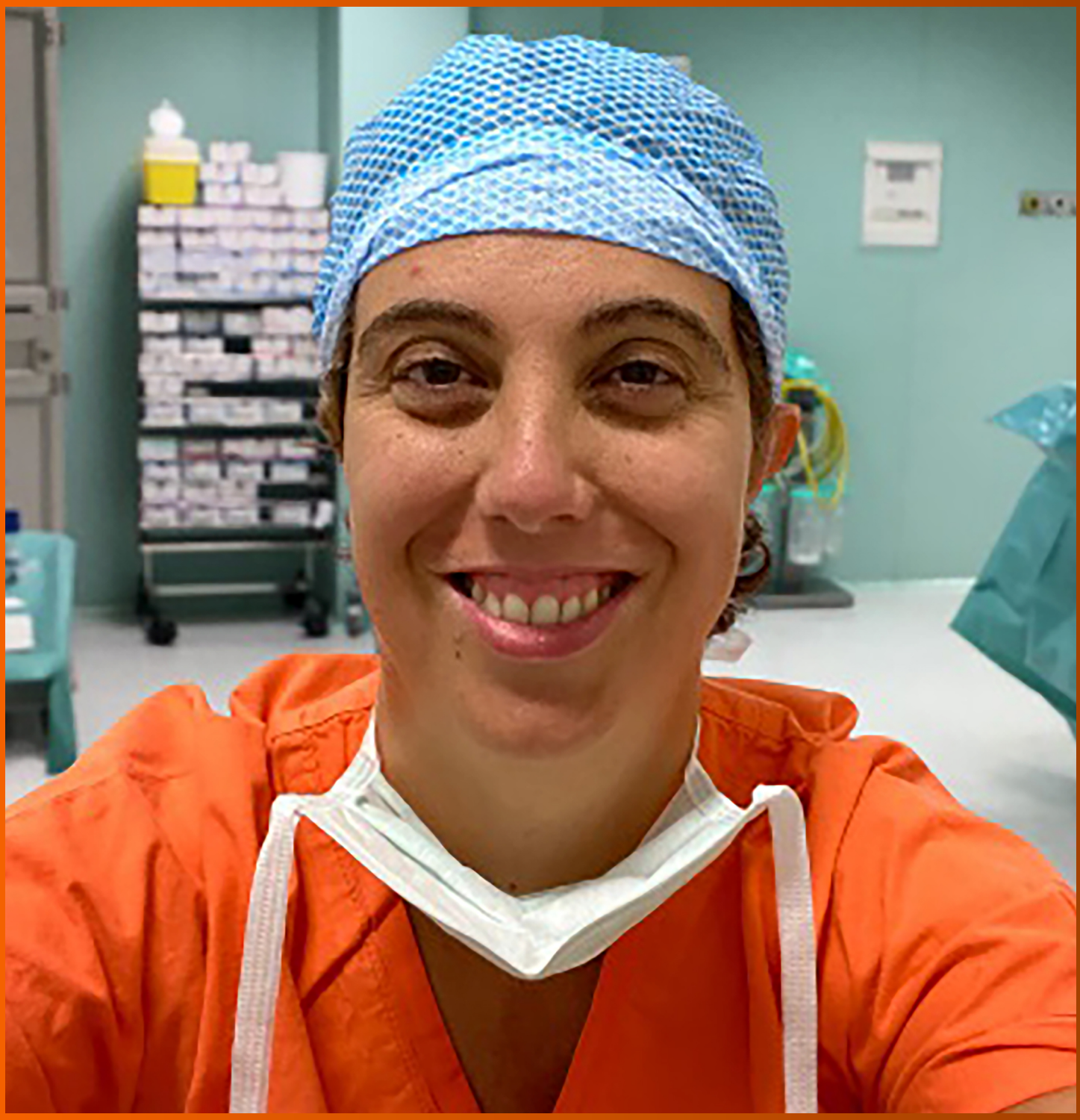
ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2021 September 27; 13(9): 885-1109



Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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## RESPONSIBLE EDITORS FOR THIS ISSUE

**Production Editor:** *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Shu-You Peng, Varut Lohsiriwat, Jin Gu

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-9366/editorialboard.htm

**PUBLICATION DATE**
September 27, 2021



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*World J Gastrointest Surg* 2021 September 27; 13(9): 885-903

DOI: 10.4240/wjgs.v13.i9.885

ISSN 1948-9366 (online)

*REVIEW*

# Neoadjuvant treatment: A window of opportunity for nutritional prehabilitation in patients with pancreatic ductal adenocarcinoma

Ilaria Trestini, Marco Cintoni, Emanuele Rinninella, Futura Grassi, Salvatore Paiella, Roberto Salvia, Emilio Bria, Carmelo Pozzo, Sergio Alfieri, Antonio Gasbarrini, Giampaolo Tortora, Michele Milella, Maria Cristina Mele

**ORCID number:** Ilaria Trestini 0000-0002-4958-9771; Marco Cintoni 0000-0002-9610-0748; Emanuele Rinninella 0000-0002-9165-2367; Futura Grassi 0000-0001-6234-3541; Salvatore Paiella 0000-0001-6893-8618; Roberto Salvia 0000-0002-3514-8473; Emilio Bria 0000-0002-2333-704X; Carmelo Pozzo 0000-0003-4004-9098; Sergio Alfieri 0000-0002-7813-4426; Antonio Gasbarrini 0000-0002-7278-4823; Giampaolo Tortora 0000-0002-1378-4962; Michele Milella 0000-0002-3826-5237; Maria Cristina Mele 0000-0002-8463-7062.

**Author contributions:** Trestini I and Cintoni M were involved in the collection and synthesis of all data and manuscript writing; Rinninella E, Grassi F, Paiella S, Salvia R, Pozzo C, Alfieri S, and Gasbarrini A oversaw the project progress and were involved in the final editing of the manuscript; Bria E, Tortora G, and Milella M were involved in the writing and revision of the manuscript; Mele MC was involved in the idea, writing, and revision of the manuscript; All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** Trestini I reported speakers' fees from Mylan and Fresenius Kabi. Bria E received speakers' and travels' fee from MSD, Astra-

**Ilaria Trestini, Michele Milella,** Section of Oncology, Department of Medicine, Pancreas Institute, University of Verona Hospital Trust, Verona 37126, Italy

**Marco Cintoni,** Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Roma 00133, Italy

**Emanuele Rinninella, Futura Grassi,** UOC Nutrizione Clinica, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico A. Gemelli IRCCS, Roma 00168, Italy

**Emanuele Rinninella, Sergio Alfieri, Antonio Gasbarrini, Maria Cristina Mele,** Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Roma 00168, Italy

**Salvatore Paiella, Roberto Salvia,** General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona Hospital Trust, Verona 37126, Italy

**Emilio Bria, Carmelo Pozzo, Giampaolo Tortora,** Oncologia Medica Unit, Comprehensive Cancer Center, Fondazione Policlinico Universitario A Gemelli IRCCS, Roma 00167, Italy

**Emilio Bria, Carmelo Pozzo, Giampaolo Tortora,** Oncologia Medica Unit, Università Cattolica del Sacro Cuore, Roma 00168, Italy

**Sergio Alfieri,** Digestive Surgery Unit and Pancreatic Surgery Gemelli Center Director, Fondazione Policlinico Universitario A Gemelli IRCCS, Roma 00167, Italy

**Antonio Gasbarrini,** UOC di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A Gemelli IRCCS, Roma 00167, Italy

**Maria Cristina Mele,** UOSD Nutrizione Avanzata in Oncologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A Gemelli IRCCS, Roma 00167, Italy

**Corresponding author:** Marco Cintoni, MD, Doctor, Scuola di Specializzazione in Scienza dell'Alimentazione, Università di Roma Tor Vergata, Viale Oxford 81, Roma 00133, Italy. marco.cintoni@gmail.com

## Abstract

Patients affected by pancreatic ductal adenocarcinoma (PDAC) frequently present

Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche; consultant's fee from Roche, Pfizer; institutional research grants from Astra-Zeneca, Roche. Bria E is currently supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) under Investigator Grant (IG) No. IG20583. Bria E is currently supported by Institutional funds of Università Cattolica del Sacro Cuore (UCSC-project D1-2018/2019). Tortora G is supported by AIRC, IG18599, AIRC 5x1000 21052. Milella M reported personal fees from Pfizer, EUSA Pharma and Astra Zeneca. Other Authors declare no conflict of interest.



**Manuscript source:** Invited manuscript

**Specialty type:** Nutrition and dietetics

**Country/Territory of origin:** Italy

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 12, 2021
**Peer-review started:** February 12, 2021
**First decision:** May 13, 2021
**Revised:** May 28, 2021
**Accepted:** July 20, 2021
**Article in press:** July 20, 2021
**Published online:** September 27,

with advanced disease at the time of diagnosis, limiting an upfront surgical approach. Neoadjuvant treatment (NAT) has become the standard of care to downstage non-metastatic locally advanced PDAC. However, this treatment increases the risk of a nutritional status decline, which in turn, may impact therapeutic tolerance, postoperative outcomes, or even prevent the possibility of surgery. Literature on prehabilitation programs on surgical PDAC patients show a reduction of postoperative complications, length of hospital stay, and readmission rate, while data on prehabilitation in NAT patients are scarce and randomized controlled trials are still missing. Particularly, appropriate nutritional management represents an important therapeutic strategy to promote tissue healing and to enhance patient recovery after surgical trauma. In this regard, NAT may represent a new interesting window of opportunity to implement a nutritional prehabilitation program, aiming to increase the PDAC patient's capacity to complete the planned therapy and potentially improve clinical and survival outcomes. Given these perspectives, this review attempts to provide an in-depth view of the nutritional derangements during NAT and nutritional prehabilitation program as well as their impact on PDAC patient outcomes.

**Key Words:** Pancreatic cancer; Neoadjuvant treatment; Pancreatic cancer surgery; Nutritional status; Nutritional prehabilitation; Malnutrition



**Core Tip:** Among pancreatic ductal adenocarcinoma patients with resectable or borderline resectable disease, and those with locally advanced disease with a feasibility of surgical resection of up to 30%, neoadjuvant treatment (NAT) has become the standard of care. NAT may impair functional reserve and lead to nutritional depletion, which may affect therapeutic tolerance, postoperative outcomes or even prevent the possibility of surgery. This review suggests that NAT timeframe may provide a valuable opportunity for nutritional prehabilitation program to minimize the NAT-related nutritional derangements, increase patient's capacity to complete planned therapy, promote tissue healing, and enhance patient's recovery, thus potentially improve outcomes.

**Citation:** Trestini I, Cintoni M, Rinninella E, Grassi F, Paiella S, Salvia R, Bria E, Pozzo C, Alfieri S, Gasbarrini A, Tortora G, Milella M, Mele MC. Neoadjuvant treatment: A window of opportunity for nutritional prehabilitation in patients with pancreatic ductal adenocarcinoma. *World J Gastrointest Surg* 2021; 13(9): 885-903
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/885.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.885

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), with 458918 new cases in 2018, represents the 14th neoplasia in incidence, and with a 95% overall mortality rate, is the 7th leading cause of cancer-related death[1].

### *Current PDAC treatment*

Surgical resection is the only potentially curative treatment for PDAC[2]. Nevertheless, an upfront surgical approach is often unfeasible, because most patients are diagnosed with an advanced PDAC stage, due to a lack of early symptoms and to the fast tumor progression[2]. In this context, neoadjuvant treatment (NAT) consisting of chemotherapy and/or chemoradiation has become the standard of care to downstage non-metastatic locally advanced PDAC patients[3]. Moreover, NAT is gaining popularity in both borderline and fully resectable patients to allow a more accurate and complete cytoreduction (R0)[4-6]. Resection rates range from 26% to 60% in patients showing a good NAT response, rising to 67.8% in patients with anatomically borderline resectable disease[7], with a high percentage of R0 resections and a more

2021

**P-Reviewer:** Koustas E
**S-Editor:** Zhang H
**L-Editor:** Filipodia
**P-Editor:** Ma YJ

than doubled median overall survival (OS)[8,9]. Adjuvant treatment after surgery, using a combination of chemotherapy and radiotherapy, is used to increase the local control of disease[3].

### *Impact of nutritional issues on PDAC*

Common presentation hallmarks of PDAC are unintentional weight loss (WL) and malnutrition, defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"[10], and sustained by cancer-induced metabolic changes and by a reduced nutrient intake[11]. Moreover, the loss of parenchyma and/or obstruction of the main pancreatic duct may affect both the production of enzymes and their transportation into the duodenum, resulting in nutrients maldigestion and/or malabsorption[12].

Over 80% of PDAC patients present with WL at diagnosis, and more than one-third reports a WL > 10% of their usual body weight[13]; moreover, NAT may worsen nutritional status, impairing postoperative outcomes and even delaying or preventing surgical intervention[14,15]. Malnutrition in PDAC patients may reach high rates (up to 80%) at diagnosis, and it is associated with a worse performance status and a worse OS[16].

Sarcopenia, defined as "a progressive and generalized skeletal muscle (SKM) disorder that is associated with increased likelihood of adverse outcomes"[17], is another frequent condition reported in more than 50% of PDAC patients[18]. It is associated with poorer surgical outcomes and a higher length of hospital stay (LOS) [19], and has been identified as a relevant prognostic factor for OS in patients treated with both gemcitabine (GEM) based and FOLFIRINOX-like (leucovorin, fluorouracil, irinotecan, and oxaliplatin) chemotherapies[20-22].

Improvement of patient nutritional status during NAT and prior to surgery may lead to better surgical outcomes and be an important part of oncological management [23,24]. The best nutritional strategy to manage PDAC patients is still under debate, even if an appropriate nutritional support represents an important therapeutic strategy in the preoperative period[23]. While cancer-related malnutrition is still an underrecognized and undertreated burden in clinical practice[25,26], emerging data show that early closing of the nutritional gap during anticancer treatment can stabilize WL, improve treatment tolerability, reduce the performance status deterioration, and ameliorate survival rate[27,28].

The aim of this review is to explore if the NAT period may represent an exploitable therapeutic window to perform a nutritional prehabilitation program improving clinical and survival outcomes.

## METHODOLOGY

This review was conducted on Medline, from inception to January 2021, aiming to identify published studies exploring the role of nutritional status and preoperative nutritional prehabilitation on the outcomes in pancreatic cancer (PC) patients. The inclusion criteria for the studies were as follows: observational, prospective and retrospective studies, case-control studies, cohort studies, narrative reviews, systematic reviews, and meta-analyses; studies including information about nutritional status and/or nutritional prehabilitation on PC patients; exclusive PC studies; and studies written in English. All studies that did not fall into the previous criteria were excluded from the review process.

## NUTRITIONAL STATUS CHANGES DURING NEOADJUVANT TREATMENT AND THEIR POTENTIAL RELATIONSHIPS WITH THERAPEUTIC OUTCOMES

Approximately one-third of PDAC patients are diagnosed with locally advanced disease, which prevents an immediate surgical approach[29]. In this setting, NAT has become the standard of care as either exclusive treatment or to achieve resectability[9, 30,31], while its use in "borderline" and "resectable" disease is still under debate, even if it has become more popular[32].

This therapeutic implementation represents an additional nutritional concern; in fact, NAT cause several side effects, such as oral ulceration, xerostomia, dysgeusia, indigestion, nausea, vomiting, diarrhea, and alteration of intestinal motility, leading to a reduced food intake, with significant consequences on body composition, and in particular on SKM mass[33]. This in turn, may impact NAT completion, postoperative outcomes or even impede the possibility of surgery[10,34].

A prospective study including patients with upper gastrointestinal cancers found that NAT-treated patients experienced greater losses in the SKM area measured at L3 vertebra by computed tomography (CT) scan, compared with patients receiving palliative chemotherapy (-6.6 $cm^2$, 95% confidence interval [CI] -10.2 to -3.1; $P < 0.001$ and -1.2 kg, 95%CI -1.8 to -0.5; $P < 0.001$, respectively)[35].

Naumann *et al*[35] analyzed 100 consecutive locally advanced PDAC patients, treated with 4 wk of GEM-based NAT and found that body weight (mean weight from 69.0 kg to 66.4 kg; $P < 0.0001$), body mass index (BMI) (mean BMI from 24.3 kg/$m^2$ to 23.4 kg/$m^2$; $P < 0.0001$), and CT-derived subcutaneous adipose tissue (SAT) area (mean SAT from 167.1 $cm^2$ to 139.5 $cm^2$; $P < 0.0001$) significantly decreased after NAT. Interestingly, there was no significant correlation between increasing extent of WL and survival (WL < 2.5%: median survival of 10.8 mo (range 3.2–46.8); 2.5% ≤ WL < 5.0%: 10.9 mo (range 5.0–27.6); 5.0% ≤ WL < 7.5%: 10.0 mo (range 3.1–26.5); 7.5% ≤ WL < 10.0%: 8.4 mo (range 3.1–16.3); WL ≥ 10.0%: 7.3 mo (range 6.1–10.2)[36]. A retrospective analysis of 89 patients with potentially resectable PDAC, who received a 12-wk regimen of neoadjuvant GEM/cisplatin followed by short-course radiotherapy with concurrent GEM as part of a phase II study, reported a significant depletion of SKM, (median SKM area/height$^2$from 47.5 $cm^2/m^2$ to 46.3 $cm^2/m^2$; $P = 0.01$), visceral adipose tissue (VAT) (median VAT area/height$^2$ from 45.1 $cm^2/m^2$ to 41.2 $cm^2/m^2$; $P = 0.01$), and SAT (median SAT area/height$^2$ from 53.0 $cm^2/m^2$ to 48.7 $cm^2/m^2$; $P = 0.02$). Progressive SKM during NAT was related to a shorter disease-free survival (DFS) (hazard ratio [HR] 0.89, 95%CI 0.80-1.00; $P = 0.04$), while VAT loss was associated with both shorter progression-free survival (HR 0.98, 95%CI 0.96-0.99; $P = 0.01$) and OS (HR 0.97, 95%CI 0.95-0.99; $P = 0.001$)[37]. Another retrospective study evaluated 127 PDAC patients who achieved resectability following approximately 5 mo of NAT, using an array of different chemotherapy regimens (mostly GEM- or fluorouracil-based regimens), found minimal changes in SKM (−0.5 ± 7.8%; $P > 0.05$), VAT (−1.8 ± 62.6%; $P < 0.001$), and SAT (−4.8 ± 27.7%; $P < 0.001$)[38]. A more recent retrospective analysis of 147 locally advanced PDAC patients, treated with NAT, showed a mean WL of 3.7 kg ($P < 0.0001$), a mean SKM area reduction of 4.2 $cm^2$ ($P < 0.0001$), while a WL > 5% and a SKM loss were associated with a worse OS (14.5 mo *vs* 20.3 mo; $P = 0.04$ and 15.1 mo *vs* 22.2 mo; $P = 0.007$, respectively)[39]. Similarly, Naumann *et al*[39] observed a significant decrease in weight (mean relative WL of 5.3%; $P < 0.001$), as well as in SAT (from 142.1 $cm^2$ to 115.2 $cm^2$; $P < 0.0001$), VAT (from 114.7 $cm^2$ to 95.0 $cm^2$; $P < 0.0001$) and SKM (from 126.0 $cm^2$ to 121.5 $cm^2$; $P < 0.0001$) during NAT among 141 PDAC patients. Moreover, WL > 5% (HR 2.8, 95%CI 1.28-5.91; $P = 0.009$) and a reduction in SKM > 5% (HR 5.54, 95%CI 2.56-12.45; $P < 0.001$) were independently associated with survival[40].

A large multicenter study by Sandini *et al*[40] including 193 PDAC patients who received NAT (64.2% of patients receiving FOLFIRINOX and 44.6% also undergoing chemoradiotherapy) observed a significant loss of adipose tissue during treatment (median total adipose tissue area from 284 $cm^2$ to 250 $cm^2$; $P < 0.001$), with no wasting of lean body mass (median SKM from 122.1 $cm^2$ to 123 $cm^2$; $P = 0.001$). Furthermore, the authors found that an SKM increase was associated with a higher resectability rate (OR 3.7; $P = 0.006$), suggesting that anabolic potential was preserved in this subset of patients and that the ability to enhance muscle tissue may be related to the treatment response[41]. Conversely, a more recent prospective analysis of 67 PDAC patients reported a deterioration in SKM (median SKM from 128.4 $cm^2$ to 120 $cm^2$; $P < 0.001$), and adipose tissue (intra-muscular adipose tissue, VAT, and SAT) during NAT, using different chemotherapy regimens (FOLFIRINOX: 44% of patients; GEM-based chemotherapy: 47%) ($P < 0.0001$). In addition, loss of lean tissue (mean fat-free mass loss 2.6 kg, HR 1.1, $P = 0.003$, mean SKM loss 1.5 kg, HR 1.21; $P = 0.001$) and loss of fat mass (mean loss 2.8 kg HR 1.09, $P = 0.004$) during treatment were related to a higher mortality risk. In multivariable analysis, the preservation of muscle during NAT was predictive of better survival (HR 1.21, 95%CI 1.08-1.35; $P = 0.025$)[42]. An overview of these studies is reported in Table 1.

In PDAC patients treated with NAT, these data highlight that anthropometric, as well as CT-scan derived body composition parameters can be useful to identify high-risk nutritional phenotypes. In the same setting, the inability to maintain body weight and SKM is associated with poor survival outcomes, while the preservation of body

**Table 1 Prognostic role of nutritional status changes during neoadjuvant therapy in patients with pancreatic cancer**

| Ref. | Number of patients enrolled | Neoadjuvant treatment | Body composition changes (*P* value) | Body parameters and clinical outcomes (HR; *P* value) |
|---|---|---|---|---|
| Naumann *et al*[35], 2013, Retrospective | 100 | Gemcitabine-based chemoradiation | Weight decrease ($P < 0.0001$), BMI decrease ($P < 0.0001$), SAT decrease ($P < 0.0001$) | WL tended to negatively impact on OS ($P > 0.05$) |
| Cooper *et al*[36], 2015, Retrospective | 89 | Gemcitabine and Cisplatin followed by Gemcitabine-based chemoradiation | SKM area/height$^2$ decrease ($P = 0.01$), VAT area/height$^2$ decrease ($P = 0.01$), SAT/height$^2$ decrease ($P = 0.02$) | Loss of SKM was related to a shorter DFS (HR 0.89, $P = 0.04$), loss of VAT was related to shorter PFS (HR 0.97, $P = 0.01$) and OS (HR 0.97, $P = 0.001$) |
| Cloyd *et al*[37], 2018, Retrospective | 127 | Gemcitabine, Capecitabine or 5-FU based chemoradiation | SKM stability ($P > 0.05$), VAT decrease ($P < 0.001$), SAT decrease ( $P = 0.02$) | Body composition changes during were not associated with OS ($P > 0.05$) |
| Sandini *et al*[40], 2018, Retrospective | 193 | FOLFIRINOX-based chemoradiotherapy | TAT area decrease ($P < 0.001$), VAT area decrease ($P < 0.0001$), SKM area increase ($P < 0.0001$) | SKM area/height$^2$ was higher in patients who underwent resection ($P = 0.004$) |
| Naumann *et al*[38], 2019, Retrospective | 147 | Gemcitabine-based chemoradiation | Weight decrease ($P < 0.0001$), SKM area decrease ($P < 0.0001$) | WL > 5% was associated with poor OS (HR 1.56, $P = 0.028$), SKM area loss > 5% was associated with poor OS (HR 1.50, $P = 0.036$) |
| Griffin *et al*[41], 2019, Retrospective | 78 | FOLFIRINOX and gemcitabine-based treatments | SKM area decrease ($P < 0.0001$), VAT decrease ($P < 0.0001$), SAT decrease ($P < 0.0001$) | Loss of lean mass was related to poor OS (HR 1.1, $P = 0.003$), loss of SKM was related to poor OS (HR 1.21, $P = 0.001$) |
| Naumann *et al*[39], 2019, Retrospective | 141 | Gemcitabine-based chemoradiation | Weight decrease ($P < 0.001$), BMI decrease ($P < 0.0001$), SAT, VAT and SKM areas decrease ($P < 0.0001$) | WL > 5% was associated with worse OS (HR 2.8, $P = 0.009$), SKM area loss > 5% was associated with poor OS (HR 5.54, $P < 0.001$) |

BMI: Body mass index; DFS: Disease-free survival; HR: Hazard ratio; IMAT: Intramuscular adipose tissue; OS: Overall survival; PFS: Progression-free survival; SAT: Subcutaneous adipose tissue; SKM: Skeletal muscle; TAT: Total adipose tissue; VAT: Visceral adipose tissue; WL: Weight loss.

composition compartments represents a positive prognostic feature. However, this topic deserves well-designed and adequately sized trials to confirm these preliminary data.

## EFFECT OF MALNUTRITION ON SURGICAL AND SURVIVAL OUTCOMES

### *Postoperative complications*

Pancreatic surgery is associated with a relatively high risk of postoperative complications (POCs), due to its technical complexity and to the anatomical location of the pancreas. Most frequent POCs are postoperative pancreatitis (incidence up to 25%-30%)[43,44], delayed gastric emptying (incidence 20%-30%)[45,46], and postoperative pancreatic fistula (10%-15%)[47,48]. Other less common POCs are represented by post pancreatectomy hemorrhage (PPH), intra-abdominal abscesses, anastomotic leakage, venous thrombosis, and biliary stenosis[49,50].

Several studies have highlighted the impact of malnutrition on the incidence of POC. In a retrospective study performed by Kanda *et al*[51] in 2011, a low prognostic nutritional index (PNI), based on serum albumin concentration and total lymphocyte count, was independently associated with the development of POC, particularly postoperative fistula (HR 2.52, 95%CI 1.37-4.63). La Torre *et al*[52] retrospectively correlated nutritional status, assessed by the Malnutrition Universal Screening Tool (MUST), with POC and found that MUST was an independent predictor of overall morbidity (HR 2.66, 95%CI 1.36-8.57; $P = 0.001$) in 143 PDAC patients. In a prospective study published by Darnis *et al*[53] the Nutritional Index Risk resulted an independent factor for the development of PPH ($P = 0.048$). Nanashima *et al*[54] performed a prospective study of 222 PDAC patients to evaluate the relationship between PNI and POC, finding a lower PNI value in patients who developed POC, without statistically significant differences. In a very recent study, Mackay *et al*[55] performed a nationwide analysis of 1306 PDAC patients and found an incidence of 24% of severe POC, which was identified among the independent factors for not receiving adjuvant

chemotherapy (OR 0.32), in particular pancreatic fistula (OR 0.51) and PPH (OR 0.36).

Body composition, particularly the presence of sarcopenia, is also associated with POC development[56]. Amini *et al*[57,58] reported that sarcopenia, assessed by total psoas volume, was associated with higher risk of POC (OR 1.79). Nishida *et al*[59] performed a retrospective study finding a higher rate of major POC and particularly of pancreatic fistula development (OR 2.87) in sarcopenic patients (assessed by the SKM index). However, a recent meta-analysis of 42 studies with 7619 patients involved, showed that preoperative sarcopenia was not associated with overall POC development nor with pancreatic fistula[60].

### *Survival outcomes*

Preoperative nutritional status may play a crucial role in survival rate after surgical oncologic resection. A recent meta-analysis by Liu *et al*[61], including 11 studies with 2123 PDAC patients, indicated that a low PNI was a significant independent predictor of a worse OS (HR 1.57, 95%CI 1.40-1.77; $P < 0.001$). Furthermore, preoperative PNI was found to be an independent risk factor for failure to complete planned adjuvant chemotherapy (OR 6.47; $P = 0.033$)[62].

Serum albumin may be associated with the nutritional status and is a prognostic factor for several cancers[63-65]. Hendifar *et al*[66], in a cohort of 106 patients with resected PDAC, the authors observed that a decrease in serum albumin was significantly correlated with a worse DFS (HR 2.2; $P = 0.024$) and preoperative albumin was correlated with a worse OS (HR 0.48; $P = 0.008$), while preoperative BMI and BMI changes during therapies were not associated with survival outcome, in line with previous analyses[67].

A recent systematic review of PDAC patients showed that sarcopenia was independently associated with a shorter OS in five of eight studies, many of which used measurements of total psoas area or total psoas index for comparison, without identifying an optimal cut-off, that indeed varied widely[56]. Another systematic review and meta-analysis by Bundred *et al*[60] reported that preoperative sarcopenia was related to lower OS in both resectable (HR 1.95; $P < 0.001$) and in actually resected patients (HR 1.78; $P < 0.001$), even if the conclusions were limited by the high heterogeneity ($I^2$: 92%) between studies, due to the different methods of body composition assessment.

Regarding DFS, a retrospective analysis by Okumura *et al*[68] determined that a low preoperative SKM was a negative independent prognostic factor both for OS (HR 2.0; $P < 0.001$) and DFS (HR 1.6; $P = 0.007$), the completion rate of adjuvant chemotherapy in patients with low psoas muscle mass index was significantly lower (65.6% *vs* 80.1%; $P < 0.001$) but upon multivariate analysis, only a low PNI remained an independent prognostic factor for worse OS and DFS. In line with these findings, Sugimoto *et al* retrospectively showed that the measure of height-adjusted and sex-standardized amount of the SKM area was related to both OS (HR 1.36; $P = 0.035$) and DFS (HR 0.84; $P = 0.007$) in patients undergoing upfront surgical resection for PDAC[69].

Sarcopenic obesity (defined as the presence of sarcopenia in an obese patient)[70] was significantly associated with a worse OS (12.9 mo *vs* 20.7 mo; $P = 0.04$) in the study by Cooper *et al*[36] in patients with potentially resectable PDAC treated within a phase II trial of NAT. A meta-analysis by Mintziras *et al*[18] including 11 studies comprising 2297 PDAC patients, found that sarcopenia was significantly associated with a poor OS (HR 1.49; $P < 0.001$) and the mortality risk was even higher in sarcopenic obese patients (HR 2.01; $P < 0.001$). Recently, a retrospective analysis of PDAC patients that underwent pancreatic resection, confirmed that sarcopenic obese patients had a worse OS (14 *vs* 23 mo; $P = 0.007$)[19].

## EVIDENCE FOR POTENTIAL CLINICAL BENEFIT WITH PREOPERATIVE NUTRITIONAL PREHABILITATION

In the Enhanced Recovery After Surgery (ERAS) era, the "prehabilitation," an intervention aimed at enhancing a patient's functional capacity to enable him/her to better cope with a stressful event, has become an evolving area of interest[71]. In this context, preoperative nutritional therapy is increasingly recognized as a crucial component to optimize nutrient stores in preparation for the metabolic demands of surgical trauma, conditioning patients to become stronger for an earlier recovery[23]. Major surgery involves several metabolic and nutritional changes, through the activation of an inflammatory cascade and the release of stress hormones and cytokines, whose intensity is correlated with the degree of tissue injury[72]. Therefore,

an adequate preoperative physiological reserve is required to meet the functional demands of the surgical stress and to support the stress-induced mobilization of nutritional substrates[73]. Of note, patients with low preoperative reserves, including malnourished, frail and sarcopenic ones, may exhaust their nutritional reserves rapidly and, therefore, they cannot respond to the increased requirements following surgery[23].

Pancreatic surgery is identified as one of the most challenging surgical areas, due to the magnitude of the dissection and resection, the anatomical location, the resultant global stress, and the relatively high rate of morbidity[34,74]. Several studies have reported improved postoperative outcomes and shorter LOS in patients treated according to ERAS principles, as compared to those receiving conventional care[61,75,76]. As many patients scheduled for PDAC surgery are nutritionally depleted, particular attention should be paid to the preoperative nutritional optimization in this clinical scenario[77], as recommended by evidence-based guidelines for preoperative care for pancreaticoduodenectomy by the ERAS Society, the European Society for Clinical Nutrition and Metabolism (ESPEN), and the International Association for Surgical Metabolism and Nutrition, published in 2013[78]. Preoperative care should include careful nutritional assessment, detection of body composition parameters, and thus a personalized preoperative nutritional optimization[79]. Oral feeding remains the best approach[80], while the role of oral nutritional supplements (ONSs) in malnourished patients is well established, and the ONS role in well-nourished ones is still debated.

According to ERAS Society guidelines, routine use of preoperative enteral nutrition is not recommended, but there is a low-level evidence suggesting that a preoperative nutritional support may be indicated in patients with malnutrition[78]. A recent systematic review of studies conducted on ERAS protocols for patients scheduled for pancreaticoduodenectomy since 2013 emphasized the role of preoperative oral immuno-nutrition in the prevention of incisional wound infections, as well as in the reduction of surgical stress, and suggested that preoperative enteral nutrition should be applied for 10 to 14 d before surgery in patients with severe malnutrition[81].

The recently published International Study Group on Pancreatic Surgery consensus statement regarding nutritional support for pancreatic surgery established that nutritional counselling and ONSs are recommended in patients with moderate malnutrition with no evidence of gastric obstruction, or in those who have a moderate risk of nutritional worsening in the early postoperative period. An aggressive preoperative nutritional support by enteral or parenteral feeding should be considered if at least one of the following criteria, reflecting severe malnutrition, is met[34]: WL > 15% within 6 mo; BMI < 18.5 kg/m$^2$; subjective global assessment grade "C" or nutritional risk score ≥ 5; and serum albumin < 30 g/dL (with no evidence of hepatic or renal dysfunction).

The benefit of preoperative nutritional intervention combined with physical exercise is still a subject of debate. In this regard, a recent Asian analysis among 108 patients undergoing hepato-pancreato-biliary surgeries for malignancy showed that the implementation of prehabilitation, integrating preoperative exercise and nutritional therapy, has the potential to improve outcome, preventing serum albumin deterioration (median, 0.10 *vs* -0.30; $P = 0.001$), increasing total muscle/fat ratio (median, 1.83 *vs* 1.75; $P < 0.001$), shortening postoperative LOS (median, 23 d *vs* 30 d; $P = 0.045$), leading to a potential positive economic impact[82].

Focusing on prehabilitation in 40 patients (45% PDAC) undergoing pancreaticoduodenectomy, a recent randomized controlled trial by Ausania *et al*[83] estimated the effect of preoperative nutritional support, control of diabetes and exocrine pancreatic insufficiency and physical, as well as respiratory training. Although prehabilitation was not associated with a lower POC incidence, a lower rate of delayed gastric emptying (5.6% *vs* 40.9%; $P = 0.01$) and a lower clinically relevant pancreatic fistula rate (11.1% *vs* 27.3%; $P$ = n.s.) were found in the prehabilitation group. However, this study had several limitations in terms of methodology and was potentially flawed by the short prehabilitation time (patients receiving only 7 d of prehabilitation were included).

In this context, Okumura *et al*[68] suggested that although the ideal period of preoperative nutritional and exercise therapeutic protocols is not established, at least 1 mo before surgery is required to improve nutritional status. Unfortunately, routine nutritional assessment within the ERAS programs is only partially implemented, probably due to insufficient awareness about nutritional issues among health professionals, lack of structured collaboration between surgeons and clinical nutrition specialists, and the absence of dedicated resources[79].

Studies evaluating nutritional optimization before surgery for PDAC are producing encouraging early results, but definitive clinical evidence is very limited. Further studies on this topic are eagerly warranted.

## NUTRITIONAL MANAGEMENT

Nutritional management should be started preoperatively to optimize nutritional status in preparation for the increased metabolic requirements of surgical injury. An overview of the suggested nutritional interventions during NAT for PDAC is shown in Figure 1 and in Table 2. An accurate identification of patients at high nutritional risk or already malnourished is crucial to choose the optimal type and timing of nutritional intervention[84]. There are many nutritional risk tools that can be used in clinical practice. Of note, none of the available clinic-biological scores for nutritional assessment meets the diagnostic performance criteria to predict POC after pancreatic surgery, and the proportion of patients at high risk for deranged nutritional status varies using different scores[85].

The inconsistency in predicting poor outcomes with different nutritional screening tools may lead to either insufficient or excessive nutritional treatments, with potentially harmful effects. In this regard, the new Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis and grading of malnutrition have been introduced and recently validated in a large population of patients undergoing abdominal surgery, including pancreatic resections[86]. According to GLIM criteria, a patient can be defined malnourished if, after a positive risk screening test for malnutrition, presents at least one phenotypic criterion (non-intentional WL, low BMI, or reduced muscle mass) and one etiologic criterion (reduced food intake/assimilation, or inflammation/disease burden)[87].

Numerous studies have shown the prognostic impact of body composition assessment by CT-scan in oncological patients and in those undergoing cancer treatments[88-91]. Especially, in patients undergoing NAT, CT scans are usually performed several times during treatment. Therefore, CT scan-based body composition analysis could be easily implemented in routine clinical practice.

### *Energy intake*

Energy balance in catabolic condition, as in PDAC patients, is deeply influenced by changes in dietary intake[92], therapy-linked factors[93], and decreased levels of physical activity[94].

Okusaka *et al*[95] found that a longer survival time was associated with a high energy intake in patients affected by advanced PDAC ($P$ = 0.02). Moreover, Bye *et al*[96] in their work, found a correlation between PDAC-specific symptoms (*e.g.*, pain, fatigue, nausea), WL, and poor energy intake. The caloric requirement of PDAC patients should be assessed in a personalized way and when energy expenditure is not measured individually, ESPEN guidelines suggest an intake of 25-30 kcal/kg/day[97].

In conclusion, assessment of energy intake should be guaranteed in PDAC patients with the aim to elaborate a personalized nutritional strategy in order to decrease the risk of WL and consequently malnutrition.

### *Protein intake*

Recent literature data on nutritional support in oncological patients attribute high relevance to correct protein intake (PI), with the aim to promote muscle anabolism [98]. Sarcopenic patients, similar to oncological ones, have poor protein stores and this could contribute to increased POC, LOS and mortality[23]. The most recent and interesting theories affirm that the best way to prepare the patient to the surgical trauma should be a multimodal approach, which includes nutritional changes, psychological support, and physical training[99,100]. ESPEN guidelines on nutrition in cancer patients set the PI target to 1.2-1.5 g/kg per day. However, it is not clarified if there are specific amino acid mixtures that can improve clinical outcomes in this setting[97].

Several studies have highlighted the role of branched-chain amino acids (BCAAs) to decrease muscle catabolism[101]. Between the first studies conducted on this field of research, Tayek *et al*[102] found a higher response in terms of protein accretion and albumin synthesis using BCAA-enriched parenteral nutrition (PN) formulas with respect to standard PN. More recently, Deutz *et al*[103] conducted a randomized, controlled, double-blind study on 25 cancer patients, with the interventional group receiving a functional food enriched with 40 g of protein and leucine. In this group, the rate of muscle protein synthesis was higher than the control group ($P$ = 0.02). β-

**Table 2 Nutritional recommendation during neoadjuvant therapy in patients with pancreatic cancer**

| Nutritional recommendation during neoadjuvant therapy in patients with pancreatic cancer | |
|---|---|
| Energy intake | Total energy expenditure should be measured; otherwise, 25 to 30 kcal/kg/d should be guaranteed |
| Protein intake | 1.2-1.5 g/kg/d should be prescribed |
| Fish oil | Fish oil supplementation may improve the metabolic derangements |
| PERT | Tumor in the head: start PERT immediately |
| | Tumor in the body/tail: Perform PEI test before prescribing PERT |
| Immunonutrition | Immunonutrition-based supplements may improve clinical outcomes |

PERT: Pancreatic enzymes replacement therapy; PEI: Pancreatic exocrine insufficiency.

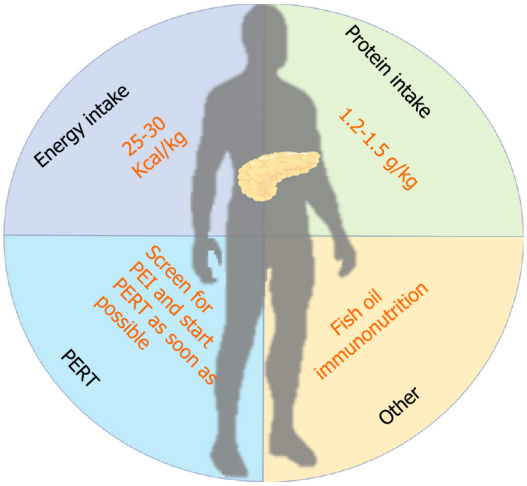


**Figure 1 Suggested nutritional interventions during neoadjuvant treatment for pancreatic ductal adenocarcinoma.** PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

hydroxy-β-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine, which induces an anabolic effect in cancer patients, promoting regenerative events, suppressing protein degradation, and activating anabolic signaling pathways[104]. In many murine preclinical studies HMB showed the potential to reduce WL, tumor weight, and to attenuate protein degradation[105,106]. In the study by May *et al*[107], which also included advanced PDAC patients, the authors found an increase of fat-free mass (FFM) in patients treated with a mixture of HMB (3 g/d), L-arginine (14 g/d), and L-glutamine (14 g/d) *vs* the control group. On the other hand, a randomized, double-blind, placebo-controlled trial performed by Berk *et al*[108], showed no statistical differences in FFM among patients treated with the same mixture. Despite the lack of a strong evidence from the literature, it is advisable to refer to ESPEN guidelines and recommend a PI of 1.2-1.5 g/kg per day in PDAC patients.

### *Fish oil*

Fish oil (FO) is an anti-inflammatory nutraceutical, which is often used to improve the imbalance between omega-3 (w-3 FA) and omega-6 fatty acids (w-6 FA) in oncologic patients among others[109]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the w-3 FA acids found in FO that are able to induce an anti-inflammatory response[110]. Moreover, many epidemiological studies have suggested that a high consumption of FO and therefore of w-3 FA reduces the risk of pancreatic cancer[111]. These molecules are also involved in the synthesis of cell membranes[112], hormones, receptors, prostaglandins, and leukotrienes[113]. Moreover, EPA and DHA show anabolic effects when used on sarcopenic patients like oncological ones[114]. Barber [115] analyzed the impact of FO on patients with cancer cachexia, concluding that FO had the potential to normalize the metabolic derangements of oncological patients.

For all of these reasons, FO can be useful both in surgical and medical patients affected by PDAC, through oral, enteral, or parenteral administration. Werner *et al* [116] performed a randomized, double-blind, and controlled trial, comparing the administration of 500 mg FO (60% of FO and 40% of medium-chain triglycerides, 6.9 g/100 g of EPA and 13.6 g/100 g DHA) *vs* 500 mg marine phospholipids (8.5 g/100 g EPA and 12.3 g/100 g DHA) three times per day for 6 consecutive weeks. The authors found a stabilization of body weight after 6 wk in both groups ($P = 0.001$ and $P = 0.003$, respectively). Moreover, they found a significant increase in the amount of anti-inflammatory EPA and DHA, a decrease of the pro-inflammatory arachidonic acid and an increase in high-density lipoprotein in the patient's plasma of FO group. Arshad *et al* [117] described a reduction in the concentration of pro-inflammatory cytokines and growth factors using intravenous omega-3 enriched lipid emulsion with improvement in survival outcomes, in patients affected by locally advanced or metastatic PDAC eligible for GEM treatment.

### *Pancreatic enzyme replacement*

Pancreatic exocrine insufficiency (PEI) is a frequent condition that can profoundly affect the nutritional status of PDAC patients. PEI is defined as the clinical condition in which the quantity of enzymes secreted by the pancreas are not sufficient to guarantee the physiological digestive processes and can be caused by lack of production by the pancreas and/or by the obstruction of ducts by external causes, such as tumors[118]. Symptoms of PEI may vary from micronutrient deficiency to abdominal pain, flatulence, WL, and steatorrhea, defined as the presence of more than 7 g fat in the feces per day[119,120]. PEI in PDAC patients ranges from 30% to 100%, according to the method used to diagnose the condition[121].

Pancreatic enzyme replacement therapy (PERT) can improve the malabsorption-related symptoms through the amelioration of protein and fat digestion processes[122, 123].

In the paper by Roberts *et al*[124], the use of PERT was associated with an increase of survival among PDAC patients (survival time ratio: 2.62, 95%CI 2.27-3.02). Landers *et al*[125] performed a pilot study to determine the efficacy of PERT in metastatic PDAC patients, using 50.000 IU of pancrealipase for each meal and 25.000 IU for each snack, showing an improvement of symptoms and quality of life (QoL) assessed at 1 and 3 wk after the start of treatment. A retrospective analysis by Domínguez-Muñoz *et al*[126] was conducted among 160 patients with unresectable PDAC. The authors divided into two groups the study population: the first group followed the standard of care, while the second one was screened for PEI and started PERT if necessary. Survival in the second group was longer than in the first one (HR 2.117, 95%CI 1.493-3.002; $P < 0.001$). Moreover, also in patients with significant WL at diagnosis, PERT was associated with longer survival (HR 2.52, 95%CI 1.55-4.11; $P < 0.001$). PERT is, therefore, useful to treat malnutrition in PDAC patients affected by PEI, and is associated with an improvement in QoL and survival[127]. Nevertheless, the optimal dose and optimal timing of PERT administration in PDAC patients is not well defined [128]. A very recent position paper by Pezzilli *et al*[12] aimed to give recommendations on PERT in the PDAC setting, concluding that patients with head PDAC should be given enzymes, while a diagnostic evaluation should be performed using fecal elastase in patients affected by body or tail neoplasm prior to giving them PERT. Moreover, in the next few months, a Cochrane Systematic Review on this issue is planning to be published[129].

In conclusion, due to the underrecognition of this condition and its metabolic consequences, PEI should be investigated in all patients affected by PDAC, and PERT should be started as soon as possible, when necessary.

### *Immunonutrition*

Immunonutrition (IN) can be defined as modulation of the activity of the immune system by specific food or nutrients, called immunonutrients; the most important are w-3 FA, glutamine, arginine, and nucleotides[130].

The role of the IN has been studied only in a few series in the surgical setting. In 2011 Klek *et al*[131] performed a prospective, randomized, double-blind clinical trial evaluating the impact of IN on surgical patients affected by PDAC or gastric cancer, finding differences in postoperative LOS ($P = 0.006$), infectious POC ($P = 0.04$), overall morbidity ($P = 0.01$), and mortality ($P = 0.03$). The group of Shirakawa *et al*[132] also found a lower rate of incisional wound infection in the IN group *vs* standard therapy ( $P = 0.012$). Gade *et al*[133] performed a randomized controlled trial enrolling 35 surgical patients, with the aim to define the effect of 7 d of oral IN supplementation in PDAC patients. However, the author found no statistically significant improvements

in the IN group. Silvestri *et al*[134] studied the impact of oral IN in non-malnourished PDAC patients undergoing pancreaticoduodenectomy and found a significative impact on LOS ($P$ = 0.035) and infectious POC ($P$ = 0.034). On the contrary, no differences in terms of mortality and overall morbidity rate were found. While IN in surgical PDAC patients reduces POC, LOS, and improves survival rate, no data were found in the recent literature on IN use during NAT.

## NAT AS A WINDOW OF OPPORTUNITY FOR NUTRITIONAL PREHABILITATION

Patients undergoing multimodal oncological care are at increased risk of progressive nutritional worsening, with deleterious effects on surgical and oncological outcomes [135,136]. In this setting, current standard of care creates a minimum timeframe of four to 6 mo for NAT completion. This time period could thus represent a valuable opportunity for prehabilitation, to minimize the nutritional/metabolic impact of NAT, but published literature is scarce on this topic[34,137]. Indeed, most studies investigating ERAS programs/prehabilitation for PDAC excluded patients who had received preoperative NAT[82,84].

Recently, a prospective randomized control study by Akita *et al*[138] aimed at exploring whether a nutritional intervention consisting in 560 kcal/day of EPA-enriched nutritional supplements might impact on nutritional status in PDAC patients who received GEM-based neoadjuvant chemoradiotherapy. The authors reported that the psoas major muscle area ratio was significantly higher in the nutritional intervention group (median, 0.96 *vs* 0.89; $P$ = 0.001), and that patients who consumed ≥ 50% of the EPA-enriched supplement presented significantly higher SKM ratios ($P$ = 0.042). With regards to patients following NAT for locally advanced PDAC, a recent prospective analysis evaluated the impact of the preoperative IN supplementation on surgical outcomes in subjects undergoing irreversible electroporation surgery. Patients receiving IN presented a lower decrease in nutritional risk index (-12.6 *vs* -16.2; $P$ = 0.03), serum albumin levels (-1.1 *vs* -1.5; $P$ < 0.01), and experienced a statistically significant decrease in POC ($P$ = 0.05) and LOS (10.7 *vs* 17.4; $P$ = 0.01)[139].

Only a preliminary prospective study has reported the feasibility of a preoperative prehabilitation program, including nutritional counselling by a dietitian, of IN for 5 d before surgery and an exercise program, in patients with borderline resectable PDAC who received NAT[82].

In other areas of surgery, multimodal prehabilitation in patients receiving NAT has recently generated growing interest and seems to have a potential clinical benefit. Recently, a retrospective study of 22 patients, planning to undergo NAT for esophageal cancer, found a trend to a lower WL (3.0% *vs* 4.4%; $P$ = 0.05) and a lower percentage of patients requiring postsurgical readmission rates at 30-d and 90-d (0.0% *vs* 18.2%; $P$ = 0.14 and 18.2% *vs* 27.3%; $P$ = 0.6, respectively) in those submitted to a structured prehabiliation program, which included tailored nutritional counselling, psychological support and supervised physical exercise[140].

## CONCLUSION

Despite the lack of high-quality clinical evidence, many PDAC patients with resectable, borderline resectable, and locally advanced disease, nowadays undergo NAT as part of an integrated, multimodal, treatment program. Since NAT may provide an interesting window of opportunity to implement nutritional prehabilitation in PDAC patients and the limited available data on this issue suggest a reduction in POC, LOS and readmission rates, well-designed, controlled, randomized clinical trials are needed to establish new recommendations in this NAT setting.

## ACKNOWLEDGEMENTS

The authors gratefully want to thank Mr. Philip Egger for his kindly revision of the English language and style.

## REFERENCES


1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Ghaneh P**, Kleeff J, Halloran CM, Raraty M, Jackson R, Melling J, Jones O, Palmer DH, Cox TF, Smith CJ, O'Reilly DA, Izbicki JR, Scarfe AG, Valle JW, McDonald AC, Carter R, Tebbutt NC, Goldstein D, Padbury R, Shannon J, Dervenis C, Glimelius B, Deakin M, Anthoney A, Lerch MM, Mayerle J, Oláh A, Rawcliffe CL, Campbell F, Strobel O, Büchler MW, Neoptolemos JP; European Study Group for Pancreatic Cancer. The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma. *Ann Surg* 2019; **269**: 520-529 [PMID: 29068800 DOI: 10.1097/SLA.0000000000002557]

3 **Dobiasch S**, Goerig NL, Fietkau R, Combs SE. Essential role of radiation therapy for the treatment of pancreatic cancer : Novel study concepts and established treatment recommendations. *Strahlenther Onkol* 2018; **194**: 185-195 [PMID: 29094172 DOI: 10.1007/s00066-017-1227-5]

4 **NCCN clinical practice guidelines in oncology**. Pancreatic adenocarcinoma. National Comprehensive Cancer Network. Version 1. 2020 [Internet]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

5 **Uzunoglu FG**, Welte MN, Gavazzi F, Maggino L, Perinel J, Salvia R, Janot M, Reeh M, Perez D, Montorsi M, Zerbi A, Adham M, Uhl W, Bassi C, Izbicki JR, Malleo G, Bockhorn M. Evaluation of the MDACC clinical classification system for pancreatic cancer patients in an European multicenter cohort. *Eur J Surg Oncol* 2019; **45**: 793-799 [PMID: 30585172 DOI: 10.1016/j.ejso.2018.12.012]

6 **Maggino L**, Malleo G, Marchegiani G, Viviani E, Nessi C, Ciprani D, Esposito A, Landoni L, Casetti L, Tuveri M, Paiella S, Casciani F, Sereni E, Binco A, Bonamini D, Secchettin E, Auriemma A, Merz V, Simionato F, Zecchetto C, D'Onofrio M, Melisi D, Bassi C, Salvia R. Outcomes of Primary Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma. *JAMA Surg* 2019; **154**: 932-942 [PMID: 31339530 DOI: 10.1001/jamasurg.2019.2277]

7 **Janssen QP**, Buettner S, Suker M, Beumer BR, Addeo P, Bachellier P, Bahary N, Bekaii-Saab T, Bali MA, Besselink MG, Boone BA, Chau I, Clarke S, Dillhoff M, El-Rayes BF, Frakes JM, Grose D, Hosein PJ, Jamieson NB, Javed AA, Khan K, Kim KP, Kim SC, Kim SS, Ko AH, Lacy J, Margonis GA, McCarter MD, McKay CJ, Mellon EA, Moorcraft SY, Okada KI, Paniccia A, Parikh PJ, Peters NA, Rabl H, Samra J, Tinchon C, van Tienhoven G, van Veldhuisen E, Wang-Gillam A, Weiss MJ, Wilmink JW, Yamaue H, Homs MYV, van Eijck CHJ, Katz MHG, Groot Koerkamp B. Neoadjuvant FOLFIRINOX in Patients With Borderline Resectable Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis. *J Natl Cancer Inst* 2019; **111**: 782-794 [PMID: 31086963 DOI: 10.1093/jnci/djz073]

8 **Habermehl D**, Kessel K, Welzel T, Hof H, Abdollahi A, Bergmann F, Rieken S, Weitz J, Werner J, Schirmacher P, Büchler MW, Debus J, Combs SE. Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer. *Radiat Oncol* 2012; **7**: 28 [PMID: 22385572 DOI: 10.1186/1748-717X-7-28]

9 **Hackert T**, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, Strobel O, Jäger D, Ulrich A, Büchler MW. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. *Ann Surg* 2016; **264**: 457-463 [PMID: 27355262 DOI: 10.1097/SLA.0000000000001850]

10 **Cederholm T**, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017; **36**: 49-64 [PMID: 27642056 DOI: 10.1016/j.clnu.2016.09.004]

11 **Fearon K**, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12**: 489-495 [PMID: 21296615 DOI: 10.1016/S1470-2045(10)70218-7]

12 **Pezzilli R**, Caccialanza R, Capurso G, Brunetti O, Milella M, Falconi M. Pancreatic Enzyme Replacement Therapy in Pancreatic Cancer. *Cancers (Basel)* 2020; **12** [PMID: 31979186 DOI: 10.3390/cancers12020275]

13 **Gilliland TM**, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, Silberfein EJ, Choi EA, Hsu C, McElhany AL, Barakat O, Fisher W, Van Buren G. Nutritional and Metabolic Derangements in Pancreatic Cancer and Pancreatic Resection. *Nutrients* 2017; **9** [PMID: 28272344 DOI: 10.3390/nu9030243]

14 **Ferrone CR**, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, Sabbatino F, Santos DD, Allen JN, Blaszkowsky LS, Clark JW, Faris JE, Goyal L, Kwak EL, Murphy JE, Ting DT, Wo JY, Zhu AX, Warshaw AL, Lillemoe KD, Fernández-del Castillo C. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015; **261**: 12-17 [PMID: 25599322 DOI: 10.1097/SLA.0000000000000867]

15 **Trestini I**, Paiella S, Sandini M, Sperduti I, Elio G, Pollini T, Melisi D, Auriemma A, Soldà C, Bonaiuto C, Tregnago D, Avancini A, Secchettin E, Bonamini D, Lanza M, Pilotto S, Malleo G, Salvia R, Bovo C, Gianotti L, Bassi C, Milella M. Prognostic Impact of Preoperative Nutritional Risk in Patients Who Undergo Surgery for Pancreatic Adenocarcinoma. *Ann Surg Oncol* 2020; **27**: 5325-5334 [PMID: 32388740 DOI: 10.1245/s10434-020-08515-5]

16 **Bicakli DH**, Uslu R, Güney SC, Coker A. The Relationship Between Nutritional Status, Performance Status, and Survival Among Pancreatic Cancer Patients. *Nutr Cancer* 2020; **72**: 202-208 [PMID: 31271302 DOI: 10.1080/01635581.2019.1634217]

17 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 601 [PMID: 31081853 DOI: 10.1093/ageing/afz046]

18 **Mintziras I**, Miligkos M, Wächter S, Manoharan J, Maurer E, Bartsch DK. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: Systematic review and meta-analysis. *Int J Surg* 2018; **59**: 19-26 [PMID: 30266663 DOI: 10.1016/j.ijsu.2018.09.014]

19 **Gruber ES**, Jomrich G, Tamandl D, Gnant M, Schindl M, Sahora K. Sarcopenia and sarcopenic obesity are independent adverse prognostic factors in resectable pancreatic ductal adenocarcinoma. *PLoS One* 2019; **14**: e0215915 [PMID: 31059520 DOI: 10.1371/journal.pone.0215915]

20 **Park I**, Choi SJ, Kim YS, Ahn HK, Hong J, Sym SJ, Park J, Cho EK, Lee JH, Shin YJ, Shin DB. Prognostic Factors for Risk Stratification of Patients with Recurrent or Metastatic Pancreatic Adenocarcinoma Who Were Treated with Gemcitabine-Based Chemotherapy. *Cancer Res Treat* 2016; **48**: 1264-1273 [PMID: 27034148 DOI: 10.4143/crt.2015.250]

21 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

22 **Kurita Y**, Kobayashi N, Tokuhisa M, Goto A, Kubota K, Endo I, Nakajima A, Ichikawa Y. Sarcopenia is a reliable prognostic factor in patients with advanced pancreatic cancer receiving FOLFIRINOX chemotherapy. *Pancreatology* 2019; **19**: 127-135 [PMID: 30473464 DOI: 10.1016/j.pan.2018.11.001]

23 **Gillis C**, Wischmeyer PE. Pre-operative nutrition and the elective surgical patient: why, how and what? *Anaesthesia* 2019; **74** Suppl 1: 27-35 [PMID: 30604414 DOI: 10.1111/anae.14506]

24 **Weimann A**. Is there a rationale for perioperative nutrition therapy in the times of ERAS? [Internet]. Vol. 4, Innovative Surgical Sciences. De Gruyter; 2019; 152–157. [cited 2020 Jun 12]. Available from: https://www.degruyter.com/view/journals/iss/4/4/article-p152.xml

25 **Paiella S**, Trestini I, Milella M, Salvia R. ASO Author Reflections: Preoperative Nutritional Care: The 'Cinderella' of Surgical Management in Patients with Pancreatic Cancer. *Ann Surg Oncol* 2020; **27**: 5335-5336 [PMID: 32356267 DOI: 10.1245/s10434-020-08547-x]

26 **Mele MC**, Rinninella E, Cintoni M, Pulcini G, Di Donato A, Grassi F, Trestini I, Pozzo C, Tortora G, Gasbarrini A, Bria E. Nutritional Support in Lung Cancer Patients: The State of the Art. *Clin Lung Cancer* 2020 [PMID: 33303399 DOI: 10.1016/j.cllc.2020.10.008]

27 **Laviano A**, Di Lazzaro L, Koverech A. Nutrition support and clinical outcome in advanced cancer patients. *Proc Nutr Soc* 2018; **77**: 388-393 [PMID: 30001763 DOI: 10.1017/S0029665118000459]

28 **Trestini I**, Carbognin L, Sperduti I, Bonaiuto C, Auriemma A, Melisi D, Salvatore L, Bria E, Tortora G. Prognostic impact of early nutritional support in patients affected by locally advanced and metastatic pancreatic ductal adenocarcinoma undergoing chemotherapy. *Eur J Clin Nutr* 2018; **72**: 772-779 [PMID: 29581564 DOI: 10.1038/s41430-018-0155-5]

29 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

30 **Neoptolemos JP**, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, Carter R, Tebbutt NC, Dervenis C, Smith D, Glimelius B, Charnley RM, Lacaine F, Scarfe AG, Middleton MR, Anthoney A, Ghaneh P, Halloran CM, Lerch MM, Oláh A, Rawcliffe CL, Verbeke CS, Campbell F, Büchler MW; European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012; **308**: 147-156 [PMID: 22782416 DOI: 10.1001/jama.2012.7352]

31 **Heinrich S**, Pestalozzi B, Lesurtel M, Berrevoet F, Laurent S, Delpero JR, Raoul JL, Bachellier P, Dufour P, Moehler M, Weber A, Lang H, Rogiers X, Clavien PA. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). *BMC Cancer* 2011; **11**: 346 [PMID: 21831266 DOI: 10.1186/1471-2407-11-346]

32 **Salvia R**, Malleo G, Maggino L, Milella M, Bassi C. Pancreatic ductal adenocarcinoma: time for a neoadjuvant revolution? *Updates Surg* 2020; **72**: 321-324 [PMID: 32445032 DOI: 10.1007/s13304-020-00798-3]

33 **Gianotti L**, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, Griffin O, Fingerhut A,

Probst P, Abu Hilal M, Marchegiani G, Nappo G, Zerbi A, Amodio A, Perinel J, Adham M, Raimondo M, Asbun HJ, Sato A, Takaori K, Shrikhande SV, Del Chiaro M, Bockhorn M, Izbicki JR, Dervenis C, Charnley RM, Martignoni ME, Friess H, de Pretis N, Radenkovic D, Montorsi M, Sarr MG, Vollmer CM, Frulloni L, Büchler MW, Bassi C. Nutritional support and therapy in pancreatic surgery: A position paper of the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2018; **164**: 1035-1048 [PMID: 30029989 DOI: 10.1016/j.surg.2018.05.040]

34 **Nitta H**, Baba H, Sugimori K, Furuse J, Ohkawa S, Yamamoto K, Minami H, Shimokawa M, Wakabayashi GO, Aiba K; CINV Study Group of Japan. Chemotherapy-induced Nausea and Vomiting in Patients with Hepatobiliary and Pancreatic Cancer Treated with Chemotherapy: A Prospective Observational Study by the CINV Study Group of Japan. *Anticancer Res* 2016; **36**: 1929-1935 [PMID: 27069182 DOI: 10.1002/jcsm.12267]

35 **Naumann P**, Habermehl D, Welzel T, Debus J, Combs SE. Outcome after neoadjuvant chemoradiation and correlation with nutritional status in patients with locally advanced pancreatic cancer. *Strahlenther Onkol* 2013; **189**: 745-752 [PMID: 23896631 DOI: 10.1007/s00066-013-0393-3]

36 **Cooper AB**, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, Balachandran A, Garg N, Ngo-Huang A, Varadhachary G, Evans DB, Lee JE, Aloia T, Conrad C, Vauthey JN, Fleming JB, Katz MH. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. *Ann Surg Oncol* 2015; **22**: 2416-2423 [PMID: 25519927 DOI: 10.1245/s10434-014-4285-2]

37 **Cloyd JM**, Nogueras-González GM, Prakash LR, Petzel MQB, Parker NH, Ngo-Huang AT, Fogelman D, Denbo JW, Garg N, Kim MP, Lee JE, Tzeng CD, Fleming JB, Katz MHG. Anthropometric Changes in Patients with Pancreatic Cancer Undergoing Preoperative Therapy and Pancreatoduodenectomy. *J Gastrointest Surg* 2018; **22**: 703-712 [PMID: 29230694 DOI: 10.1007/s11605-017-3618-4]

38 **Naumann P**, Eberlein J, Farnia B, Hackert T, Debus J, Combs SE. Continued Weight Loss and Sarcopenia Predict Poor Outcomes in Locally Advanced Pancreatic Cancer Treated with Chemoradiation. *Cancers (Basel)* 2019; **11** [PMID: 31126040 DOI: 10.3390/cancers11050709]

39 **Naumann P**, Eberlein J, Farnia B, Liermann J, Hackert T, Debus J, Combs SE. Cachectic Body Composition and Inflammatory Markers Portend a Poor Prognosis in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiation. *Cancers (Basel)* 2019; **11** [PMID: 31717736 DOI: 10.3390/cancers11111655]

40 **Sandini M**, Patino M, Ferrone CR, Alvarez-Pérez CA, Honselmann KC, Paiella S, Catania M, Riva L, Tedesco G, Casolino R, Auriemma A, Salandini MC, Carrara G, Cristel G, Damascelli A, Ippolito D, D'Onofrio M, Lillemoe KD, Bassi C, Braga M, Gianotti L, Sahani D, Fernández-Del Castillo C. Association Between Changes in Body Composition and Neoadjuvant Treatment for Pancreatic Cancer. *JAMA Surg* 2018; **153**: 809-815 [PMID: 29801062 DOI: 10.1001/jamasurg.2018.0979]

41 **Griffin OM**, Duggan SN, Ryan R, McDermott R, Geoghegan J, Conlon KC. Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. *Pancreatology* 2019; **19**: 850-857 [PMID: 31362865 DOI: 10.1016/j.pan.2019.07.039]

42 **Connor S**. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB (Oxford)* 2016; **18**: 642-651 [PMID: 27485058 DOI: 10.1016/j.hpb.2016.05.006]

43 **Lermite E**, Sommacale D, Piardi T, Arnaud JP, Sauvanet A, Dejong CH, Pessaux P. Complications after pancreatic resection: diagnosis, prevention and management. *Clin Res Hepatol Gastroenterol* 2013; **37**: 230-239 [PMID: 23415988 DOI: 10.1016/j.clinre.2013.01.003]

44 **Hüttner FJ**, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Büchler MW, Diener MK. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev* 2016; **2**: CD006053 [PMID: 26905229 DOI: 10.1002/14651858.CD006053.pub6]

45 **McEvoy SH**, Lavelle LP, Hoare SM, O'Neill AC, Awan FN, Malone DE, Ryan ER, McCann JW, Heffernan EJ. Pancreaticoduodenectomy: expected post-operative anatomy and complications. *Br J Radiol* 2014; **87**: 20140050 [PMID: 25026968 DOI: 10.1259/bjr.20140050]

46 **Kawaida H**, Kono H, Hosomura N, Amemiya H, Itakura J, Fujii H, Ichikawa D. Surgical techniques and postoperative management to prevent postoperative pancreatic fistula after pancreatic surgery. *World J Gastroenterol* 2019; **25**: 3722-3737 [PMID: 31391768 DOI: 10.3748/wjg.v25.i28.3722]

47 **Bassi C**, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8-13 [PMID: 16003309 DOI: 10.1016/j.surg.2005.05.001]

48 **Bhosale P**, Fleming J, Balachandran A, Charnsangavej C, Tamm EP. Complications of Whipple surgery: imaging analysis. *Abdom Imaging* 2013; **38**: 273-284 [PMID: 22623029 DOI: 10.1007/s00261-012-9912-4]

49 **Hafezi-Nejad N**, Fishman EK, Zaheer A. Imaging of post-operative pancreas and complications after pancreatic adenocarcinoma resection. *Abdom Radiol (NY)* 2018; **43**: 476-488 [PMID: 29094173 DOI: 10.1007/s00261-017-1378-y]

50 **Onodera T**, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi* 1984; **85**: 1001-1005 [PMID: 6438478]

51 **Kanda M**, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative

outcome in pancreatic cancer. *Br J Surg* 2011; **98**: 268-274 [PMID: 20960457 DOI: 10.1002/bjs.7305]

52 **La Torre M**, Ziparo V, Nigri G, Cavallini M, Balducci G, Ramacciato G. Malnutrition and pancreatic surgery: prevalence and outcomes. *J Surg Oncol* 2013; **107**: 702-708 [PMID: 23280557 DOI: 10.1002/jso.23304]

53 **Darnis B**, Lebeau R, Chopin-Laly X, Adham M. Postpancreatectomy hemorrhage (PPH): predictors and management from a prospective database. *Langenbecks Arch Surg* 2013; **398**: 441-448 [PMID: 23435636 DOI: 10.1007/s00423-013-1047-8]

54 **Nanashima A**, Hiyoshi M, Imamura N, Yano K, Hamada T, Hamada R, Nagatomo K, Ikenoue M, Tobinaga S, Nagayasu T. Clinical significance of preoperative nutritional parameter and patient outcomes after pancreatectomy: A retrospective study at two academic institute. *Ann Hepatobiliary Pancreat Surg* 2019; **23**: 168-173 [PMID: 31225419 DOI: 10.14701/ahbps.2019.23.2.168]

55 **Mackay TM**, Smits FJ, Roos D, Bonsing BA, Bosscha K, Busch OR, Creemers GJ, van Dam RM, van Eijck CHJ, Gerhards MF, de Groot JWB, Groot Koerkamp B, Haj Mohammad N, van der Harst E, de Hingh IHJT, Homs MYV, Kazemier G, Liem MSL, de Meijer VE, Molenaar IQ, Nieuwenhuijs VB, van Santvoort HC, van der Schelling GP, Stommel MWJ, Ten Tije AJ, de Vos-Geelen J, Wit F, Wilmink JW, van Laarhoven HWM, Besselink MG; Dutch Pancreatic Cancer Group. The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis. *HPB (Oxford)* 2020; **22**: 233-240 [PMID: 31439478 DOI: 10.1016/j.hpb.2019.06.019]

56 **Chan MY**, Chok KSH. Sarcopenia in pancreatic cancer - effects on surgical outcomes and chemotherapy. *World J Gastrointest Oncol* 2019; **11**: 527-537 [PMID: 31367272 DOI: 10.4251/wjgo.v11.i7.527]

57 **Amini N**, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, Rezaee N, Weiss MJ, Wolfgang CL, Makary MM, Kamel IR, Pawlik TM. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. *J Gastrointest Surg* 2015; **19**: 1593-1602 [PMID: 25925237 DOI: 10.1007/s11605-015-2835-y]

58 **Amini N**, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, Rezaee N, Weiss MJ, Wolfgang CL, Makary MM, Kamel IR, Pawlik TM. Erratum to: Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. *J Gastrointest Surg* 2016; **20**: 1082 [PMID: 26984695 DOI: 10.1007/s11605-016-3126-y]

59 **Nishida Y**, Kato Y, Kudo M, Aizawa H, Okubo S, Takahashi D, Nakayama Y, Kitaguchi K, Gotohda N, Takahashi S, Konishi M. Preoperative Sarcopenia Strongly Influences the Risk of Postoperative Pancreatic Fistula Formation After Pancreaticoduodenectomy. *J Gastrointest Surg* 2016; **20**: 1586-1594 [PMID: 27126054 DOI: 10.1007/s11605-016-3146-7]

60 **Bundred J**, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. *HPB (Oxford)* 2019; **21**: 1603-1612 [PMID: 31266698 DOI: 10.1016/j.hpb.2019.05.018]

61 **Liu J**, Jiang S, Yang X, Li X, Wang N. The Significant Value of Preoperative Prognostic Nutritional Index for Survival in Pancreatic Cancers: A Meta-analysis. *Pancreas* 2018; **47**: 793-799. [PMID: 29985846 DOI: 10.1097/MPA.0000000000001089]

62 **Akahori T**, Sho M, Tanaka T, Kinoshita S, Nagai M, Nishiwada S, Nishiofuku H, Ohbayashi C, Kichikawa K, Nakajima Y. Factors associated with failure to complete adjuvant chemotherapy in pancreatic cancer. *Am J Surg* 2016; **211**: 787-792 [PMID: 26846177 DOI: 10.1016/j.amjsurg.2015.10.034]

63 **Nicholson JP**, Wolmarans MR, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000; **85**: 599-610 [PMID: 11064620 DOI: 10.1093/bja/85.4.599]

64 **Carr BI**, Guerra V. Serum albumin levels in relation to tumor parameters in hepatocellular carcinoma patients. *Int J Biol Markers* 2017; **32**: e391-e396 [PMID: 28862714 DOI: 10.5301/ijbm.5000300]

65 **Danan D**, Shonka DC Jr, Selman Y, Chow Z, Smolkin ME, Jameson MJ. Prognostic value of albumin in patients with head and neck cancer. *Laryngoscope* 2016; **126**: 1567-1571 [PMID: 26864349 DOI: 10.1002/lary.25877]

66 **Hendifar A**, Osipovl A, Khanujal J, Nissen N, Naziri J, Yang W, Li Q, Tuli R. Influence of Body Mass Index and Albumin on Perioperative Morbidity and Clinical Outcomes in Resected Pancreatic Adenocarcinoma. *PLoS One* 2016; **11**: e0152172 [PMID: 27015568 DOI: 10.1371/journal.pone.0152172]

67 **Vos T**, GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545-1602 [PMID: 27733282 DOI: 10.1016/S0140-6736(16)31678-6]

68 **Okumura S**, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, Hammad A, Mori A, Takaori K, Uemoto S. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* 2015; **157**: 1088-1098 [PMID: 25799468 DOI: 10.1016/j.surg.2015.02.002]

69 **Sugimoto M**, Farnell MB, Nagorney DM, Kendrick ML, Truty MJ, Smoot RL, Chari ST, Moynagh MR, Petersen GM, Carter RE, Takahashi N. Decreased Skeletal Muscle Volume Is a Predictive Factor for Poorer Survival in Patients Undergoing Surgical Resection for Pancreatic Ductal

Adenocarcinoma. *J Gastrointest Surg* 2018; **22**: 831-839 [PMID: 29392613 DOI: 10.1007/s11605-018-3695-z]

70 **Kamarajah SK**, Bundred J. Comments on: Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: Systematic review and meta-analysis. *Int J Surg* 2019; **66**: 99-100 [PMID: 30836140 DOI: 10.1016/j.ijsu.2019.02.015]

71 **Ljungqvist O**, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg* 2017; **152**: 292-298 [PMID: 28097305 DOI: 10.1001/jamasurg.2016.4952]

72 **Pillinger NL**, Robson JL, Kam P. Nutritional prehabilitation: physiological basis and clinical evidence. *Anaesth Intensive Care* 2018; **46**: 453-462 [PMID: 30189818 DOI: 10.1177/0310057X1804600505]

73 **Gillis C**, Carli F. Promoting Perioperative Metabolic and Nutritional Care. *Anesthesiology* 2015; **123**: 1455-1472 [PMID: 26248016 DOI: 10.1097/ALN.0000000000000795]

74 **Ji HB**, Zhu WT, Wei Q, Wang XX, Wang HB, Chen QP. Impact of enhanced recovery after surgery programs on pancreatic surgery: A meta-analysis. *World J Gastroenterol* 2018; **24**: 1666-1678 [PMID: 29686474 DOI: 10.3748/wjg.v24.i15.1666]

75 **Rinninella E**, Persiani R, D'Ugo D, Pennestrì F, Cicchetti A, Di Brino E, Cintoni M, Miggiano GAD, Gasbarrini A, Mele MC. NutriCatt protocol in the Enhanced Recovery After Surgery (ERAS) program for colorectal surgery: The nutritional support improves clinical and cost-effectiveness outcomes. *Nutrition* 2018; **50**: 74-81 [PMID: 29547797 DOI: 10.1016/j.nut.2018.01.013]

76 **Ardito F**, Lai Q, Rinninella E, Mimmo A, Vellone M, Panettieri E, Adducci E, Cintoni M, Mele MC, Gasbarrini A, Giuliante F. The impact of personalized nutritional support on postoperative outcome within the enhanced recovery after surgery (ERAS) program for liver resections: results from the NutriCatt protocol. *Updates Surg* 2020; **72**: 681-691 [PMID: 32410162 DOI: 10.1007/s13304-020-00787-6]

77 **Goonetilleke KS**, Siriwardena AK. Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. *JOP* 2006; **7**: 5-13 [PMID: 16407613]

78 **Lassen K**, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, Parks RW, Fearon KC, Lobo DN, Demartines N, Braga M, Ljungqvist O, Dejong CH; Enhanced Recovery After Surgery (ERAS) Society, for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN). Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *World J Surg* 2013; **37**: 240-258 [PMID: 22956014 DOI: 10.1007/s00268-012-1771-1]

79 **Sandrucci S**, Beets G, Braga M, Dejong K, Demartines N. Perioperative nutrition and enhanced recovery after surgery in gastrointestinal cancer patients. A position paper by the ESSO task force in collaboration with the ERAS society (ERAS coalition). *Eur J Surg Oncol* 2018; **44**: 509-514 [PMID: 29398322 DOI: 10.1016/j.ejso.2017.12.010]

80 **West MA**, Wischmeyer PE, Grocott MPW. Prehabilitation and Nutritional Support to Improve Perioperative Outcomes. *Curr Anesthesiol Rep* 2017; **7**: 340-349 [PMID: 29200973 DOI: 10.1007/s40140-017-0245-2]

81 **Xu X**, Zheng C, Zhao Y, Chen W, Huang Y. Enhanced recovery after surgery for pancreaticoduodenectomy: Review of current evidence and trends. *Int J Surg* 2018; **50**: 79-86 [PMID: 29081374 DOI: 10.1016/j.ijsu.2017.10.067]

82 **Nakajima H**, Yokoyama Y, Inoue T, Nagaya M, Mizuno Y, Kadono I, Nishiwaki K, Nishida Y, Nagino M. Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy. *Ann Surg Oncol* 2019; **26**: 264-272 [PMID: 30367303 DOI: 10.1245/s10434-018-6943-2]

83 **Ausania F**, Senra P, Meléndez R, Caballeiro R, Ouviña R, Casal-Núñez E. Prehabilitation in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. *Rev Esp Enferm Dig* 2019; **111**: 603-608 [PMID: 31232076 DOI: 10.17235/reed.2019.6182/2019]

84 **Weimann A**, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, Laviano A, Ljungqvist O, Lobo DN, Martindale R, Waitzberg DL, Bischoff SC, Singer P. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr* 2017; **36**: 623-650 [PMID: 28385477 DOI: 10.1016/j.clnu.2017.02.013]

85 **Probst P**, Haller S, Bruckner T, Ulrich A, Strobel O, Hackert T, Diener MK, Büchler MW, Knebel P. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS Pancreas). *Br J Surg* 2017; **104**: 1053-1062 [PMID: 28369809 DOI: 10.1002/bjs.10525]

86 **Skeie E**, Tangvik RJ, Nymo LS, Harthug S, Lassen K, Viste A. Weight loss and BMI criteria in GLIM's definition of malnutrition is associated with postoperative complications following abdominal resections - Results from a National Quality Registry. *Clin Nutr* 2020; **39**: 1593-1599 [PMID: 31375303 DOI: 10.1016/j.clnu.2019.07.003]

87 **Cederholm T**, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats A, Crivelli A, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A, Mogensen KM, Morley JE, Muscaritoli M, Nyulasi I, Pirlich M, Pisprasert V, de van der Schueren MAE, Siltharm S, Singer P, Tappenden K, Velasco N, Waitzberg D, Yamwong P, Yu J, Van Gossum A, Compher C; GLIM Core Leadership Committee; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr* 2019; **38**: 1-9 [PMID: 30181091 DOI: 10.1016/j.clnu.2018.08.002]

88 **Malietzis G**, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT. The role of body composition

evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. *Eur J Surg Oncol* 2015; **41**: 186-196 [PMID: 25468746 DOI: 10.1016/j.ejso.2014.10.056]

89 **Shachar SS**, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer* 2016; **57**: 58-67 [PMID: 26882087 DOI: 10.1016/j.ejca.2015.12.030]

90 **Rinninella E**, Cintoni M, Raoul P, Pozzo C, Strippoli A, Bria E, Tortora G, Gasbarrini A, Mele MC. Muscle mass, assessed at diagnosis by L3-CT scan as a prognostic marker of clinical outcomes in patients with gastric cancer: A systematic review and meta-analysis. *Clin Nutr* 2020; **39**: 2045-2054 [PMID: 31718876 DOI: 10.1016/j.clnu.2019.10.021]

91 **Rinninella E**, Fagotti A, Cintoni M, Raoul P, Scaletta G, Scambia G, Gasbarrini A, Mele MC. Skeletal muscle mass as a prognostic indicator of outcomes in ovarian cancer: a systematic review and meta-analysis. *Int J Gynecol Cancer* 2020; **30**: 654-663 [PMID: 32241875 DOI: 10.1136/ijgc-2020-001215]

92 **Baracos VE**, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers* 2018; **4**: 17105 [PMID: 29345251 DOI: 10.1038/nrdp.2017.105]

93 **Purcell SA**, Elliott SA, Baracos VE, Chu QS, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. *Eur J Clin Nutr* 2016; **70**: 1230-1238 [PMID: 27273068 DOI: 10.1038/ejcn.2016.96]

94 **Ngo-Huang A**, Holmes HM, des Bordes JKA, Parker NH, Fogelman D, Petzel MQB, Song J, Bruera E, Katz MHG. Association between frailty syndrome and survival in patients with pancreatic adenocarcinoma. *Cancer Med* 2019; **8**: 2867-2876 [PMID: 31033241 DOI: 10.1002/cam4.2157]

95 **Okusaka T**, Okada S, Ishii H, Ikeda M, Kosakamoto H, Yoshimori M. Prognosis of advanced pancreatic cancer patients with reference to calorie intake. *Nutr Cancer* 1998; **32**: 55-58 [PMID: 9824858 DOI: 10.1080/01635589809514717]

96 **Bye A**, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. *Support Care Cancer* 2013; **21**: 219-227 [PMID: 22684989 DOI: 10.1007/s00520-012-1514-8]

97 **Arends J**, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017; **36**: 11-48 [PMID: 27637832 DOI: 10.1016/j.clnu.2016.07.015]

98 **Baracos VE**. Skeletal muscle anabolism in patients with advanced cancer. *Lancet Oncol* 2015; **16**: 13-14 [PMID: 25524803 DOI: 10.1016/S1470-2045(14)71185-4]

99 **Carli F**, Gillis C, Scheede-Bergdahl C. Promoting a culture of prehabilitation for the surgical cancer patient. *Acta Oncol* 2017; **56**: 128-133 [PMID: 28067101 DOI: 10.1080/0284186X.2016.1266081]

100 **Carli F**, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, Stein B, Charlebois P, Ghitulescu G, Morin N, Jagoe T, Scheede-Bergdahl C, Minnella EM, Fiore JF Jr. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. *JAMA Surg* 2020; **155**: 233-242 [PMID: 31968063 DOI: 10.1001/jamasurg.2019.5474]

101 **Holeček M**. Branched-chain amino acids in health and disease: Metabolism, alterations in blood plasma, and as supplements. *Nutr Metab (Lond)* 2018; **15**: 33 [DOI: 10.1186/s12986-018-0271-1]

102 **Tayek JA**, Bistrian BR, Hehir DJ, Martin R, Moldawer LL, Blackburn GL. Improved protein kinetics and albumin synthesis by branched chain amino acid-enriched total parenteral nutrition in cancer cachexia. A prospective randomized crossover trial. *Cancer* 1986; **58**: 147-157 [PMID: 3085914 DOI: 10.1002/1097-0142(19860701)58:1<147::aid-cncr2820580126>3.0.co;2-i]

103 **Deutz NE**, Safar A, Schutzler S, Memelink R, Ferrando A, Spencer H, van Helvoort A, Wolfe RR. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. *Clin Nutr* 2011; **30**: 759-768 [PMID: 21683485 DOI: 10.1016/j.clnu.2011.05.008]

104 **Kim JS**, Khamoui AV, Jo E, Park BS, Lee WJ. β-Hydroxy-β-methylbutyrate as a countermeasure for cancer cachexia: a cellular and molecular rationale. *Anticancer Agents Med Chem* 2013; **13**: 1188-1196 [PMID: 23919746 DOI: 10.2174/18715206113139990321]

105 **Eley HL**, Russell ST, Tisdale MJ. Mechanism of attenuation of muscle protein degradation induced by tumor necrosis factor-alpha and angiotensin II by beta-hydroxy-beta-methylbutyrate. *Am J Physiol Endocrinol Metab* 2008; **295**: E1417-E1426 [PMID: 18840762 DOI: 10.1152/ajpendo.90567.2008]

106 **Aversa Z**, Bonetto A, Costelli P, Minero VG, Penna F, Baccino FM, Lucia S, Rossi Fanelli F, Muscaritoli M. β-hydroxy-β-methylbutyrate (HMB) attenuates muscle and body weight loss in experimental cancer cachexia. *Int J Oncol* 2011; **38**: 713-720 [PMID: 21184031 DOI: 10.3892/ijo.2010.885]

107 **May PE**, Barber A, D'Olimpio JT, Hourihane A, Abumrad NN. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg* 2002; **183**: 471-479 [PMID: 11975938 DOI: 10.1016/s0002-9610(02)00823-1]

108 **Berk L**, James J, Schwartz A, Hug E, Mahadevan A, Samuels M, Kachnic L; RTOG. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer* 2008;

**16**: 1179-1188 [PMID: 18293016 DOI: 10.1007/s00520-008-0403-7]
109 **Bosaeus I**. Nutritional support in multimodal therapy for cancer cachexia. *Support Care Cancer* 2008; **16**: 447-451 [PMID: 18196284 DOI: 10.1007/s00520-007-0388-7]
110 **Calder PC**. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans* 2017; **45**: 1105-1115 [PMID: 28900017 DOI: 10.1042/BST20160474]
111 **Park M**, Kim H. Anti-cancer Mechanism of Docosahexaenoic Acid in Pancreatic Carcinogenesis: A Mini-review. *J Cancer Prev* 2017; **22**: 1-5 [PMID: 28382280 DOI: 10.15430/JCP.2017.22.1.1]
112 **Cholewski M**, Tomczykowa M, Tomczyk M. A Comprehensive Review of Chemistry, Sources and Bioavailability of Omega-3 Fatty Acids. *Nutrients* 2018; **10** [PMID: 30400360 DOI: 10.3390/nu10111662]
113 **Nabavi SF**, Bilotto S, Russo GL, Orhan IE, Habtemariam S, Daglia M, Devi KP, Loizzo MR, Tundis R, Nabavi SM. Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. *Cancer Metastasis Rev* 2015; **34**: 359-380 [PMID: 26227583 DOI: 10.1007/s10555-015-9572-2]
114 **Di Girolamo FG**, Situlin R, Mazzucco S, Valentini R, Toigo G, Biolo G. Omega-3 fatty acids and protein metabolism: enhancement of anabolic interventions for sarcopenia. *Curr Opin Clin Nutr Metab Care* 2014; **17**: 145-150 [PMID: 24500439 DOI: 10.1097/MCO.0000000000000032]
115 **Barber MD**. Cancer cachexia and its treatment with fish-oil-enriched nutritional supplementation. *Nutrition* 2001; **17**: 751-755 [PMID: 11527672 DOI: 10.1016/s0899-9007(01)00631-1]
116 **Werner K**, Küllenberg de Gaudry D, Taylor LA, Keck T, Unger C, Hopt UT, Massing U. Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil - a randomized controlled double-blind trial. *Lipids Health Dis* 2017; **16**: 104 [PMID: 28578704 DOI: 10.1186/s12944-017-0495-5]
117 **Arshad A**, Chung WY, Steward W, Metcalfe MS, Dennison AR. Reduction in circulating pro-angiogenic and pro-inflammatory factors is related to improved outcomes in patients with advanced pancreatic cancer treated with gemcitabine and intravenous omega-3 fish oil. *HPB (Oxford)* 2013; **15**: 428-432 [PMID: 23458624 DOI: 10.1111/hpb.12002]
118 **Nikfarjam M**, Wilson JS, Smith RC; Australasian Pancreatic Club Pancreatic Enzyme Replacement Therapy Guidelines Working Group. Diagnosis and management of pancreatic exocrine insufficiency. *Med J Aust* 2017; **207**: 161-165 [PMID: 28814218 DOI: 10.5694/mja16.00851]
119 **Löhr JM**, Oliver MR, Frulloni L. Synopsis of recent guidelines on pancreatic exocrine insufficiency. *United European Gastroenterol J* 2013; **1**: 79-83 [PMID: 24917944 DOI: 10.1177/2050640613476500]
120 **Sabater L**, Ausania F, Bakker OJ, Boadas J, Domínguez-Muñoz JE, Falconi M, Fernández-Cruz L, Frulloni L, González-Sánchez V, Lariño-Noia J, Lindkvist B, Lluís F, Morera-Ocón F, Martín-Pérez E, Marra-López C, Moya-Herraiz Á, Neoptolemos JP, Pascual I, Pérez-Aisa Á, Pezzilli R, Ramia JM, Sánchez B, Molero X, Ruiz-Montesinos I, Vaquero EC, de-Madaria E. Evidence-based Guidelines for the Management of Exocrine Pancreatic Insufficiency After Pancreatic Surgery. *Ann Surg* 2016; **264**: 949-958 [PMID: 27045859 DOI: 10.1097/SLA.0000000000001732]
121 **Vujasinovic M**, Valente R, Del Chiaro M, Permert J, Löhr JM. Pancreatic Exocrine Insufficiency in Pancreatic Cancer. *Nutrients* 2017; **9** [PMID: 28241470 DOI: 10.3390/nu9030183]
122 **Dominguez-Muñoz JE**. Management of pancreatic exocrine insufficiency. *Curr Opin Gastroenterol* 2019; **35**: 455-459 [PMID: 31219829 DOI: 10.1097/MOG.0000000000000562]
123 **Forsmark CE**. Diagnosis and Management of Exocrine Pancreatic Insufficiency. *Curr Treat Options Gastroenterol* 2018; **16**: 306-315 [PMID: 30027527 DOI: 10.1007/s11938-018-0186-y]
124 **Roberts KJ**, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study. *Pancreatology* 2019; **19**: 114-121 [PMID: 30385188 DOI: 10.1016/j.pan.2018.10.010]
125 **Landers A**, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. *Palliat Care* 2019; **12**: 1178224218825270 [PMID: 30799929 DOI: 10.1177/1178224218825270]
126 **Domínguez-Muñoz JE**, Nieto-Garcia L, López-Díaz J, Lariño-Noia J, Abdulkader I, Iglesias-Garcia J. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: a retrospective analysis. *BMC Cancer* 2018; **18**: 534 [PMID: 29728096 DOI: 10.1186/s12885-018-4439-x]
127 **Layer P**, Kashirskaya N, Gubergrits N. Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency. *World J Gastroenterol* 2019; **25**: 2430-2441 [PMID: 31171887 DOI: 10.3748/wjg.v25.i20.2430]
128 **Barkin JA**, Westermann A, Hoos W, Moravek C, Matrisian L, Wang H, Shemanski L, Barkin JS, Rahib L. Frequency of Appropriate Use of Pancreatic Enzyme Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients. *Pancreas* 2019; **48**: 780-786 [PMID: 31210656 DOI: 10.1097/MPA.0000000000001330]
129 **Nofal YH**, Abu Dail Y, Assaf Y, Abo Samra H, Abbas F, Hamzeh A, Alhaj Hasan N. Pancreatic enzyme replacement therapy for steatorrhoea in pancreatic cancer. *Database Syst Rev* 2018; **2**: CD012952 [DOI: 10.1002/14651858.CD012952]
130 **Grimble RF**. Basics in clinical nutrition: Immunonutrition-Nutrients which influence immunity: Effect and mechanism of action. *Educational Paper* 2009; **4**: E10-13 [DOI: 10.1016/j.eclnm.2008.07.015]
131 **Klek S**, Sierzega M, Szybinski P, Szczepanek K, Scislo L, Walewska E, Kulig J. The

immunomodulating enteral nutrition in malnourished surgical patients - a prospective, randomized, double-blind clinical trial. *Clin Nutr* 2011; **30**: 282-288 [PMID: 21074910 DOI: 10.1016/j.clnu.2010.10.001]

132 **Shirakawa H**, Kinoshita T, Gotohda N, Takahashi S, Nakagohri T, Konishi M. Compliance with and effects of preoperative immunonutrition in patients undergoing pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci* 2012; **19**: 249-258 [PMID: 21667052 DOI: 10.1007/s00534-011-0416-3]

133 **Gade J**, Levring T, Hillingsø J, Hansen CP, Andersen JR. The Effect of Preoperative Oral Immunonutrition on Complications and Length of Hospital Stay After Elective Surgery for Pancreatic Cancer--A Randomized Controlled Trial. *Nutr Cancer* 2016; **68**: 225-233 [PMID: 26943500 DOI: 10.1080/01635581.2016.1142586]

134 **Silvestri S**, Franchello A, Deiro G, Galletti R, Cassine D, Campra D, Bonfanti D, De Carli L, Fop F, Fronda GR. Preoperative oral immunonutrition versus standard preoperative oral diet in well nourished patients undergoing pancreaticoduodenectomy. *Int J Surg* 2016; **31**: 93-99 [PMID: 27267949 DOI: 10.1016/j.ijsu.2016.05.071]

135 **Versteijne E**, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, Buijsen J, Busch OR, Creemers GM, van Dam RM, Eskens FALM, Festen S, de Groot JWB, Groot Koerkamp B, de Hingh IH, Homs MYV, van Hooft JE, Kerver ED, Luelmo SAC, Neelis KJ, Nuyttens J, Paardekooper GMRM, Patijn GA, van der Sangen MJC, de Vos-Geelen J, Wilmink JW, Zwinderman AH, Punt CJ, van Eijck CH, van Tienhoven G; Dutch Pancreatic Cancer Group. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020; **38**: 1763-1773 [PMID: 32105518 DOI: 10.1200/JCO.19.02274]

136 **Versteijne E**, van Eijck CH, Punt CJ, Suker M, Zwinderman AH, Dohmen MA, Groothuis KB, Busch OR, Besselink MG, de Hingh IH, Ten Tije AJ, Patijn GA, Bonsing BA, de Vos-Geelen J, Klaase JM, Festen S, Boerma D, Erdmann JI, Molenaar IQ, van der Harst E, van der Kolk MB, Rasch CR, van Tienhoven G; Dutch Pancreatic Cancer Group (DPCG). Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials* 2016; **17**: 127 [PMID: 26955809 DOI: 10.1186/s13063-016-1262-z]

137 **Ngo-Huang A**, Parker N, Martinez VA, Petzel MQ, Fogelman D, Holmes HM, Dhah SS, Katz M. Poster 68 Feasibility of a Prehabilitation Program for Patients with Potentially Resectable Pancreatic Cancer: Pilot Study. *PM R* 2016; **8**: S183 [PMID: 27672836 DOI: 10.1016/j.pmrj.2016.07.111]

138 **Akita H**, Takahashi H, Asukai K, Tomokuni A, Wada H, Marukawa S, Yamasaki T, Yanagimoto Y, Takahashi Y, Sugimura K, Yamamoto K, Nishimura J, Yasui M, Omori T, Miyata H, Ochi A, Kagawa A, Soh Y, Taniguchi Y, Ohue M, Yano M, Sakon M. The utility of nutritional supportive care with an eicosapentaenoic acid (EPA)-enriched nutrition agent during pre-operative chemoradiotherapy for pancreatic cancer: Prospective randomized control study. *Clin Nutr ESPEN* 2019; **33**: 148-153 [PMID: 31451252 DOI: 10.1016/j.clnesp.2019.06.003]

139 **Martin RC 2nd**, Agle S, Schlegel M, Hayat T, Scoggins CR, McMasters KM, Philips P. Efficacy of preoperative immunonutrition in locally advanced pancreatic cancer undergoing irreversible electroporation (IRE). *Eur J Surg Oncol* 2017; **43**: 772-779 [PMID: 28162818 DOI: 10.1016/j.ejso.2017.01.002]

140 **Dewberry LC**, Wingrove LJ, Marsh MD, Glode AE, Schefter TE, Leong S, Purcell WT, McCarter MD. Pilot Prehabilitation Program for Patients With Esophageal Cancer During Neoadjuvant Therapy and Surgery. *J Surg Res* 2019; **235**: 66-72 [PMID: 30691852 DOI: 10.1016/j.jss.2018.09.060]

World Journal of Gastrointestinal Surgery

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*World J Gastrointest Surg* 2021 September 27; 13(9): 904-922

DOI: 10.4240/wjgs.v13.i9.904

ISSN 1948-9366 (online)

*REVIEW*

# Current trends in three-dimensional visualization and real-time navigation as well as robot-assisted technologies in hepatobiliary surgery

Yun Wang, Di Cao, Si-Lin Chen, Yu-Mei Li, Yun-Wen Zheng, Nobuhiro Ohkohchi

**ORCID number:** Yun Wang 0000-0002-9281-0048; Di Cao 0000-0002-9711-5001; Si-Lin Chen 0000-0002-2622-2010; Yu-Mei Li 0000-0002-9501-5314; Yun-Wen Zheng 0000-0001-9002-3190; Nobuhiro Ohkohchi 0000-0003-2779-1247.

**Author contributions:** Zheng YW designed the study; Wang Y drafted the manuscript; Zheng YW, Wang Y, Cao D and Chen SL contributed to reviewing and revising the manuscript; Zheng YW, Wang Y, Li YM and Ohkohchi N discussed the draft; all authors approved the final manuscript; Zheng YW, Li YM and Ohkohchi N are senior authors and co-correspondents of this work.

**Supported by** National Natural Science Foundation of China, No. 82070638 and No. 81770621; and JSPS KAKENHI, No. JP18H02866.

**Conflict-of-interest statement:** The authors declare no potential financial interests.



**Yun Wang, Di Cao, Si-Lin Chen, Yu-Mei Li, Yun-Wen Zheng,** Institute of Regenerative Medicine, and Affiliated Hospital of Jiangsu University, Jiangsu University, Zhenjiang 212001, Jiangsu Province, China

**Yun-Wen Zheng, Nobuhiro Ohkohchi,** Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8575, Ibaraki, Japan

**Yun-Wen Zheng,** Guangdong Provincial Key Laboratory of Large Animal Models for Biomedicine, and School of Biotechnology and Heath Sciences, Wuyi University, Jiangmen 529020, Guangdong Province, China

**Yun-Wen Zheng,** School of Medicine, Yokohama City University, Yokohama 234-0006, Kanagawa, Japan

**Corresponding author:** Yun-Wen Zheng, PhD, Associate Professor, Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Faculty of Medicine, University of Tsukuba, Tennodai 1-1-1, Tsukuba 305-8575, Ibaraki, Japan. ywzheng@md.tsukuba.ac.jp

## Abstract

With the continuous development of digital medicine, minimally invasive precision and safety have become the primary development trends in hepatobiliary surgery. Due to the specificity and complexity of hepatobiliary surgery, traditional preoperative imaging techniques such as computed tomography and magnetic resonance imaging cannot meet the need for identification of fine anatomical regions. Imaging-based three-dimensional (3D) reconstruction, virtual simulation of surgery and 3D printing optimize the surgical plan through preoperative assessment, improving the controllability and safety of intraoperative operations, and in difficult-to-reach areas of the posterior and superior liver, assistive robots reproduce the surgeon's natural movements with stable cameras, reducing natural vibrations. Electromagnetic navigation in abdominal surgery solves the problem of conventional surgery still relying on direct visual observation or preoperative image assessment. We summarize and compare these recent trends in digital medical solutions for the future development and refinement of digital medicine in hepatobiliary surgery.

**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Japan

**Peer-review report's scientific quality classification**
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 14, 2021
**Peer-review started:** February 14, 2021
**First decision:** April 6, 2021
**Revised:** April 19, 2021
**Accepted:** August 2, 2021
**Article in press:** August 2, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Kaya B, Yang HX
**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Ma YJ

**Key Words:** Hepatobiliary surgery; Three-dimensional visualization; Three-dimensional printing; Electromagnetic tracking; Real-time navigation; Robot-assisted surgery



**Core Tip:** This paper analyzes the latest trends in three-dimensional visualization, robot-assisted surgery, and electromagnetic intraoperative navigation in hepatobiliary surgery and summarizes the advantages and limitations of existing technologies and potential solution strategies. It also analyzes existing real-time intraoperative navigation, compares optical tracking navigation to electromagnetic tracking navigation with a focus on the advantages and existing limitations, and attempts to improve the program as an educational learning tool for new physicians. Additionally, it aims to popularize hepatobiliary surgery as digital medicine and tries to illustrate a direction for the advancement and development of digital medicine in hepatobiliary surgery.

**Citation:** Wang Y, Cao D, Chen SL, Li YM, Zheng YW, Ohkohchi N. Current trends in three-dimensional visualization and real-time navigation as well as robot-assisted technologies in hepatobiliary surgery. *World J Gastrointest Surg* 2021; 13(9): 904-922
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/904.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.904

## INTRODUCTION

The safety and effectiveness of hepatobiliary surgery is based on knowledge of the detailed anatomy of the hepatobiliary structures, but the structure of the liver is complex and the vascularity and anatomy of the bile ducts at the hilum are prone to variation[1]. Traditional surgery based on two-dimensional (2D) images to visualize the three-dimensional (3D) spatial relationships of anatomical structures in the mind in order to complete the operation, but it's a significant challenge for new inexperienced surgeons. 3D visualization, digital imaging and 3D printing can clearly show the 3D spatial relationship of the lesion site, which can help with difficult intrahepatic vein reconstruction and blood supply assessment as well as biliary vein drainage problems, enabling surgeons to better plan their operations and pushing surgery towards precision and minimally invasive surgery. The development of robot-assisted surgery can overcome the disadvantages of traditional laparoscopy in hepatobiliary surgery, such as inadequate depth perception, inevitable hand tremors, and the surgeon's greater susceptibility to fatigue after prolonged surgery, helping surgeons to be more flexible in operating on delicate sites[2,3]. Intraoperative navigation reduces the practical uncertainty of the operation and the deformation and displacement of tissues, and evolving digital medicine is helping surgeons to optimize preoperative planning, perform precise and safe intraoperative procedures and carry out accurate postoperative analysis[4,5].

## THREE-DIMENSINAL VISUALIZATION IMAGES AND THEIR EXTENSION

The segmental anatomy of the liver and the anatomy of the blood vessels and bile ducts are diverse and the presence of various anatomical variants requires individualized surgical plans to ensure that the operation is carried out safely. Experienced surgeons can sketch a 3D image in their minds based on preoperative 2D images such as computed tomography (CT) plane magnetic resonance imaging (MRI) to complete the operation successfully, but it is a significant challenge for surgeons new to the profession[6,7]. 3D visualization and 3D printing technologies can clearly show the specific spatial anatomy of a lesion and can help young surgeons optimize their surgical plans, which can be used for liver resection, liver transplantation, radiofrequency ablation, transjugular intrahepatic portosystemic shunts, gallstones, gallbladder cancer and many other diseases[4,8,9]. Especially in the case of malignant liver tumor resection, the application of 3D visualization and 3D printing technology

allows for accurate preoperative assessment, simulation and optimization of the surgical plan to ensure that the operation is carried out safely[10].

### 3D visualization

With the rapid development of digital medicine, 3D visualization images are increasingly used in the diagnosis and treatment of hepatobiliary diseases, and more and more companies are developing 3D visualization software for medical use, such as Liversim, Mint Liver, *etc.*[11]. A large amount of fine stereoscopic data helps surgeons to clearly identify the anatomical relationship of the lesion before surgery, helping the team to share accurate 3D surgical images[12]. Particularly for surgery on hepatobiliary malignancies, 3D visualization technology also allows for a comprehensive assessment of the vasculature and evaluation of variants, which helps the surgery to unfold safely[13,14].

As shown in Table 1, Miyamoto *et al*[15] used 3D visualization images to diagnose parabile ducts in patients with cholangiocarcinoma that could not be detected by multilayer spiral CT and magnetic resonance cholangiopancreatography. Zeng *et al*[16] conducted a retrospective study of patients with type-III hilar cholangiocarcinoma using 3D modelling, demonstrating the safety and efficacy of 3D visualization. Nakayama *et al*[13] retrospectively analyzed 240 consecutive patients undergoing liver resection and demonstrated the effectiveness of 3D simulation to help surgeons effectively reduce operative time. Lin *et al*[17] explored the value of 3D visualization in pancreatic resection and validated the effectiveness of 3D visualization images to help surgeons plan surgery.

### Advantages and limitations of 3D visualization

The development and application of visualization images has changed the paradigm of surgery and can also help inexperienced surgeons to learn with simulation, improved safety, reduced intraoperative risk and to some extent reduced postoperative complications[12,17,18].

However, the current 3D visualization techniques still have some limitations[18]. First, the process of medical image reconstruction mainly includes image data preprocessing, segmentation and annotation, alignment and fusion, 3D reconstruction, visual image display, *etc.* Each step of the process affects the results of 3D reconstruction, and the quality of the raw data acquired during the process and the different capabilities of the various reconstruction software applications also affect the outcome of 3D reconstruction. Second, although the reconstructed images produced by current visualization software are generally better than the image post-processing software that comes with CT or MRI, they are based on secondary processing of the original CT or MRI images, which inevitably results in partial loss of the original data during the image processing, thus affecting the fineness and clarity of the reconstructed images [18]. Future research should maximize the preservation of raw data, optimize the algorithms of various reconstruction techniques, improve the fidelity of the reconstruction and increase the accuracy of the 3D visualized images. Third, the reconstruction of images is currently time-consuming, taking at least one to two hours, future research could be technically optimized to reduce the reconstruction time[19]. Fourth, soft tissue organs such as the liver surface, intrahepatic structures and the bile duct tree are usually deformed intraoperatively due to changes in position and surgical procedures[20]. Although studies have also described calibration algorithms based on deformed organs, the currently available DIR algorithms still have limitations when dealing with complex deformations including volume changes, and optimization solutions for variable organ alignment remain a difficult area for future research, and further development and testing studies are needed in the future[21].

### 3D printing

3D printing is an extension and expansion of 3D visualization technology. High-fidelity 3D printed models can realistically reflect the 3D spatial relationships of fine anatomical areas such as lesion sites and blood vessels, allowing for multi-dimensional predictions of surgical procedures before surgery, achieving a leap from 3D images to solid 3D physical models[22,23].

The use of 3D printing in liver surgery has become widespread, and studies have shown good results with negative margins for using this technique in the treatment of small liver cancers[24]. Joo *et al*[25] applied a 3D-printed transparent liver model. The 3D technique was also applied by Fang *et al*[26] in surgeries on liver diseases such as intrahepatic bile duct stones and liver malignancies. He *et al*[27] also applied 3D printing in liver resection and autologous liver transplantation for vesicular encapsu-

**Table 1 Three-dimensional visualization and robot-assisted surgery in recent years**

| | Surgical site | Sample size | Patient type of disease | Imaging systems | Incidence of complications (%) | Summary of technology | Ref. |
|---|---|---|---|---|---|---|---|
| 3D visualization | Bile duct department | 1 | Extrahepatic cholangiocarcinoma combined with paracolic bile duct | Synapse Vincent | 0 | Accuracy and reliability | Miyamoto *et al*[15], 2014 |
| | Hepatic portal | 47 | Type-III cholangiocarcinoma of the porta hepatis | MI-3DVS | | Safety, effectiveness, and feasibility | Zeng *et al*[16], 2016 |
| | Liver | 120 | Hepatocellular carcinoma, bile duct cancer, liver transplantation | Synapse Vincent | 10.8 | Time savings | Nakayama *et al*[13], 2017 |
| | Pancreas | 64 | Pancreatic cancer, biliary tract cancer, neuroendocrine tumors, IPMN | Synapse Vincent | 14 | Safety, effectiveness, and feasibility | Miyamoto *et al*[100], 2018 |
| | Pancreas | 44 | Pancreatic cancer | MVT | | Safety, effectiveness, and feasibility | Lin *et al*[17], 2020 |
| Robot-assisted | Major and minor liver resections | 40 | Hemangioma, HCC, hydatid cyst, cholangiocarcinoma | da Vinci Surgical System | 12.5 | Safety and feasibility | Troisi *et al* [37], 2013 |
| | Major liver resection | 25 | Fatty liver, hepatic hemangioma, giant adenoma, HCC, secondary liver carcinoma | da Vinci Surgical System | 9.3 | Safety and feasibility | Spampinato *et al*[33], 2014 |
| | Wedge resection of the liver | 20 | HCC, secondary liver carcinoma, hepatic hemangioma, liver stones | da Vinci Surgical System | 9.5 | Safety and feasibility | Felli *et al*[47], 2015 |
| | Cholecystectomy | 38 | Benign biliary disease | da Vinci Surgical System | 0 | Safety and effectiveness | Gustafson *et al*[51], 2016 |
| | Cholecystectomy | 1833 | Benign gallbladder disease | da Vinci Surgical System, Zeus system, AESPO | 9.3 | No superiority over laparoscopy | Han *et al* [101], 2018 |
| | Major and minor liver resections | 1312 | Liver tumors | da Vinci Surgical System | 17.8 | No superiority over laparoscopy | Zhang *et al* [2], 2020 |

MVT: A three-dimensional multi-touch visualization table introduced by Sectra in 2010 at the Radiological Society of North America. IPMN: Intraductal papillary mucinous neoplasm; HCC: Hepatocellular carcinoma; 3D: Three-dimensional.

lation disease with satisfactory surgical results. Yang *et al*[28] used HepaRG cells and bioink to construct 3D bioprinted hepatic-like biotin, demonstrating that 3D bioprinting can be used to generate human liver tissue as an alternative transplant donor for therapy.

As shown in Table 2, current 3D printing enables the adjustment and placement of 3D printed models in optimal anatomical positions, facilitating both the placement of surgical instruments and the intuitive real-time navigation of key steps in surgery. It also allows rapid identification and precise positioning of key sites, optimizing the plane of surgical resection, the separation of important vessels and the precise removal of lesions, thereby improving surgical precision and safety and reducing surgical risk [29]. A number of studies have shown that 3D printing can produce implant shapes that precisely match their anatomical characteristics, ensuring that implant surgery is carried out safely[30,31].

Despite these advantages, 3D printing has a number of limitations. First, 3D printing devices take longer to plan and produce, often delays surgery and therefore are unsuitable for emergency surgery. Second, the issue of the material of the model is also a key point to be examined, as the visceral soft tissue organs are deformable and rigid models cannot reproduce the compliance of the tissue[32,33]. Fragile models are also unsuitable for surgery, and certain models cannot be handled by the surgeon during surgery because the particular material cannot be sterilized[34,35]. Third, the design and manufacture of 3D models for transplantation is more challenging,

**Table 2 Advantages and current limitations of existing three-dimensional printing**

| Advantages | Limitations |
|---|---|
| (1) Realistic spatially dissected views | (1) Time-consuming production |
| (2) Intuitive real-time navigation for rapid identification and location | (2) Rigid model with poor soft tissue compliance |
| (3) Improved surgical safety | (3) Fragility |
| (4) Less time consumed and fewer complications | (4) High cost |
| (5) Novel educational techniques | (5) Issues of specificity, safety, and sustainability of implantable 3D-printed products |

3D: Three-dimensional.

requiring consideration not only of the specificity of soft tissue organs, but also of the safety and sustainability of 3D printed products. Fourth, the high additional cost is also one of the disadvantages of current3D printing that cannot be ignored, of course, it is believed that with the development of bioprinting technology, these issues may be addressed to some extent[34].

## ROBOT-ASSISTED HPATOBILIARY SURGERY

Precision and minimally invasive surgery have long been the pursuit of surgical procedures, and with the development of surgical anatomy and perioperative care, enhanced imaging modalities such as 3D visualization, and advances in laparoscopic surgery and robotic devices, minimally invasive surgery is becoming the gold standard in specific areas of gastrointestinal surgery[36-38]. However, the straight instruments of the laparoscope allow only four degrees of freedom, and the surgeon's inevitable physical hand tremors are magnified by the long laparoscopic tube. These factors, combined with the 2D field of view, the narrow space and the lack of depth perception, add to the difficulty of laparoscopic surgery, and prolonged procedures are more likely to lead to surgeon fatigue[2]. The robot-assisted surgical system offers many advantages over laparoscopic surgery, including the filtering out of physiological hand tremors based on simulated surgeon wrist movements, a stable camera platform, a 3D surgical field of view and visual magnification, seven degrees of freedom of dexterity, and reduced surgical fatigue for the surgeon[39].

### *Operation of robotic surgery: Indications and contraindications*

Currently, most robot-assisted minimally invasive surgery is performed using the Da Vinci Si Surgical System telesurgery system, in which the surgeon sits at a console and operates several master robots, with intraoperative manipulation and view capture performed by three robotic instrument arms and one camera arm[40]. The stable platform's 3D field of view and flexible robot arm help surgeons better expose anatomical structures for selective control, dissection, and handling[39]. The robotic platform also enables near-infrared fluorescence imaging using indocyanine green (ICG) to assess tissue perfusion and identify lymphatic structures, distinguishing between healthy liver and tumor tissue[41]. The use of ICG fluorescence imaging also improves the discrimination between biliary tract and vascular structures, facilitating the identification of resection lines and helping the surgeon to maintain an accurate resection plane intraoperatively[42]. The use of these devices together allows for better control of the vascular system and fine structures such as the bile ducts, reducing intraoperative risks and intraoperative complications.

According to the available guidelines, indications for robotic hepatectomy include malignant tumors of the liver such as primary liver cancer, secondary liver cancer, and other rare malignant tumors of the liver, as well as benign diseases including adenomas, cavernous hemangiomas with symptoms or over 10 cm in diameter, focal nodular hyperplasia, cystic diseases such as hepatic echinococcosis, and intrahepatic bile duct stones requiring hepatic resection involving combined organ resection[43]. Indications for machine bile duct resection include intra- and extra-hepatic bile duct stones requiring combined hepatic segmental surgery or lobectomy for gallbladder cancer without abdominal implant metastases or large vessel invasion, type I, II and III

cholangiocarcinoma of the porta hepatis, *etc*.[44-46]. Contraindications for robotic surgery include, in addition to the same contraindications as for open hepatobiliary resection, severe cardiopulmonary disease that does not tolerate pneumoperitoneum, intra-abdominal adhesions that are difficult to separate and reveal the lesion in two or more operations, lesions that are close to or that directly invade large blood vessels, invasion of the hilum, invasion of the portal vein, hepatic artery and other blood vessels, or lesions that require extensive hilar lymph node dissection[32].

### Robotic surgery in hepatobiliary surgery

As shown in Table 1, Troisi *et al*[37] reviewed liver resections in 40 patients, comparing robot-assisted surgery with laparoscopic surgery, where the robotic platform provided some reduction in complications compared to laparoscopic surgery, and in difficult posterior and superior segments, robot-assisted surgery appeared to be more advantageous and confirmed the safety and feasibility of robot-assisted surgery[37]. Spampinato *et al*[33] conducted a retrospective analysis of the perioperative outcomes of robot-assisted major hepatectomy *vs* laparoscopic major hepatectomy, which confirmed the safety of robot-assisted surgery. Felli *et al*[47] demonstrated the safety of robotic surgery through initial experience with 20 consecutive robotic liver resections. Zhang *et al*[2] conducted a meta-analysis in which robot-assisted surgery had advantages over laparoscopic hepatectomy in major hepatectomy. It has also been shown that the proportion of major resections was higher in the more difficult posterior epigastric group than in the laparoscopic group, and that surgeons subjectively preferred robot-assisted surgery[3]. Kamiński *et al*[48] compared laparoscopic cholecystectomy with robotic cholecystectomy and showed no statistical difference between the two groups in terms of operative time and major bleeding complications, and found that the robotic approach may help in the management of bile duct injuries.

In addition, single-incision robotic cholecystectomy recapitulates the advantages of single-incision surgery, which is based on the same principles as multi-port laparoscopic cholecystectomy and offers the advantages of high definition and stereoscopic vision[49]. It overcomes some of the limitations of conventional laparoscopy through a clear 3D view, redistribution of instruments and optimized engineering design, making it safe and feasible to operate on different gallbladder lesions[49-51]. Gustafson *et al*[51] compared 38 laparoscopic procedures with 44 robotic single-incision cholecystectomies and found no significant differences between the two groups in terms of either transit rate, length of stay, incidence of incisional hernias requiring repair, or intraoperative and postoperative complications.

### Advantages

With the growing trend towards minimally invasive surgery continues to develop, robot-assisted surgery is increasingly being used in hepatobiliary surgery, where it offers potential advantages over other techniques, and studies have shown its advantages in facilitating bile duct reconstruction and vascular anastomosis, and large hepatectomy, and resection of lesions located in highly complex areas[52-54].

First, robotic-assisted technology has more precise resolution, greater magnification, smaller instruments and greater mobility, making it more advantageous in delicate areas such as the liver portal[3], studies have shown that robotic surgery can reduce abdominal wall trauma and improve post-operative diaphragm function, thereby reducing respiratory complications, among other things. Second, the robotic system reproduces the surgeon's natural movements through a steady camera, reducing surgeon fatigue and filtering out physiological tremors, improving precision, accuracy and safety in surgery[43]. Third, the flexible robotic arm can help surgeons perform more precise and safer dissections and sutures, especially in the event of acute bleeding, and the resting position of the robotic arm to stop bleeding allows for safer transfer of open surgery[47]. Previous studies have also shown that intraoperative blood loss is reduced in robotic surgery compared to traditional laparoscopic or open techniques[52]. Fourth, improved venous drainage and reduced bile duct injury are both potential advantages of robotic surgery, which can reduce postoperative pain and complications such as ascites bile duct injury in cirrhotic patients and effectively improve their postoperative quality of life[55]. Fifth, robotic surgery can be used in conjunction with fluoroscopic techniques, with the robotic console providing fluoroscopic cholangiograms that are more conducive to a safe procedure[49].

In recent years, the use of two important phases of minimally invasive hepatectomy — hilar resection and hepatic cavity resection — has improved with the spread of robotic surgery and surgeons' increased level of experience[49]. As surgeons gain experience, the learning curve for robotic surgical approaches is likely to decrease[56].

In addition, as robotic surgery and open surgery share a common skill principle, even new surgeons with less experience may have a shorter learning curve on the operating table and a correspondingly shorter operating time[57].

### *Limitations*

Current robotic surgery is not mature and still has many limitations. First, compared to laparoscopic techniques, robotic surgery is not as resource efficient, as robotic surgery lacks compression options to control acute bleeding, it usually requires at least two experienced hepatobiliary surgeons to interact with coordination at the console and around the patient for safety reasons. In this regard, there is a need for a technical solution for simpler and faster instrument changes that can be performed independently by the surgeon at the console, thus increasing the efficiency of surgical resources[3]. Second, tactile sensitivity is also one of the primary issues facing surgeons, as the robotic arm has no tactile feedback, in order to avoid tissue damage, the instruments should always be in the surgeon's field of view as blind movements of the instruments can cause damage to surrounding organs and structures, so robotic surgery requires higher quality intraoperative images[47]. Okuda *et al*[58] have developed new forceps with force sensors that can analyze the gripping force generated by forceps during laparoscopic surgery and display it graphically on a laptop display, providing real-time feedback to the surgical staff. Experiments have shown that this measurement is accurate and feasible and that this new device with force sensors will also provide real-world feedback during endoscopic surgery, providing practical haptic feedback to aid robot-assisted surgical systems (such as the da Vinci Surgical System) is expected to overcome the lack of haptic feedback in robotic surgery. Third, the choice of anatomical approach is one of the limitations of current robotic surgery. Although the bipolar-based "vascular closure" has multiple degrees of freedom, their branches are too wide for precise and substantial dissection, and the longer time required to change instruments and applicators in robotic surgery compared to open and laparoscopic liver surgery also contributes to the longer operative times, and in these areas there is still a need for some technical adjustments to be made[36,59]. The restricted placement of casing needles is also an issue of concern and solution. Ideally, for optimal setup in the cross-section, four 8 mm robotic trocar needles should be placed in a hypothetical straight line at a distance of approximately 7 cm from each other; however, for setup of the upper segment, especially for severe underlying lesions such as large steatotic livers, trocar needle placement may be limited, increasing the postoperative complications of robotic surgery[60]. Fourth, the long operating time remains a drawback of robotic surgery as the preoperative assembly of the robotic system is very time-consuming[2]. The learning curve for robotic surgery inevitably leads to some increased operative times and the need for resident involvement in all procedures, although the learning curve for robots appears to be faster than for laparoscopy, training in advanced laparoscopic techniques is still required before starting robotic hepatobiliary surgery[60]. Reports of robotic hepatectomy at this stage may be somewhat selective and there may be serious adverse events that are not published. The next step is also the need for standardized training in robotic surgery, such as dedicated robotic surgery training using virtual reality training tables or robotic dual consoles, which is the basis for establishing a successful robotic surgery[61,62]. One of the problems with robotic surgery is its high cost, as many hospitals cannot afford this new technology due to the high cost of purchasing and maintaining robots, but in recent years, as surgeons have gained experience, operating times have been reduced and patient lengths of stay have become less decisive in terms of cost[56]. Despite these reports, more prospective randomized studies are needed to assess the true costs of robotic surgery in different procedures, combining robotic surgery with accelerated recovery and perioperative care could theoretically significantly reduce the patient's length of stay and therefore offset the existing high costs[3]. In addition, there is a lack of communication between clinicians and those developing the technology. Clinicians should communicate fully with technicians to inform them of their needs and the advantages and disadvantages of the existing technology so that they can target improvements to facilitate continuous technological progress, optimization of image processing, develop new computer interfaces to facilitate interfacing, and even add modules with sensory haptics to overcome the lack of tactile feedback and assess pathology based on accurate 3D reconstruction, *etc.*

## REAL-TIME NAVIGATION

Accurate surgical navigation, which can better guide surgeons and improve surgical safety, has received widespread attention with the development of computer science and imaging technology. Surgical navigation refers to the use of medical imaging equipment and computer image processing methods to visualize the patient's preoperative multimodal image data before surgery, to precisely match the patient's anatomy during surgery using rapid alignment procedures, and to obtain and display the position of surgical instruments in space in real time using a 3D positioning system [63-65].

The accuracy of the tracking technique is an important basis for the reliability of the navigation procedure, and the accuracy of the tracking system largely reflects the quality and performance of the surgical navigation system. To date, optical tracking system (OTS) and electromagnetic tracking system (EMT) are the two main tracking techniques used in surgical navigation. Table 3 compares some of the basic characteristics of OTS and EMT.

The OTS is used to locate visual markers by means of a camera. Its high tracking accuracy and robustness are widely used to estimate the position of surgical tools relative to the target area, with great accuracy and tracking volume, but its main limitation is that a visible line of sight between the intraoperative marker site and the camera is required. Without a line of sight, optical tracking cannot be achieved, and the tip of the knife is usually the location to be tracked and typically needs to be placed near the end of a rigid instrument. As only rigid instruments can be used due to the possibility of tip shift of the tracker, the use of optical tracking is limited, so optical navigation systems are mainly used to track rigid objects, for example in orthopedic surgery[66,67].

The EMT uses a known magnetic field geometry to determine the attitude of the sensor measuring the magnetic flux or field to achieve attitude measurement and dynamic tracking of the target, with the advantages of real-time positioning, high accuracy and no fear of obstruction[68]. EMT provides a solution for precise positioning when line of sight cannot be established, enabling small electromagnetic (EM) sensors to be positioned independently of line of sight in a given EM field, facilitating fast and accurate tracking[66], this avoids the limitations of line of sight establishment problems, and the small size of the sensor allows it to be embedded in the tip of the surgical instrument, reducing tracking errors caused by the large distance between the sensor and the tip of the positioning instrument[66]. Therefore, EM surgical navigation systems are commonly used in endoscopic surgery and abdominal surgery[69].

### *Real-time navigation and the applications mediated by EM tracking*

The implementation of EM tracking-mediated real-time navigation consists of three important steps: (1) Preoperative acquisition of 3D visualization images of organ tissues; (2) Alignment of the virtual 3D visualization images with the real intraoperative images using real-time EM tracking technology and tracking and matching of the virtual 3D images with the changing real images; and (3) Overlay of the virtual images with the real images through augmented reality so that the real environment and virtual images are superimposed on the same screen in real time. As shown in Figure 1, these superimposed virtual images materialize and visualize the intraoperative hepatobiliary structures, helping the surgeon to better judge their spatial relationships and thus making the operation run more smoothly[70-72]. Augmented reality allows the 3D visualization of the hepatobiliary model to be projected onto the surgical area for precise alignment of the coverage area, avoiding hand-eye coordination problems for the surgeon in traditional laparoscopic surgery[73].

A real-time ultrasound and preoperative CT or MRI image fusion system has been developed in recent years to construct preoperative CT or MRI image datasets as tomographic images and fuse them with real-time acquired ultrasound images with high precision and dynamics[1]. Although this method of navigation is feasible, the inevitable problem of poor accuracy when tracking and locating ultrasound is due to the effect of temperature and air displacement on ultrasonic positioning.

Today, as EM navigation procedures continue to evolve, a number of manufacturers have developed different stand-alone EM tracking systems for medical applications, with the main commercial EM tracking devices currently used in clinical applications being the NDI Aurora (NDI Medical, Canada), the Polhemus Fastack (Polhemus, Canada), and the Ascension MiniBIRD (Ascension Technologies, United States)[74].

**Table 3 Comparison of optical and electromagnetic tracking navigation**

| Item | Optical tracking | Electromagnetic tracking |
|---|---|---|
| Tracking accuracy | High | Low |
| Robustness relative to environmental conditions | High | Low |
| Visible line of sight | Need for | No need for |
| Tracking of rigid objects | Suitable for | Unsuitable for |
| Electromagnetic field | No need for | Need for |
| Interference from magnetic field | Nothing | Notable |
| Common uses in the surgeries: | | |
| Neurosurgery | + | |
| Orthopedic | + | |
| Endoscopic abdominal | | + |

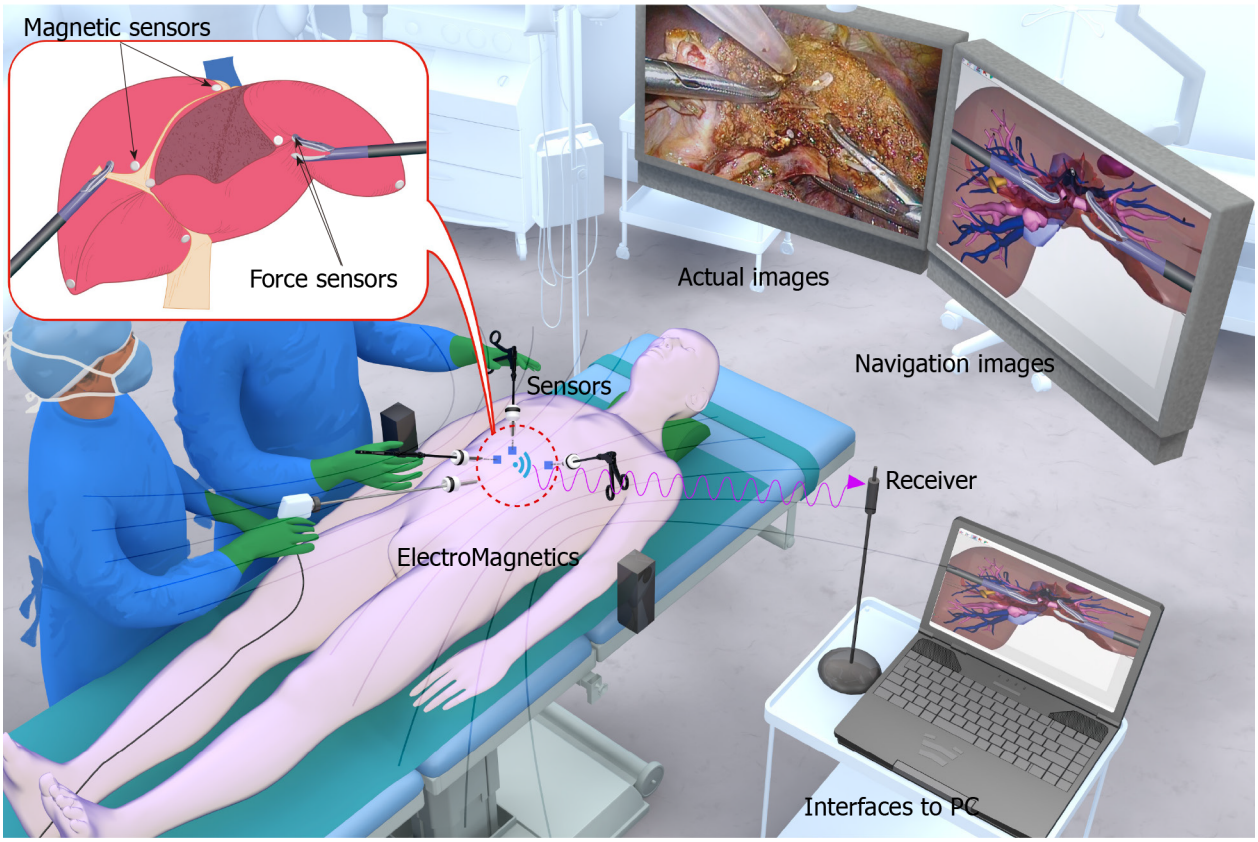


**Figure 1 Intraoperative schematic of the electromagnetic tracking procedure.** It shows a schematic diagram based on electromagnetic tracking navigation under a developing work by the Ohkohchi team which is used to track the position of the micro electro mechanical system (MEMS) within the magnetic field in real time without the need for line of sight and send the real-time information to a computer workstation, fuse the real-time intraoperative actual procedure and visual images with the preoperative computed tomography or magnetic resonance imaging pictures to form a three-dimensional reconstruction image, and display the real intraoperative actual procedure and visual images and the corresponding reconstruction images side-by-side on a TV monitor to achieve real-time navigation of the surgical site (this is the project of "Development of Real-time Navigation System for Laparoscopic Hepatectomy", University of Tsukuba, Japan, 2017.4-2020.3).

Song *et al*[75] proposed a magnetic tracking-based planar shape-sensing and navigation system for a flexible surgical robot applied to transoral surgery. The permanent magnets were mounted at the distal end of the robot to provide 3D localization and 2D orientation estimation, so there was no need to mount the sensors on the robot. Navigation validation on an experimental platform showed that the approach was feasible and can work in the surgical environment, despite localization errors within the tracking system and the robot[75].

Kok *et al*[76] evaluated the feasibility and safety of an internally developed EM navigation system for real-time rectal tumor tracking using the NDI Aurora V2 EM tracking system (Northern Digital Inc, Waterloo, Ontario, Canada), employing a patient tracker with an EM sensor (Philips Traxtal/Percunav, Philips, Best, the Netherlands) patient tracker to determine the patient's position during surgery and to place tracking sensors on the tumor to adjust for real-time tumor motion, providing continuous interpretable navigation data for rectal surgery, this prospective study demonstrates that real-time tumor tracking with EM navigation is feasible, safe and accurate and provides direction for wider clinical implementation and contributes to further research to improve workflow and demonstrate clinical benefit[76].

The Ohkochi team at the University of Tsukuba, Japan, in collaboration with LEXI at University of Tokyo, have developed a new forceps with a powerful sensor that connects a micro electromechanical systems triaxial pressure sensor to the forceps tip to measure the pressure exerted by an endoscopic surgical forceps, the gripping force generated by the forceps with the pressure sensor during laparoscopic surgery was measured and analyzed in real time using quantitative data with temperature-compensated triaxial forces displayed graphically on a laptop computer display, providing real-time feedback to the surgical staff on pressure changes due to complex movements, the results show that this measurement is accurate and feasible, and this is the first study to report on the measurement of complex movements during actual surgery, Okuda *et al*[58] are working on the development of a position sensor system by combining it with a pressure-sensing system, when the data obtained from the device with the pressure sensor is combined with the real-time navigation system, it can display the magnitude of the grip force based on the information provided about the position of the operating site, helping the surgeon to control the intraoperative operation when the pressure is too high and causes damage to the internal soft tissue organs. This will be a breakthrough in traditional navigation surgery, overcoming the lack of tactile feedback from existing navigation[58].

### Advantages

Real-time navigation based on EM tracking offers the possibility of navigation in minimally invasive abdominal surgery without the line-of-sight interference problems of optical systems. It provides real-time accurate spatial 3D measurements in the presence of obstruction, allowing real-time unobstructed tracking of miniaturized sensors embedded in surgical tools, probes, needles, guidewires and catheters, which can even be placed at the tips of flexible machinery, helping surgeons to achieve real-time precise navigation of the surgical area and improve the safety of the procedure [66].

EM tracking in surgical navigation provides a non-invasive, radiation-free way to navigate intraoperatively in real-time without any invasive procedures such as portal venipuncture or hepatic dissection, showing the fine anatomy of the lesion in real time, combines flexibly with surgical instruments, solves the surgeon's hand-eye coordination problem, and improves the accuracy and controllability of surgical navigation[77]. In addition, real-time navigation allows the intraoperative surgical team to share intraoperative information to ensure that the operation is carried out safely.

### Limitations

First, EMT are highly sensitive to EM interference and magnetic field distortions[66]. Second, existing EM tracking systems do not provide for accurate position tracking at longer distances from the source, some current studies have confirmed that the stability of EM navigation systems needs further improvement, these systems can operate with a limited amount of tracking but their accuracy decreases as the distance between the transmitter and receiver increases, the accuracy of AR navigation decreases when the EM sensor is far from the magnetic field generator and it is difficult to have systems that can track small sensors with a volume greater than 1 cubic metre[78]. Third, in addition to technical shortcomings, EM tracking technology lacks environmental robustness and accuracy compared to optical tracking navigation, and the robustness of EM tracking can be a problem in some environments, so all systems need to be carefully evaluated in clinical practice[79]. The development of customized systems for different environments and applications may offer some solutions for increasing the robustness of EM tracking technology[66]. Fourth, although the ideal navigation system is easy to use for those unfamiliar with intrahepatic anatomy, current navigation systems sometimes require manual intraoperative adjustment, which takes time and requires an in-depth knowledge of hepatobiliary anatomy, and therefore still requires the surgeon to be very familiar with the

anatomy in order to ensure a smooth operation[80]. Fifthly, the issue of alignment in real-time surgery has always been a challenge[70]. Sixth, the time-consuming problem of superimposing reconstructed images onto real-time intraoperative images is also a current technical challenge[81]. The construction of superimposed images is still time-consuming and labor-intensive in routine use, and although currently available simulation software programs have reduced surgery time by up to one hour, skilled surgeons still need three to four hours to construct overlay images[82]. There is therefore an urgent need to develop new techniques to reduce the time taken to superimpose images, and in the future it is also hoped that technicians will be able to provide more information on pathological or biological conditions in addition to the superimposed images to enrich the usefulness of the navigation system. Seventh, in terms of image display technology, although various methods are used in navigational surgery, such as monitor-based video fluoroscopic and projection-based systems, there are still problems to overcome such as limited resolution, overlapping distorted images and cumbersome operation[83]. Eighth, the cost of navigation equipment is relatively high and it is believed that as the price of equipment decreases it will be able to drive more hospitals to perform procedures with real-time navigation and more surgeons to participate. However, many clinicians are not aware of the advances in augmented reality technology, so there needs to be a full exchange of information and communication of needs between clinicians and technicians in the clinical setting to develop technology that meets clinicians' expectations, which will help create new inventions and facilitate the advancement and development of navigation[84].

### *Problem analysis and anticipation of improvements*

The accuracy and distortion of EM tracking has been a central issue of research. The accuracy of EM tracking is affected by a variety of factors, and existing EM tracking systems have multiple sources of error, physical laws, design limitations, and manufacturing imperfections or environmental noise can all lead to positioning errors. The intraoperative alignment of deformed organs is also another challenge in navigation technology due to the effects of intraoperative manipulation and respiratory activity, and the clarity and resolution of reconstructed images based on real-time intraoperative images is also of concern to researchers. Despite some attempts to compensate for the tracking, alignment and reconstruction of images, there are still some issues to be resolved[85,86].

**Accuracy and distortion:** In EMT, errors can be classified as (1) inherent system errors, (2) field distortion errors, and (3) motion-induced errors. Inherent system errors are static errors that can occur when the sensor is placed at a fixed point or when the system is updated; distortion errors refer to disturbances in the secondary and unwanted magnetic fields which can be caused by eddy currents induced by ferromagnetic or conductive materials or by external currents, and they can also originate from the FG field generator and sensor design; motion-induced errors can be caused by changes in the speed of the sensor and the environment during the measurement[79,87].

Upgrading the system to avoid eddy currents and performing a system calibration function can help to some extent with inherent system errors[79,88]. Static pre-calibration processes are cumbersome and ineffective for most dynamic clinical procedures, and often require too many EM sensors to compensate for field distortion in dynamic environments, making them inefficient. A fusion-based approach has also been applied that combines measurements from multiple redundant EM sensors with the motion model of the instrument being tracked, which uses both localization and mapping (SLAM) algorithms to create field distortion maps and compensate for EM tracking errors in real time, however, it requires a large surgical space to complement the tracking technique or an excessive number of redundant sensors, and increases time of calibration. Too many devices also have an impact on the surgeon's surgical space, and their computational complexity, convergence and performance in dynamic environments and spaces still need to be considered by technicians in the future[89].

**Alignment errors:** The main problem with navigational surgery in hepatobiliary surgery are the accuracy, complexity and time-consuming nature of alignment. First, the EM transmitter should be placed as close as possible to the operating table to avoid interference with alignment accuracy caused by longer distances, second, a suitable probe point should be selected. For transabdominal scans, the ideal location for the probe point is below the glabella, whereas for intraoperative scans, the probe point should be set on the surface of the liver, preferably in the easily recognizable round ligament at the inferior edge of the fissure, the tip of the main portal vein near the

tumor can also be used as an important intraoperative landmark, as can the branching vessels near the tumor for precise intraoperative adjustment[90]. In addition, intraoperative control of ventilation or reduction of tidal volume can reduce respiratory-related alignment errors to some extent, and deformed livers can also be monitored in real time using respiratory gating techniques to compensate for errors in the tracking position of EM sensors[91]. It is also necessary to calibrate the camera and the spatial relationship between the camera lens and the solenoid and to manually verify the reference boundary markers, all of the aforementioned techniques can help to improve the accuracy of the alignment[92].

Image reconstruction has also been investigated using surface data obtained from a flexible liver model that simulates deformation, and this data was then used to construct a sample library to predict liver displacement and deformation in alignment, including changes in the shape and internal relative position of the internal structures of the liver[93,94]. However, due to the movement of the diaphragm during breathing and the pulling of instruments can lead to changes in the position and shape of the liver and the occurrence of biliary tract deformities, this leads to incorrect positioning in the navigation system[90]. Although interactive and automated alignment systems have been developed that allow for periodically repeated real-time image acquisition to accommodate alignment difficulties caused by liver deformation and displacement, these systems require a hybrid operating room with CT or MRI equipment and have not been performed in human hepatobiliary surgery[95]. There are also reports of proposed 3D dense surface reconstruction algorithms that can localize hidden structures in intestinal surgery and gallbladder surgery, as well as enhanced block mapping algorithms and reimage mapping techniques that facilitate the implementation of dynamic alignment and aid in alignment studies of variable organs, although there are reports of these studies using existing engineering techniques and mathematical algorithms to solve organ deformation problems, the required methods and algorithms are complex and still need to be simplified and optimized[95].

**Superimposed images:** Reconstructed images can be displayed in a variety of ways, either video-based or projection-based. Video-based reconstructed image display is commonly used for laparoscopic, robotic and endoscopic procedures[57]. The external video monitor displays the actual surgical scene, and the virtual 3D reconstructed image in the video has poor resolution, requiring tracking and correction of multiple anatomical structures to compensate for changes in the surgeon's field of view and changes in the projected image due to changes in the curvature of the surface of the organ being tracked, this adds to the complexity of constructing the image[1,96,97]. The projection-based reconstructed image also interferes with the surgeon's depth perception, as the image is disturbed and lost when the projector's beam is interrupted by the surgeon's body or robotic arm, and the constructed image is distorted when the beam is not projected on a flat area[98,99]. The development of 3D future holographic projection technology may address the issues of overlapping image interference and diminished depth perception, thereby improving projection-based displays in intraoperative navigation[70]. There is also a transparent display in use that reflects the image in a translucent mirror, allowing the surgeon to view the reconstructed image while also looking directly into the surgical field. It does not require additional video compositing, making it more convenient than conventional video displays and avoids the problem of distortion of the projected image due to changes in the curvature of the object's surface, in addition it does not require special glasses or sensing devices, future research will require improved transparent display methods and more advanced naked eye 3D to provide doctors with a more accurate display of spatial images[29].

## CONCLUSION

In Table 4, we summarize the advantages and existing limitations of the latest trends in existing digital healthcare such as 3D visualization of images as well as robot-assisted surgery and real-time EM-based intraoperative navigation. Visualization techniques are more widely used in clinical practice, providing a 3D view of the lesion area and clearer spatial anatomical relationships through the preoperative sharing of accurate 3D surgical images. By creating conditions for complex and precise procedures, such techniques also help surgeons to optimize their surgical plans before surgery and to carry out preoperative simulations through software, which not only reduces surgery time but also reduces intraoperative risks and postoperative complic-

**Table 4 Advantages and limitations of three-dimensional visualization, robot-assisted surgery, and electromagnetic tracking navigation**

| | Advantages | Limitations |
|---|---|---|
| 3D visualization | Realistic spatially dissected views | Complex and time-consuming reconstruction process |
| | Accurate 3D preoperative images | Possible loss of raw data due to operational errors |
| | Possibility of complicated surgery | Distortion in reconstructed images |
| | Optimization of preoperative assessment | Poor accuracy of reconstructed images |
| | Time-saving simulation | Complex algorithms and imperfect display techniques |
| | Less time consumed and fewer complications | Registration of mutable organs |
| | Novel educational techniques | High cost |
| Robot-assisted | Better micro-invasiveness | Inefficient surgical resources |
| | Smaller equipment for wider scope | Lack of tactile feedback |
| | Larger and clearer 3D views | Limitations in the choice of anatomical methods |
| | Micro-invasiveness | Restrictions on the placement of casing needles |
| | Improved venous drainage | Time-consuming operation |
| | More accurate resolution and greater magnification | Prolonged Pringle operation in the hilar region |
| | Filtering of natural tremor | Potential bleeding tendency of the clamping and squeezing technique |
| | Better ergonomics of the operator | High cost |
| Electromagnetic tracking real-time navigation | No requirement for any other invasive operations | Magnetic field interference and tracking errors |
| | No line of sight restrictions | Low tracking accuracy and robustness relative to environmental conditions |
| | Real-time intraoperative tracking and navigation | Low stability of electromagnetic navigation system |
| | Display of intraoperative fine anatomy | High cost |
| | Improved safety of surgical operations | Registration of mutable organs |
| | Identification of lesions that are not visually detectable | Accuracy of navigation issues |
| | Simultaneous sharing of intraoperative information | Time-consuming reconstruction image overlay |
| | Increased hand-eye coordination for doctors | Low resolution and distortion of the reconstructed image |
| | | Insufficient communication between technicians and surgeons |
| | | Tedious operation |

3D: Three-dimensional.

ations, improves patient prognosis, and can be used as a new teaching technique for new doctors. However, it is still time consuming and costly to plan and produce 3D models, and rigid models do not reproduce the compliance of soft tissues, implantable organs, and the specificity of 3D-printed products. The specificity, safety, and sustainability of 3D-printed products remain to be addressed. Robotic surgery, which is more minimally invasive than traditional laparoscopic or open surgery, with smaller instruments and a greater degree of motion, a clearer 3D field of view, more precise resolution, and greater magnification. Additionally, it offers filtering out of natural tremors, better ergonomics for the operator, the advantage of highly complex site resections, and improved venous drainage to reduce postoperative complications and help improve patients' quality of life. However, at this stage, robotic surgery is not mature and still has many limitations. Current limitations of robotic surgery include inefficient surgical resources, lack of tactile feedback, limited choice of anatomical approach, limitations in trocar placement, excessive operative time, long assembly time of the robotic system, time-consuming docking procedures, potential tendency to

prolong pulmonary portal Pringle surgery, potential bleeding from the clamp squeeze technique, and high costs. Real-time navigation based on EM tracking has the advantage of not requiring any invasive operations and is not limited by line of sight, allowing for real-time intraoperative tracking and navigation, sharing of intraoperative information in real time, display of intraoperative fine anatomy, identification of lesions that cannot be detected by the naked eye, and lessening of hand-eye coordination issues during laparoscopic surgery. The development of sensors is expected to improve the accuracy of navigation for the safe unfolding of hepatobiliary surgery, but at this stage there are also problems with EM navigation systems that are not very stable, as well as low tracking accuracy, poor robustness to environmental conditions, magnetic field interference and tracking errors, poor navigation accuracy, a time-consuming reconstructed image superimposition process, low resolution of reconstructed images, large distortion, and intraoperative variable organ alignment problems. There are problems to be solved, and insufficient information exchange between the technician and the clinician remains problematic.

It is noteworthy that in previous studies we have found that surgeons tend to focus on the surgical procedure to the neglect of post-operative care. The final healing after surgery is the result of a combination of factors such as the quality of surgery, intraoperative blood loss, the size of the resected lesion, the patient's underlying preoperative disease or comorbidities, and the patient's physical condition. The concept of Enhanced Recovery After Surgery was first developed by Danish surgeon Henrik Kehlet, based on the principles of reducing the stress of surgery, shortening the length of hospital stay and reducing perioperative complications, leading to rapid recovery. The concept is also considered to be a safe and effective treatment combining existing surgical options with accelerated recovery perioperative care. This could theoretically significantly reduce the length of a patient's hospital stay, which could to some extent offset the existing high costs. The price of various technologies — be it robotic surgery, 3D printing or EM navigation tracking — will certainly come down in the future. This will require a concerted effort and adequate communication between the entire healthcare industry, corporate bodies and technicians in order to target technological improvements and facilitate the continued progress of digital healthcare. Despite the opportunities and challenges, digital healthcare is sure to flourish in the future.

## ACKNOWLEDGEMENTS

We thank Dr. Kim J of University of Tsukuba Faculty of Medicine for designing the figure image.

## REFERENCES

1 **Miyata A**, Arita J, Kawaguchi Y, Hasegawa K, Kokudo N. Simulation and navigation liver surgery: an update after 2,000 virtual hepatectomies. *Glob Health Med* 2020; **2**: 298-305 [PMID: 33330824 DOI: 10.35772/ghm.2020.01045]

2 **Zhang L**, Yuan Q, Xu Y, Wang W. Comparative clinical outcomes of robot-assisted liver resection *vs* laparoscopic liver resection: A meta-analysis. *PLoS One* 2020; **15**: e0240593 [PMID: 33048989 DOI: 10.1371/journal.pone.0240593]

3 **Schmelzle M**, Krenzien F, Schöning W, Pratschke J. [Possibilities and limits of robotic liver surgery - Current status 2020]. *Chirurg* 2021; **92**: 107-114 [PMID: 33095282 DOI: 10.1007/s00104-020-01300-w]

4 **Fang C**, Zhang P, Qi X. Digital and intelligent liver surgery in the new era: Prospects and dilemmas. *EBioMedicine* 2019; **41**: 693-701 [PMID: 30773479 DOI: 10.1016/j.ebiom.2019.02.017]

5 **Kochanski RB**, Lombardi JM, Laratta JL, Lehman RA, O'Toole JE. Image-Guided Navigation and Robotics in Spine Surgery. *Neurosurgery* 2019; **84**: 1179-1189 [PMID: 30615160 DOI: 10.1093/neuros/nyy630]

6 **Mathew RP**, Venkatesh SK. Liver vascular anatomy: a refresher. *Abdom Radiol (NY)* 2018; **43**: 1886-1895 [PMID: 29696320 DOI: 10.1007/s00261-018-1623-z]

7 **Shimoda M**, Hariyama M, Oshiro Y, Suzuki S. Development of new software enabling automatic identification of the optimal anatomical liver resectable region, incorporating preoperative liver function. *Oncol Lett* 2019; **18**: 6639-6647 [PMID: 31788120 DOI: 10.3892/ol.2019.11006]

8 **Su L**, Dong Q, Zhang H, Zhou X, Chen Y, Hao X, Li X. Clinical application of a three-dimensional imaging technique in infants and young children with complex liver tumors. *Pediatr Surg Int* 2016; **32**: 387-395 [PMID: 26809670 DOI: 10.1007/s00383-016-3864-7]

9 **Witowski J**, Budzyński A, Grochowska A, Ballard DH, Major P, Rubinkiewicz M, Złahoda-Huzior A, Popiela TJ, Wierdak M, Pędziwiatr M. Decision-making based on 3D printed models in

laparoscopic liver resections with intraoperative ultrasound: a prospective observational study. *Eur Radiol* 2020; **30**: 1306-1312 [PMID: 31773294 DOI: 10.1007/s00330-019-06511-2]

10 **Okuda Y**, Taura K, Seo S, Yasuchika K, Nitta T, Ogawa K, Hatano E, Uemoto S. Usefulness of operative planning based on 3-dimensional CT cholangiography for biliary malignancies. *Surgery* 2015; **158**: 1261-1271 [PMID: 26054319 DOI: 10.1016/j.surg.2015.04.021]

11 **Pianka F**, Baumhauer M, Stein D, Radeleff B, Schmied BM, Meinzer HP, Müller SA. Liver tissue sparing resection using a novel planning tool. *Langenbecks Arch Surg* 2011; **396**: 201-208 [PMID: 21161546 DOI: 10.1007/s00423-010-0734-y]

12 **Fang CH**, Zhang P, Zhou WP, Zhou J, Dai CL, Liu JF, Jia WD, Liang X, Zeng SL, Wen S. [Efficacy of three-dimensional visualization technology in the precision diagnosis and treatment for primary liver cancer: a retrospective multicenter study of 1 665 cases in China]. *Zhonghua Wai Ke Za Zhi* 2020; **58**: 375-382 [PMID: 32393005 DOI: 10.3760/cma.j.cn112139-20200220-00105]

13 **Nakayama K**, Oshiro Y, Miyamoto R, Kohno K, Fukunaga K, Ohkohchi N. The Effect of Three-Dimensional Preoperative Simulation on Liver Surgery. *World J Surg* 2017; **41**: 1840-1847 [PMID: 28271263 DOI: 10.1007/s00268-017-3933-7]

14 **Zhu W**, He SS, Zeng SL, Zhang P, Yang J, Xiang N, Zeng N, Fan YF, Wen S, Fang CH, Zhang K. [Three-dimensional visual assessment and virtual reality study of centrally located hepatocellular carcinoma on the axis of blood vessels]. *Zhonghua Waike Zazhi* 2019; **57**: 358-365 [PMID: 31091591]

15 **Miyamoto R**, Oshiro Y, Hashimoto S, Kohno K, Fukunaga K, Oda T, Ohkohchi N. Three-dimensional imaging identified the accessory bile duct in a patient with cholangiocarcinoma. *World J Gastroenterol* 2014; **20**: 11451-11455 [PMID: 25170235 DOI: 10.3748/wjg.v20.i32.11451]

16 **Zeng N**, Tao H, Fang C, Fan Y, Xiang N, Yang J, Zhu W, Liu J, Guan T, Xiang F. Individualized preoperative planning using three-dimensional modeling for Bismuth and Corlette type III hilar cholangiocarcinoma. *World J Surg Oncol* 2016; **14**: 44 [PMID: 26911245 DOI: 10.1186/s12957-016-0794-8]

17 **Lin C**, Gao J, Zheng H, Zhao J, Yang H, Lin G, Li H, Pan H, Liao Q, Zhao Y. Three-Dimensional Visualization Technology Used in Pancreatic Surgery: a Valuable Tool for Surgical Trainees. *J Gastrointest Surg* 2020; **24**: 866-873 [PMID: 31012044 DOI: 10.1007/s11605-019-04214-z]

18 **Fang C**, An J, Bruno A, Cai X, Fan J, Fujimoto J, Golfieri R, Hao X, Jiang H, Jiao LR, Kulkarni AV, Lang H, Lesmana CRA, Li Q, Liu L, Liu Y, Lau W, Lu Q, Man K, Maruyama H, Mosconi C, Örmeci N, Pavlides M, Rezende G, Sohn JH, Treeprasertsuk S, Vilgrain V, Wen H, Wen S, Quan X, Ximenes R, Yang Y, Zhang B, Zhang W, Zhang P, Zhang S, Qi X. Consensus recommendations of three-dimensional visualization for diagnosis and management of liver diseases. *Hepatol Int* 2020; **14**: 437-453 [PMID: 32638296 DOI: 10.1007/s12072-020-10052-y]

19 **Yamada Y**, Matsumoto S, Mori H, Takaji R, Kiyonaga M, Hijiya N, Tanoue R, Tomonari K, Tanoue S, Hongo N, Ohta M, Seike M, Inomata M, Murakami K, Moriyama M. Periportal lymphatic system on post-hepatobiliary phase Gd-EOB-DTPA-enhanced MR imaging in normal subjects and patients with chronic hepatitis C. *Abdom Radiol (NY)* 2017; **42**: 2410-2419 [PMID: 28444420 DOI: 10.1007/s00261-017-1155-y]

20 **Chen-Yoshikawa TF**, Hatano E, Yoshizawa A, Date H. Clinical application of projection mapping technology for surgical resection of lung metastasis. *Interact Cardiovasc Thorac Surg* 2017; **25**: 1010-1011 [PMID: 29049837 DOI: 10.1093/icvts/ivx247]

21 **Sen A**, Anderson BM, Cazoulat G, McCulloch MM, Elganainy D, McDonald BA, He Y, Mohamed ASR, Elgohari BA, Zaid M, Koay EJ, Brock KK. Accuracy of deformable image registration techniques for alignment of longitudinal cholangiocarcinoma CT images. *Med Phys* 2020; **47**: 1670-1679 [PMID: 31958147 DOI: 10.1002/mp.14029]

22 **Lopez-Lopez V**, Robles-Campos R, García-Calderon D, Lang H, Cugat E, Jiménez-Galanes S, Férnandez-Cebrian JM, Sánchez-Turrión V, Fernández-Fernández JM, Barrera-Gómez MÁ, de la Cruz J, Lopez-Conesa A, Brusadin R, Gomez-Perez B, Parrilla-Paricio P. Applicability of 3D-printed models in hepatobiliary surgey: results from "LIV3DPRINT" multicenter study. *HPB (Oxford)* 2021; **23**: 675-684 [PMID: 33071150 DOI: 10.1016/j.hpb.2020.09.020]

23 **Yang T**, Lin S, Xie Q, Ouyang W, Tan T, Li J, Chen Z, Yang J, Wu H, Pan J, Hu C, Zou Y. Impact of 3D printing technology on the comprehension of surgical liver anatomy. *Surg Endosc* 2019; **33**: 411-417 [PMID: 29943060 DOI: 10.1007/s00464-018-6308-8]

24 **Igami T**, Nakamura Y, Hirose T, Ebata T, Yokoyama Y, Sugawara G, Mizuno T, Mori K, Nagino M. Application of a three-dimensional print of a liver in hepatectomy for small tumors invisible by intraoperative ultrasonography: preliminary experience. *World J Surg* 2014; **38**: 3163-3166 [PMID: 25145821 DOI: 10.1007/s00268-014-2740-7]

25 **Joo I**, Kim JH, Park SJ, Lee K, Yi NJ, Han JK. Personalized 3D-Printed Transparent Liver Model Using the Hepatobiliary Phase MRI: Usefulness in the Lesion-by-Lesion Imaging-Pathologic Matching of Focal Liver Lesions-Preliminary Results. *Invest Radiol* 2019; **54**: 138-145 [PMID: 30379728 DOI: 10.1097/RLI.0000000000000521]

26 **Fang C**, Fang Z, Fan Y, Li J, Xiang F, Tao H. [Application of 3D visualization, 3D printing and 3D laparoscopy in the diagnosis and surgical treatment of hepatic tumors]. *Nanfang Yike Daxue Xuebao* 2015; **35**: 639-645 [PMID: 26018255]

27 **He YB**, Bai L, Li T, Ji XW, Tuerganaili A, Jiang Y, Zhao JM, Shao YM, Liu WY, Wen H. [Application of three-dimensional visualization technology in surgical treatment for patients with hepatic alveolar echinococcosis]. *Zhonghua Wai Ke Za Zhi* 2016; **54**: 704-709 [PMID: 27587215

DOI: 10.3760/cma.j.issn.0529-5815.2016.09.011]

28 **Yang H**, Sun L, Pang Y, Hu D, Xu H, Mao S, Peng W, Wang Y, Xu Y, Zheng YC, Du S, Zhao H, Chi T, Lu X, Sang X, Zhong S, Wang X, Zhang H, Huang P, Sun W, Mao Y. Three-dimensional bioprinted hepatorganoids prolong survival of mice with liver failure. *Gut* 2021; **70**: 567-574 [PMID: 32434830 DOI: 10.1136/gutjnl-2019-319960]

29 **Tang R**, Ma L, Li A, Yu L, Rong Z, Zhang X, Xiang C, Liao H, Dong J. Choledochoscopic Examination of a 3-Dimensional Printing Model Using Augmented Reality Techniques: A Preliminary Proof of Concept Study. *Surg Innov* 2018; **25**: 492-498 [PMID: 29909727 DOI: 10.1177/1553350618781622]

30 **Suh YJ**, Lim TH, Choi HS, Kim MS, Lee SJ, Kim SH, Park CH. 3D Printing and NIR Fluorescence Imaging Techniques for the Fabrication of Implants. *Materials (Basel)* 2020; **13** [PMID: 33126650 DOI: 10.3390/ma13214819]

31 **van Doremalen RFM**, van der Linde RA, Kootstra JJ, van Helden SH, Hekman EEG. Can 3D-printing avoid discomfort-related implant removal in midshaft clavicle fractures? *Arch Orthop Trauma Surg* 2020 [PMID: 33128609 DOI: 10.1007/s00402-020-03654-6]

32 **Liu R**, Wakabayashi G, Kim HJ, Choi GH, Yiengpruksawan A, Fong Y, He J, Boggi U, Troisi RI, Efanov M, Azoulay D, Panaro F, Pessaux P, Wang XY, Zhu JY, Zhang SG, Sun CD, Wu Z, Tao KS, Yang KH, Fan J, Chen XP. International consensus statement on robotic hepatectomy surgery in 2018. *World J Gastroenterol* 2019; **25**: 1432-1444 [PMID: 30948907 DOI: 10.3748/wjg.v25.i12.1432]

33 **Spampinato MG**, Coratti A, Bianco L, Caniglia F, Laurenzi A, Puleo F, Ettorre GM, Boggi U. Perioperative outcomes of laparoscopic and robot-assisted major hepatectomies: an Italian multi-institutional comparative study. *Surg Endosc* 2014; **28**: 2973-2979 [PMID: 24853851 DOI: 10.1007/s00464-014-3560-4]

34 **Huber T**, Huettl F, Tripke V, Baumgart J, Lang H. Experiences With Three-dimensional Printing in Complex Liver Surgery. *Ann Surg* 2021; **273**: e26-e27 [PMID: 33074891 DOI: 10.1097/SLA.0000000000004348]

35 **Kuroda S**, Kihara T, Akita Y, Kobayashi T, Nikawa H, Ohdan H. Simulation and navigation of living donor hepatectomy using a unique three-dimensional printed liver model with soft and transparent parenchyma. *Surg Today* 2020; **50**: 307-313 [PMID: 31471747 DOI: 10.1007/s00595-019-01868-9]

36 **Gavriilidis P**, Roberts KJ, Aldrighetti L, Sutcliffe RP. A comparison between robotic, laparoscopic and open hepatectomy: A systematic review and network meta-analysis. *Eur J Surg Oncol* 2020; **46**: 1214-1224 [PMID: 32312592 DOI: 10.1016/j.ejso.2020.03.227]

37 **Troisi RI**, Patriti A, Montalti R, Casciola L. Robot assistance in liver surgery: a real advantage over a fully laparoscopic approach? *Int J Med Robot* 2013; **9**: 160-166 [PMID: 23526589 DOI: 10.1002/rcs.1495]

38 **Milone M**, Manigrasso M, Burati M, Velotti N, Milone F, De Palma GD. Surgical resection for rectal cancer. Is laparoscopic surgery as successful as open approach? *PLoS One* 2018; **13**: e0204887 [PMID: 30300377 DOI: 10.1371/journal.pone.0204887]

39 **Lafaro KJ**, Stewart C, Fong A, Fong Y. Robotic Liver Resection. *Surg Clin North Am* 2020; **100**: 265-281 [PMID: 32169180 DOI: 10.1016/j.suc.2019.11.003]

40 **Fahrner R**, Rauchfuß F, Bauschke A, Kissler H, Settmacher U, Zanow J. Robotic hepatic surgery in malignancy: review of the current literature. *J Robot Surg* 2019; **13**: 533-538 [PMID: 30895519 DOI: 10.1007/s11701-019-00939-w]

41 **Achterberg FB**, Sibinga Mulder BG, Meijer RPJ, Bonsing BA, Hartgrink HH, Mieog JSD, Zlitni A, Park SM, Farina Sarasqueta A, Vahrmeijer AL, Swijnenburg RJ. Real-time surgical margin assessment using ICG-fluorescence during laparoscopic and robot-assisted resections of colorectal liver metastases. *Ann Transl Med* 2020; **8**: 1448 [PMID: 33313193 DOI: 10.21037/atm-20-1999]

42 **Pesce A**, La Greca G. Is it still reasonable to raise doubts on ICG-fluorescence cholangiography during laparoscopic cholecystectomy? *Updates Surg* 2020; **72**: 1285-1286 [PMID: 32537686 DOI: 10.1007/s13304-020-00830-6]

43 **Di Benedetto F**, Petrowsky H, Magistri P, Halazun KJ. Robotic liver resection: Hurdles and beyond. *Int J Surg* 2020; **82S**: 155-162 [PMID: 32504813 DOI: 10.1016/j.ijsu.2020.05.070]

44 **Nota CLMA**, Smits FJ, Woo Y, Borel Rinkes IHM, Molenaar IQ, Hagendoorn J, Fong Y. Robotic Developments in Cancer Surgery. *Surg Oncol Clin N Am* 2019; **28**: 89-100 [PMID: 30414684 DOI: 10.1016/j.soc.2018.07.003]

45 **Na KJ**, Kang CH. Robotic thymectomy for advanced thymic epithelial tumor: indications and technical aspects. *J Thorac Dis* 2020; **12**: 63-69 [PMID: 32190355 DOI: 10.21037/jtd.2019.09.27]

46 **Sanford DE**. An Update on Technical Aspects of Cholecystectomy. *Surg Clin North Am* 2019; **99**: 245-258 [PMID: 30846033 DOI: 10.1016/j.suc.2018.11.005]

47 **Felli E**, Santoro R, Colasanti M, Vennarecci G, Lepiane P, Ettorre GM. Robotic liver surgery: preliminary experience in a tertiary hepato-biliary unit. *Updates Surg* 2015; **67**: 27-32 [PMID: 25750057 DOI: 10.1007/s13304-015-0285-4]

48 **Kamiński JP**, Bueltmann KW, Rudnicki M. Robotic *vs* laparoscopic cholecystectomy inpatient analysis: does the end justify the means? *J Gastrointest Surg* 2014; **18**: 2116-2122 [PMID: 25319034 DOI: 10.1007/s11605-014-2673-3]

49 **Escobar-Dominguez JE**, Hernandez-Murcia C, Gonzalez AM. Description of robotic single site cholecystectomy and a review of outcomes. *J Surg Oncol* 2015; **112**: 284-288 [PMID: 25973731

DOI: 10.1002/jso.23931]
50 **Gonzalez A**, Murcia CH, Romero R, Escobar E, Garcia P, Walker G, Gallas M, Dickens E, McIntosh B, Norwood W, Kim K, Rabaza J, Parris D. A multicenter study of initial experience with single-incision robotic cholecystectomies (SIRC) demonstrating a high success rate in 465 cases. *Surg Endosc* 2016; **30**: 2951-2960 [PMID: 26541728 DOI: 10.1007/s00464-015-4583-1]
51 **Gustafson M**, Lescouflair T, Kimball R, Daoud I. A comparison of robotic single-incision and traditional single-incision laparoscopic cholecystectomy. *Surg Endosc* 2016; **30**: 2276-2280 [PMID: 26675933 DOI: 10.1007/s00464-015-4223-9]
52 **Guerra F**, Di Marino M, Coratti A. Robotic Surgery of the Liver and Biliary Tract. *J Laparoendosc Adv Surg Tech A* 2019; **29**: 141-146 [PMID: 30118390 DOI: 10.1089/lap.2017.0628]
53 **Zhao ZM**, Yin ZZ, Meng Y, Jiang N, Ma ZG, Pan LC, Tan XL, Chen X, Liu R. Successful robotic radical resection of hepatic echinococcosis located in posterosuperior liver segments. *World J Gastroenterol* 2020; **26**: 2831-2838 [PMID: 32550758 DOI: 10.3748/wjg.v26.i21.2831]
54 **Nota CL**, Woo Y, Raoof M, Boerner T, Molenaar IQ, Choi GH, Kingham TP, Latorre K, Borel Rinkes IHM, Hagendoorn J, Fong Y. Robotic Versus Open Minor Liver Resections of the Posterosuperior Segments: A Multinational, Propensity Score-Matched Study. *Ann Surg Oncol* 2019; **26**: 583-590 [PMID: 30334196 DOI: 10.1245/s10434-018-6928-1]
55 **Giulianotti PC**, Bianco FM, Daskalaki D, Gonzalez-Ciccarelli LF, Kim J, Benedetti E. Robotic liver surgery: technical aspects and review of the literature. *Hepatobiliary Surg Nutr* 2016; **5**: 311-321 [PMID: 27500143 DOI: 10.21037/hbsn.2015.10.05]
56 **Gonzalez-Ciccarelli LF**, Quadri P, Daskalaki D, Milone L, Gangemi A, Giulianotti PC. Robotic approach to hepatobiliary surgery. *Chirurg* 2017; **88**: 19-28 [PMID: 27481268 DOI: 10.1007/s00104-016-0223-0]
57 **Becker F**, Morgül H, Katou S, Juratli M, Hölzen JP, Pascher A, Struecker B. Robotic Liver Surgery - Current Standards and Future Perspectives. *Z Gastroenterol* 2021; **59**: 56-62 [PMID: 33429451 DOI: 10.1055/a-1329-3067]
58 **Okuda Y**, Nakai A, Sato T, Kurata M, Shimoyama I, Oda T, Ohkohci N. New device with force sensors for laparoscopic liver resection - investigation of grip force and histological damage. *Minim Invasive Ther Allied Technol* 2020; 1-6 [PMID: 32468887 DOI: 10.1080/13645706.2020.1755313]
59 **Ban D**, Ishikawa Y, Tanabe M. Can robotic liver resection compensate for weaknesses of the laparoscopic approach? *Hepatobiliary Surg Nutr* 2020; **9**: 385-387 [PMID: 32509837 DOI: 10.21037/hbsn.2019.11.02]
60 **Schmelzle M**, Schöning W, Pratschke J. [Liver Surgery - Setup, Port Placement, Structured Surgical Steps - Standard Operating Procedures in Robot-Assisted Liver Surgery]. *Zentralbl Chir* 2020; **145**: 246-251 [PMID: 32498105 DOI: 10.1055/a-1135-9162]
61 **Lai ECH**, Tang CN. Training robotic hepatectomy: the Hong Kong experience and perspective. *Hepatobiliary Surg Nutr* 2017; **6**: 222-229 [PMID: 28848744 DOI: 10.21037/hbsn.2017.01.21]
62 **Wang RS**, Ambani SN. Robotic Surgery Training: Current Trends and Future Directions. *Urol Clin North Am* 2021; **48**: 137-146 [PMID: 33218588 DOI: 10.1016/j.ucl.2020.09.014]
63 **Quero G**, Lapergola A, Soler L, Shahbaz M, Hostettler A, Collins T, Marescaux J, Mutter D, Diana M, Pessaux P. Virtual and Augmented Reality in Oncologic Liver Surgery. *Surg Oncol Clin N Am* 2019; **28**: 31-44 [PMID: 30414680 DOI: 10.1016/j.soc.2018.08.002]
64 **Schoeb DS**, Schwarz J, Hein S, Schlager D, Pohlmann PF, Frankenschmidt A, Gratzke C, Miernik A. Mixed reality for teaching catheter placement to medical students: a randomized single-blinded, prospective trial. *BMC Med Educ* 2020; **20**: 510 [PMID: 33327963 DOI: 10.1186/s12909-020-02450-5]
65 **Tarassoli SP**. Artificial intelligence, regenerative surgery, robotics? *Ann Med Surg (Lond)* 2019; **41**: 53-55 [PMID: 31049197 DOI: 10.1016/j.amsu.2019.04.001]
66 **Sorriento A**, Porfido MB, Mazzoleni S, Calvosa G, Tenucci M, Ciuti G, Dario P. Optical and Electromagnetic Tracking Systems for Biomedical Applications: A Critical Review on Potentialities and Limitations. *IEEE Rev Biomed Eng* 2020; **13**: 212-232 [PMID: 31484133 DOI: 10.1109/RBME.2019.2939091]
67 **O'Donoghue K**, Jaeger HA, Cantillon-Murphy P. A Radiolucent Electromagnetic Tracking System for Use with Intraoperative X-ray Imaging. *Sensors (Basel)* 2021; **21** [PMID: 34065968 DOI: 10.3390/s21103357]
68 **Wagner M**, Gondan M, Zöllner C, Wünscher JJ, Nickel F, Albala L, Groch A, Suwelack S, Speidel S, Maier-Hein L, Müller-Stich BP, Kenngott HG. Electromagnetic organ tracking allows for real-time compensation of tissue shift in image-guided laparoscopic rectal surgery: results of a phantom study. *Surg Endosc* 2016; **30**: 495-503 [PMID: 26099616 DOI: 10.1007/s00464-015-4231-9]
69 **Leong F**, Garbin N, Natali CD, Mohammadi A, Thiruchelvam D, Oetomo D, Valdastri P. Magnetic Surgical Instruments for Robotic Abdominal Surgery. *IEEE Rev Biomed Eng* 2016; **9**: 66-78 [PMID: 26829803 DOI: 10.1109/RBME.2016.2521818]
70 **Tang R**, Ma LF, Rong ZX, Li MD, Zeng JP, Wang XD, Liao HE, Dong JH. Augmented reality technology for preoperative planning and intraoperative navigation during hepatobiliary surgery: A review of current methods. *Hepatobiliary Pancreat Dis Int* 2018; **17**: 101-112 [PMID: 29567047 DOI: 10.1016/j.hbpd.2018.02.002]
71 **Zhang W**, Zhu W, Yang J, Xiang N, Zeng N, Hu H, Jia F, Fang C. Augmented Reality Navigation for Stereoscopic Laparoscopic Anatomical Hepatectomy of Primary Liver Cancer: Preliminary Experience. *Front Oncol* 2021; **11**: 663236 [PMID: 33842378 DOI: 10.3389/fonc.2021.663236]

72 **Bari H**, Wadhwani S, Dasari BVM. Role of artificial intelligence in hepatobiliary and pancreatic surgery. *World J Gastrointest Surg* 2021; **13**: 7-18 [PMID: 33552391 DOI: 10.4240/wjgs.v13.i1.7]

73 **Cong X**, Li T. Design and Development of Virtual Medical System Interface Based on VR-AR Hybrid Technology. *Comput Math Methods Med* 2020; **2020**: 7108147 [PMID: 32908580 DOI: 10.1155/2020/7108147]

74 **Attivissimo F**, Lanzolla AML, Carlone S, Larizza P, Brunetti G. A novel electromagnetic tracking system for surgery navigation. *Comput Assist Surg (Abingdon)* 2018; **23**: 42-52 [PMID: 30497291 DOI: 10.1080/24699322.2018.1529199]

75 **Song S**, Zhang C, Liu L, Meng MQ. Preliminary study on magnetic tracking-based planar shape sensing and navigation for flexible surgical robots in transoral surgery: methods and phantom experiments. *Int J Comput Assist Radiol Surg* 2018; **13**: 241-251 [PMID: 28983750 DOI: 10.1007/s11548-017-1672-8]

76 **Kok END**, Eppenga R, Kuhlmann KFD, Groen HC, van Veen R, van Dieren JM, de Wijkerslooth TR, van Leerdam M, Lambregts DMJ, Heerink WJ, Hoetjes NJ, Ivashchenko O, Beets GL, Aalbers AGJ, Nijkamp J, Ruers TJM. Accurate surgical navigation with real-time tumor tracking in cancer surgery. *NPJ Precis Oncol* 2020; **4**: 8 [PMID: 32285009 DOI: 10.1038/s41698-020-0115-0]

77 **Krumb H**, Hofmann S, Kügler D, Ghazy A, Dorweiler B, Bredemann J, Schmitt R, Sakas G, Mukhopadhyay A. Leveraging spatial uncertainty for online error compensation in EMT. *Int J Comput Assist Radiol Surg* 2020; **15**: 1043-1051 [PMID: 32440957 DOI: 10.1007/s11548-020-02189-w]

78 **Andria G**, Attivissimo F, Di Nisio A, Lanzolla AML, Ragolia MA. Assessment of Position Repeatability Error in an Electromagnetic Tracking System for Surgical Navigation. *Sensors (Basel)* 2020; **20** [PMID: 32053941 DOI: 10.3390/s20040961]

79 **Franz AM**, Haidegger T, Birkfellner W, Cleary K, Peters TM, Maier-Hein L. Electromagnetic tracking in medicine--a review of technology, validation, and applications. *IEEE Trans Med Imaging* 2014; **33**: 1702-1725 [PMID: 24816547 DOI: 10.1109/TMI.2014.2321777]

80 **Robu MR**, Edwards P, Ramalhinho J, Thompson S, Davidson B, Hawkes D, Stoyanov D, Clarkson MJ. Intelligent viewpoint selection for efficient CT to video registration in laparoscopic liver surgery. *Int J Comput Assist Radiol Surg* 2017; **12**: 1079-1088 [PMID: 28401399 DOI: 10.1007/s11548-017-1584-7]

81 **Oldhafer KJ**, Peterhans M, Kantas A, Schenk A, Makridis G, Pelzl S, Wagner KC, Weber S, Stavrou GA, Donati M. [Navigated liver surgery : Current state and importance in the future]. *Chirurg* 2018; **89**: 769-776 [PMID: 30225532 DOI: 10.1007/s00104-018-0713-3]

82 **Liu W**, Sawant A, Ruan D. Prediction of high-dimensional states subject to respiratory motion: a manifold learning approach. *Phys Med Biol* 2016; **61**: 4989-4999 [PMID: 27299958 DOI: 10.1088/0031-9155/61/13/4989]

83 **Yasuda J**, Okamoto T, Onda S, Fujioka S, Yanaga K, Suzuki N, Hattori A. Application of image-guided navigation system for laparoscopic hepatobiliary surgery. *Asian J Endosc Surg* 2020; **13**: 39-45 [PMID: 30945434 DOI: 10.1111/ases.12696]

84 **Okamoto T**, Onda S, Yanaga K, Suzuki N, Hattori A. Clinical application of navigation surgery using augmented reality in the abdominal field. *Surg Today* 2015; **45**: 397-406 [PMID: 24898629 DOI: 10.1007/s00595-014-0946-9]

85 **Kügler D**, Krumb H, Bredemann J, Stenin I, Kristin J, Klenzner T, Schipper J, Schmitt R, Sakas G, Mukhopadhyay A. High-precision evaluation of electromagnetic tracking. *Int J Comput Assist Radiol Surg* 2019; **14**: 1127-1135 [PMID: 30982148 DOI: 10.1007/s11548-019-01959-5]

86 **Krumb H**, Das D, Chadda R, Mukhopadhyay A. CycleGAN for interpretable online EMT compensation. *Int J Comput Assist Radiol Surg* 2021; **16**: 757-765 [PMID: 33719026 DOI: 10.1007/s11548-021-02324-1]

87 **Gherardini M**, Clemente F, Milici S, Cipriani C. Localization accuracy of multiple magnets in a myokinetic control interface. *Sci Rep* 2021; **11**: 4850 [PMID: 33649463 DOI: 10.1038/s41598-021-84390-8]

88 **Andrews CM**, Henry AB, Soriano IM, Southworth MK, Silva JR. Registration Techniques for Clinical Applications of Three-Dimensional Augmented Reality Devices. *IEEE J Transl Eng Health Med* 2021; **9**: 4900214 [PMID: 33489483 DOI: 10.1109/JTEHM.2020.3045642]

89 **Sadjadi H**, Hashtrudi-Zaad K, Fichtinger G. Simultaneous Electromagnetic Tracking and Calibration for Dynamic Field Distortion Compensation. *IEEE Trans Biomed Eng* 2016; **63**: 1771-1781 [PMID: 26595908 DOI: 10.1109/TBME.2015.2502138]

90 **Lv A**, Li Y, Qian HG, Qiu H, Hao CY. Precise Navigation of the Surgical Plane with Intraoperative Real-time Virtual Sonography and 3D Simulation in Liver Resection. *J Gastrointest Surg* 2018; **22**: 1814-1818 [PMID: 30039451 DOI: 10.1007/s11605-018-3872-0]

91 **Hostettler A**, Nicolau SA, Rémond Y, Marescaux J, Soler L. A real-time predictive simulation of abdominal viscera positions during quiet free breathing. *Prog Biophys Mol Biol* 2010; **103**: 169-184 [PMID: 20883713 DOI: 10.1016/j.pbiomolbio.2010.09.017]

92 **Zhu H**, Rohling RN, Salcudean SE. Hand-eye coordination-based implicit re-calibration method for gaze tracking on ultrasound machines: a statistical approach. *Int J Comput Assist Radiol Surg* 2020; **15**: 837-845 [PMID: 32323208 DOI: 10.1007/s11548-020-02143-w]

93 **Heiselman JS**, Jarnagin WR, Miga MI. Intraoperative Correction of Liver Deformation Using Sparse Surface and Vascular Features *via* Linearized Iterative Boundary Reconstruction. *IEEE Trans Med Imaging* 2020; **39**: 2223-2234 [PMID: 31976882 DOI: 10.1109/TMI.2020.2967322]

94 **Heiselman JS**, Miga MI. Strain Energy Decay Predicts Elastic Registration Accuracy From Intraoperative Data Constraints. *IEEE Trans Med Imaging* 2021; **40**: 1290-1302 [PMID: 33460370 DOI: 10.1109/TMI.2021.3052523]

95 **Miyata A**, Arita J, Shirata C, Abe S, Akamatsu N, Kaneko J, Kokudo N, Hasegawa K. Quantitative Assessment of the Accuracy of Real-Time Virtual Sonography for Liver Surgery. *Surg Innov* 2020; **27**: 60-67 [PMID: 31516065 DOI: 10.1177/1553350619875301]

96 **Ivashchenko OV**, Kuhlmann KFD, van Veen R, Pouw B, Kok NFM, Hoetjes NJ, Smit JN, Klompenhouwer EG, Nijkamp J, Ruers TJM. CBCT-based navigation system for open liver surgery: Accurate guidance toward mobile and deformable targets with a semi-rigid organ approximation and electromagnetic tracking of the liver. *Med Phys* 2021; **48**: 2145-2159 [PMID: 33666243 DOI: 10.1002/mp.14825]

97 **Luo H**, Yin D, Zhang S, Xiao D, He B, Meng F, Zhang Y, Cai W, He S, Zhang W, Hu Q, Guo H, Liang S, Zhou S, Liu S, Sun L, Guo X, Fang C, Liu L, Jia F. Augmented reality navigation for liver resection with a stereoscopic laparoscope. *Comput Methods Programs Biomed* 2020; **187**: 105099 [PMID: 31601442 DOI: 10.1016/j.cmpb.2019.105099]

98 **Onda S**, Okamoto T, Kanehira M, Fujioka S, Suzuki N, Hattori A, Yanaga K. Short rigid scope and stereo-scope designed specifically for open abdominal navigation surgery: clinical application for hepatobiliary and pancreatic surgery. *J Hepatobiliary Pancreat Sci* 2013; **20**: 448-453 [PMID: 23269461 DOI: 10.1007/s00534-012-0582-y]

99 **Eck U**, Winkler A. [Display technologies for augmented reality in medical applications]. *Unfallchirurg* 2018; **121**: 278-285 [PMID: 29464292 DOI: 10.1007/s00113-018-0463-1]

100 **Miyamoto R**, Oshiro Y, Sano N, Inagawa S, Ohkohchi N. Three-dimensional surgical simulation of the bile duct and vascular arrangement in pancreatoduodenectomy: A retrospective cohort study. *Ann Med Surg (Lond)* 2018; **36**: 17-22 [PMID: 30370052 DOI: 10.1016/j.amsu.2018.09.043]

101 **Han C**, Shan X, Yao L, Yan P, Li M, Hu L, Tian H, Jing W, Du B, Wang L, Yang K, Guo T. Robotic-assisted *vs* laparoscopic cholecystectomy for benign gallbladder diseases: a systematic review and meta-analysis. *Surg Endosc* 2018; **32**: 4377-4392 [PMID: 29956028 DOI: 10.1007/s00464-018-6295-9]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 923-940

DOI: 10.4240/wjgs.v13.i9.923

ISSN 1948-9366 (online)

*REVIEW*

# How can probiotic improve irritable bowel syndrome symptoms?

Indira Benjak Horvat, Ivana Gobin, Andrea Kresović, Goran Hauser

**ORCID number:** Indira Benjak Horvat 0000-0002-9740-3310; Ivana Gobin 0000-0002-8956-4675; Andrea Kresović 0000-0001-7570-3139; Goran Hauser 0000-0002-4758-1717.

**Author contributions:** Hauser G and Gobin I conceived the original idea; Benjak Horvat I, Gobin I and Kresović A performed a comprehensive review of all available literature, synthesised the data; Benjak Horvat I, Gobin I and Kresović A wrote the manuscript; Benjak Horvat I, Gobin I and Hauser G contributed to the study design and manuscript structure and performed a final critical appraisal of the manuscript; all authors read and approved the final manuscript.

**Conflict-of-interest statement:** We declare that there is no conflict of interest.



**Indira Benjak Horvat,** Department of Gastroenterology, Varaždin General Hospital, Varažin 42000, Croatia

**Ivana Gobin,** Department of Microbiology and Parasitology, Faculty of Medicine, University of Rijeka, Rijeka 51000, Croatia

**Andrea Kresović,** Department of Gastroenterology, Clinical Hospital Center Rijeka, Rijeka 51000, Croatia

**Goran Hauser,** Department of Gastroenterology, Faculty of Medicine, Clinical Hospital Center Rijeka, University of Rijeka, Rijeka 51000, Croatia

**Corresponding author:** Ivana Gobin, PhD, Associate Professor, Department of Microbiology and Parasitology, Faculty of Medicine, University of Rijeka, Braće Branchetta 20, Rijeka 51000, Croatia. ivana.gobin@uniri.hr

## Abstract

The onset and manifestations of irritable bowel syndrome (IBS) is associated with several factors, and the pathophysiology involves various central and peripheral mechanisms. Most studies indicate that the management of gut microbiota could significantly affect the improvement of subjective disorders in patients with IBS. Numerous clinical trials have assessed the efficacy of probiotics for IBS with controversial conclusions. Several clinical trials have suggested that probiotics can improve global IBS symptoms, while others only improve individual IBS symptoms, such as bloating scores and abdominal pain scores. Only a few clinical trials have found no apparent effect of probiotics on IBS symptoms. Generally, probiotics appear to be safe for patients with IBS. However, the question of which probiotics should be used for certain IBS subtypes remains unresolved. In everyday practice, the dose of the recommended probiotic remains questionable, as well as how long the probiotic should be used in therapy. The use of probiotics in the M subtype and non-classified IBS is particularly problematic, in which combination therapy should be recommended due to the change in symptoms. Therefore, new approaches are needed in the design of clinical studies that should address certain subtypes of IBS.

**Key Words:** Irritable bowel syndrome; Obstipation; Diarrhoea; Abdominal pain; Probiotic; Prebiotic; Symbiotic; Microbiota

**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Croatia

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 14, 2021
**Peer-review started:** February 14, 2021
**First decision:** March 16, 2021
**Revised:** March 22, 2021
**Accepted:** August 6, 2021
**Article in press:** August 6, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Frascio M, Sahin Y
**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Li JH

**Core Tip:** The onset and manifestations of irritable bowel syndrome (IBS) is associated with a number of factors, and the pathophysiology involves various central and peripheral mechanisms. The results of most studies indicate that influencing the gut microbiota could significantly affect the improvement of subjective disorders in patients with IBS. The most important open questions are the design of a clinical study in which the IBS subgroup is not initially defined and whether all IBS subtypes can be treated with the same probiotic or combination of probiotics. IBS subtype-designed clinical studies are urgently needed as a good foundation to define recommendations and guidelines for the use of probiotics in IBS.

**Citation:** Benjak Horvat I, Gobin I, Kresović A, Hauser G. How can probiotic improve irritable bowel syndrome symptoms? *World J Gastrointest Surg* 2021; 13(9): 923-940
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/923.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.923

## INTRODUCTION

Irritable bowel syndrome (IBS) is a brain-gut disorder characterised by chronic abdominal pain and discomfort that involves a change in the bowel habits and includes the absence of an organic pathological process. Other related symptoms include abdominal distension, bloating, flatulence, diarrhoea, constipation, or a combination of two symptoms. According to these bowel habit patterns, the disease is divided into subtypes: C-IBS (IBS with predominant constipation), D-IBS (IBS with predominant diarrhoea), and M-IBS (IBS with mixed bowel habits) and U-IBS (IBS unclassified). Patients with U-IBS meet the diagnostic criteria for IBS, but bowel habits cannot be accurately categorised into the above explained three subtypes[1,2].

There are no objective tests used to diagnose the disease; therefore, diagnosis is based on symptoms taken as criteria for determining IBS. These symptoms were adopted in 1988 in Rome at the World Congress of Gastroenterologists and revised several times, and based on basic science research and clinical trials, Roman IV criteria were adopted and have been in force since 2016[3,4] (Table 1).

Although the pathophysiology of IBS has not been fully elucidated, nowdays, we can claim with certainty that IBS is an unexplained brain–gut disorder (Figure 1).

The pathophysiology of IBS includes central and peripheral mechanisms. Central mechanisms involve a number of factors, including genetic (mutation of SCN5A, which belongs to a family of genes that provide instructions for making sodium channels) and altered serotonin metabolism; alterations in brain-gut function (stress and visceral hypersensitivity) and dietary influence [gluten and fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)]. Peripheral mechanisms involve changes in gastrointestinal motility, intestinal permeability, local immune response disorder, low-grade inflammation, disordered bile salt metabolism, post-infectious changes, chronic infections and disturbances in the intestinal microbiota[5,6] (Figure 1).

## CHANGES OF THE BOWEL MICROBIOTA AND IBS

Intestinal microbiota has been associated with numerous syndromes and thus, with IBS; therefore, there is a growing interest in modulating the microbiota as one of the treatment options. Because microbiota is connected with the central nervous system across the axis referred to as the gut-brain axis, additional changes in this relationship are imposed as a major factor in the pathophysiology of IBS, which acts through central and peripheral mechanisms and metabolic products of microbes in the gastrointestinal system. This, in turn, causes an altered perception of visceral events, so the individual perceives them as hyperalgesia or allodynia[7-10].

It is estimated that there are more than 100 trillion bacteria in the body of an adult; 80% of which are in the digestive system, which, in turn, contains more than 100 species of bacteria[11]. *Bacteroidetes* and *Firmicutes* predominate, and the amounts of *Proteobacteria*, *Actinomyces*, *Fusobacterium* and *Verrucomicrobia* are relatively small[12].

**Table 1 Summary of diagnostic criteria used to define irritable bowel syndrome**

| Diagnostic criteria | Symptoms included in criteria |
|---|---|
| Rome 1 (1990) | Abdominal pain or discomfort relived with defecation; Abdominal pain or discomfort associated with a change in stool frequency or consistency; In addition, two or more of the following on at least 5% of occasions or days for 3 mo: (1) Altered stool frequency and form; (2) Altered stool passage; (3) Passage of mucus; and (4) Bloating or distension |
| Rome II (1999) | Abdominal discomfort or pain that has two or three features for 1 wk (need to be consecutive) in the last year; Relieved with defecation; Onset associated with a change in the frequency of stools; Onset associated with a change in the form of stools |
| Rome III (2006) | Recurrent abdominal pain or discomfort three days per month in the last 3 mo associated with two or more of: (1) Improvement in defecation; (2) Onset associated with a change in the frequency of stools; and (3) Onset associated with a change in the form of stools |
| Rome IV (2016) | Recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, associated with 2 or more of the following[1]: (1) Related to defecation (*i.e.*, either increasing or improving pain); (2) Associated with a change in stool frequency; and (3) Associated with a change in stool form (appearance) |

[1]Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo before diagnosis.

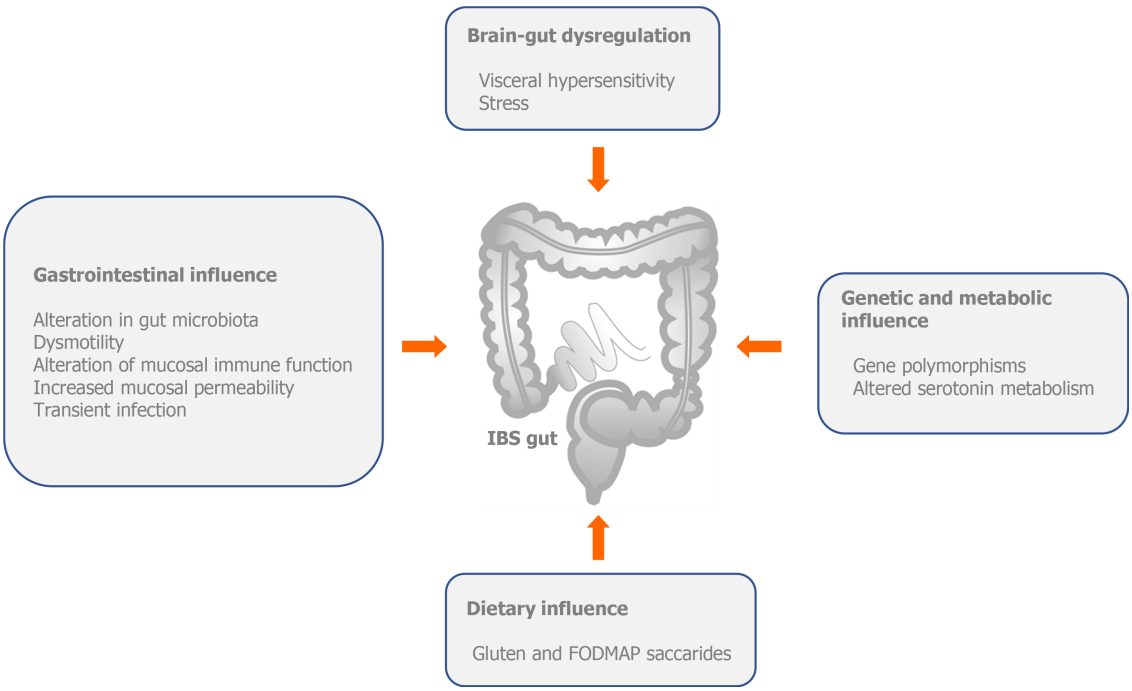


**Figure 1 Pathophysiology of irritable bowel syndrome.** IBS: Irritable bowel syndrome.

During life, and due to a number of environmental factors, the diversity and numerical proportion of individual strains change and there is a possibility that antibiotics and probiotics may affect the intestinal dysbiosis and microbial imbalance that may exist in IBS. Previous studies indicate a high percentage of dysbiosis in IBS patients compared to the general population[13,14]. Generally, the composition and activities of *Lactobacillus* and *Bifidobacterium* are heavily compromised in IBS patients[15]. Tap *et al*[16] reported that the severity of IBS was positively correlated with low microbial richness, absence of *Methanobacteriales* and the number of *Bacteroides* enterotypes. Pozuelo *et al*[17] found a lower abundance of butyrate-producing and methane-producing bacteria in IBS-D and IBS-M patients. Lower counts of methanogens may explain the symptoms of flatulence or excess gas in the abdomen. Dysbiosis in IBS patients is presented with an increase in abundance of *Proteobacteria* (*Veillonella*) and *Firmicutes* (*Lactobacillus* and *Ruminococcus)* and with decreased *Bifidobacterium*, *Faecalibacterium*, *Erysipelotrichaceae* and methanogens[18,19].

One of the approaches of treating IBS is the rationale use of probiotics due to their potential to correct dysbiosis (qualitative and quantitative changes in the gut microbiota) or stabilise the host microbiota (Figure 2).

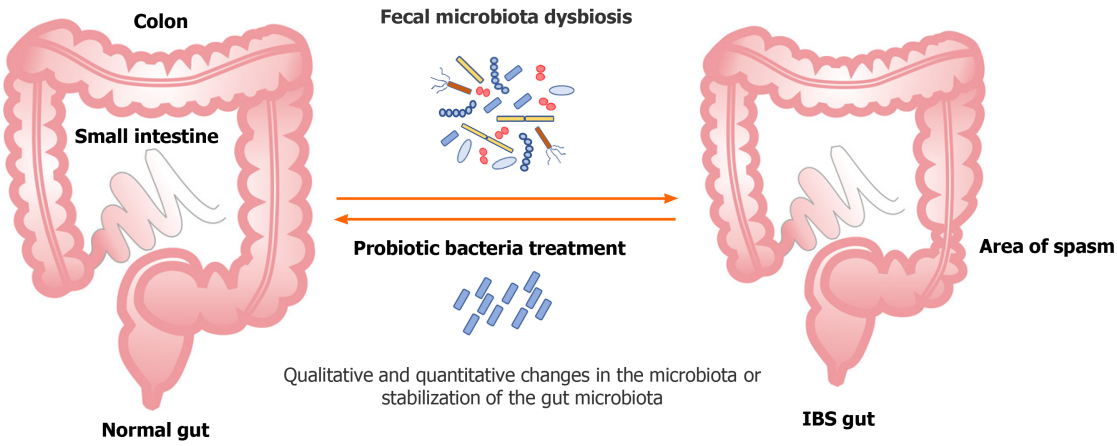


**Figure 2 Probiotics in the management of irritable bowel syndrome.** IBS: Irritable bowel syndrome.

There are more evidence and assumptions regarding how the gut microbiota is associated with IBS formation, either directly or indirectly. It is known that 10% of patients who develop some forms of IBS previously had an episode of infectious diarrhoea (postinfectious IBS), during which changes in the normal gut microbiota occur[20-22]. An association between broad-spectrum antibiotics and IBS is also described[23]. The microbiota interacts extensively with external factors, which occur due to some forms of diet[24].

## BRAIN-GUT DYSREGULATION

Patients with IBS are more likely than healthy populations to develop depression and anxiety, and it is well known that gut microbiota even affects mood and behaviour in humans[25,26]. The microbiota is a separate variable and the axis is called the microbiota-brain axis. The most important communication pathway in this relationship is the tenth cerebral nerve, the vagus nerve. The observed benefits, which arose due to the ingestion of *Lactobacillus rhamnosus* (*L. rhamnosus*) JB-1, resulted in a reduction in anxiety and depression-like behaviour, disappeared after vagotomy in mice. At the brain level, probiotic-induced changes in GABA receptor (receptor for neurotransmitter gamma-aminobutyric acid) expression are also involved in the pathogenesis of anxiety and depression, and disappear in vagotomised mice[27].

After fecal transplantation of microbiota from depressed patients into animals, certain characteristics of depression began to manifest in the recipients (rodents), such as anhedonia and anxiety-like behaviour, and the door to a wide range of assumptions to be investigated opened[28]. An experiment was performed on healthy young students taking probiotic supplements and a reduction in cognitive response to sadness in the form of decreased aggressive thoughts was found after four weeks[29]. As a stress index in some experiments, cortisol level were considered a sign of stress, and levels decreased with improved emotional response in those taking probiotics [30]. These findings, as well as the results of many other studies in the field, were the inspiration for transferring this information to the model of patients with IBS, given the association of the gastrointestinal system, microbiota, brain, and neurotransmitters, which is formed, in part, depending on the composition of microorganisms in the intestine and disturbed axis in these patients.

The high ratio of *Firmicutes*:*Bacteroides* in patients with IBS correlates with depression and anxiety[31], and the result of an additional study shows that the use of prebiotics (defined as selectively fermented carbohydrate ingredients that cause specific changes in the composition and/or activity of the gut microbiota, and thus contribute to host health[32]) and galactooligosaccharides reduce anxiety for four weeks and has a positive effect on quality of life. Another study included the species *Bifidobacterium longum* (*B. longum*) and measured anxiety, depression, IBS symptoms, somatisation, and quality of life in the first, sixth, and tenth weeks. As early as the sixth week, subjects reported a reduction in depressive symptoms and improvement in quality of life, but there was no effect on IBS symptoms or anxiety. Functional magnetic resonance imaging showed a reduced response to negative emotional stimuli

in multiple areas of the brain, including the amygdala and frontolimbic area. Decreased levels of methylamine and aromatic amino acid metabolites were found in the urine of these subjects[33]. Nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide ($H_2S$), hydrogen, methane, and ammonia may be of microbial origin and are normally created in our body, but also imported with various external factors, such as a red meat-enriched diet. $H_2S$ gas has been recognised as a neuromodulator/neurotransmitter that influences intestinal inflammation and sensitivity and is a product of the intestinal microbiota. Therefore, it plays an important role in modulating visceral pain[34-39].

## THE ROLE OF GUT MICROBIOTA IN VISCERAL SENSITIVITY

It has already been mentioned that there is evidence of direct modulation of several systems involved in visceral hypersensitivity; for example, *via* local expression of cannabinoid receptor type 2 and tryptophan hydrolase 1 isoform, and that patients with IBS, in whom hypersensitivity exists, have functional dysbiosis. Probiotics (*Lactobacillus reuteri*) directly alter the visceral perception of nociceptive stimulants[40]. *Lactobacillus reuteri* inhibits the autonomic nervous system response to colorectal distension in mice[41]. Only a few studies have been performed in humans to confirm these results in animal models. By importing unfermented dairy products containing *Bifidobacterium animalis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and *Lactococcus lactis*, the possibility of influencing the activity of areas of the brain, which control the central processing and processing of emotions and sensations, is opened [42].

## THE ROLE OF GUT MICROBIOTA IN INTESTINAL MOTILITY

There are many variables that affect the survival of gut microbiota, especially high oxygen, pH, salt and bile contents, which are all under the influence of intestinal motility.

The change in motility in patients with IBS is manifested by stronger and faster postprandial intestinal muscle contractions in IBS-D and faster passage through the gastrointestinal system and irregular luminal contractions. *Bacteroides thetaiotaomicron* has been shown to alter the expression of a gene involved in neurotransmission and smooth muscle function[43], *Escherichia coli* Nissle 1917[44] improves contractility of colon, and *L. rhamnosus* causes a disorder of contractility stimulated by acetilcolin[45]. Therefore, we can ask ourselves whether the import of probiotics or prebiotics could affect the above mentioned functions *via* bacteria already present in our bowels.

## THE ROLE OF MICROBIOTA IN EPITHELIAL BARRIER MODULATION, INTESTINAL INFLAMMATION, AND IMMUNE SYSTEM ACTIVATION

Recent findings suggest that probiotics have a good effect on the stabilisation of gut microbiota in patients with IBS[46] and modulation of the immune response in the form of normalisation of the interleukin (IL)-10/IL-12 ratio produced by mononuclear cells[47]. In patients with diarrhoeal disease, there are indications of disorders of the function of the intestinal mucosal barrier, which is measured by an increase in intestinal permeability. This leads to an increase in the number of T lymphocytes, mast cells, and enterochromaffin cells[48]. These changes indicate that IBS could have a low-grade inflammatory component in pathophysiology. Several sources report the ability of probiotics to modulate the innate and acquired immune responses with a tendency to achieve a balance between proinflammatory and anti-inflammatory cytokines[46]. A possible therapeutic option would be to use probiotics that interact with the host epithelium to resolve possible inflammation and preserve barrier function. It has been shown that, in adults, *Lactobacillus gasseri* KS-13, *B. longum* MM2 175, and *Bifidobacterium bifidum* G9-1 change the profile of cytokines by stimulating the production of less inflammatory cytokines[49]; and *Saccharomyces boulardii* reduces pro-inflammatory IL-8 and tumor necrosis factor alpha and increases the level of anti-inflammatory IL-10 [50]. The authors of one study[51] concluded that the use of probiotics resulted in reduced intestinal barrier permeability, which may be consistent with these claims.

## POSSIBLE THERAPEUTIC OPTIONS AND OBJECTIVES IN THE TREATMENT OF IBS WITH PROBIOTICS

One of the generally accepted definitions of probiotics is that they are living microorganisms that contribute to the well-being and health of a host when administered in an adequate dose[52]. *Lactobacillus* and *Bifidobacterium* are the most common species that are put in the center of studies in the context of IBS because of their numerical superiority over the rest, as well as the number of aerobes *vs* anaerobes[53,54]. In 2007, Rousseaux *et al*[55] demonstrated that direct contact of certain probiotic bacteria [*Lactobacillus acidophilus* (*L. acidophilus*)] with epithelial cells induces the expression of opioid and cannabinoid receptors in the gut and contributes to the modulation and restoration of the normal perception of visceral pain. Lactic acid bacteria (LAB) are currently the most widely studied, and this group of probiotics consists of approximately 20 genera. The most common are *Aerococcus*, *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus* and *Weisella*. *Bifidobacterium* species does not belong to this group and has its own mode of sugar fermentation[56]. LABs are part of the gut microbiota, and they have antimicrobial action because they create an unsuitable environment for the growth of undesirable microorganisms, compete for nutrients and binding sites to the intestinal epithelium, produce products of toxic microbes for foreign microbes and prevent pathogens from settling and feeding in our bodies[57].

## EFFECT OF PROBIOTICS ON OVERALL IBS SYMPTOMS

Several studies had their limitations in the form of inconsistencies in reports, variable treatment periods, small number of subjects and heterogeneous groups of patients, according to the form of the syndrome (diarrhoeal/constipation). *In vitro* and *in vivo* studies have shown that the probiotic combination VSL#3 [*L. acidophilus*, *Lactobacillus plantarum* (*L. plantarum*), *Lactobacillus casei* (*L. casei*), and *Lactobacillus delbrueckii subspecies bulgaricus* (*L. delbrueckii spp. bulgaricus*), *Bifidobacterium breve* (*B. breve*), *B. longum*, and *Bifidobacterium infantis* (*B. infantis*) and *Streptococcus salivarius ssp. thermophiles*] is likely to modulate the host immune response, intestinal microbiota, anti-inflammatory pathways, responses to visceral pain, and epithelial barrier function[58-62]. It also has different effects on different types of disease. Kim *et al*[63] found that the combination of probiotics VSL#3 slowed intestinal passage compared to placebo, indicating that the aforementioned probiotic is likely to have a better effect on the diarrhoeal form of the disease. The diversity and richness of gut microbiota has been shown to be associated with slower intestinal passage[64], whereas in softer stools, this diversity is significantly reduced[65].

Several studies have included a prepared, specific combination of eight different strains, consisting mainly of LAB and *Bifidobacterium* (including *B. longum, B. infantis*, *B. breve*, *L. acidophilus*, *L. casei*, *L. delbrueckii spp. bulgaricus*, *L. plantarum* and *Streptococcus salivarius*), that showed efficacy in patients with IBS in the form of reduction of bloating and abdominal symptoms[66-70].

The most commonly used probiotic bacteria in studies are *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and *Streptococcus*, and in most studies that included these probiotics, there was a marked improvement in the reduction of abdominal pain and discomfort. Individual studies and the applied probiotic species/strains and the results are shown in Table 2. Diagnostic criteria of IBS were Rome III and IV, with duration of therapy of at least six weeks.

The results of several dozen examined studies showed a reduction in abdominal distension and bloating. In a meta-analysis of 42 randomised controlled trials, 34 reported improvements in at least one symptom[90]. No significant difference was observed in the individual groups of probiotics used: *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, or in a combination of the above[47,49,91,92]. The main limitation of most of the clinical studies is that the patient groups were heterogeneous; however, the overall result of all the analyses was the alleviation of general symptomatology.

A meta-analysis of the efficacy of *B. infantis* 35624 in the IBS was performed. As in the studies already mentioned, the efficacy targets were symptoms related to abdominal pain, bloating and bowel emptying habits, and respondent satisfaction with the management of these symptoms. The analysis included three studies conducted based on the use of *B. infantis* and two additional probiotics. The results showed a significant improvement in all examined parametres in terms of the mixture of probiotics together with *B. infantis*, but not equally effective if *B. infantis* was solely

**Table 2 Outcomes of randomized controlled trials of probiotics versus placebo in different type of irritable bowel syndrome**

| Ref. | Type of IBS (%) | Sample size | Probiotic | Outcome by the type of IBS (probiotic group) | Common outcome (probiotic group) |
|---|---|---|---|---|---|
| Sinn *et al*[71], 2008 | D: 20; C: 27; M: 62.5 | 40 | *L.acidophillus* SDC 2012, 2013 | Not specified | Reduction of abdominal pain (28%), bowel habit satisfaction (18.2%), reduction of straining at stool (25.4%) |
| Hong *et al* [72], 2009 | D: 45.7; C: 20; M: 8.6; Non classified: 25.7 | 70 | *Bifidobacterium bifidum* BGN4, *B. lactis* AD011, *Lactobacillus acidophilus* AD031, *L. casei* IBS041 | Not specified | Reduction of pain score (-31.9), defecation and discomfort (-29.2), no significant change in QOL and bowel habits (defecation frequency and stoll consistency) |
| Guglielmetti *et al*[73], 2011 | D: 21.3; C: 19.7; M: 58.2; NC: 0.8 | 122 | *Bifidobacterium bifidum* MIMBb75 | Not specified | Improved global IBS symptoms by -0.88 points, reduction in pain/discomfort by -0.82 points, distention/bloating by -0.92 points, urgency by -0.76 points (Likert scale) |
| Cui and Hu [74], 2012 | D: 48.3; C: 20; M: 11.7; NC: 10 | 60 | *Bifidobacterium longum* and *Lactobacillus acidophilus* | Not specified | Improvement in frequency of abdominal pain (23% *vs* 6%), abdominal distension (27% *vs* 7%), bowel habits (26% *vs* 8%), dissatisfaction with defecation (20% *vs* 10%). |
| Dapoigny *et al* [75], 2012 | D: 30; C: 22; M: 34; NC: 14 | 50 | *Lactobacillus casei rhamnosus* LCR35 | D: significant reduction in abdominal pain; M: no relevant difference between groups | No clinicaly relevant changes overall |
| Ducrottéet al [76], 2012 | All types | 214 | *Lactobacillus* plantarum 299v | Not specified | Mean frequency of abdominal pain was reduced significantly by 51.9%, reductions in stool frequency, bloating and feeling of incomplete emptying, significant reduction of the daily number of stools |
| Amirimani *et al*[77], 2013 | All types | 102 | *Lactobacillus reuteri* | Not specified | Increased frequency of defecation, no significat difference in bloating, urgency,abdominal pain, stool shape. Study did not clasiffy between D and C subtype |
| Begtrup *et al* [78], 2013 | D: 40; C: 19; M: 38; NC: 2 | 131 | *L. paracasei ssp paracasei* F19, *L. Acidophilus;* La5 *and Bifidobacterium* Bb12 | Not specified | Adequate relief of symptoms at least 50% of the time (52% *vs* 41%), No difference in diarrhea, bloating and satiety |
| Roberts *et al* [79], 2013 | D and C | 179 | *Bifidobacterium lactis* CNCM I-2494, *S.thermophilus, L.bulgaris* | Not specified | Improvements in symptoms scores, bloating, flatulence, ease of bowel movement and quality of life (48% *vs* 33%) |
| Jafari *et al*[80], 2014 | All types | 108 | Probio-Tec® Quatro-cap-4 | Not specified | Decrease in VAS score for abdominal pain and bloating, decrease in feeling incomplete defecation |
| Ludidi *et al* [81], 2014 | All types | 40 | *Bifidobacterium lactis* W52, *Lactobacillus casei* W56, *L. salivarius* W57, *Lactococcus lactis* W58, *L. acidophilus* NCFM, *and L. rhamnosus* W71 | Not specified | Decrease in visceral hypersensitivity in both groups,decreased pain in both groups, no significat difference in overal symptom improval |
| Pedersen *et al* [82], 2014 | D: 38; C: 17.3; M: 40.7; NC: 4 | 81 | *Lactobacillus rhamnosus* GG | Not specified | Improvement in IBS-SSS score nad QOL score. Low FODMAP diet showed efficient in IBS-C, and probiotic in IBC-D |
| Sisson *et al* [83], 2014 | D: 37.6; C: 21.5; M: 35.5; NC: 5.4 | 186 | *Lactobacillus rhamnosus* NCIMB 30174, *L. plantarum* NCIMB 30173, *L. Acidophilus* NCIMB 30175, *Enterococcus faecium* NCIMB 30176 | Not specified | Reduction in IBS-SSS score (abdominal paion, bloating, bowel habit satisfaction)-63.3 *vs* -28.3. No difference in QOL score |
| Yoon *et al*[84], 2014 | D: 53.1; C: 40.8; M: 6.1 | 49 | *Bifidobacterium bifidum* (KCTC 12199BP), *B. lactis* (KCTC 11904BP), *B. longum* (KCTC 12200BP), *L. acidophilus* (KCTC | Not specified | Global relief of IBS symptoms (68% *vs* 37.5%), reduced abdominal pain and discomfort. No difference in |

| | | | | | |
|---|---|---|---|---|---|
| | | | 11906BP), *L. rhamnosus* (KCTC 12202BP) *and Streptococcus thermophilus* (KCTC 11870BP) | | stool consistency. Changes in the fecal microbiota genome (detected by PCR test) |
| Pineton de Chambrun *et al*[85], 2015 | D: 28.5; C: 46.9; M: 24.6 | 179 | *Saccharomyces cerevisiae* CNCM I-3856 | Not specified | Same results regarding abdominal pain and discomfort in both groups, but probiotic group showed improvement in during the second month of use |
| Yoon *et al*[86], 2015 | D: 48.1; C: 18.5; M: 21; NC: 12.4 | 80 | *Bifidobacterium bifidum* (KCTC 12199BP), *B. lactis* (KCTC11904BP), *B. longum (* KCTC 12200BP), *Lactobacillus acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), *Streptococcusthermophilus* | Not specified | Increase in probiotic strains in stool samples, higher adequate symptom relief (but not statisticaly relevant), improvement in the diarhea symptom score |
| Lyra *et al*[87], 2016 | D: 38.9; C: 16.6; M: 44; NC: 0.5 | 391 | *Lactobacillus acidophilus* NCFM (ATCC 700396) | Not specified | No difference in both groups in IBS-SSS score |
| Spiller *et al* [88], 2016 | D: 20.8; C: 47.4; M: 31.7 | 379 | *Saccharomyces cerevisiase* I-3856 | Reduced abdominal pain and bloating in IBS-C | No overall benefit in all subtypes, but significant improvement in C subtype |
| Preston *et al* [89], 2018 | D: 46.4; C: 35.7; M: 18.6 | 113 | *Lactobacillus acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2 | Improvement of IBS-SSS score for female D subtype by 50% to 144%. Better satisfation with bowel habits in C subtype. Better QOL in IBS-D females. Impruvment in number of days without pain M subtype | No improvement in IBS-SSS score overall or QOL overall |

IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System; NC: Non classified irritable bowel syndrome; D: Diarrhea irritable bowel syndrome; C: Constipation irritable bowel syndrome; M: Mixed irritable bowel syndrome; QOL: Quality of life.

used. According to that analysis, treatment with a mixture of probiotics that also contain this bacterium could have an effect in treating the disease. However, it should be considered that the number of participants in the examination was too small, and certainly, the stated claims should be further examined[50].

An interesting fact is the analysis of several studies that show that the use of one probiotic, rather than a combination of several, taken in a short period and in a low dose, proved to be better in the final general condition, general feeling of patients after treatment (testing) and improvement in their quality of life. Yoon *et al*[84] hypothesised that multi-strain-containing probiotics may result in different effects and benefits on IBS symptoms, as each bacterial species produces a different effect in the gastrointestinal system, and two or more probiotic species in combination have a synergistic effect. However, research has also shown that competition between introduced combined species or strains is possible, which can lead to negative effects. Analysis of gut microbiota before and after probiotic administration showed that different strains have different viabilities and overdoses can disturb living conditions by competition[81].

## EFFECT OF PROBIOTIC DOSE ON IBS SYMPTOMS

The question of the dosage of the individual probiotics that needs to be applied to achieve the final desired effects was raised. Initially, an answer is not offered; significant is that an adequate dose is needed for the desired effect. There are several variables that could affect the effective dose of probiotics: Desired effect, specific strain, probiotic carrier, and the mode of application. In a unique study, the combination of two strains of *L. plantarum* and one strain of *Pediococcus acidilactici* (confirmed to reduce inflammation and frequency of diarrhoea in animal models of intestinal inflammation) were applied in two doses: 1-3 × $10^{10}$ CFU (colony forming unit) per capsule and 3-6 × $10^{9}$ CFU per capsule, in equal representation of each probiotic. The results are such that all patients, regardless of the dose of I.31 (as the combination of probiotics is called), indicating that the achievement effect is attained even at lower values, reported a better quality of life after three weeks of intolerance to mixtures, while reduction of anxiety was reported only after six weeks. Interestingly, the effect was achieved earlier when a higher dose was administered[93]. We must, however, emphasise that although the authors claim they tested high and low doses of

probiotics, $10^9$ bacteria per capsule can in no way be considered low dose. The difference between these two doses is too small and the authors should have used a slightly lower dose to examine whether probiotic dose influences IBS.

Liang *et al*[94] analyzed several clinical trials, with a primary goal to clarify the effective dose of applied probiotics which, in this case, is a combination of *Lactobacillus* and *Bifidobacterium*. Their conclusion is comparable to previous studies, with an observed improvement in global symptoms that was achieved even at low doses. In most studies, a dose of $10^9$CFU/d to $10^{10}$ CFU/d of the tested strains is the recommended dose, based on comparisons of the accompanying studies.

According to Lorenzo-Zúñiga *et al*[93], probiotics do not follow pharmacological rules in achieving the effect of saturation, but this effect is attained according to the principle of synergism or antagonism, in which negative effects are caused. High doses of probiotics can cause short-term discomfort in the gastrointestinal system due to excessive fermentation of carbohydrates, which is a feature of the most studied and represented strains in patients with IBS[95].

In other medical cases, conditions and diseases, the doses of specific probiotic strains have been studied. Namely, the results of one study showed that *L. rhamnosus* GG has a greater effect in acute gastroenteritis in children when administered at a dose greater than $10^{10}$ CFU/d[96]. *S. boulardii* administered in patients with diarrhoea, after low and high doses, achieved an equal effect[97]. In addition, no difference was found in the dose-dependent effect for *Lactobacillus reuteri* DSM17938 on diarrhoea[98].

In 2006, in a meta-analysis of antibiotic-related diarrhoea and necrotising enterocolitis, a result based on 25 studies involving 13 probiotic products reported that probiotic doses less than $10^{10}$ CFU did not result in treatment success. The results were confirmed in later meta-analyses[99].

## APPLICATION OF PROBIOTICS IN TREATMENT OF C-IBS

Significantly less research regarding the effectiveness of probiotics have been conducted in patients with C-IBS. Based on the Bristol stool scale, study participants described their stool as hard or lumpy (≥ 25% of all stools) and fluffy or watery (< 25% of all stools).

It is known that in these patients, there exists an increased number of bacteria that produce methane[100] and the amount of gas released is directly correlated with the severity of severe constipation[101], which is consistent with the slower passage through the intestine in these cases, with reduced segmental contraction and attenuated propulsion. Given these facts, the effect of *B. lactis* DN-173 010 on distension, bloating, and other IBS symptoms was examined[102]. Patients complained of a visible increase in abdominal volume at least twice a week and met other Roman III. The dose of *B. lactis* was $1.25 \times 10^{10}$ CFU/g, and *S. thermophilus* and *L. bulgaricus* ($1.2 \times 10^9$ CFU/g) were added; in fact, fermented milk and yogurts were found to contain these probiotics. The results showed that fermented dairy products reduced abdominal distension and accelerated intestinal passage. Reduced bloating was also reported, as were other IBS symptoms. There are fewer studies involving subjects who have constipation-like problems, and one of these studies was published in 2014. The results are impressive and show that probiotics have significantly reduced the passage time by 12.4 h and increased stool frequency by 1.3 wkly bowel movements. Success is related to the administration of *B. lactis* (increasing weekly bowel movements by 1.5 movements), but not to *L. casei* Shirota (recorded decreased weekly bowel movements per week to 0.2). Stool consistency was better during intake of *B. lactis*, but not *L. casei* Shirota strain[103]. Health-related quality of life was also a frequently examined aspect in patients, making it the primary subject of the study by Guyonnet *et al*[104], because they believed that the patient's perception of symptoms and the impact of difficulties on daily life are extremely important. In general, patients with more severe disease and frequent symptomatology felt relief, but were reluctant to report it. This was in contrast to those subjects who had moderate or mild disease and did not experience significant improvement, but reported a change in symptom severity. Interestingly, in a number of studies, placebo groups also reported positive effects, which is an increasingly central point of the study (Table 3).

**Table 3 Outcomes of randomized controlled trials of probiotics versus placebo in the C and D type of irritable bowel syndrome**

| Ref. | Type of IBS | Sample size | Probiotic | Outcome by the type of IBS (probiotic group) |
|---|---|---|---|---|
| Agrawal *et al* [102], 2009 | C | 34 | *Bifidobacterium lactis* DN-173 010 | Reduction in bloating and distension (-1.52 cm), reduction of orocaecal (-1.2 h) and colonic (-12.2 h) transit times, reduction of pain and discomfort (-0.5) |
| Michail *et al* [105], 2011 | D | 24 | *VSL*#3: *Lactobacillus acidophilus*, *L. plantarum*, *L. casei*, and *L. delbrueckii ssp. bulgaricus*, *Bifidobacterium breve*, *B. longum*, and *B. infantis* and *Streptococcus salivarius ssp. thermophilus* | Significant decreases in the bloating, diarrhea, satiety and QOL in both groups (placebo and probiotic) |
| Ki Cha *et al*[106], 2012 | D | 50 | *Lactobacillus acidophilus*, *L. plantarum*, *L. rhamnosus*, *Bifidobacterium breve*, *B. lactis*, *B. longum* and *Streptococcus thermophilus* | Symptoms (abdominal pain, abdominal discomfort, loose/watery stool, urgency, mucus in stool, bloating, and passage of gas) relief was higher (> 50%), improved stool consistency |
| Abbas *et al*[50], 2014 | D | 72 | *Saccharomyces boulardii* | Decrease in the blood and tissue levels of proinflammatory cytokines IL-8 and TNF-a and and increase in the anti-inflammatory IL-10, improvement in body image and food avoidance |
| Lorenzo-Zúñiga *et al*[93], 2014 | D | 84 | *Lactobacillus plantarum* (CECT7484 and CECT7485), *Pediococcus acidilactici* (CECT7483) | Improved QOL score, improvement in gut-related anxiety (VSI scale) |
| Majeed *et al* [107], 2016 | D | 36 | *Bacillus coagulans* MTCC 5856 | Decrase in bloating, diarhea, vomiting, abdominal pain, improvement in Bristol stool score |
| Mezzasalma *et al* [108],2019 | C | 150 | *Lactobacillus acidophilus*, *L. reuteri*, *L.s plantarum*, *L.s rhamnosus*, *Bifidobacterium animalis subps. lactis* | QOL improved in probiotic group, incresead healthier characteristic in stool samples |
| Hod *et al*[109], 2017 | D | 107 | *Lactobacillus rhamnosus LR5*, *L. casei LC5*, *L. paracasei LPC5*, *L. plantarum LP3*, *L. acidophilus LA1*, *Bifidobacterium bifidum*, *BF3*, *B. longum BG7*, *B. breve BR3*, *B. infantis BT1*, *Streptococcus thermophilus ST3*, *L. bulgaricus LG1*, *Lactococcus lactis* | No difference between groups overall, no CRP and fecal calprotectin levels difference |
| Ishaque *et al* [110],2018 | D | 360 | Bio-Kult® | Reduced overal IBS-SSS score by 145 point in 30 d, reduced number of bowel movements, symptom free patients (33.7% *vs* 12.8%) |
| Khodadoostan *et al*[111],2018 | D | 67 | *Lactobacillus casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaricus*, *Bifidobacterium breve*, *B. longum*, and *Streptococcus thermophilus* with prebiotic of *ructooligosaccharides* | Improvement in stool consistency adn defecation rate after 3 mo, decrease in abdominal pain after 6 mo |
| Sun *et al*[112], 2018 | D | 200 | *Clostridium butyricum* | Reduction in IBS-SSS score (-62.12 *vs* -40.74), no difference in abdominal pain and bloating, improvement in QOL, no change in Bristol stool scale. |

IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System; D: Diarrhea irritable bowel syndrome; C: Constipation irritable bowel syndrome; QOL: Quality of life.

## APPLICATION OF PROBIOTICS IN TREATMENT OF D-IBS

The symptoms of this form of the disease are similar to those in other subtypes, with more frequent bowel movements and increased peristalsis, which results in softer stools or diarrhoea. It is also characterised by the urgency for defecation. According to the Bristol stool scale, patients define this form of the disease as the presence of fluffy or watery stools (≤ 25% of all stools) and hard or lumpy stools (< 25% of all stools). When using a mixture of *L. plantarum* ($5 \times 10^7$ CFU/mL) and 3.6 g of fibre, the results showed that the presence of gas/wind was significantly lower, intensity of abdominal pain was reduced and overall function of the gastrointestinal system was much better after one year of using symbiotics[113]. These effects can be explained by slowing down the passage through the intestine, facilitating the flow, electrolyte reabsorption and consequently, reducing diarrhoea. The combination of the probiotics *L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *B. breve*, *B. lactis*, *B. longum* and *S. thermophilus* in a dose of $1.0 \times 10^{10}$ CFU also produced promising results. The application lasted for eight weeks, and the effect manifested as alleviation of overall symptoms and improvement in stool consistency, although no specific effect on individual symptoms was observed[106]. However, regarding the primary symptom of this subgroup, diarrhoea, probiotics did not prove effective in reducing the number of diarrhoeal stools. Several studies have been conducted, testing different probiotics, but the results have not been successful[46,78,114]. Moreover, in one study, an even more significant

deterioration was reported[115]. In contrast, in this subtype of disease, *Bacillus coagulans* MTCC 5856, at a dose of 2 × $10^9$ CFU/d for 90 d of use, proved to be quite successful. All symptoms in patients belonging to the D-IBS group were significantly alleviated, including diarrhoea[107].

The aim of one study was to evaluate the change in the frequency and intensity of abdominal pain in patients with a predominantly diarrhoeal form of the disease. A combination of strains were evaluated in the study: *Bacillus subtilis* PXN 21, *B. bifidum* PXN 23, *B. breve* PXN 25, *B. infantis* PXN 27, *B. longum* PXN 30, *L. acidophilus* PXN 35, *L. delbrueckii* spp. *bulgaricus* PXN39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57), *Lactococcus lactis* PXN 63, and *S. thermophilus* PXN 66 at 2 million colonies per capsule, twice daily for 16 wk. After this treatment, patients reported a reduction in the intensity of abdominal pain, as well as other symptoms comprising the IBS-SSS (Irritable Bowel Syndrome Severity Scoring System), including the intensity of abdominal pain, number of days of abdominal pain during the last 10 d, severity of abdominal distension, discomfort during urination, and reduced quality of life. The participants were examined every month for five months, and during these controls, the results showed an improvement in all examined elements of the disease, compared to the initial condition and results of the group of patients receiving placebo. This study included a large number of subjects (360 patients) that were relatively homogeneous with a certain subtype of the disease, resulting in a more relevant study compared to a large number of other processed analyses[110]. In Figure 3, exhibited is the effect of probiotics on different IBS type symptoms.

## THE ROLE OF PREBIOTICS ON IBS SYMPTOMS

Unlike probiotics, prebiotics are not metabolised in the intestines of the host, and their ultimate purpose is to positively impact the microenvironment of the digestive system. The best known prebiotics are oligofructose, inulin, galactooligosaccharides, lactulose, and oligosaccharides from breast milk. In fact, these compounds are an integral part of the food we eat every day. Some of the positive effects include an increase in the number of bifidobacteria, calcium absorption, and fecal mass, shortening of the retention time of fecal mass in the intestines, and a possible decrease in blood lipids [32]. Several studies have investigated the effect of prebiotics[47], revealing the importance of choice of prebiotic, as well as the dose, since doses that were too small could be useless, and larger ones can stimulate gas production, which worsens symptoms[116-118].

## SIDE EFFECTS OF PROBIOTICS

Most of the studies highlighted in this article did not report side effects or listed them as "unimportant". In fact, it is an interesting that probiotics, prebiotics and symbiotics used in the treatment of IBS can sometimes cause, or even worsen, some symptoms. This phenomenon is most commonly observed in D-IBS, in which the use of prebiotics and fibre could lead to worsening of symptoms. These side effects include gas production, bloating, softer stools and abdominal pain; all of which are mostly temporary[119].

## CONCLUSION

There exist several variables that affect changes in the microbiota (*i.e.*, differences in sample storage, DNA extraction, and analytical methods), as well as the diet of individuals, which were not strictly regulated in any studies. Many foods serve as prebiotics and may also contain probiotics. It has been proven that the application of multiple strains of probiotic bacteria, or even multiple species, is much more effective than the application of only one probiotic strain. It is difficult to predict which strain or species most contributed to the welfare of IBS patients. Several groups investigated the effect of a particular strain on a specific symptom, which could be considered a good research direction and a way to prove the effectiveness of a particular probiotic on the symptom that causes the most discomfort to an individual patient. A major drawback of these studies, however, is the design of clinical studies in which the types of IBS are

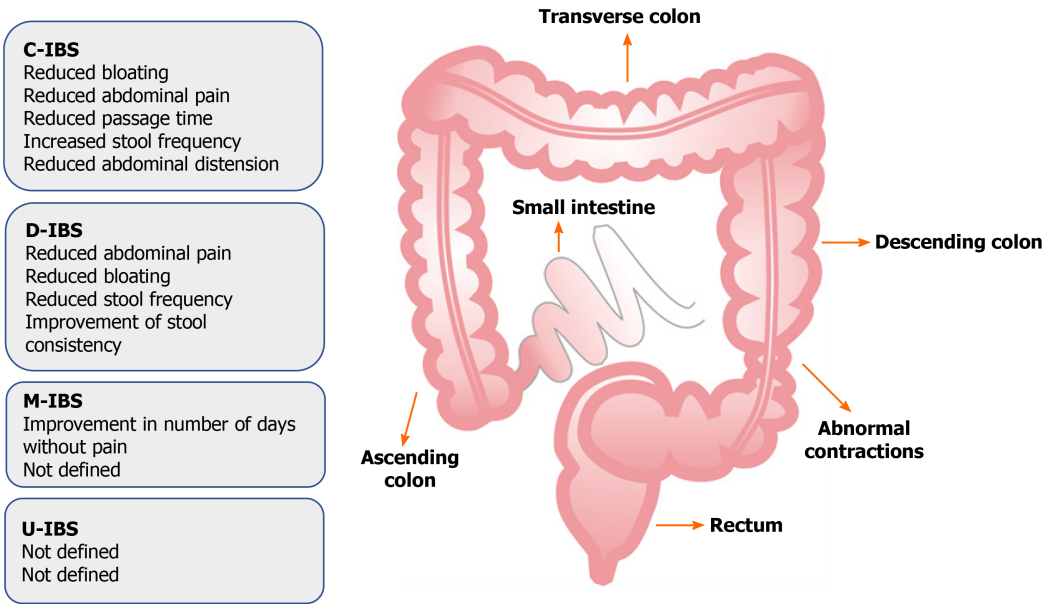


**Figure 3 Effect of probiotic bacteria on different irritable bowel syndrome type symptoms.** C-IBS: Irritable bowel syndrome with predominant constipation; D-IBS: Irritable bowel syndrome with predominant diarrhea; M-IBS: Irritable bowel syndrome with mixed bowel habits; U-IBS: Irritable bowel syndrome unclassified.

not clearly defined, or the analysis of IBS types is performed after the study is completed. In most of the clinical studies, a small number of patients were grouped into IBS subtypes, which made it difficult to draw conclusions. In addition, it is unlikely that the same probiotic or multispecies probiotic preparation will influence all four types of IBS. The biggest unknown remains as the mixed and unclassified types of IBS, which are present in small numbers in the conducted studies. The way to design a suitable study for mixed and unclassified types of IBS is questionable, as we do not currently have a probiotic or symbiotic that would affect the modification of the various symptoms that occur in these types of IBS. The solution may be to group patients with specific subtype and gather critical mass. Furthermore, numerous studies have shown the impact of probiotics on certain areas of the brain and their activity. Studies of this type certainly have their limitations, mostly related to the complicated interrelationships of the intestinal brain axis, such as those present in patients with IBS, which are not easy to transfer to an animal model and then map to human subjects. The need to understand the connection between the intestinal microbiota and functional diseases of the gastrointestinal system is central to the research in this field of medicine. The cognition that controlling the intake of dietary supplements can affect bowel functions, as well as the psychological manifestations of the disease, is the basis for setting new therapeutic options in the treatment of IBS and other similar disorders of the gastrointestinal system.

## ACKNOWLEDGEMENTS

We would like to thank Darko Rodi for helping with the illustrations.

## REFERENCES

1 **Thompson WG**, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45** Suppl 2: II43-II47 [PMID: 10457044 DOI: 10.1136/gut.45.2008.ii43]
2 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]
3 **Saha L**. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. *World J Gastroenterol* 2014; **20**: 6759-6773 [PMID: 24944467 DOI: 10.3748/wjg.v20.i22.6759]
4 **Lacy BE**, Mearin F, Lembo AJ, Simren M, Spiller R. Bowel Disorders. *Gastroenterol* 2016; **150**:

1393-1407
5 **Mearin F**, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. *Gastroenterology* 2016 [PMID: 27144627 DOI: 10.1053/j.gastro.2016.02.031]
6 **Holtmann GJ**, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2016; **1**: 133-146 [PMID: 28404070 DOI: 10.1016/S2468-1253(16)30023-1]
7 **Parkes GC**, Brostoff J, Whelan K, Sanderson JD. Gastrointestinal microbiota in irritable bowel syndrome: their role in its pathogenesis and treatment. *Am J Gastroenterol* 2008; **103**: 1557-1567 [PMID: 18513268 DOI: 10.1111/j.1572-0241.2008.01869.x]
8 **Bhattarai Y**, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? *Am J Physiol Gastrointest Liver Physiol* 2017; **312**: G52-G62 [PMID: 27881403 DOI: 10.1152/ajpgi.00338.2016]
9 **Mayer EA**, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994; **107**: 271-293 [PMID: 8020671 DOI: 10.1016/0016-5085(94)90086-8]
10 **Distrutti E**, Salvioli B, Azpiroz F, Malagelada JR. Rectal function and bowel habit in irritable bowel syndrome. *Am J Gastroenterol* 2004; **99**: 131-137 [PMID: 14687154 DOI: 10.1046/j.1572-0241.2003.04012.x]
11 **Lozupone CA**, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012; **489**: 220-230 [PMID: 22972295 DOI: 10.1038/nature11550]
12 **Grenham S**, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. *Front Physiol* 2011; **2**: 94 [PMID: 22162969 DOI: 10.3389/fphys.2011.00094]
13 **Collins SM**. A role for the gut microbiota in IBS. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 497-505 [PMID: 24751910 DOI: 10.1038/nrgastro.2014.40]
14 **Chong PP**, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The Microbiome and Irritable Bowel Syndrome - A Review on the Pathophysiology, Current Research and Future Therapy. *Front Microbiol* 2019; **10**: 1136 [PMID: 31244784 DOI: 10.3389/fmicb.2019.01136]
15 **Bellini M**, Gambaccini D, Stasi C, Urbano MT, Marchi S, Usai-Satta P. Irritable bowel syndrome: a disease still searching for pathogenesis, diagnosis and therapy. *World J Gastroenterol* 2014; **20**: 8807-8820 [PMID: 25083055]
16 **Tap J**, Derrien M, Törnblom H, Brazeilles R, Cools-Portier S, Doré J, Störsrud S, Le Nevé B, Öhman L, Simrén M. Identification of an Intestinal Microbiota Signature Associated With Severity of Irritable Bowel Syndrome. *Gastroenterology* 2017; **152**: 111-123.e8 [PMID: 27725146 DOI: 10.1053/j.gastro.2016.09.049]
17 **Pozuelo M**, Panda S, Santiago A, Mendez S, Accarino A, Santos J, Guarner F, Azpiroz F, Manichanh C. Reduction of butyrate- and methane-producing microorganisms in patients with Irritable Bowel Syndrome. *Sci Rep* 2015; **5**: 12693 [PMID: 26239401 DOI: 10.1038/srep12693]
18 **Tana C**, Umesaki Y, Imaoka A, Handa T, Kanazawa M, Fukudo S. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. *Neurogastroenterol Motil* 2010; **22**: 512-519, e114 [PMID: 19903265 DOI: 10.1111/j.1365-2982.2009.01427.x]
19 **Rajilić-Stojanović M**, Biagi E, Heilig HG, Kajander K, Kekkonen RA, Tims S, de Vos WM. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology* 2011; **141**: 1792-1801 [PMID: 21820992 DOI: 10.1053/j.gastro.2011.07.043]
20 **Thabane M**, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; **26**: 535-544 [PMID: 17661757 DOI: 10.1111/j.1365-2036.2007.03399.x]
21 **Spiller R**, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology* 2009; **136**: 1979-1988 [PMID: 19457422 DOI: 10.1053/j.gastro.2009.02.074]
22 **Jalanka-Tuovinen J**, Salojärvi J, Salonen A, Immonen O, Garsed K, Kelly FM, Zaitoun A, Palva A, Spiller RC, de Vos WM. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. *Gut* 2014; **63**: 1737-1745 [PMID: 24310267 DOI: 10.1136/gutjnl-2013-305994]
23 **Villarreal AA**, Aberger FJ, Benrud R, Gundrum JD. Use of broad-spectrum antibiotics and the development of irritable bowel syndrome. *WMJ* 2012; **111**: 17-20 [PMID: 22533211]
24 **Rajilić-Stojanović M**, Jonkers DM, Salonen A, Hanevik K, Raes J, Jalanka J, de Vos WM, Manichanh C, Golic N, Enck P, Philippou E, Iraqi FA, Clarke G, Spiller RC, Penders J. Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? *Am J Gastroenterol* 2015; **110**: 278-287 [PMID: 25623659 DOI: 10.1038/ajg.2014.427]
25 **Mayer EA**, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *J Neurosci* 2014; **34**: 15490-15496 [PMID: 25392516 DOI: 10.1523/JNEUROSCI.3299-14.2014]
26 **Tillisch K**, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* 2013; **144**: 1394-1401, 1401.e1 [PMID: 23474283 DOI: 10.1053/j.gastro.2013.02.043]
27 **Bravo JA**, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse *via* the vagus nerve. *Proc Natl Acad Sci U S A* 2011; **108**: 16050-16055

[PMID: 21876150 DOI: 10.1073/pnas.1102999108]
28 **Kelly JR**, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, Kennedy PJ, Beers S, Scott K, Moloney G, Hoban AE, Scott L, Fitzgerald P, Ross P, Stanton C, Clarke G, Cryan JF, Dinan TG. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *J Psychiatr Res* 2016; **82**: 109-118 [PMID: 27491067 DOI: 10.1016/j.jpsychires.2016.07.019]
29 **Steenbergen L**, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behav Immun* 2015; **48**: 258-264 [PMID: 25862297 DOI: 10.1016/j.bbi.2015.04.003]
30 **Messaoudi M**, Violle N, Bisson JF, Desor D, Javelot H, Rougeot C. Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. *Gut Microbes* 2011; **2**: 256-261 [PMID: 21983070 DOI: 10.4161/gmic.2.4.16108]
31 **Jeffery IB**, O'Toole PW, Öhman L, Claesson MJ, Deane J, Quigley EM, Simrén M. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut* 2012; **61**: 997-1006 [PMID: 22180058 DOI: 10.1136/gutjnl-2011-301501]
32 **Hauser G**, Benjak Horvat I, Zelić M, Prusac M, Škopić OV. Probiotici i prebiotici – koncept. *Medicus* 2020; **29**: 95-114
33 **Pinto-Sanchez MI**, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, Martin FP, Cominetti O, Welsh C, Rieder A, Traynor J, Gregory C, De Palma G, Pigrau M, Ford AC, Macri J, Berger B, Bergonzelli G, Surette MG, Collins SM, Moayyedi P, Bercik P. Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology* 2017; **153**: 448-459.e8 [PMID: 28483500 DOI: 10.1053/j.gastro.2017.05.003]
34 **Medani M**, Collins D, Docherty NG, Baird AW, O'Connell PR, Winter DC. Emerging role of hydrogen sulfide in colonic physiology and pathophysiology. *Inflamm Bowel Dis* 2011; **17**: 1620-1625 [PMID: 21674719 DOI: 10.1002/ibd.21528]
35 **Schemann M**, Grundy D. Role of hydrogen sulfide in visceral nociception. *Gut* 2009; **58**: 744-747 [PMID: 19433593 DOI: 10.1136/gut.2008.167858]
36 **Distrutti E**. Hydrogen sulphide and pain. *Inflamm Allergy Drug Targets* 2011; **10**: 123-132 [PMID: 21275898 DOI: 10.2174/187152811794776240]
37 **Distrutti E**, Cipriani S, Renga B, Mencarelli A, Migliorati M, Cianetti S, Fiorucci S. Hydrogen sulphide induces micro opioid receptor-dependent analgesia in a rodent model of visceral pain. *Mol Pain* 2010; **6**: 36 [PMID: 20540729 DOI: 10.1186/1744-8069-6-36]
38 **Distrutti E**, Sediari L, Mencarelli A, Renga B, Orlandi S, Antonelli E, Roviezzo F, Morelli A, Cirino G, Wallace JL, Fiorucci S. Evidence that hydrogen sulfide exerts antinociceptive effects in the gastrointestinal tract by activating KATP channels. *J Pharmacol Exp Ther* 2006; **316**: 325-335 [PMID: 16192316 DOI: 10.1124/jpet.105.091595]
39 **Oleskin AV**, Shenderov BA. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. *Microb Ecol Health Dis* 2016; **27**: 30971 [PMID: 27389418 DOI: 10.3402/mehd.v27.30971]
40 **Perez-Burgos A**, Wang L, McVey Neufeld KA, Mao YK, Ahmadzai M, Janssen LJ, Stanisz AM, Bienenstock J, Kunze WA. The TRPV1 channel in rodents is a major target for antinociceptive effect of the probiotic Lactobacillus reuteri DSM 17938. *J Physiol* 2015; **593**: 3943-3957 [PMID: 26084409 DOI: 10.1113/JP270229]
41 **Kamiya T**, Wang L, Forsythe P, Goettsche G, Mao Y, Wang Y, Tougas G, Bienenstock J. Inhibitory effects of Lactobacillus reuteri on visceral pain induced by colorectal distension in Sprague-Dawley rats. *Gut* 2006; **55**: 191-196 [PMID: 16361309 DOI: 10.1136/gut.2005.070987]
42 **Zhou L**, Foster JA. Psychobiotics and the gut-brain axis: in the pursuit of happiness. *Neuropsychiatr Dis Treat* 2015; **11**: 715-723 [PMID: 25834446 DOI: 10.2147/NDT.S61997]
43 **Hooper LV**, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**: 881-884 [PMID: 11157169 DOI: 10.1126/science.291.5505.881]
44 **Bär F**, Von Koschitzky H, Roblick U, Bruch HP, Schulze L, Sonnenborn U, Böttner M, Wedel T. Cell-free supernatants of Escherichia coli Nissle 1917 modulate human colonic motility: evidence from an *in vitro* organ bath study. *Neurogastroenterol Motil* 2009; **21**: 559-566, e16 [PMID: 19220758 DOI: 10.1111/j.1365-2982.2008.01258.x]
45 **Guarino MP**, Altomare A, Stasi E, Marignani M, Severi C, Alloni R, Dicuonzo G, Morelli L, Coppola R, Cicala M. Effect of acute mucosal exposure to Lactobacillus rhamnosus GG on human colonic smooth muscle cells. *J Clin Gastroenterol* 2008; **42** Suppl 3 Pt 2: S185-S190 [PMID: 18685510 DOI: 10.1097/MCG.0b013e31817e1cac]
46 **Kajander K**, Myllyluoma E, Rajilić-Stojanović M, Kyrönpalo S, Rasmussen M, Järvenpää S, Zoetendal EG, de Vos WM, Vapaatalo H, Korpela R. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. *Aliment Pharmacol Ther* 2008; **27**: 48-57 [PMID: 17919270 DOI: 10.1111/j.1365-2036.2007.03542.x]
47 **O'Mahony L**, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005; **128**: 541-551 [PMID:

15765388 DOI: 10.1053/j.gastro.2004.11.050]
48 **Dunlop SP**, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, Spiller RC. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006; **101**: 1288-1294 [PMID: 16771951 DOI: 10.1111/j.1572-0241.2006.00672.x]
49 **Spaiser SJ**, Culpepper T, Nieves C Jr, Ukhanova M, Mai V, Percival SS, Christman MC, Langkamp-Henken B. Lactobacillus gasseri KS-13, Bifidobacterium bifidum G9-1, and Bifidobacterium longum MM-2 Ingestion Induces a Less Inflammatory Cytokine Profile and a Potentially Beneficial Shift in Gut Microbiota in Older Adults: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. *J Am Coll Nutr* 2015; **34**: 459-469 [PMID: 25909149 DOI: 10.1080/07315724.2014.983249]
50 **Abbas Z**, Yakoob J, Jafri W, Ahmad Z, Azam Z, Usman MW, Shamim S, Islam M. Cytokine and clinical response to Saccharomyces boulardii therapy in diarrhea-dominant irritable bowel syndrome: a randomized trial. *Eur J Gastroenterol Hepatol* 2014; **26**: 630-639 [PMID: 24722560 DOI: 10.1097/MEG.0000000000000094]
51 **Zeng J**, Li YQ, Zuo XL, Zhen YB, Yang J, Liu CH. Clinical trial: effect of active lactic acid bacteria on mucosal barrier function in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2008; **28**: 994-1002 [PMID: 18671775 DOI: 10.1111/j.1365-2036.2008.03818.x]
52 **Hill C**, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 506-514 [PMID: 24912386 DOI: 10.1038/nrgastro.2014.66]
53 **Ford AC**, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Moayyedi P. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**: 1547-61; quiz 1546, 1562 [PMID: 25070051 DOI: 10.1038/ajg.2014.202]
54 **Moraes-Filho JP**, Quigley EM. THE INTESTINAL MICROBIOTA AND THE ROLE OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME: a review. *Arq Gastroenterol* 2015; **52**: 331-338 [PMID: 26840477 DOI: 10.1590/S0004-28032015000400015]
55 **Rousseaux C**, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel JF, Ardid D, Desreumaux P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med* 2007; **13**: 35-37 [PMID: 17159985 DOI: 10.1038/nm1521]
56 **Axelsson L**. Lactid acid bacteria: Classification and physiology. In: Salminen S, von Wright A, Ouwehand A. Lactic acid bacteria: Microbiological and funcional aspects. 3rd ed. New York: Marcel Dekker Inc, 2004: 3-66
57 **Šušković J**, Brkić B, Matošić S. Mehanizam probiotičkog djelovanja bakterija mliječne Kiseline. *Mljekarstvo* 1997; **47**: 57-73
58 **Dai C**, Zheng CQ, Meng FJ, Zhou Z, Sang LX, Jiang M. VSL#3 probiotics exerts the anti-inflammatory activity *via* PI3k/Akt and NF-κB pathway in rat model of DSS-induced colitis. *Mol Cell Biochem* 2013; **374**: 1-11 [PMID: 23271629 DOI: 10.1007/s11010-012-1488-3]
59 **Distrutti E**, Cipriani S, Mencarelli A, Renga B, Fiorucci S. Probiotics VSL#3 protect against development of visceral pain in murine model of irritable bowel syndrome. *PLoS One* 2013; **8**: e63893 [PMID: 23691109 DOI: 10.1371/journal.pone.0063893]
60 **Do EJ**, Hwang SW, Kim SY, Ryu YM, Cho EA, Chung EJ, Park S, Lee HJ, Byeon JS, Ye BD, Yang DH, Park SH, Yang SK, Kim JH, Myung SJ. Suppression of colitis-associated carcinogenesis through modulation of IL-6/STAT3 pathway by balsalazide and VSL#3. *J Gastroenterol Hepatol* 2016; **31**: 1453-1461 [PMID: 26711554 DOI: 10.1111/jgh.13280]
61 **Dolpady J**, Sorini C, Di Pietro C, Cosorich I, Ferrarese R, Saita D, Clementi M, Canducci F, Falcone M. Oral Probiotic VSL#3 Prevents Autoimmune Diabetes by Modulating Microbiota and Promoting Indoleamine 2,3-Dioxygenase-Enriched Tolerogenic Intestinal Environment. *J Diabetes Res* 2016; **2016**: 7569431 [PMID: 26779542 DOI: 10.1155/2016/7569431]
62 **Madsen K**, Cornish A, Soper P, McKaigney C, Jijon H, Yachimec C, Doyle J, Jewell L, De Simone C. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology* 2001; **121**: 580-591 [PMID: 11522742 DOI: 10.1053/gast.2001.27224]
63 **Kim HJ**, Vazquez Roque MI, Camilleri M, Stephens D, Burton DD, Baxter K, Thomforde G, Zinsmeister AR. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil* 2005; **17**: 687-696 [PMID: 16185307 DOI: 10.1111/j.1365-2982.2005.00695.x]
64 **Roager HM**, Hansen LB, Bahl MI, Frandsen HL, Carvalho V, Gøbel RJ, Dalgaard MD, Plichta DR, Sparholt MH, Vestergaard H, Hansen T, Sicheritz-Pontén T, Nielsen HB, Pedersen O, Lauritzen L, Kristensen M, Gupta R, Licht TR. Colonic transit time is related to bacterial metabolism and mucosal turnover in the gut. *Nat Microbiol* 2016; **1**: 16093 [PMID: 27562254 DOI: 10.1038/nmicrobiol.2016.93]
65 **Vandeputte D**, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. *Gut* 2016; **65**: 57-62 [PMID: 26069274 DOI: 10.1136/gutjnl-2015-309618]
66 **Wong RK**, Yang C, Song GH, Wong J, Ho KY. Melatonin regulation as a possible mechanism for

probiotic (VSL#3) in irritable bowel syndrome: a randomized double-blinded placebo study. *Dig Dis Sci* 2015; **60**: 186-194 [PMID: 25092036 DOI: 10.1007/s10620-014-3299-8]

67 **Aragon G**, Graham DB, Borum M, Doman DB. Probiotic therapy for irritable bowel syndrome. *Gastroenterol Hepatol (N Y)* 2010; **6**: 39-44 [PMID: 20567539]

68 **Kim HJ**, Camilleri M, McKinzie S, Lempke MB, Burton DD, Thomforde GM, Zinsmeister AR. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; **17**: 895-904 [PMID: 12656692 DOI: 10.1046/j.1365-2036.2003.01543.x]

69 **Guandalini S**, Magazzù G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, Sibal A, Romano C, Canani RB, Lionetti P, Setty M. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. *J Pediatr Gastroenterol Nutr* 2010; **51**: 24-30 [PMID: 20453678 DOI: 10.1097/MPG.0b013e3181ca4d95]

70 **Staudacher HM**, Lomer MCE, Farquharson FM, Louis P, Fava F, Franciosi E, Scholz M, Tuohy KM, Lindsay JO, Irving PM, Whelan K. A Diet Low in FODMAPs Reduces Symptoms in Patients With Irritable Bowel Syndrome and A Probiotic Restores Bifidobacterium Species: A Randomized Controlled Trial. *Gastroenterology* 2017; **153**: 936-947 [PMID: 28625832 DOI: 10.1053/j.gastro.2017.06.010]

71 **Sinn DH**, Song JH, Kim HJ, Lee JH, Son HJ, Chang DK, Kim YH, Kim JJ, Rhee JC, Rhee PL. Therapeutic effect of Lactobacillus acidophilus-SDC 2012, 2013 in patients with irritable bowel syndrome. *Dig Dis Sci* 2008; **53**: 2714-2718 [PMID: 18274900 DOI: 10.1007/s10620-007-0196-4]

72 **Hong KS**, Kang HW, Im JP, Ji GE, Kim SG, Jung HC, Song IS, Kim JS. Effect of probiotics on symptoms in korean adults with irritable bowel syndrome. *Gut Liver* 2009; **3**: 101-107 [PMID: 20431731 DOI: 10.5009/gnl.2009.3.2.101]

73 **Guglielmetti S**, Mora D, Gschwender M, Popp K. Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life--a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011; **33**: 1123-1132 [PMID: 21418261 DOI: 10.1111/j.1365-2036.2011.04633.x]

74 **Cui S**, Hu Y. Multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. *Int J Clin Exp Med* 2012; **5**: 238-244 [PMID: 22837798]

75 **Dapoigny M**, Piche T, Ducrotte P, Lunaud B, Cardot JM, Bernalier-Donadille A. Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: a randomized, double-blind study. *World J Gastroenterol* 2012; **18**: 2067-2075 [PMID: 22563194 DOI: 10.3748/wjg.v18.i17.2067]

76 **Ducrotté P**, Sawant P, Jayanthi V. Clinical trial: Lactobacillus plantarum 299v (DSM 9843) improves symptoms of irritable bowel syndrome. *World J Gastroenterol* 2012; **18**: 4012-4018 [PMID: 22912552 DOI: 10.3748/wjg.v18.i30.4012]

77 **Amirimani B**, Nikfam S, Albaji M, Vahedi S, Nasseri-Moghaddam S, Sharafkhah M, Ansari R, Vahedi H. Probiotic vs. Placebo in Irritable Bowel Syndrome:A Randomized Controlled Trial. *Middle East J Dig Dis* 2013; **5**: 98-102 [PMID: 24829677]

78 **Begtrup LM**, de Muckadell OB, Kjeldsen J, Christensen RD, Jarbøl DE. Long-term treatment with probiotics in primary care patients with irritable bowel syndrome--a randomised, double-blind, placebo controlled trial. *Scand J Gastroenterol* 2013; **48**: 1127-1135 [PMID: 23957590 DOI: 10.3109/00365521.2013.825314]

79 **Roberts LM**, McCahon D, Holder R, Wilson S, Hobbs FD. A randomised controlled trial of a probiotic 'functional food' in the management of irritable bowel syndrome. *BMC Gastroenterol* 2013; **13**: 45 [PMID: 23496803 DOI: 10.1186/1471-230X-13-45]

80 **Jafari E**, Vahedi H, Merat S, Momtahen S, Riahi A. Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. *Arch Iran Med* 2014; **17**: 466-470 [PMID: 24979556]

81 **Ludidi S**, Jonkers DM, Koning CJ, Kruimel JW, Mulder L, van der Vaart IB, Conchillo JM, Masclee AA. Randomized clinical trial on the effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients. *Neurogastroenterol Motil* 2014; **26**: 705-714 [PMID: 24588932 DOI: 10.1111/nmo.12320]

82 **Pedersen N**, Andersen NN, Végh Z, Jensen L, Ankersen DV, Felding M, Simonsen MH, Burisch J, Munkholm P. Ehealth: low FODMAP diet *vs* Lactobacillus rhamnosus GG in irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 16215-16226 [PMID: 25473176 DOI: 10.3748/wjg.v20.i43.16215]

83 **Sisson G**, Ayis S, Sherwood RA, Bjarnason I. Randomised clinical trial: A liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome--a 12 wk double-blind study. *Aliment Pharmacol Ther* 2014; **40**: 51-62 [PMID: 24815298 DOI: 10.1111/apt.12787]

84 **Yoon JS**, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, Lee HL, Yoon BC, Choi HS, Chung WS, Seo JG. Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol Hepatol* 2014; **29**: 52-59 [PMID: 23829297 DOI: 10.1111/jgh.12322]

85 **Pineton de Chambrun G**, Neut C, Chau A, Cazaubiel M, Pelerin F, Justen P, Desreumaux P. A randomized clinical trial of Saccharomyces cerevisiae *vs* placebo in the irritable bowel syndrome. *Dig Liver Dis* 2015; **47**: 119-124 [PMID: 25488056 DOI: 10.1016/j.dld.2014.11.007]

86 **Yoon H**, Park YS, Lee DH, Seo JG, Shin CM, Kim N. Effect of administering a multi-species

probiotic mixture on the changes in fecal microbiota and symptoms of irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Clin Biochem Nutr* 2015; **57**: 129-134 [PMID: 26388670 DOI: 10.3164/jcbn.15-14]

87 **Lyra A**, Hillilä M, Huttunen T, Männikkö S, Taalikka M, Tennilä J, Tarpila A, Lahtinen S, Ouwehand AC, Veijola L. Irritable bowel syndrome symptom severity improves equally with probiotic and placebo. *World J Gastroenterol* 2016; **22**: 10631-10642 [PMID: 28082816 DOI: 10.3748/wjg.v22.i48.10631]

88 **Spiller R**, Pélerin F, Cayzeele Decherf A, Maudet C, Housez B, Cazaubiel M, Jüsten P. Randomized double blind placebo-controlled trial of Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation. *United European Gastroenterol J* 2016; **4**: 353-362 [PMID: 27403301 DOI: 10.1177/2050640615602571]

89 **Preston K**, Krumian R, Hattner J, de Montigny D, Stewart M, Gaddam S. Lactobacillus acidophilus CL1285, Lactobacillus casei LBC80R and Lactobacillus rhamnosus CLR2 improve quality-of-life and IBS symptoms: a double-blind, randomised, placebo-controlled study. *Benef Microbes* 2018; **9**: 697-706 [PMID: 29888656 DOI: 10.3920/BM2017.0105]

90 **Clarke G**, Cryan JF, Dinan TG, Quigley EM. Review article: probiotics for the treatment of irritable bowel syndrome--focus on lactic acid bacteria. *Aliment Pharmacol Ther* 2012; **35**: 403-413 [PMID: 22225517 DOI: 10.1111/j.1365-2036.2011.04965.x]

91 **Martoni CJ**, Evans M, Chow CT, Chan LS, Leyer G. Impact of a probiotic product on bowel habits and microbial profile in participants with functional constipation: A randomized controlled trial. *J Dig Dis* 2019; **20**: 435-446 [PMID: 31271261 DOI: 10.1111/1751-2980.12797]

92 **Ghouri YA**, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. *Clin Exp Gastroenterol* 2014; **7**: 473-487 [PMID: 25525379 DOI: 10.2147/CEG.S27530]

93 **Lorenzo-Zúñiga V**, Llop E, Suárez C, Alvarez B, Abreu L, Espadaler J, Serra J. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol* 2014; **20**: 8709-8716 [PMID: 25024629 DOI: 10.3748/wjg.v20.i26.8709]

94 **Liang D**, Longgui N, Guoqiang X. Efficacy of different probiotic protocols in irritable bowel syndrome: A network meta-analysis. *Medicine (Baltimore)* 2019; **98**: e16068 [PMID: 31277101 DOI: 10.1097/MD.0000000000016068]

95 **Staudacher HM**, Whelan K. The low FODMAP diet: recent advances in understanding its mechanisms and efficacy in IBS. *Gut* 2017; **66**: 1517-1527 [PMID: 28592442 DOI: 10.1136/gutjnl-2017-313750]

96 **Szajewska H**, Gyrczuk E, Horvath A. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2013; **162**: 257-262 [PMID: 22981952 DOI: 10.1016/j.jpeds.2012.08.004]

97 **Szajewska H**, Kołodziej M. Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2015; **42**: 793-801 [PMID: 26216624 DOI: 10.1111/apt.13344]

98 **Urbańska M**, Gieruszczak-Białek D, Szajewska H. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. *Aliment Pharmacol Ther* 2016; **43**: 1025-1034 [PMID: 26991503 DOI: 10.1111/apt.13590]

99 **Ouwehand AC**. A review of dose-responses of probiotics in human studies. *Benef Microbes* 2017; **8**: 143-151 [PMID: 28008787 DOI: 10.3920/BM2016.0140]

100 **Pimentel M**, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003; **48**: 86-92 [PMID: 12645795 DOI: 10.1023/a:1021738515885]

101 **Chatterjee S**, Park S, Low K, Kong Y, Pimentel M. The degree of breath methane production in IBS correlates with the severity of constipation. *Am J Gastroenterol* 2007; **102**: 837-841 [PMID: 17397408 DOI: 10.1111/j.1572-0241.2007.01072.x]

102 **Agrawal A**, Houghton LA, Morris J, Reilly B, Guyonnet D, Goupil Feuillerat N, Schlumberger A, Jakob S, Whorwell PJ. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2009; **29**: 104-114 [PMID: 18801055 DOI: 10.1111/j.1365-2036.2008.03853.x]

103 **Pimentel M**, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003; **98**: 412-419 [PMID: 12591062 DOI: 10.1111/j.1572-0241.2003.07234.x]

104 **Guyonnet D**, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier CH, Matuchansky C. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. *Aliment Pharmacol Ther* 2007; **26**: 475-486 [PMID: 17635382 DOI: 10.1111/j.1365-2036.2007.03362.x]

105 **Michail S**, Kenche H. Gut microbiota is not modified by Randomized, Double-blind, Placebo-controlled Trial of VSL#3 in Diarrhea-predominant Irritable Bowel Syndrome. *Probiotics Antimicrob Proteins* 2011; **3**: 1-7 [PMID: 22247743 DOI: 10.1007/s12602-010-9059-y]

106 **Ki Cha B**, Mun Jung S, Hwan Choi C, Song ID, Woong Lee H, Joon Kim H, Hyuk J, Kyung Chang S, Kim K, Chung WS, Seo JG. The effect of a multispecies probiotic mixture on the symptoms and

fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Clin Gastroenterol* 2012; **46**: 220-227 [PMID: 22157240 DOI: 10.1097/MCG.0b013e31823712b1]

107 **Majeed M**, Nagabhushanam K, Natarajan S, Sivakumar A, Ali F, Pande A, Majeed S, Karri SK. Bacillus coagulans MTCC 5856 supplementation in the management of diarrhea predominant Irritable Bowel Syndrome: a double blind randomized placebo controlled pilot clinical study. *Nutr J* 2016; **15**: 21 [PMID: 26922379 DOI: 10.1186/s12937-016-0140-6]

108 **Mezzasalma V**, Manfrini E, Ferri E, Sandionigi A, Ferla B, Schiano I, Michelotti A, Nobile V, Labra M, Di Gennaro P. Corrigendum to "A Randomized, Double-Blind, Placebo-Controlled Trial: The Efficacy of Multispecies Probiotic Supplementation in Alleviating Symptoms of Irritable Bowel Syndrome Associated with Constipation". *Biomed Res Int* 2019; **2019**: 9042956 [PMID: 31093503 DOI: 10.1155/2019/9042956]

109 **Hod K**, Sperber AD, Ron Y, Boaz M, Dickman R, Berliner S, Halpern Z, Maharshak N, Dekel R. A double-blind, placebo-controlled study to assess the effect of a probiotic mixture on symptoms and inflammatory markers in women with diarrhea-predominant IBS. *Neurogastroenterol Motil* 2017; **29** [PMID: 28271623 DOI: 10.1111/nmo.13037]

110 **Ishaque SM**, Khosruzzaman SM, Ahmed DS, Sah MP. A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult®) in the management of diarrhea-predominant irritable bowel syndrome. *BMC Gastroenterol* 2018; **18**: 71 [PMID: 29801486 DOI: 10.1186/s12876-018-0788-9]

111 **Khodadoostan M**, Shavakhi A, Sherafat Z. Effect of Probiotic Administration Immediately and 1 Month after Colonoscopy in Diarrhea-predominant Irritable Bowel Syndrome Patients. *Adv Biomed Res* 2018; **7**: 94 [PMID: 30050882 DOI: 10.4103/abr.abr_216_17]

112 **Sun YY**, Li M, Li YY, Li LX, Zhai WZ, Wang P, Yang XX, Gu X, Song LJ, Li Z, Zuo XL, Li YQ. The effect of Clostridium butyricum on symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *Sci Rep* 2018; **8**: 2964 [PMID: 29445178 DOI: 10.1038/s41598-018-21241-z]

113 **Nobaek S**, Johansson ML, Molin G, Ahrné S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* 2000; **95**: 1231-1238 [PMID: 10811333 DOI: 10.1111/j.1572-0241.2000.02015.x]

114 **Ringel-Kulka T**, Palsson OS, Maier D, Carroll I, Galanko JA, Leyer G, Ringel Y. Probiotic bacteria Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07 *vs* placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. *J Clin Gastroenterol* 2011; **45**: 518-525 [PMID: 21436726 DOI: 10.1097/MCG.0b013e31820ca4d6]

115 **Ligaarden SC**, Axelsson L, Naterstad K, Lydersen S, Farup PG. A candidate probiotic with unfavourable effects in subjects with irritable bowel syndrome: a randomised controlled trial. *BMC Gastroenterol* 2010; **10**: 16 [PMID: 20144246 DOI: 10.1186/1471-230X-10-16]

116 **Hasler WL**. Lactulose breath testing, bacterial overgrowth, and IBS: just a lot of hot air? *Gastroenterology* 2003; **125**: 1898-900; discussion 1900 [PMID: 14724846 DOI: 10.1053/j.gastro.2003.08.038]

117 **Snook J**, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994; **8**: 511-514 [PMID: 7865643 DOI: 10.1111/j.1365-2036.1994.tb00323.x]

118 **Badiali D**, Corazziari E, Habib FI, Tomei E, Bausano G, Magrini P, Anzini F, Torsoli A. Effect of wheat bran in treatment of chronic nonorganic constipation. A double-blind controlled trial. *Dig Dis Sci* 1995; **40**: 349-356 [PMID: 7851201 DOI: 10.1007/BF02065421]

119 **Binder HJ**. Role of colonic short-chain fatty acid transport in diarrhea. *Annu Rev Physiol* 2010; **72**: 297-313 [PMID: 20148677 DOI: 10.1146/annurev-physiol-021909-135817]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 941-952

DOI: 10.4240/wjgs.v13.i9.941

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Role of minimally invasive techniques in gastrointestinal surgery: Current status and future perspectives

Shan-Ping Ye, Wei-Quan Zhu, Zhi-Xiang Huang, Dong-Ning Liu, Xiang-Qiong Wen, Tai-Yuan Li

**ORCID number:** Shan-Ping Ye 0000-0002-3588-7559; Wei-Quan Zhu 0000-0002-5579-9468; Zhi-Xiang Huang 0000-0002-9564-9923; Dong-Ning Liu 0000-0002-9496-9458; Xiang-Qiong Wen 0000-0002-3084-279X; Tai-Yuan Li 0000-0003-2623-4211.

**Author contributions:** Ye SP and Zhu WQ wrote the paper; Ye SP and Li TY proofread and revised the manuscript; Liu DN, Huang ZX, and Wen XQ collected the data and conducted the analysis of pooled data.

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.



**Manuscript source:** Invited

**Shan-Ping Ye, Dong-Ning Liu, Tai-Yuan Li,** Department of General Surgery, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Shan-Ping Ye, Tai-Yuan Li,** Institute of Digestive Surgery, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Wei-Quan Zhu, Zhi-Xiang Huang, Xiang-Qiong Wen,** Jiangxi Medical College of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Corresponding author:** Tai-Yuan Li, MD, PhD, Chief Doctor, Department of General Surgery, The First Affiliated Hospital of Nanchang University, No. 17 Yongwaizheng Street, Nanchang 330006, Jiangxi Province, China. litaiyuanyfy@sina.com

## Abstract

In recent years, the incidence of gastrointestinal cancer has remained high. Currently, surgical resection is still the most effective method for treating gastrointestinal cancer. Traditionally, radical surgery depends on open surgery. However, traditional open surgery inflicts great trauma and is associated with a slow recovery. Minimally invasive surgery, which aims to reduce postoperative complications and accelerate postoperative recovery, has been rapidly developed in the last two decades; it is increasingly used in the field of gastrointestinal surgery and widely used in early-stage gastrointestinal cancer. Nevertheless, many operations for gastrointestinal cancer treatment are still performed by open surgery. One reason for this may be the challenges of minimally invasive technology, especially when operating in narrow spaces, such as within the pelvis or near the upper edge of the pancreas. Moreover, some of the current literature has questioned oncologic outcomes after minimally invasive surgery for gastrointestinal cancer. Overall, the current evidence suggests that minimally invasive techniques are safe and feasible in gastrointestinal cancer surgery, but most of the studies published in this field are retrospective studies and case-matched studies. Large-scale randomized prospective studies are needed to further support the application of minimally invasive surgery. In this review, we summarize several common minimally invasive methods used to treat gastrointestinal cancer and discuss the advances in the minimally invasive treatment of gastrointestinal cancer in detail.

**Key Words:** Gastrointestinal neoplasms; Laparoscopy; Minimally invasive surgical procedures; Robotic surgical procedures; Therapeutics

manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 7, 2021
**Peer-review started:** February 7, 2021
**First decision:** April 6, 2021
**Revised:** April 15, 2021
**Accepted:** July 27, 2021
**Article in press:** July 27, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Cazorla E
**S-Editor:** Yan JP
**L-Editor:** Wang TQ
**P-Editor:** Li JH



**Core Tip:** The incidence of gastrointestinal tumors is high. Minimally invasive surgery has changed the traditional treatment of these patients. Minimally invasive surgery is a revolutionary treatment for gastrointestinal tumors that can reduce surgical complications and accelerate postoperative recovery. Here, we discuss the role and prospect of minimally invasive surgery in the treatment of gastrointestinal tumors.

**Citation:** Ye SP, Zhu WQ, Huang ZX, Liu DN, Wen XQ, Li TY. Role of minimally invasive techniques in gastrointestinal surgery: Current status and future perspectives. *World J Gastrointest Surg* 2021; 13(9): 941-952
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/941.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.941

## INTRODUCTION

With the development of science and technology, minimally invasive surgery is a new option for the radical treatment of tumors. Minimally invasive surgery is gaining increasing popularity for the treatment of gastrointestinal cancer, including endoscopic resection, laparoscopic resection, and da Vinci surgical system resection. Minimally invasive techniques have resulted in less blood loss and fewer complications than conventional surgery.

Minimally invasive surgery is not just about minimizing trauma but also about achieving a complete radical tumor removal. To achieve this goal, high-definition, high-magnification devices have been developed for use in gastrointestinal cancer surgery, allowing surgeons to perform more accurate resection and avoid unnecessary damage compared with traditional surgery because the tumor and surrounding structures can be better visualized.

For any minimally invasive technique, there is always a learning curve to overcome and sufficient evidence to substantiate its effectiveness; equally important is whether the benefits of these techniques are worth the added cost and time.

## ENDOSCOPY TECHNOLOGY IN GASTROINTESTINAL CANCER

### *Endoscopic resection of early gastric cancer*

Endoscopic resection may be presently thought of as an option for the majority of early gastric malignancy cases and could be recognized as a definitive treatment unless it is thought that there is a significant risk of lymph node metastasis[1-3]. The most risky component of lymph hub metastasis is lymphatic vessels in the vicinity of the tumor. Other risk factors include submucosal intrusion (T1b), poor differentiation, ulceration, and a large tumor[1]. Several studies have reported no significant difference in long-term overall survival or tumor-specific survival between patients with early gastric cancer treated endoscopically and those who underwent conventional surgical resection[4,5].

There are currently two primary endoscopic resection techniques: Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR is robust and technically reproducible with a short learning curve, whereas ESD is technically more demanding and therefore has a much longer learning curve. However, ESD normally brings about *en bloc* specimens, higher extent of complete resections, and fewer nearby recurrences[6,7]. Asian and European guidelines recommend ESD as the endoscopic resection method of choice for early gastric cancer[1,8,9].

### *Endoscopic resection in early colorectal cancer*

The detection rate of early colorectal cancer has increased due to the improvements in quality of life and the emphasis on medical check-ups. Early (T1) colorectal cancers with a low risk of lymphatic metastasis can be treated by endoscopic techniques[10-12]. Unfortunately, most patients with early-stage colorectal cancer do not receive adequate endoscopic treatment evaluation and still undergo surgical treatment[13,14].

Endoscopic resection of stage T1 colorectal cancer depends on the tumor size and the depth of invasion. When submucosal invasion is highly suspected, ESD and endoscopic full-thickness resection are better choices than EMR[15-17]. A number of studies have shown that endoscopic treatment of patients with stage T1 colorectal cancer is safe and feasible, and there is no significant difference between the results of endoscopic treatment and surgical treatment[18-21]. Although endoscopic treatment requires adequate physician proficiency and proper assessment of the tumor stage, the advantages of endoscopic treatment in terms of a lower cost and faster postoperative recovery are enormous. Therefore, doctors should properly recognize the advantages of endoscopic treatment and should consider whether endoscopic treatment can benefit their patients with early colorectal cancer.

## LAPAROSCOPIC TECHNIQUES IN GASTROINTESTINAL SURGERY

Laparoscopy is a landmark advance in the history of minimally invasive surgery, and its use is intended to help minimize surgical trauma, reduce pain, and accelerate recovery of bowel function and general mobility after surgery. All of these factors have the potential to shorten the length of hospital stay and reduce patient suffering.

### *Laparoscopic gastric cancer surgery*

Since Kitano *et al*[22] first reported laparoscopic-assisted gastrectomy for early gastric cancer in 1994, laparoscopic gastric cancer surgery has developed rapidly, especially in East Asian countries with a high incidence of gastric cancer, such as China, Japan, and Korea. Despite the rapid development of laparoscopic gastric cancer surgery, the clinical issues surrounding laparoscopic gastric cancer surgery still require more solid medical evidence, mainly due to insufficient evidence of its long-term oncologic efficacy and the optimal extent of lymph node dissection[23].

The KLASS-02-Randomized Clinical Trial of Korean[24] followed and observed 1050 patients in terms of the 3-year relapse-free survival rate. A total of 492 patients underwent laparoscopic surgery and 482 patients underwent open surgery. The 3-year relapse-free survival rate of the laparoscopy group was 80.3%, and this rate of the open group was 81.3%. It was concluded that for patients with locally advanced gastric cancer, the recurrence-free survival rate of laparoscopic distal gastrectomy combined with D2 lymphadenectomy is similar to that of open surgery.

The Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group established the largest multicenter cohort of laparoscopic gastric cancer, the CLASS-01 Randomized Clinical Trial Effect of Laparoscopic *vs* Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer[25]. This study showed that the 3-year disease-free survival rate of laparoscopic distal gastrectomy was not less than that of open distal gastrectomy.

These studies are inadequate and have limitations, such as geographical differences between the East and the West, but they provide a scientific basis and clinical experience for the promotion of laparoscopic gastric cancer surgery[24-32] (Table 1).

### *Laparoscopic colorectal cancer surgery*

Surgery is the main treatment for colorectal cancer, and minimally invasive surgery is the mainstream developmental direction of surgery in recent years. Laparoscopic colorectal cancer surgery has become the standard technique for the treatment of colon cancer in many countries around the world and has been shown to be safe and feasible in randomized trials and population-based studies due to its short-term efficacy[33-44]. However, more evidence is needed to determine its long-term efficacy, especially for advanced colorectal tumors[45] (Table 2).

The operation for rectal cancer is very complicated and is related to the accessibility of the pelvis and its complex anatomical structure. The surgical treatment of rectal cancer has a greater technical challenge than colon cancer, mainly due to the anatomical limitations of the pelvis and the protection by the pelvic plexus[46]. However, laparoscopic surgery has significant advantages compared to open surgery. Although most studies show no difference in short- and long-term outcomes between laparoscopic and open surgery for rectal cancer, it is still a debated issue. Some studies suggest that the long-term efficacy of laparoscopic rectal cancer resection is yet to be determined and is not superior to that of open surgery[47]. In general, an increasing number of studies have confirmed the efficacy and advantages of laparoscopy in colorectal cancer surgery, and it has been widely used.

**Table 1 Studies on laparoscopic surgery in gastric cancer**

| Ref. | Study type | Comparison | Group | Endpoints | Results |
|---|---|---|---|---|---|
| Kim *et al*[31], KLASS-01-RCT, 2019 | Randomized clinical trial | Laparoscopic distal gastrectomy *vs* open distal gastrectomy on long-term survival among patients with stage I gastric cancer | LADG ($n$ = 706); ODG ($n$ = 711) | 5-yr overall survival rate and 5-yr cancer-specific survival rate | No significant difference between the two groups in the 5-yr overall survival rate (94.2% *vs* 93.3%) or 5-yr cancer-specific survival rate (97.1% *vs* 97.2%) |
| Lee *et al*[30], KLASS-02-RCT, 2019 | Multicenter randomized controlled trial | Laparoscopic distal gastrectomy (LDG) *vs* open distal gastrectomy (ODG) for D2 lymphadenectomy | LADG ($n$ = 526); ODG ($n$ = 524) | Thirty-day morbidity, 90-d mortality, postoperative pain, and recovery | Laparoscopic distal gastrectomy was associated with a lower complication rate, faster recovery, and less pain ($P$ < 0.05), and there was no significant difference in mean number of totally retrieved lymph nodes (46.6 *vs* 47.4, $P$ = 0.451) |
| Hyung *et al* [24], KLASS-02-RCT, 2020 | Randomized clinical trial | Laparoscopic distal gastrectomy surgery *vs* open distal gastrectomy surgery for locally advanced gastric cancer | LADG ($n$ = 492); ODG ($n$ = 482) | 3-yr relapse-free survival rate | No significant difference between the two groups in the 3-yr relapse-free survival rate (80.3% *vs* 81.3%) |
| Yu *et al*[25], The CLASS-01 RCT, 2019 | Randomized clinical trial | Laparoscopic distal gastrectomy surgery *vs* open distal gastrectomy for early-stage gastric cancer | LADG ($n$ = 519); ODG ($n$ = 520) | 3-year disease-free survival rate | No significant difference between the two groups in 3-year disease-free survival rate (83.1% *vs* 85.2%) |
| Liu *et al*[27], The CLASS-02, 2020 | Multicenter randomized clinical trial | Laparoscopic total gastrectomy (LTG) *vs* open total gastrectomy (OTG) for patients with clinical stage I gastric cancer | LTG ($n$ = 105); OTG ($n$ = 109) | Morbidity and mortality within 30 d following surgeries; recovery courses; postoperative hospital stays | No significant difference in morbidity and mortality within 30 d following surgeries |
| Katai *et al* [26], JCOG0912, 2020 | A multicenter, non-inferiority, phase 3 randomized controlled trial | Laparoscopy-assisted distal gastrectomy (LADG) *vs* open distal gastrectomy (ODG) for patients with clinical stage I gastric cancer | LADG ($n$ = 462); ODG ($n$ = 459) | Relapse-free survival | LADG was non-inferior to ODG for relapse-free survival (94% *vs* 95.1%, $P$ < 0.05), and LADG should be considered a standard treatment option |
| Kinoshitaet al [28], LOC-A Study, 2019 | Multicenter cohort study | Laparoscopic gastrectomy (LC) *vs* open gastrectomy (OP) for locally advanced gastric cancer | LC ($n$ = 305); Op ( $n$ = 305) | 5-yr overall survival; recurrence rate; hazard ratio for recurrence (HR) | No significant difference between the two groups in the 5-yr overall survival (53.0% *vs* 54.2%) and recurrence rate (30.8% *vs* 29.8%) |
| Park *et al*[29], COACT 1001, 2018 | Randomized phase II multicenter clinical trial | Laparoscopy-assisted distal gastrectomy (LADG) with D2 lymph node dissection *vs* open distal gastrectomy (ODG) for the treatment of advanced gastric cancer | LADG ($n$ = 105); ODG ($n$ = 99) | Noncompliance rate of the lymph node dissection; 3-yr disease-free survival (DFS), 5-yr overall survival, complications, and surgical stress response | No significant difference between the two groups in the noncompliance rate of lymph node dissection (47.0% *vs* 43.2%) and 3-yr DFS (80.1% *vs* 81.9%) |

LADG: Laparoscopy-assisted distal gastrectomy; ODG: Open distal gastrectomy; LC: Laparoscopic gastrectomy; OP: Open gastrectomy; DFS: Disease-free survival; HR: Hazard ratio; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; LDG: Laparoscopic distal gastrectomy.

### *Three-dimensional laparoscopic imaging systems*

Minimally invasive laparoscopic techniques are now rapidly gaining popularity, but conventional laparoscopy provides only a two-dimensional (2D) view. Three-dimensional (3D) laparoscopy overcomes this disadvantage and offers the advantage of a greater field of view[48]. Some studies have shown that 3D laparoscopic surgery provides better depth perception, significantly reduces the operative time and intraoperative blood loss, and shortens the surgeon's learning curve[48-51]. However, there is a lack of prospective evidence on the safety and efficacy of 3D technology in the long term. Despite the controversy, the benefits of 3D laparoscopy are undeniable and it has a promising future.

## APPLICATION STATUS OF ROBOTIC SURGICAL SYSTEMS IN GASTROINTESTINAL SURGERY

To overcome the shortcomings of laparoscopic techniques, especially when working in confined spaces such as the pelvis, da Vinci robotic surgery system robots, which are precise, stable, and flexible and can be operated remotely and gradually, are becoming a new option for minimally invasive surgery. The da Vinci robotic surgery system developed by the US Intuitive Surgical Company received US FDA marketing

**Table 2 Studies on laparoscopic surgery in colorectal cancer**

| Ref. | Study type | Comparison | Group | Endpoints | Results |
|---|---|---|---|---|---|
| Bonjer *et al*[44], 2015 | Randomized clinical trial | Laparoscopic *vs* open surgery for rectal cancer | LC ($n$ = 699); OP ( $n$ = 345) | Locoregional recurrence 3 yr after index surgery, and disease-free and overall survival | No significant difference between the two groups in locoregional recurrence 3 yr after index surgery, or disease-free and overall survival (86.7% *vs* 83.6%) |
| Fleshman *et al*[43], ACOSOG Z6051 Randomized Controlled Trial, 2019 | Randomized clinical trial | Laparoscopic-assisted resection *vs* open resection of stage II or III rectal cancer | LC ($n$ = 243); OP ( $n$ = 243) | Disease-free survival and local recurrence | No significant difference between the two groups in disease-free survival and local recurrence |
| Park *et al*[39], 2020 | Multicenter comparative study | Laparoscopic *vs* open surgery for small T4 colon cancer | LC ($n$ = 149); OP ( $n$ = 300) | Blood loss, length of hospital stay, postoperative morbidity, and overall survival or disease-free survival | No significant difference between the two groups in overall survival or disease-free survival, and LC was associated with favorable short-term oncologic outcomes in patients with tumors ≤ 4.0 cm |
| Li *et al*[40], 2021 | Multicenter comparative study | Laparoscopic *vs* open surgery for transverse colon cancer | LC ($n$ = 181); OP ( $n$ = 235) | Operation time, postoperative hospitalization, lymph node retrieval, 5-yr overall survival | LC was associated with statistically longer operation time (209.96 *vs* 173.31 min, $P$ = 0.002) and shorter postoperative hospitalization (12.05 *vs* 14.44 d, $P$ = 0.001), but there was no significant difference in lymph node retrieval and 5-yr overall survival |
| Garbarino *et al*[42], 2021 | Propensity score-matched analysis | Laparoscopic *vs* open surgery for rectal resection | LC ($n$ = 181); OP ( $n$ = 2 35) | Operative time, postoperative morbidity, hospital stay, safe oncological adequateness | LC was associated with shorter hospital stay ($P$ < 0.001), but there was no significant difference in safe oncological adequateness |

LC: Laparoscopic gastrectomy; OP: Open gastrectomy.

approval in July 2000 and began to be used in clinical applications. In 2002, Weber *et al*[52] reported the first robotic system-assisted surgery for benign colonic disease, and in the same year, Hashizume *et al*[53] also reported robotic colorectal surgery for malignant disease. With the development of the technology, it has been widely used in gastrointestinal surgery, hepatobiliary surgery, urology, gynecology, *etc*.[54]. However, the high cost and a lack of evidence of efficacy are limitations.

### *Robotic surgery in gastric cancer*

Despite the lack of more robust multicenter evidence, robotic surgery has been increasingly used as a minimally invasive means for treating gastric cancer because of the potential surgical advantages that it may have over conventional laparoscopy. However, Kim *et al*[55] showed that there was no significant difference between the two in terms of surgical blood loss, number of intermediate openings, time to oral feeding, or the length of hospital stay. At the same time, Uyama *et al*[56] showed that robotic gastric cancer surgery is safe and effective for stage I/II gastric cancer and can reduce the incidence of early postoperative complications compared to laparoscopic surgery. The short-term efficacy of robotic gastric cancer surgery is therefore good, but more evidence is still needed to prove it.

### *Robotics surgery in colorectal cancer*

Current evidence suggests that the short-term efficacy of robotic-assisted colorectal cancer surgery is good and it may have potential minimally invasive advantages[57-61]. Robotic surgery for rectal cancer has been promoted as an improved minimally invasive procedure due to the flexibility of the da Vinci robot for operating in confined spaces such as the pelvis. Some prospectively randomized studies have shown that the clinical outcomes of robotic surgical resection of rectal cancer are similar to those of laparoscopic and open surgery[62-69]. There is also literature confirming that robotic rectal cancer surgery is closely associated with better short-term outcomes than laparoscopic surgery, and it has advantages in protecting the pelvic nerves, resulting in fewer short-term postoperative complications and shorter hospital stays[70,71].

Crippa *et al*[71] analyzed 600 patients. The number of patients undergoing robotic surgery was 317 (52.8%), and the laparoscopic group consisted of 283 (47.2%) patients. Both groups were similar in terms of age, sex, and body mass index (BMI). The overall incidence of short-term complications in patients undergoing robotic surgery was lower than that in the laparoscopic group (37.2% *vs* 51.2%; $P$ < 0.001). However, larger

prospectively randomized trials are needed to support its use. There is no denying that robotic flexibility may be more promising than laparoscopy in rectal cancer surgery.

## NATURAL ORIFICE SPECIMEN EXTRACTION SURGERY

The aim of minimal invasiveness is to reduce trauma. To avoid the need for an auxiliary abdominal incision, natural orifice specimen extraction surgery (NOSES) is a newly developed method that extracts specimens through natural orifices *via* the trans-anal or transvaginal route to reduce trauma and to avoid auxiliary abdominal incisions[72]. Trans-anal removal of specimens is mainly used for left-sided colectomies and rectal procedures, and transvaginal removal is used for all colonic procedures, especially right-sided colectomies and large specimens[73,74]. It is seldom used for operations on the stomach, but the study by Jeong *et al*[73] concluded that in carefully selected elderly women with early gastric cancer, transvaginal specimen collection may be a safe and feasible procedure.

The NOSES technique is currently used mainly in colorectal cancer surgery, especially rectal surgery. Many studies have shown that the NOSES technique is safe and feasible for colorectal cancer; although it may increase the probability of contamination of the surgical area, this does not appear to translate into a higher incidence of infection[75-81]. Colorectal resection with NOSES is more advantageous in terms of postoperative recovery, postoperative pain, esthetics, and complications (Figure 1). However, not every patient is suitable for NOSES. Patients with stage T4 tumors and large tumors should not undergo NOSES. Trans-anal specimens are suitable for both men and women, but the tumor size should be less than 3 cm, whereas transvaginal specimens are suitable for women and the tumor size should be no larger than 5 cm. In addition, the BMI of the patient should be less than 30 kg/m$^2$ for anal specimens and less than 35 kg/m$^2$ for transvaginal specimens[82,83]. Hence, the NOSES procedure indications should be strictly observed.

## CONCLUSION

Advances in minimally invasive techniques have opened a new era in gastrointestinal treatment. For gastrointestinal tumors, the most important treatment is surgical resection. However, it is often overlooked that early-stage gastrointestinal cancer can be treated endoscopically with a good result. To obtain the best prognosis and minimal trauma, it is very important to choose an appropriate surgical method.

For advanced tumors, total resection including regional lymph nodes should be performed. The emergence of laparoscopic surgery has brought innovation to minimally invasive surgery. As laparoscopic techniques continue to mature and surgeons become more skilled, surgeons can do even more with a laparoscopic view. There are many reported studies showing that the efficacy of total laparoscopic surgery is positive; completely laparoscopic surgery reduces the size of the secondary incision and reduces trauma[84-90].

A 3D laparoscopic imaging system is a further improvement on conventional laparoscopic techniques, and with improved laparoscopic views, it may help to shorten the learning curve of surgeons. Laparoscopic surgery has been recognized in the early treatment of gastrointestinal cancer, and its use in the treatment of most advanced tumors has also been affirmed. We look forward to international multicenter research evidence.

To improve the inadequacy of laparoscopic techniques, especially when operating in a narrow space, such as the pelvis and at the superior margin of the pancreas, surgeons started using robotic surgery systems. Among them, the da Vinci robot surgery system is used most often, and its technology is relatively mature, which offers the advantages of anti-shaking, three-dimensional vision, and operational flexibility, taking minimally invasive surgery to new levels of precision[91,92]. At present, the research on da Vinci robots is mainly retrospective. From the results, some short-term curative effects are better than those of laparoscopy, and the long-term curative effect is equivalent. However, these results need further confirmation in randomized clinical trial results. Additionally, one of the greatest drawbacks of the da Vinci robotic surgical system is its cost. The da Vinci surgical system is the only surgical robot available on the market today, and it has a high upfront cost. At the same time, surgeons need to go through a long learning curve to use the robotic system, meaning that the da Vinci system costs considerable time and money upfront,

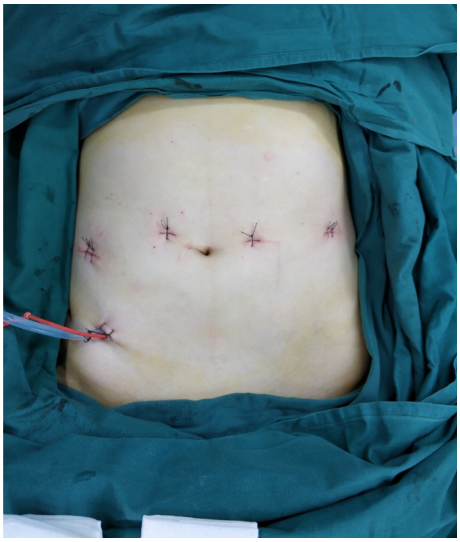

**Figure 1 Rectal cancer resection by natural orifice specimen extraction surgery without incision.**

which is a major reason for its need for further development. Hence, before large-scale randomized clinical trial research is confirmed, we recommend that gastrointestinal surgery with rich experience in laparoscopy be carried out.

The future of surgical robots will move toward miniaturization and intelligence, and with the maturity of 5G technology, artificial intelligence technology and 5G technology have the potential to be combined with robotic surgical systems to help surgeons operate remotely, improve medical conditions, reduce healthcare costs, and benefit more patients.

In summary, minimally invasive surgery is the goal of surgeons. Combined with our experience, robotic surgery systems may be used increasingly widely. As interest and research in minimally invasive surgery continue to grow, the role of minimally invasive techniques in gastrointestinal surgery will become increasingly important.

## REFERENCES


1 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

2 **Pimentel-Nunes P**, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, Amato A, Berr F, Bhandari P, Bialek A, Conio M, Haringsma J, Langner C, Meisner S, Messmann H, Morino M, Neuhaus H, Piessevaux H, Rugge M, Saunders BP, Robaszkiewicz M, Seewald S, Kashin S, Dumonceau JM, Hassan C, Deprez PH. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; **47**: 829-854 [PMID: 26317585 DOI: 10.1055/s-0034-1392882]

3 **Hatta W**, Gotoda T, Koike T, Masamune A. History and future perspectives in Japanese guidelines for endoscopic resection of early gastric cancer. *Dig Endosc* 2020; **32**: 180-190 [PMID: 31529716 DOI: 10.1111/den.13531]

4 **Choi KS**, Jung HY, Choi KD, Lee GH, Song HJ, Kim DH, Lee JH, Kim MY, Kim BS, Oh ST, Yook JH, Jang SJ, Yun SC, Kim SO, Kim JH. EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. *Gastrointest Endosc* 2011; **73**: 942-948 [PMID: 21392757 DOI: 10.1016/j.gie.2010.12.032]

5 **Choi IJ**, Lee JH, Kim YI, Kim CG, Cho SJ, Lee JY, Ryu KW, Nam BH, Kook MC, Kim YW. Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. *Gastrointest Endosc* 2015; **81**: 333-41.e1 [PMID: 25281498 DOI: 10.1016/j.gie.2014.07.047]

6 **Facciorusso A**, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest Endosc* 2014; **6**: 555-563 [PMID: 25400870 DOI: 10.4253/wjge.v6.i11.555]

7 **Park YM**, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. *Surg Endosc* 2011; **25**: 2666-2677 [PMID: 21424201 DOI: 10.1007/s00464-011-1627-z]

8 **Shahidi N**, Bourke MJ. ESD, not EMR, should be the first-line therapy for early gastric neoplasia. *Gut* 2020; **69**: 1-2 [PMID: 31481547 DOI: 10.1136/gutjnl-2019-319646]

9 **Smyth E**, Schöder H, Strong VE, Capanu M, Kelsen DP, Coit DG, Shah MA. A prospective evaluation of the utility of 2-deoxy-2-[(18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer* 2012; **118**: 5481-5488 [PMID: 22549558 DOI: 10.1002/cncr.27550]

10 **Hassan I**, Wise PE, Margolin DA, Fleshman JW. The Role of Transanal Surgery in the Management of T1 Rectal Cancers. *J Gastrointest Surg* 2015; **19**: 1704-1712 [PMID: 26048145 DOI: 10.1007/s11605-015-2866-4]

11 **Aepli P**, Criblez D, Baumeler S, Borovicka J, Frei R. Endoscopic full thickness resection (EFTR) of colorectal neoplasms with the Full Thickness Resection Device (FTRD): Clinical experience from two tertiary referral centers in Switzerland. *United European Gastroenterol J* 2018; **6**: 463-470 [PMID: 29774161 DOI: 10.1177/2050640617728001]

12 **Ferlitsch M**, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, Jover R, Langner C, Bronzwaer M, Nalankilli K, Fockens P, Hazzan R, Gralnek IM, Gschwantler M, Waldmann E, Jeschek P, Penz D, Heresbach D, Moons L, Lemmers A, Paraskeva K, Pohl J, Ponchon T, Regula J, Repici A, Rutter MD, Burgess NG, Bourke MJ. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017; **49**: 270-297 [PMID: 28212588 DOI: 10.1055/s-0043-102569]

13 **Moss A**, Nalankilli K. Completing the circle of informed consent for EMR versus surgery for nonmalignant large or complex colorectal polyps. *Gastrointest Endosc* 2016; **84**: 304-306 [PMID: 27425800 DOI: 10.1016/j.gie.2016.02.039]

14 **Keswani RN**, Law R, Ciolino JD, Lo AA, Gluskin AB, Bentrem DJ, Komanduri S, Pacheco JA, Grande D, Thompson WK. Adverse events after surgery for nonmalignant colon polyps are common and associated with increased length of stay and costs. *Gastrointest Endosc* 2016; **84**: 296-303.e1 [PMID: 26828760 DOI: 10.1016/j.gie.2016.01.048]

15 **Backes Y**, Schwartz MP, Ter Borg F, Wolfhagen FHJ, Groen JN, de Vos Tot Nederveen Cappel WH, van Bergeijk J, Geesing JMJ, Spanier BWM, Didden P, Vleggaar FP, Lacle MM, Elias SG, Moons LMG; Dutch T1 CRC Working Group. Multicentre prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large non-pedunculated colorectal polyps using narrow band imaging (the OPTICAL study). *Gut* 2019; **68**: 271-279 [PMID: 29298873 DOI: 10.1136/gutjnl-2017-314723]

16 **Hayashi N**, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013; **78**: 625-632 [PMID: 23910062 DOI: 10.1016/j.gie.2013.04.185]

17 **Sano Y**, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, Fujii T, Ikematsu H, Uraoka T, Kobayashi N, Nakamura H, Hotta K, Horimatsu T, Sakamoto N, Fu KI, Tsuruta O, Kawano H, Kashida H, Takeuchi Y, Machida H, Kusaka T, Yoshida N, Hirata I, Terai T, Yamano HO, Kaneko K, Nakajima T, Sakamoto T, Yamaguchi Y, Tamai N, Nakano N, Hayashi N, Oka S, Iwatate M, Ishikawa H, Murakami Y, Yoshida S, Saito Y. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; **28**: 526-533 [PMID: 26927367 DOI: 10.1111/den.12644]

18 **van de Ven SEM**, Backes Y, Hilbink M, Seerden TCJ, Kessels K, de Vos Tot Nederveen Cappel WH, Groen JN, Wolfhagen FHJ, Geesing JMJ, Borg FT, van Bergeijk J, Spanier BWM, Mundt MW, Pullens HJM, Boonstra JJ, Opsteeg B, van Lent AUG, Schrauwen RWM, Laclé MM, Moons LMG, Terhaar Sive Droste JS; Dutch T1 CRC Working Group. Periprocedural adverse events after endoscopic resection of T1 colorectal carcinomas. *Gastrointest Endosc* 2020; **91**: 142-152.e3 [PMID: 31525362 DOI: 10.1016/j.gie.2019.08.046]

19 **Kuellmer A**, Mueller J, Caca K, Aepli P, Albers D, Schumacher B, Glitsch A, Schäfer C, Wallstabe I, Hofmann C, Erhardt A, Meier B, Bettinger D, Thimme R, Schmidt A; FTRD study group. Endoscopic full-thickness resection for early colorectal cancer. *Gastrointest Endosc* 2019; **89**: 1180-1189.e1 [PMID: 30653939 DOI: 10.1016/j.gie.2018.12.025]

20 **Bosch SL**, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. *Endoscopy* 2013; **45**: 827-834 [PMID: 23884793 DOI: 10.1055/s-0033-1344238]

21 **Dang H**, de Vos Tot Nederveen Cappel WH, van der Zwaan SMS, van den Akker-van Marle ME, van Westreenen HL, Backes Y, Moons LMG, Holman FA, Peeters KCMJ, van der Kraan J, Langers AMJ, Lijfering WM, Hardwick JCH, Boonstra JJ. Quality of life and fear of cancer recurrence in T1 colorectal cancer patients treated with endoscopic or surgical tumor resection. *Gastrointest Endosc* 2019; **89**: 533-544 [PMID: 30273589 DOI: 10.1016/j.gie.2018.09.026]

22 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]

23 **Smyth EC**, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020; **396**: 635-648 [PMID: 32861308 DOI: 10.1016/S0140-6736(20)31288-5]

24 **Hyung WJ**, Yang HK, Park YK, Lee HJ, An JY, Kim W, Kim HI, Kim HH, Ryu SW, Hur H, Kim MC, Kong SH, Cho GS, Kim JJ, Park DJ, Ryu KW, Kim YW, Kim JW, Lee JH, Han SU; Korean Laparoendoscopic Gastrointestinal Surgery Study Group. Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial. *J Clin Oncol* 2020; **38**: 3304-3313 [PMID: 32816629 DOI: 10.1200/JCO.20.01210]

25 **Yu J**, Huang C, Sun Y, Su X, Cao H, Hu J, Wang K, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du

X, Hu Y, Liu H, Zheng C, Li P, Xie J, Liu F, Li Z, Zhao G, Yang K, Liu C, Li H, Chen P, Ji J, Li G; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *JAMA* 2019; **321**: 1983-1992 [PMID: 31135850 DOI: 10.1001/jama.2019.5359]

26 **Katai H**, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, Ito S, Takagi M, Takagane A, Teshima S, Koeda K, Nunobe S, Yoshikawa T, Terashima M, Sasako M. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 142-151 [PMID: 31757656 DOI: 10.1016/S2468-1253(19)30332-2]

27 **Liu F**, Huang C, Xu Z, Su X, Zhao G, Ye J, Du X, Huang H, Hu J, Li G, Yu P, Li Y, Suo J, Zhao N, Zhang W, Li H, He H, Sun Y; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Morbidity and Mortality of Laparoscopic vs Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASS02 Multicenter Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1590-1597 [PMID: 32815991 DOI: 10.1001/jamaoncol.2020.3152]

28 **Kinoshita T**, Uyama I, Terashima M, Noshiro H, Nagai E, Obama K, Tamamori Y, Nabae T, Honda M, Abe T; LOC-A Study Group. Long-term Outcomes of Laparoscopic Versus Open Surgery for Clinical Stage II/III Gastric Cancer: A Multicenter Cohort Study in Japan (LOC-A Study). *Ann Surg* 2019; **269**: 887-894 [PMID: 29697447 DOI: 10.1097/SLA.0000000000002768]

29 **Park YK**, Yoon HM, Kim YW, Park JY, Ryu KW, Lee YJ, Jeong O, Yoon KY, Lee JH, Lee SE, Yu W, Jeong SH, Kim T, Kim S, Nam BH; COACT group. Laparoscopy-assisted versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: Results From a Randomized Phase II Multicenter Clinical Trial (COACT 1001). *Ann Surg* 2018; **267**: 638-645 [PMID: 28187041 DOI: 10.1097/SLA.0000000000002168]

30 **Lee HJ**, Hyung WJ, Yang HK, Han SU, Park YK, An JY, Kim W, Kim HI, Kim HH, Ryu SW, Hur H, Kong SH, Cho GS, Kim JJ, Park DJ, Ryu KW, Kim YW, Kim JW, Lee JH, Kim MC; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Short-term Outcomes of a Multicenter Randomized Controlled Trial Comparing Laparoscopic Distal Gastrectomy With D2 Lymphadenectomy to Open Distal Gastrectomy for Locally Advanced Gastric Cancer (KLASS-02-RCT). *Ann Surg* 2019; **270**: 983-991 [PMID: 30829698 DOI: 10.1097/SLA.0000000000003217]

31 **Kim HH**, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Hyung WJ; Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 506-513 [PMID: 30730546 DOI: 10.1001/jamaoncol.2018.6727]

32 **Hyung WJ**, Yang HK, Han SU, Lee YJ, Park JM, Kim JJ, Kwon OK, Kong SH, Kim HI, Lee HJ, Kim W, Ryu SW, Jin SH, Oh SJ, Ryu KW, Kim MC, Ahn HS, Park YK, Kim YH, Hwang SH, Kim JW, Cho GS. A feasibility study of laparoscopic total gastrectomy for clinical stage I gastric cancer: a prospective multi-center phase II clinical trial, KLASS 03. *Gastric Cancer* 2019; **22**: 214-222 [PMID: 30128720 DOI: 10.1007/s10120-018-0864-4]

33 **Veldkamp R**, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM; COlon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; **6**: 477-484 [PMID: 15992696 DOI: 10.1016/S1470-2045(05)70221-7]

34 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718-1726 [PMID: 15894098 DOI: 10.1016/S0140-6736(05)66545-2]

35 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]

36 **Jayne DG**, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg* 2010; **97**: 1638-1645 [PMID: 20629110 DOI: 10.1002/bjs.7160]

37 **Fleshman J**, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Nelson H; Clinical Outcomes of Surgical Therapy Study Group. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg* 2007; **246**: 655-62; discussion 662 [PMID: 17893502 DOI: 10.1097/SLA.0b013e318155a762]

38 **Bagshaw PF**, Allardyce RA, Frampton CM, Frizelle FA, Hewett PJ, McMurrick PJ, Rieger NA, Smith JS, Solomon MJ, Stevenson AR; Australasian Laparoscopic Colon Cancer Study Group. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. *Ann Surg* 2012; **256**: 915-919 [PMID: 23154392 DOI: 10.1097/SLA.0b013e3182765ff8]

39 **Park SS**, Lee JS, Park HC, Park SC, Sohn DK, Oh JH, Han KS, Lee DW, Lee DE, Kang SB, Park KJ, Jeong SY; Seoul Colorectal Research Group (SECOG). Favorable short-term oncologic outcomes following laparoscopic surgery for small T4 colon cancer: a multicenter comparative study. *World J Surg Oncol* 2020; **18**: 299 [PMID: 33187538 DOI: 10.1186/s12957-020-02074-5]

40 **Li Z**, Zou Z, Lang Z, Sun Y, Zhang X, Dai M, Mao S, Han Z. Laparoscopic versus open radical

resection for transverse colon cancer: evidence from multi-center databases. *Surg Endosc* 2021; **35**: 1435-1441 [PMID: 33507386 DOI: 10.1007/s00464-021-08285-5]

41 **Hewett PJ**, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson AR. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. *Ann Surg* 2008; **248**: 728-738 [PMID: 18948799 DOI: 10.1097/SLA.0b013e31818b7595]

42 **Garbarino GM**, Canali G, Tarantino G, Costa G, Ferri M, Balducci G, Pilozzi E, Berardi G, Mercantini P. Laparoscopic versus open rectal resection: a 1:2 propensity score-matched analysis of oncological adequateness, short- and long-term outcomes. *Int J Colorectal Dis* 2021; **36**: 801-810 [PMID: 33483843 DOI: 10.1007/s00384-021-03841-w]

43 **Fleshman J**, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, Peters WR Jr, Maun DC, Chang GJ, Herline A, Fichera A, Mutch MG, Wexner SD, Whiteford MH, Marks J, Birnbaum E, Margolin DA, Larson DW, Marcello PW, Posner MC, Read TE, Monson JRT, Wren SM, Pisters PWT, Nelson H. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. *Ann Surg* 2019; **269**: 589-595 [PMID: 30080730 DOI: 10.1097/SLA.0000000000003002]

44 **Bonjer HJ**, Deijen CL, Haglind E; COLOR II Study Group. A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer. *N Engl J Med* 2015; **373**: 194 [PMID: 26154803 DOI: 10.1056/NEJMc1505367]

45 **Fleshman J**, Branda M, Sargent DJ, Boller AM, George V, Abbas M, Peters WR Jr, Maun D, Chang G, Herline A, Fichera A, Mutch M, Wexner S, Whiteford M, Marks J, Birnbaum E, Margolin D, Larson D, Marcello P, Posner M, Read T, Monson J, Wren SM, Pisters PW, Nelson H. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. *JAMA* 2015; **314**: 1346-1355 [PMID: 26441179 DOI: 10.1001/jama.2015.10529]

46 **van der Sijp MP**, Bastiaannet E, Mesker WE, van der Geest LG, Breugom AJ, Steup WH, Marinelli AW, Tseng LN, Tollenaar RA, van de Velde CJ, Dekker JW. Differences between colon and rectal cancer in complications, short-term survival and recurrences. *Int J Colorectal Dis* 2016; **31**: 1683-1691 [PMID: 27497831 DOI: 10.1007/s00384-016-2633-3]

47 **Cleary RK**, Morris AM, Chang GJ, Halverson AL. Controversies in Surgical Oncology: Does the Minimally Invasive Approach for Rectal Cancer Provide Equivalent Oncologic Outcomes Compared with the Open Approach? *Ann Surg Oncol* 2018; **25**: 3587-3595 [PMID: 30187281 DOI: 10.1245/s10434-018-6740-y]

48 **Zheng CH**, Lu J, Zheng HL, Li P, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Tu RH, Huang CM. Comparison of 3D laparoscopic gastrectomy with a 2D procedure for gastric cancer: A phase 3 randomized controlled trial. *Surgery* 2018; **163**: 300-304 [PMID: 29195739 DOI: 10.1016/j.surg.2017.09.053]

49 **Storz P**, Buess GF, Kunert W, Kirschniak A. 3D HD versus 2D HD: surgical task efficiency in standardised phantom tasks. *Surg Endosc* 2012; **26**: 1454-1460 [PMID: 22179446 DOI: 10.1007/s00464-011-2055-9]

50 **Kanaji S**, Suzuki S, Harada H, Nishi M, Yamamoto M, Matsuda T, Oshikiri T, Nakamura T, Fujino Y, Tominaga M, Kakeji Y. Comparison of two- and three-dimensional display for performance of laparoscopic total gastrectomy for gastric cancer. *Langenbecks Arch Surg* 2017; **402**: 493-500 [PMID: 28314905 DOI: 10.1007/s00423-017-1574-9]

51 **Chiu CJ**, Lobo Prabhu K, Tan-Tam CC, Panton ON, Meneghetti A. Using three-dimensional laparoscopy as a novel training tool for novice trainees compared with two-dimensional laparoscopy. *Am J Surg* 2015; **209**: 824-827.e1; discussion 827 [PMID: 25795176 DOI: 10.1016/j.amjsurg.2015.01.007]

52 **Weber PA**, Merola S, Wasielewski A, Ballantyne GH. Telerobotic-assisted laparoscopic right and sigmoid colectomies for benign disease. *Dis Colon Rectum* 2002; **45**: 1689-94; discussion 1695 [PMID: 12473897 DOI: 10.1007/s10350-004-7261-2]

53 **Hashizume M**, Shimada M, Tomikawa M, Ikeda Y, Takahashi I, Abe R, Koga F, Gotoh N, Konishi K, Maehara S, Sugimachi K. Early experiences of endoscopic procedures in general surgery assisted by a computer-enhanced surgical system. *Surg Endosc* 2002; **16**: 1187-1191 [PMID: 11984681 DOI: 10.1007/s004640080154]

54 **Braumann C**, Jacobi CA, Menenakos C, Ismail M, Rueckert JC, Mueller JM. Robotic-assisted laparoscopic and thoracoscopic surgery with the da Vinci system: a 4-year experience in a single institution. *Surg Laparosc Endosc Percutan Tech* 2008; **18**: 260-266 [PMID: 18574412 DOI: 10.1097/SLE.0b013e31816f85e5]

55 **Kim HI**, Han SU, Yang HK, Kim YW, Lee HJ, Ryu KW, Park JM, An JY, Kim MC, Park S, Song KY, Oh SJ, Kong SH, Suh BJ, Yang DH, Ha TK, Kim YN, Hyung WJ. Multicenter Prospective Comparative Study of Robotic Versus Laparoscopic Gastrectomy for Gastric Adenocarcinoma. *Ann Surg* 2016; **263**: 103-109 [PMID: 26020107 DOI: 10.1097/SLA.0000000000001249]

56 **Uyama I**, Suda K, Nakauchi M, Kinoshita T, Noshiro H, Takiguchi S, Ehara K, Obama K, Kuwabara S, Okabe H, Terashima M. Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study. *Gastric Cancer* 2019; **22**: 377-385 [PMID: 30506394 DOI: 10.1007/s10120-018-00906-8]

57 **Zarak A**, Castillo A, Kichler K, de la Cruz L, Tamariz L, Kaza S. Robotic versus laparoscopic

surgery for colonic disease: a meta-analysis of postoperative variables. *Surg Endosc* 2015; **29**: 1341-1347 [PMID: 25847139 DOI: 10.1007/s00464-015-4197-7]

58 **deSouza AL**, Prasad LM, Park JJ, Marecik SJ, Blumetti J, Abcarian H. Robotic assistance in right hemicolectomy: is there a role? *Dis Colon Rectum* 2010; **53**: 1000-1006 [PMID: 20551751 DOI: 10.1007/DCR.0b013e3181d32096]

59 **Xu H**, Li J, Sun Y, Li Z, Zhen Y, Wang B, Xu Z. Robotic versus laparoscopic right colectomy: a meta-analysis. *World J Surg Oncol* 2014; **12**: 274 [PMID: 25169141 DOI: 10.1186/1477-7819-12-274]

60 **Solaini L**, Bazzocchi F, Cavaliere D, Avanzolini A, Cucchetti A, Ercolani G. Robotic versus laparoscopic right colectomy: an updated systematic review and meta-analysis. *Surg Endosc* 2018; **32**: 1104-1110 [PMID: 29218671 DOI: 10.1007/s00464-017-5980-4]

61 **Cheng CL**, Rezac C. The role of robotics in colorectal surgery. *BMJ* 2018; **360**: j5304 [PMID: 29440057 DOI: 10.1136/bmj.j5304]

62 **Feroci F**, Vannucchi A, Bianchi PP, Cantafio S, Garzi A, Formisano G, Scatizzi M. Total mesorectal excision for mid and low rectal cancer: Laparoscopic vs robotic surgery. *World J Gastroenterol* 2016; **22**: 3602-3610 [PMID: 27053852 DOI: 10.3748/wjg.v22.i13.3602]

63 **Park JS**, Choi GS, Lim KH, Jang YS, Jun SH. S052: a comparison of robot-assisted, laparoscopic, and open surgery in the treatment of rectal cancer. *Surg Endosc* 2011; **25**: 240-248 [PMID: 20552367 DOI: 10.1007/s00464-010-1166-z]

64 **D'Annibale A**, Pernazza G, Monsellato I, Pende V, Lucandri G, Mazzocchi P, Alfano G. Total mesorectal excision: a comparison of oncological and functional outcomes between robotic and laparoscopic surgery for rectal cancer. *Surg Endosc* 2013; **27**: 1887-1895 [PMID: 23292566 DOI: 10.1007/s00464-012-2731-4]

65 **Kim JY**, Kim NK, Lee KY, Hur H, Min BS, Kim JH. A comparative study of voiding and sexual function after total mesorectal excision with autonomic nerve preservation for rectal cancer: laparoscopic versus robotic surgery. *Ann Surg Oncol* 2012; **19**: 2485-2493 [PMID: 22434245 DOI: 10.1245/s10434-012-2262-1]

66 **Baik SH**, Kwon HY, Kim JS, Hur H, Sohn SK, Cho CH, Kim H. Robotic versus laparoscopic low anterior resection of rectal cancer: short-term outcome of a prospective comparative study. *Ann Surg Oncol* 2009; **16**: 1480-1487 [PMID: 19290486 DOI: 10.1245/s10434-009-0435-3]

67 **Kim MJ**, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, Sohn DK, Oh JH. Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer: A Phase II Open Label Prospective Randomized Controlled Trial. *Ann Surg* 2018; **267**: 243-251 [PMID: 28549014 DOI: 10.1097/SLA.0000000000002321]

68 **Kang J**, Yoon KJ, Min BS, Hur H, Baik SH, Kim NK, Lee KY. The impact of robotic surgery for mid and low rectal cancer: a case-matched analysis of a 3-arm comparison--open, laparoscopic, and robotic surgery. *Ann Surg* 2013; **257**: 95-101 [PMID: 23059496 DOI: 10.1097/SLA.0b013e3182686bbd]

69 **Ye SP**, Zhu WQ, Liu DN, Lei X, Jiang QG, Hu HM, Tang B, He PH, Gao GM, Tang HC, Shi J, Li TY. Robotic- *vs* laparoscopic-assisted proctectomy for locally advanced rectal cancer based on propensity score matching: Short-term outcomes at a colorectal center in China. *World J Gastrointest Oncol* 2020; **12**: 424-434 [PMID: 32368320 DOI: 10.4251/wjgo.v12.i4.424]

70 **Park SY**, Choi GS, Park JS, Kim HJ, Ryuk JP. Short-term clinical outcome of robot-assisted intersphincteric resection for low rectal cancer: a retrospective comparison with conventional laparoscopy. *Surg Endosc* 2013; **27**: 48-55 [PMID: 22752275 DOI: 10.1007/s00464-012-2405-2]

71 **Crippa J**, Grass F, Dozois EJ, Mathis KL, Merchea A, Colibaseanu DT, Kelley SR, Larson DW. Robotic Surgery for Rectal Cancer Provides Advantageous Outcomes Over Laparoscopic Approach: Results From a Large Retrospective Cohort. *Ann Surg* 2020 [PMID: 32068552 DOI: 10.1097/SLA.0000000000003805]

72 **Palanivelu C**, Rangarajan M, Jategaonkar PA, Anand NV. An innovative technique for colorectal specimen retrieval: a new era of "natural orifice specimen extraction" (N.O.S.E). *Dis Colon Rectum* 2008; **51**: 1120-1124 [PMID: 18481149 DOI: 10.1007/s10350-008-9316-2]

73 **Jeong SH**, Lee YJ, Choi WJ, Paik WY, Jeong CY, Park ST, Choi SK, Hong SC, Jung EJ, Joo YT, Ha WS. Trans-vaginal specimen extraction following totally laparoscopic subtotal gastrectomy in early gastric cancer. *Gastric Cancer* 2011; **14**: 91-96 [PMID: 21264485 DOI: 10.1007/s10120-011-0006-8]

74 **Zeng WG**, Zhou ZX. Mini-invasive surgery for colorectal cancer. *Chin J Cancer* 2014; **33**: 277-284 [PMID: 24589210 DOI: 10.5732/cjc.013.10182]

75 **Zhuang CL**, Zhang FM, Wang Z, Jiang X, Wang F, Liu ZC. Precision functional sphincter-preserving surgery (PPS) for ultralow rectal cancer: a natural orifice specimen extraction (NOSE) surgery technique. *Surg Endosc* 2021; **35**: 476-485 [PMID: 32989539 DOI: 10.1007/s00464-020-07989-4]

76 **He J**, Hu JF, Shao SX, Yao HB, Zhang XF, Yang GG, Shen Z. The Comparison of Laparoscopic Colorectal Resection with Natural Orifice Specimen Extraction versus Mini-Laparotomy Specimen Extraction for Colorectal Tumours: A Systematic Review and Meta-Analysis of Short-Term Outcomes. *J Oncol* 2020; **2020**: 6204264 [PMID: 32454825 DOI: 10.1155/2020/6204264]

77 **Zhou S**, Wang X, Zhao C, Zhou H, Pei W, Liang J, Zhou Z. Can transanal natural orifice specimen extraction after laparoscopic anterior resection for colorectal cancer reduce the inflammatory response? *J Gastroenterol Hepatol* 2020; **35**: 1016-1022 [PMID: 31692119 DOI: 10.1111/jgh.14919]

78 **Chang SC**, Chen HC, Chen YC, Ke TW, Tsai YY, Wang HM, Fingerhut A, Chen WT. Long-term Oncologic Outcomes of Laparoscopic Anterior Resections for Cancer with Natural Orifice Versus

Conventional Specimen Extraction: A Case-Control Study. *Dis Colon Rectum* 2020; **63**: 1071-1079 [PMID: 32692072 DOI: 10.1097/DCR.0000000000001622]

79 **Costantino FA**, Diana M, Wall J, Leroy J, Mutter D, Marescaux J. Prospective evaluation of peritoneal fluid contamination following transabdominal vs. transanal specimen extraction in laparoscopic left-sided colorectal resections. *Surg Endosc* 2012; **26**: 1495-1500 [PMID: 22179455 DOI: 10.1007/s00464-011-2066-6]

80 **Zhou S**, Wang X, Zhao C, Pei W, Zhou H, Liu Q, Liang J, Zhou Z. Comparison of short-term and survival outcomes for transanal natural orifice specimen extraction with conventional mini-laparotomy after laparoscopic anterior resection for colorectal cancer. *Cancer Manag Res* 2019; **11**: 5939-5948 [PMID: 31303795 DOI: 10.2147/CMAR.S209194]

81 **Park JS**, Choi GS, Kim HJ, Park SY, Jun SH. Natural orifice specimen extraction versus conventional laparoscopically assisted right hemicolectomy. *Br J Surg* 2011; **98**: 710-715 [PMID: 21305535 DOI: 10.1002/bjs.7419]

82 **Guan X**, Liu Z, Longo A, Cai JC, Tzu-Liang Chen W, Chen LC, Chun HK, Manuel da Costa Pereira J, Efetov S, Escalante R, He QS, Hu JH, Kayaalp C, Kim SH, Khan JS, Kuo LJ, Nishimura A, Nogueira F, Okuda J, Saklani A, Shafik AA, Shen MY, Son JT, Song JM, Sun DH, Uehara K, Wang GY, Wei Y, Xiong ZG, Yao HL, Yu G, Yu SJ, Zhou HT, Lee SH, Tsarkov PV, Fu CG, Wang XS; International Alliance of NOSES. International consensus on natural orifice specimen extraction surgery (NOSES) for colorectal cancer. *Gastroenterol Rep (Oxf)* 2019; **7**: 24-31 [PMID: 30792863 DOI: 10.1093/gastro/goy055]

83 **Izquierdo KM**, Unal E, Marks JH. Natural orifice specimen extraction in colorectal surgery: patient selection and perspectives. *Clin Exp Gastroenterol* 2018; **11**: 265-279 [PMID: 30087574 DOI: 10.2147/CEG.S135331]

84 **Chen K**, Pan Y, Cai JQ, Xu XW, Wu D, Yan JF, Chen RG, He Y, Mou YP. Intracorporeal esophagojejunostomy after totally laparoscopic total gastrectomy: A single-center 7-year experience. *World J Gastroenterol* 2016; **22**: 3432-3440 [PMID: 27022225 DOI: 10.3748/wjg.v22.i12.3432]

85 **Xu X**, Huang C, Mou Y, Zhang R, Pan Y, Chen K, Lu C. Intra-corporeal hand-sewn esophagojejunostomy is a safe and feasible procedure for totally laparoscopic total gastrectomy: short-term outcomes in 100 consecutive patients. *Surg Endosc* 2018; **32**: 2689-2695 [PMID: 29101569 DOI: 10.1007/s00464-017-5964-4]

86 **Ko CS**, Gong CS, Kim BS, Kim SO, Kim HS. Overlap method versus functional method for esophagojejunal reconstruction using totally laparoscopic total gastrectomy. *Surg Endosc* 2021; **35**: 130-138 [PMID: 31938929 DOI: 10.1007/s00464-020-07370-5]

87 **Kumagai K**, Hiki N, Nunobe S, Sekikawa S, Chiba T, Kiyokawa T, Jiang X, Tanimura S, Sano T, Yamaguchi T. Totally laparoscopic pylorus-preserving gastrectomy for early gastric cancer in the middle stomach: technical report and surgical outcomes. *Gastric Cancer* 2015; **18**: 183-187 [PMID: 24481853 DOI: 10.1007/s10120-014-0337-3]

88 **Sun Z**, Zheng X, Chen G, Wang L, Sang Q, Xu G, Zhang N, Aminbuhe. Technical details of and prognosis for the "China stitch", a novel technique for totally laparoscopic hand-sewn esophagojejunostomy. *Biosci Trends* 2020; **14**: 56-63 [PMID: 32092746 DOI: 10.5582/bst.2019.01329]

89 **Umemura A**, Koeda K, Sasaki A, Fujiwara H, Kimura Y, Iwaya T, Akiyama Y, Wakabayashi G. Totally laparoscopic total gastrectomy for gastric cancer: literature review and comparison of the procedure of esophagojejunostomy. *Asian J Surg* 2015; **38**: 102-112 [PMID: 25458736 DOI: 10.1016/j.asjsur.2014.09.006]

90 **Matsuda T**, Iwasaki T, Mitsutsuji M, Hirata K, Tsugawa D, Sugita Y, Shimada E, Kakeji Y. A Simple and Reliable Method for Intracorporeal Circular-Stapled Esophagojejunostomy Using a Hand-Sewn Over-and-Over Suture Technique in Laparoscopic Total Gastrectomy. *Ann Surg Oncol* 2015; **22** Suppl 3: S355 [PMID: 25948158 DOI: 10.1245/s10434-015-4541-0]

91 **Sharma NL**, Shah NC, Neal DE. Robotic-assisted laparoscopic prostatectomy. *Br J Cancer* 2009; **101**: 1491-1496 [PMID: 19861995 DOI: 10.1038/sj.bjc.6605341]

92 **Gao C**, Yang M, Wu Y, Wang G, Xiao C, Liu H, Lu C. Hybrid coronary revascularization by endoscopic robotic coronary artery bypass grafting on beating heart and stent placement. *Ann Thorac Surg* 2009; **87**: 737-741 [PMID: 19231382 DOI: 10.1016/j.athoracsur.2008.12.017]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 953-966

DOI: 10.4240/wjgs.v13.i9.953

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma

Yang Zhao, Yu Liu, Lin Zhou, Guo-Sheng Du, Qiang He

**ORCID number:** Yang Zhao 0000-0003-4901-2216; Yu Liu 0000-0002-5347-6980; Lin Zhou 0000-0001-8055-4203; Guo-Sheng Du 0000-0002-0732-031X; Qiang He 0000-0002-8900-1688.

**Author contributions:** Zhao Y performed the review of the literature and wrote the original draft; Liu Y, Zhou L, He Q, and Du GS reviewed and edited the manuscript; all authors read, revised, and approved the final manuscript.

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.



**Manuscript source:** Invited manuscript

**Yang Zhao, Yu Liu, Lin Zhou, Qiang He,** Department of Hepatobiliary and Pancreaticosplenic Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

**Guo-Sheng Du,** Department of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital, Beijing 100853, China

**Corresponding author:** Guo-Sheng Du, MD, Professor, Department of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. duguosheng309@126.com

## Abstract

The proportion of liver transplantation (LT) for hepatocellular carcinoma (HCC) has kept on increasing over the past years and account for 20%-40% of all LT. Post-transplant HCC recurrence is considered the most important factor affecting the long-term survival of patients. The use of different types of immunosuppressive agents after LT is closely associated with an increased risk for HCC recurrence. The most commonly used conventional immunosuppressive drugs include the calcineurin inhibitors tacrolimus (FK506) and mammalian target of rapamycin inhibitor rapamycin (RAPA). Compared with tacrolimus, RAPA may carry an advantage in survival benefit because of its anti-tumor effects. However, no sufficient evidence to date has proven that RAPA could increase long-term recurrence-free survival and its anti-tumor mechanism of combined therapy remains incompletely clear. In this review, we will focus on recent advances in clinical application experience and basic research results of RAPA in patients undergoing LT for HCC to further guide the clinical practice.

**Key Words:** Rapamycin; Hepatocellular carcinoma; Liver transplantation; Lenvatinib; Programmed death protein-1; Huaier granule



**Core Tip:** Although liver transplantation (LT) is the radical method for patients with hepatocellular carcinoma (HCC), especially advanced HCC, by improving the survival benefits, the postoperative tumor recurrence seriously affects the survival of the graft and patients. The rapamycin (RAPA)-based immunosuppressive regimen has been

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 21, 2021
**Peer-review started:** February 21, 2021
**First decision:** May 8, 2021
**Revised:** May 17, 2021
**Accepted:** July 26, 2021
**Article in press:** July 26, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Di Pasqua LG, Tevethia HV
**S-Editor:** Fan JR
**L-Editor:** Wang TQ
**P-Editor:** Guo X

recommended as a priority after LT due to its favorable survival benefits. In this paper, we describe the immune regulation and anti-tumor mechanism of RAPA, summarize the progress of RAPA transformation therapy after LT for HCC, further analyze the survival benefits of combined anticancer drugs and targeted drugs, and comb the prospect of immune checkpoint therapy such as programmed cell death protein 1, in order to provide a theoretical basis for RAPA transformation therapy after LT for HCC.

**Citation:** Zhao Y, Liu Y, Zhou L, Du GS, He Q. Trends of rapamycin in survival benefits of liver transplantation for hepatocellular carcinoma. *World J Gastrointest Surg* 2021; 13(9): 953-966
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/953.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.953

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer with a continuous increase in incidence over the past decades, and it is the third most common cause of cancer-related death worldwide and the second most prevalent cause of cancer-related death in men[1,2]. HCC has an insidious onset and rapid progression, and most patients with HCC have lost the chance of surgical resection at the time of diagnosis due to the accompanied severe liver cirrhosis and intrahepatic and extrahepatic metastasis. Liver transplantation (LT) is regarded as the most effective treatment for end-stage HCC that can completely remove the tumor and the "soil" of potentially inducing HCC such as liver cirrhosis and hepatitis B in comparison with liver resection and other treatment approaches[3]. According to data from multiple transplant centers worldwide[4], HCC is currently the main indication for LT and accounts for 20%-40% of all the LT cases, and this proportion continues to increase. Although the short-term prognosis of patients with HCC after LT is significantly improved, with a 5-year survival rate of more than 50%[5], the problem of HCC recurrence remains a serious challenge and it is associated with a dismal prognosis. Scientific selection of recipients in strict accordance with the standard of LT for HCC is an effective way to reduce the risk of HCC recurrence. Despite that physicians strictly adhere to Milan criteria and select recipients accurately, the 5-year recurrence rate of HCC after LT remains about 30%[6-8]. As known, there are several risk factors for post-LT recurrence. In addition to the primary tumor, calcineurin inhibitors (CNIs), a groups of routine immunosuppressive drugs, have been proved to be an independent risk factor for the recurrence of HCC[9]. The overuse of CNIs early after LT may block the recipient's immune system from detecting and killing residual HCC cells in the blood[10]. Therefore, it is a key issue to find an ideal treatment strategy that can inhibit rejection while minimizing the risk of HCC recurrence to improve the long-term survival of patients with HCC after LT.

To minimize the risk of post-LT recurrence caused by immunosuppressive drugs, mammalian target of rapamycin (mTOR) inhibitors have gradually attracted the attention of experts in the field of LT. mTOR inhibitor is a commonly used immunosuppressive drug with anti-tumor effects, which brings new choices to HCC transplant recipients and becomes a potential treatment strategy to solve the above issue[11]. Rapamycin (RAPA) is a first-generation mTOR inhibitor, which can not only prevent rejection, but also effectively inhibit the growth of tumor cells, and has less impact on renal function than CNIs. RAPA is presently employed as an immunosuppressant in recipients with abnormal renal function, intolerable adverse reactions of CNIs, and the high risk of post-LT recurrence, and it can provide sufficient immunosuppression while reducing the risk of recurrence, renal impairment, and infection [12]. Since 2011, our team has taken the lead in the application of RAPA conversion therapy in HCC transplant patients in China and recommended RAPA as the main immunosuppressive treatment strategy[13]. In recent years, the proportion of immunosuppressive regimens based on RAPA in HCC transplant patients has kept on increasing, but in the clinical treatment of such patients, there are still many controversies about the impact of RAPA on the survival benefits. In this review, we will focus on recent clinical and basic research on the application of RAPA in HCC

transplant patients, with the aim of summarizing existing evidence and areas for potential future study to guide the clinical application of RAPA more rationally and scientifically.

## MECHANISM AND APPLICATION OF RAPA

### *Development and application trends of RAPA*

RAPA is also known as sirolimus. In 1964, Canadian Wyeth Ayrest Research Institute identified an antifungal metabolite produced by Streptomyces hygroscopic AYB-944 from plant and soil samples from Rapa Nui (Easter Island) in the Pacific Ocean and named it rapamycin after Rapa Nui[14]. RAPA was initially widely used as a low-toxic and powerful antifungal agent in anti-inflammatory therapy. With the in-depth study of the pharmacological properties and molecular mechanism of RAPA, it was found that RAPA is a triene macrolide immunosuppressive drug that can exert an immunosuppressive effect by inhibiting cellular immune response[15]. In 1989, Meiser *et al*[16] began to try to use RAPA as a new immunosuppressant for the treatment of rejection after organ transplantation and now RAPA has been widely used in clinical treatment. In recent years, it has been found that RAPA has anti-tumor effects, which open up a new direction for the prevention of tumor recurrence and metastasis after organ transplantation.

RAPA exerts its immunomodulatory effect mainly by inhibiting the mTOR signal pathway, and mTOR is the target of RAPA in mammals. The essence of mTOR is a serine/threonine protease that belongs to the phosphoinositide 3-kinase (PI3K) related kinase family. It plays an important role in immune homeostasis by integrating different response signals of the microenvironment in the body. The main function of mTOR is to regulate multiple key pathways associated with cell cycle development and progression, including cell growth, proliferation, and metabolism[17]. At present, it is known that mTOR mainly exists in two structurally and functionally distinct protein complexes, mTOR complex 1 (mTORC1) and mTORC2[18]. mTORC1 is sensitive to RAPA and the activation of the mTORC1 pathway promotes a variety of pathways related to cell metabolism, such as glucose metabolism, protein synthesis, and lipid synthesis, and then regulates cell metabolic growth and proliferation activation[19]. mTORC2 is comparatively insensitive to RAPA compared with mTORC1, and it needs long-term exposure to the drug[20]. Currently, it is generally believed that most of the effects of RAPA *in vivo* are mediated by mTORC1, and P70 ribosomal protein S6 kinase (p70S6K)/protein S6 (RPS6) and eukaryotic translation initiation factor 4e binding protein 1 (4EBP1)/eukaryotic translation initiation factor 4e (eIF4E) are the main downstream targets of mTORC1 (Figure 1). RAPA can specifically block p70S6K/RPS6, but does not affect the response of 4EBP1/eIF4E[21].

### *Immunosuppressive mechanism of RAPA*

The first-generation CNIs, such as cyclosporine and tacrolimus (FK506), inhibit T cell proliferation induced by calcium-dependent signal transduction pathways, while RAPA can disrupt T cell proliferation induced by both calcium-dependent and calcium-independent signal transduction pathways[22]. The chemical structure of RAPA is similar to that of FK506, and it mainly binds to the cytoplasmic receptor FK506-binding protein-12 (FKBP-12), but the further mechanism of action of RAPA is completely different from that of FK506[23]. FK506 inhibits the interleukin-2 (IL-2) production by blocking calcineurin which is responsible for the transcriptional activation of the *IL-2* gene, which in turn, results in disrupting the IL-2-mediated calcium-dependent T cell transcription and activation signal pathway and eventually blocks T cell cycle progression from $G_0$ to $G_1$ phase[23]. Different from FK506, RAPA first binds with FKBP-12 to form an FKBP12-RAPA complex (Figure 1), which specifically acts on mTOR to phosphorylate the downstream target proteins of the mTOR. Then, it inhibits the post-IL-2 receptor signal transduction and interferes with the protein and DNA synthesis of T lymphocytes induced by IL-2. As a result, it blocks the transition from $G_1$ to S phases in the T cell proliferation cycle, thereby playing its immunosuppressive role[24]. In addition to inhibiting the proliferation of T lymphocytes, RAPA can also induce receptor immune tolerance and reduce rejection by inhibiting the maturation of dendritic cells and promoting the proliferation of regulatory T cells[25,26].

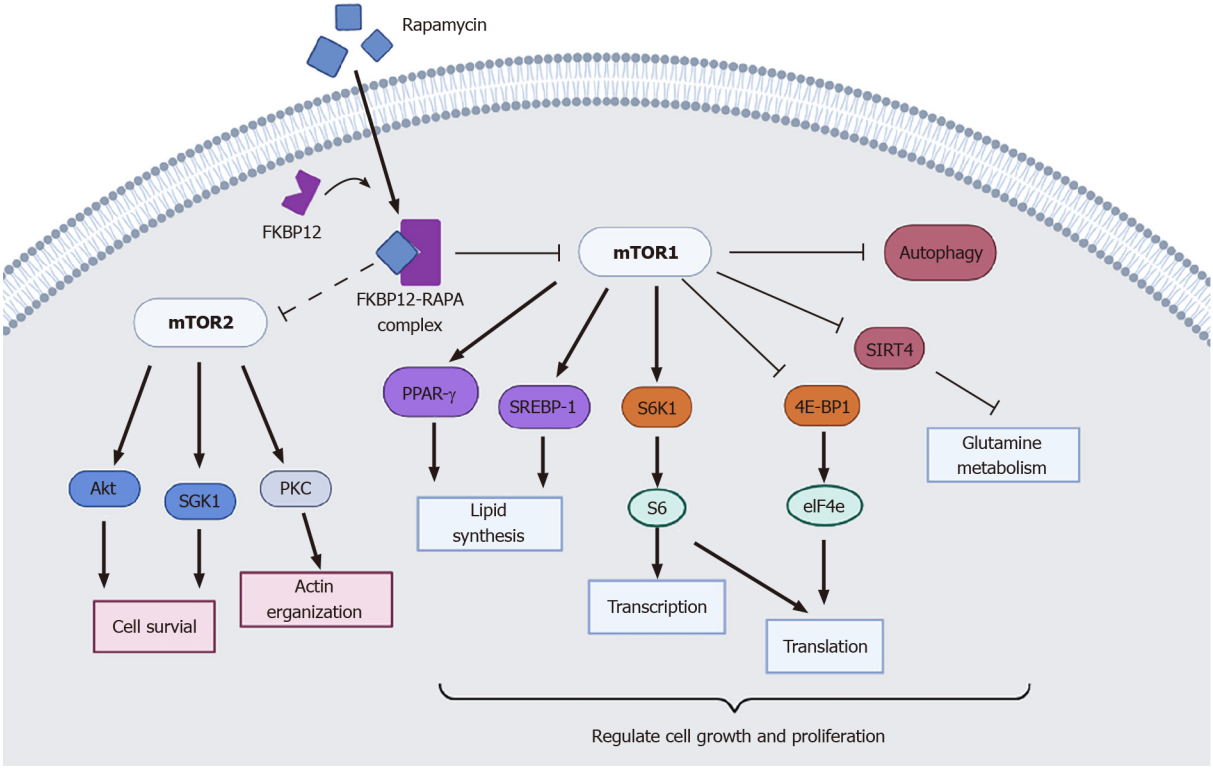


**Figure 1 Regulatory mechanism of rapamycin on mammalian target of rapamycin signaling.** Rapamycin (RAPA) inhibits mammalian target of rapamycin (mTOR) by binding to its intracellular receptor FK506-binding protein-12. mTOR exists in two functionally distinct complexes, termed mTORC1 and mTORC2. RAPA acutely inhibits mTORC1, while the mTORC2 is affected by chronic exposure. Activated mTORC1 promotes cell growth and proliferation by regulation of lipid synthesis and glutamine metabolism and inhibition of autophagy, and it also could promote mRNA translation by stimulating 4e binding protein 1 (4E-BP1) and inhibiting 4E-BP1. mTORC2 regulates actin cytoskeletal dynamics and cell survival through the above pathways. RAPA: Rapamycin; mTOR: Mammalian target of rapamycin; FKBP12: FK506-binding protein-12; S6K1: S6 kinase 1; 4E-BP1: 4e binding protein 1; PKC: Protein kinase C; PPAR: Peroxisome proliferator-activated receptors.

### *Anti-tumor mechanism of RAPA*

The anti-tumor effect of RAPA is mainly reflected in the following aspects: (1) Interfering with tumor cell proliferation and growth cycle. The mTOR signal pathway is associated with multiple key pathways of tumor development and progression. The activation of the PI3K/AKT/mTOR signal pathway can inhibit apoptosis activated by multiple factors, thereby promoting tumor cell proliferation[21]. The PI3K/AKT/mTOR signal pathway is also one of the most common activation pathways in HCC, and studies have found that mTORC1 and mTORC2 pathways are up-regulated in 40%-50% of HCC patients[27]. RAPA makes mTOR inactivate and blocks mTOR-related signal transduction to make the cell cycle arrest in the G1 phase, thereby inhibiting the proliferation of tumor cells and exerting anti-tumor effects[23]; (2) inhibiting tumor angiogenesis. RAPA can indirectly exert its anti-tumor effect by inhibiting angiogenesis[28]. New angiogenesis is an indispensable condition for tumor cell growth. Vascular endothelial growth factor (VEGF) is the central regulator of angiogenesis, and RAPA prevents new tumor angiogenesis by interfering with VEGF. This mainly inhibits tumor growth indirectly by reducing tumor blood supply; and (3) RAPA can also induce tumor cell death through apoptosis[29,30].

### *Protective mechanism of RAPA on ischemia-reperfusion injury*

Ischemia-reperfusion (IR) injury is an inevitable pathophysiological process in the process of LT, and it may lead to a slow recovery of transplanted liver function and increase the incidence of postoperative complications, even death in some cases[31]. The intracellular signal pathway that leads to IR injury is caused by the increase of reactive oxygen species (ROS). Treatment with RAPA in patients after LT can reduce the production of ROS in the liver and increase the ability of hepatocytes to scavenge ROS by inducing the high expression of heme oxygenase-1 (HO-1) and peroxiredoxin-1 in hepatocytes, thereby reducing IR injury[32,33]. In addition, maintaining an appropriate level of HO-1 in the transplanted liver may reduce the deterioration of liver function after LT[31]. Especially for HCC patients undergoing LT, the increase of

ROS promotes the survival and proliferation of HCC cells but is detrimental to normal hepatocytes[34,35]. Moreover, there is some evidence to indicate that potential IR injury and longer times of ischemia are positively correlated with post-LT tumor recurrence[32].

### *Other functional mechanisms of RAPA*

RAPA is metabolized by CYP3A4 isozymes in the intestinal wall and liver, mainly excreted by feces, and a small amount (2.2%) is excreted through urine. Therefore, patients with renal function injury caused by CNIs can be improved through the use of RAPA[12]. RAPA can also inhibit the proliferation of vascular smooth muscle cells and deactivate immune cells in vascular lesions, which has a certain degree of cardioprotective effect[36]. In addition, it was also found that RAPA has the function of neuroprotection and promotion of nerve regeneration, which provides a promising treatment strategy for diseases caused by misfolding and aggregation of proteins, such as Parkinson's disease[37].

## TRENDS OF RAPA IN SURVIVAL BENEFITS OF TRANSPLANT FOR HCC

### *Immunosuppressant and tumor relapse post-LT*

Immunosuppressive agents are necessary to inhibit graft rejection after organ transplantation. However, immunosuppression plays an important role in the development and progression of tumors. Immunosuppressive therapy after LT makes the patient in a state of immunodeficiency chronically, which weakens the immune surveillance and defense of HCC or other tumors, and increases susceptibility to infection. Ultimately, it may increase the risk of HCC recurrence and metastasis after LT. CNI is a commonly used immunosuppressive agent after transplantation. However, many research data indicated that CNI-based regimens may increase the probability of tumor recurrence and metastasis, and it also has a direct carcinogenic activity that induces the growth and progression of tumors[38,39]. The traditional treatment view holds that there is no other immunosuppressive strategy that can effectively reduce the risk of tumor recurrence except for minimizing the dose of CNI after transplantation[9]. Therefore, it is an urgent problem to be solved whether other strategies can be used to replace or reduce the dose of CNI to minimize the risk of tumor recurrence and improve the prognosis of patients.

### *Application of RAPA transformation after transplantation*

RAPA can also have anti-tumor effects by inhibiting tumor cell proliferation and angiogenesis while exerting immunosuppressive effects. RAPA conversion can effectively reduce the risk of post-LT HCC recurrence and prolong the tumor-free survival time of patients during different studies[40,41]. Subsequently, meta-analysis affirmed to varying degrees the survival benefit of RAPA in HCC patients after LT, but these studies have their limitations because of single-center experience[11,42,43]. While RAPA is considered a potential ideal immunosuppressive agent, the therapeutic effect of RAPA in clinical application is still controversial. Although RAPA treatment decreased the recurrence rate and tumor-specific mortality rate (with no statistical difference), it did not bring significant benefits to overall survival[44]. Data from the Scientific Registry of Transplant Recipients, the United States national transplant registry, showed a significant 5-year survival benefit for HCC transplant patients receiving RAPA[40]. To address controversy over whether survival benefits are associated with RAPA action targets and tissue expression levels, some researchers have done such research on HCC patients with LT.

RAPA may have significant benefits in HCC patients with over-activated mTOR pathway[44]. This view has been further confirmed in other studies. Guerrera[45] found that the overexpression of the mTOR pathway in tumor tissues was associated with an increase in post-LT recurrence, and suggested that mTOR inhibitors such as RAPA should be used in patients with histopathologically up-regulated mTOR pathway in tumors, rather than as a unified drug for all HCC transplant patients. Based on this theory, we use animal models to find that RAPA can down-regulate $Foxp3^{+}$Treg mediated tumor immune escape through the mTOR pathway. High expression of mTOR and Treg was associated with a low rat survival time[46].

### *Clinical study of RAPA conversion therapy*

A multicenter prospective randomized controlled phase 3 clinical trial (Table 1), the

**Table 1 Clinical trials with reported results for rapamycin in post-liver transplantation hepatocellular carcinoma**

| Ref. | Patients (N) | Treatment | 1-yr OS (%) | 3-yr OS (%) | 5-yr OS (%) | HCC recurrence HR (95%CI) |
|---|---|---|---|---|---|---|
| Grigg *et al*[11], 2019 | 968 | RAPA *vs* CNI | NA | NA | 67.6 *vs* 59.7 | NA |
| Zhou *et al*[13], 2018 | 36 | RAPA *vs* RAPA free | 100 *vs* 77.8 | 94.5 *vs* 0 | 77.8 *vs* 0 | NA |
| Toso *et al*[40], 2010 | 2491 | RAPA *vs* RAPA free | NA | 85.6 *vs* 79.2 | 83.1 *vs* 68.7 | NA |
| Ling *et al*[41], 2020 | 204 | RAPA *vs* RAPA free | 97.4 *vs* 82.0 | 85.5 *vs* 71.9 | NA | NA |
| Menon *et al*[42], 2013 | 474 | RAPA *vs* CNI | 94-95 *vs* 79-83 | 85 *vs* 66 | 80 *vs* 59-62 | NA |
| Liang *et al*[43], 2012 | 2815 | RAPA *vs* RAPA free | NA | NA | 81.5 *vs* 68.1 | NA |
| Yanik *et al*[44], 2016 | 3936 | RAPA *vs* RAPA free | NA | NA | 75.0 *vs* 75.0 | 0.86 *vs* 0.83 |
| Geissler *et al*[47], 2016 | 525 | RAPA *vs* RAPA free | 96.0 *vs* 91.4 | 86.1 *vs* 78.5 | 79.4 *vs* 70.3 | NA |
| Schnitzbauer *et al*[48], 2020 | 508 | RAPA > 3 mo *vs* RAPA ≤ 3 mo | 100 *vs* 89.9 | 87.7 *vs* 76.3 | 80.1 *vs* 67.0 | NA |
| Xu *et al*[49], 2016 | 142 | RAPA *vs* RAPA free | 81.1 *vs* 85.3 | 60.3 *vs* 71.2 | 40.7 *vs* 43.5 | NA |
| Na *et al*[61], 2016 | 39 | RAPA + SOR *vs* RAPA + SOR free | NA | NA | NA | NA |
| Yang *et al*[65], 2020 | 64 | RAPA *vs* TAC | 54.5 *vs* 29.0 | NA | NA | NA |

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; RAPA: Rapamycin; CNI: Calcineurin inhibitor; NA: Not applicable; SOR: Sorafenib; TAC: Tacrolimus; LT: Liver transplantation.

Siliver trial[47], showed that RAPA improved the recurrence-free survival and overall survival rates in the first 3 to 5 years in LT recipients with HCC, especially for low-risk patients defined according to the Milan criteria, but for patients with advanced HCC or a long-term survival of more than 5 years, RAPA does not significantly improve recurrence-free survival and mortality compared with traditional CNIs. This trial provides a high reference value for the clinical application of RAPA-based immunosuppressive regimens in LT patients with HCC. At the same time, it also puts forward an important problem that needs to be solved, namely, how to improve long-term HCC recurrence-free and overall survival outcomes after 5 years in HCC patients undergoing LT. Whether to combine other treatments, such as targeted therapy, to improve patient survival benefits is an issue that needs to be considered. Subsequently, Schnitzbauer *et al*[48] conducted an exploratory multivariate analysis of the data in the Siliver trial and proposed that RAPA treatment for more than 3 mo was an independent factor for overall survival, and compared with less than 3 mo of RAPA treatment, the risk of death was decreased by 30%. When another variable (AFP index) was jointly evaluated, the risk of death decreased by 41% in patients with AFP ≥ 10 ng/mL and RAPA treatment for more than 3 mo. Besides, RAPA treatment can delay tumor recurrence, and patients have a longer survival time after recurrence[48]. Coincidentally, Xu *et al*[49] found that the recurrence-free survival rate of HCC transplant patients meeting the Milan criteria was not significantly different between the RAPA group and the control group, but under the intervention of RAPA, the overall survival time of the patients after recurrence was significantly longer than that of the control group. As one of the earliest transplant centers to use RAPA conversion therapy in China[13,50], we suggested that early conversion of RAPA after transplantation can improve the survival benefits of patients. The results of our previous study showed that RAPA-based therapy improved post-LT survival rates and decreased recurrence rates compared with the control group after LT. Moreover, our previous study also indicated that the therapeutic concentration of RAPA does not depend on drug dosage, but primarily on liver and renal function, rejection status, and anti-tumor effect. Furthermore, to avoid severe adverse reactions, we also suggested that serum RAPA levels should be maintained at ≤ 10 ng/mL[13].

Taken together, it is of clinical importance to clarify the conditions under which liver transplant patients with HCC are most likely to benefit from RAPA treatment. In particular, patients with the overexpression of the mTOR pathway in HCC can significantly benefit from the treatment of RAPA. However, overexpression of the mTOR pathway is not uniformly present in all HCC tumors, and there is no clear evidence for a benefit of RAPA use for non-mTOR pathway-dependent HCC. More-

over, a few studies have found that RAPA-based immunosuppressive regimens are associated with increased mortality[51]. Poor solubility is a disadvantage of RAPA in clinical application. Additionally, RAPA is unstable in physiological conditions, and it is not suitable for oral administration because of a large decrease in hydrolytic activity under the condition of physiological PH. Besides, like other effective immunosuppressive drugs, the use of RAPA can also cause many side effects, including dyslipidemia, dysglycemia, peripheral edema, anemia, leukopenia, delayed wound healing, *etc*.[52], and these side effects are relatively mild and easy to manage. The above adverse reacations could be alleviated or disappeared after a reduction in the instillation rate or drug withdrawal. Patients with dyslipidemia or dysglycemia can choose corresponding lipid-lowering or glucose-lowering drugs, combined with diet and appropriate exercise therapy[53,54]. For patients undergoing transplant for HCC, how to establish an appropriate balance between risks and benefits still needs further research. RAPA-related derivatives have a considerable prospect in improving the poor solubility and stability of RAPA. The RAPA-derivative everolimus is also used as one of the main treatment options for HCC after LT[11]. The immune activity and anti-tumor effect of everolimus *in vivo* are similar to those of RAPA. The aqueous solubility of everolimus is superior to that of RAPA, and its blood concentration is more stable. Compared with RAPA, everolimus has higher oral bioavailability and metabolic stability[55], and it also has a more significant protective effect on renal function[56]. However, everolimus is also associated with a high incidence of adverse effects. In particular, stomatitis is a common clinical symptom in everolimus users, with a incidence up to 42.6%[57]. Besides, dyslipidemia is also more common[58]. The development of the derivatives of RAPA may produce better results in clinical application, and more in-depth research on its mechanisms is still needed in the future.

## TRENDS OF COMBINED THERAPY OF RAPA AND ANTI-TUMOR DRUGS IN SURVIVAL BENEFITS OF TRANSPLANT FOR HCC

RAPA may be a promising immunosuppressive option in patients undergoing transplant for HCC, although there is no sufficient evidence for sustained benefit of this therapy. How to improve the efficacy of RAPA in the long-term prognosis should be the main research direction in the future. So far, multiple studies have shown that the use of RAPA alone may have a limited anti-tumor effect, and it is still not completely clear whether the combination of anti-tumor drugs and RAPA can achieve better synergistic anti-tumor effects, such as molecular targeted drugs, immune checkpoint inhibitors, and anticancer traditional Chinese medicine (TCM). Such combination therapy has been reported and analyzed, and the prerequisite for combined therapy is that the anti-tumor mechanisms of the two drugs are different or have a synergistic effect, which can increase the anti-tumor effect in different degrees.

### *Combination of RAPA and molecular targeted drugs*

Till now, molecular targeted drugs are one of the first-line choices for patients with advanced HCC, but there are still many problems in the application of these drugs, such as individual differences in drug sensitivity, drug resistance, and serious side effects caused by high doses of drugs. Therefore, how to improve the sensitivity of liver cancer cells to targeted drugs while reducing drug dose is an urgent problem to be solved in clinical practice. Sorafenib (SOR) has been the main targeting drug for patients with advanced HCC since it was approved in 2007, and it can not only directly inhibit tumor cell growth by inhibiting the RAF/MEK/ERK signal transduction pathway, but also indirectly exert its anti-tumor effect by inhibiting tumor angiogenesis. Previous studies have proposed that the anti-angiogenic effect of SOR in combination with RAPA is enhanced[59]. In the clinical retrospective study, Gomez-Martin *et al*[60] reported that the combination of SOR and RAPA could achieve a better anti-tumor effect in patients with post-LT recurrence but without the chance of secondary operation, and suggested that high-risk HCC transplant patients should choose RAPA-based immunosuppressive regimen combined with SOR to prevent HCC recurrence. For patients in the palliative treatment group (mainly including arterial chemoembolization, chemotherapy, or radiotherapy after post-LT recurrence), the survival rate of patients under the combined treatment of SOR and RAPA was significantly improved, but for patients in the radical treatment group (mainly including surgical resection or ablation after post-LT recurrence), the combined treatment did not show survival benefits[61]. It is also noteworthy that some patients in the above studies had varying degrees of toxic and side effects, such as diarrhea and

proteinuria. The superposition of toxicity and side effects may be the main obstacle to limiting the combined use of SOR and RAPA, and further studies are warranted to evaluate their advantages and disadvantages in the future.

In 2017, the American Clinical Oncology Annual Meeting (ASCO) released the REFLECT data of a phase 3 clinical trial of lenvatinib[62]. Then, lenvatinib was recommended as the first-line targeted therapy for unresectable HCC by the United States Food and Drug Administration, Japan, and the Chinese Society of Clinical Oncology, breaking the dominant position of SOR in first-line therapy. Lenvatinib is a multi-target tyrosine kinase inhibitor that can inhibit VEGF receptor and fibroblast growth factor receptor, which was known as the landmark development of targeting drugs in liver cancer[63,64]. The overall survival of patients with advanced HCC treated with lenvatinib was similar to that of patients treated with SOR, and the objective remission rate (40.6% *vs* 12.4%) and progression-free survival time (7.3 mo *vs* 3.6 mo) of patients in the lenvatinib group were significantly higher than those in the SOR group[60]. Especially for Asian HCC patients, the over survival of patients in the lenvatinib group was significantly longer than that in the SOR group, which suggests that Asian HCC patients be the dominant group of patients suitable for lenvatinib treatment[62]. Yang *et al*[65] found that the post-LT recurrence patients in the SOR ineffective or tolerant group had significantly improved overall survival after switching to lenvatinib. Six of these patients received combined therapy of lenvatinib and RAPA after reoperation, and the overall survival was 80% at 2 years, which was significantly longer than that in the control group. Although the sample size of this group is small with a limited reference value, we suggest that the combined therapy of lenvatinib and RAPA may not only be a potentially beneficial choice, but also can serve as a bridge approach before LT for some advanced patients, which needs further research in the future. Our recent data showed that the application of lenvatinib in patients beyond UCSF or Hangzhou criterion can enhance the rate of LT by inhibiting tumor progression or eliminating satellite lesions (unpublished data) (Table 1).

### *Combination of RAPA and programmed death protein-1 inhibitors*

Programmed death protein-1 (PD-1) is an important negative regulatory molecule of T cells, B cells, and other immune cells, and the binding of PD-1 to programmed death ligand-1 (PD-L1) on T cell surface can inhibit T cell activation and reduce tumor-killing effect[66,67]. PD-1 is also expressed on the surface of B cells and natural killer cells, and their function will be limited after binding to PD-L1[68,69]. Therefore, blocking the PD-1/PD-L1 pathway can enhance the anti-tumor effect of immune cells and promote tumor destruction. The immune checkpoint inhibitors of the PD-1/PD-L1 pathway are a research hotspot in HCC therapy in recent years, and the high expression of PD-1/PD-L1 on HCC cells promotes the growth of tumors and is closely related to tumor invasiveness and prognosis of patients[70]. It has been proved that immune checkpoint inhibitors can provide a longer disease-free survival than other targeted therapies (such as SOR)[71,72]. However, considering the risk of rejection induced by using immune checkpoint inhibitors, its effectiveness and safety in HCC transplant patients need to be further verified. We have attempted to apply RAPA and anti PD-1 antibodies in patients with negative expression of PD-L1, and such patients obtained survival benefit with little rejection (unpublished data). This finding needs confirmation using long-term studies with a large sample size.

Although formal testing has not been conducted in HCC transplant patients, a small number of cases have reported that the use of immune checkpoint inhibitors does not cause rejection[73]. mTOR immunosuppressive agents combined with immune checkpoint inhibitors may be a potentially useful therapeutic strategy for patients with HCC after LT. The combination of the two drugs can improve the anti-tumor effects, block mTOR-related tumor growth pathways, and reduce the expression of PD-1 in different immune cells[70]. The synergistic anti-tumor mechanism of mTOR inhibitors and PD-1 blockers may lie in the complete inhibition of RPS6 and eIF4E, the downstream targets of mTORC1[70]. RPS6 and eIF4E play different roles in the development and progression of HCC with AKT/RAS activation, and the simultaneous inhibition of both can inhibit the growth of such HCC. RAPA only selectively inhibits RPS6, while PD-1 can physically bind with RPS6 and eIF4E and promote their phosphorylation. Therefore, RAPA combined with PD-1 inhibitor has a synergistic anti-tumor effect[21]. So far, there have been few reports about the clinical application of RAPA combined with a PD-1 inhibitor in HCC transplant patients, and the effectiveness and safety of the combination therapy need more data support. How to balance the changes of the anti-tumor and anti-rejection immune microenvironment needs more in-depth exploration.

### *Combination of RAPA and anti-tumor TCM*

TCM has been used to treat inflammation and cancer in China for more than 1600 years[74]. TCM has a long-lasting anti-tumor effect and low recurrence rate. Recently, it has been demonstrated that anti-tumor TCM is a promising way in the treatment of HCC. Huaier granule (PS-T) is a representative anti-tumor TCM, which has been recommended as an adjuvant drug of radiotherapy and chemotherapy by the Chinese Clinical Oncology Association. Clinically, it has a good anti-tumor effect on liver cancer, lung cancer, gastric cancer, and breast cancer[75,76]. PS-T is a multi-target drug that contains the active ingredient of proteoglycan, which can improve immune function and kill tumor cells[77]. PS-T can inhibit angiogenesis in HCC tissue by down-regulating VEGF levels[78]. It can also inhibit the tumorigenicity of cells through the mTOR signaling pathway and enhance the sensitivity of cells to RAPA [76]. Based on the above theoretical basis, the study of RAPA combined with PS-T in the treatment of LT for HCC has been carried out in many centers in China[50,79]. We believe that RAPA combined with PS-T adjuvant therapy after LT for HCC is expected to improve the quality of life and prolong the survival time of patients, and its specific mechanism needs to be further studied.

In our previous clinical study, we found that the combination of RAPA and PS-T significantly prolonged the postoperative survival time of HCC transplant patients beyond the UCSF standard, and proved the effectiveness and safety of this combination therapy[13,50]. Based on clinical research, we further found that RAPA-based therapy has an anti-tumor effect by reducing FoxP3$^+$Tregs and its inhibitory cytokines, and the application of PS-T enhances the anti-tumor effect of RAPA. This synergistic effect is mediated by the mTOR signal pathway[46]. To further verify the long-term efficacy and specific mechanism of the combination of RAPA and PS-T, it is necessary to perform multicenter, large sample randomized controlled trials.

### *Advice on RAPA application*

The unified recommended scheme for the prevention and treatment of HCC recurrence after LT has not been previously reported in the global transplantation field. Given the demonstration of the global multicenter results of RAPA and the first-line recommended use of lenvatinib as well as the comprehensive treatment strategy of early RAPA transformation combined with lenvatinib, minimizing hormone exposure and CIN dose should be adopted for HCC patients undergoing LT. RAPA can be efficient at establishing clinical immune tolerance and supporting long-time survival of the graft. Therefore, we believe that it is necessary to construct systematic and individualized prevention and treatment strategy based on RAPA, which is helpful to protect the function of grafts while preventing the recurrence of HCC. Meanwhile, the development of a comprehensive program to combat the recurrence of HCC after LT should integrate the progress of molecular targeting drugs and immunotherapy. First, for HCC patients who satisfy the Milan Criteria, we recommend the "dual regimen" of RAPA combined with lenvatinib, RAPA conversion therapy within 1 mo, no hormone during operation, and rapid decrease of the low-dose hormone after the operation. Second, for patients beyond Milan criteria and with the overexpression of the mTOR pathway and active HCC (AFP positive), we recommend the "triple regimen", that is, combination with thymalfasin based on "dual regimen". In the meantime, the regimen with no hormone during operation and rapid decrease of low dose hormone after the operation can be used. Third, for advanced HCC exceeding the UCSF standard, preoperative neoadjuvant therapy with lenvatinib can be considered to eliminate satellite lesions in the liver and residual cancer cells in the blood. The "dual regimen" combined with bevacizumab can be considered a systematic and comprehensive prevention and treatment strategy. Additionally, whether the PD-1/PD-L1 inhibitors can be used in preoperative neoadjuvant and postoperative combined treatment should be based on the expression of PD-1 in cancer tissues or PD-L1 in immune cells.

## CONCLUSION

With the increasing incidence of HCC, the selection criteria for LT recipients for HCC in many transplantation centers are gradually expanding, but the prevention and treatment strategies for post-LT recurrence are not perfect. The problem of tumor recurrence after transplantation is still an important clinical challenge. It has been more than 50 years since the advent of RAPA. From the initial antifungal agent, it has gradually become a multi-effect drug with both immunosuppressive and anti-tumor effects. A large number of studies have begun to focus on whether RAPA can bring

more survival benefits to HCC transplant patients. So far, most studies have shown that RAPA has a positive impact on the prognosis of HCC patients undergoing LT. Especially, HCC patients with overexpression of the PI3K/Akt/mTOR pathway can significantly benefit from RAPA-based immunosuppression regimen. However, there is still no consensus on the specific indications and therapeutic dose recommendations for the clinical application of RAPA. Although the research of RAPA has made gratifying achievements, whether this drug can achieve more ideal efficacy in clinical application still needs to be further explored. Given the variability of the occurrence and development of HCC and the activity of human cell signaling pathways, the application of RAPA to HCC transplant patients may be quite different. How to formulate scientific individualized drug use still requires the support of high-level evidence-based medical evidence, such as large-sample, multicenter randomized controlled trials.

The key role of the mTOR signal pathway in the development of HCC has well-proven and RAPA treatment after LT for HCC leads to higher survival rates in some groups of post-LT HCC patients. With the progress of technology and the continuous accumulation of understanding of RAPA, the research on RAPA will continue to deepen. The future research on RAPA will focus on the following aspects. First, RAPA-sensitive HCC transplant patients should be scientifically screened to maximize the clinical efficacy of RAPA. Second, chemical modification of the chemical structure of RAPA and screening of RAPA analogs are conducted to develop more functional and targeted mTOR inhibitors.

It is promising in HCC comprehensive treatment to improve and establish a treatment system to prevent tumor recurrence after LT by applying RAPA with lenvatinib treatment. In addition, the combination of RAPA and other anti-tumor drugs has a synergistic and sensitizing effect, especially for patients with advanced HCC. Future research should be directed to find and screen the patients who are suitable for the combination of immune checkpoint therapy and to improve their safety and effectiveness. Combination therapy may be an important research direction to break through the bottleneck of RAPA in LT patients with HCC. Only by carrying out targeted relevant research can we effectively promote the application of RAPA in LT for HCC.

## REFERENCES


1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7-30 [PMID: 29313949 DOI: 10.3322/caac.21442]

2 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

3 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]

4 **Sapisochin G**, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 203-217 [PMID: 28053342 DOI: 10.1038/nrgastro.2016.193]

5 **Ince V**, Ara C, Yilmaz S. Malatya and Other Criteria for Liver Transplantation in Hepatocellular Carcinoma. *J Gastrointest Cancer* 2020; **51**: 1118-1121 [PMID: 32860615 DOI: 10.1007/s12029-020-00484-y]

6 **Sapisochin G**, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, Cleary SP, Lilly L, Cattral MS, Marquez M, Selzner M, Renner E, Selzner N, McGilvray ID, Greig PD, Grant DR. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. *Hepatology* 2016; **64**: 2077-2088 [PMID: 27178646 DOI: 10.1002/hep.28643]

7 **Xu X**, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016; **65**: 1035-1041 [PMID: 25804634 DOI: 10.1136/gutjnl-2014-308513]

8 **Bhoori S**, Mazzaferro V. Current challenges in liver transplantation for hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2014; **28**: 867-879 [PMID: 25260314 DOI: 10.1016/j.bpg.2014.08.001]

9 **Rodríguez-Perálvarez M**, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J, Poyato-González A, Ferrín-Sánchez G, Montero-Álvarez JL, Patch D, Thorburn D, Briceño J, De la Mata M, Burroughs AK. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. *J Hepatol* 2013; **59**: 1193-1199 [PMID: 23867318 DOI: 10.1016/j.jhep.2013.07.012]

10 **Rodríguez-Perálvarez M**, De la Mata M, Burroughs AK. Liver transplantation: immunosuppression

and oncology. *Curr Opin Organ Transplant* 2014; **19**: 253-260 [PMID: 24685671 DOI: 10.1097/MOT.0000000000000069]

11 **Grigg SE**, Sarri GL, Gow PJ, Yeomans ND. Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2019; **49**: 1260-1273 [PMID: 30989721 DOI: 10.1111/apt.15253]

12 **Harper SJ**, Gelson W, Harper IG, Alexander GJ, Gibbs P. Switching to sirolimus-based immune suppression after liver transplantation is safe and effective: a single-center experience. *Transplantation* 2011; **91**: 128-132 [PMID: 21452417 DOI: 10.1097/tp.0b013e3181fe131b]

13 **Zhou L**, Pan LC, Zheng YG, Du GS, Fu XQ, Zhu ZD, Song JY, Liu ZJ, Su XZ, Chen W, Zheng DH, Suo LL, Yang SZ. Novel strategy of sirolimus plus thymalfasin and huaier granule on tumor recurrence of hepatocellular carcinoma beyond the UCSF criteria following liver transplantation: A single center experience. *Oncol Lett* 2018; **16**: 4407-4417 [PMID: 30214575 DOI: 10.3892/ol.2018.9226]

14 **Sehgal SN**, Baker H, Vézina C. Rapamycin (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. *J Antibiot (Tokyo)* 1975; **28**: 727-732 [PMID: 1102509 DOI: 10.7164/antibiotics.28.727]

15 **Martel RR**, Klicius J, Galet S. Inhibition of the immune response by rapamycin, a new antifungal antibiotic. *Can J Physiol Pharmacol* 1977; **55**: 48-51 [PMID: 843990 DOI: 10.1139/y77-007]

16 **Meiser BM**, Wang J, Morris RE. Rapamycin: A New and Highly Active Immunosuppressive Macrolide with an Efficacy Superior to Cyclosporine. Springer, 1989 [DOI: 10.1007/978-3-642-83755-5_159]

17 **Jung S**, Gámez-Díaz L, Proietti M, Grimbacher B. "Immune TOR-opathies," a Novel Disease Entity in Clinical Immunology. *Front Immunol* 2018; **9**: 966 [PMID: 29867948 DOI: 10.3389/fimmu.2018.00966]

18 **Linke M**, Fritsch SD, Sukhbaatar N, Hengstschläger M, Weichhart T. mTORC1 and mTORC2 as regulators of cell metabolism in immunity. *FEBS Lett* 2017; **591**: 3089-3103 [PMID: 28600802 DOI: 10.1002/1873-3468.12711]

19 **Lawrence J**, Nho R. The Role of the Mammalian Target of Rapamycin (mTOR) in Pulmonary Fibrosis. *Int J Mol Sci* 2018; **19** [PMID: 29518028 DOI: 10.3390/ijms19030778]

20 **Sarbassov DD**, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, Markhard AL, Sabatini DM. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Mol Cell* 2006; **22**: 159-168 [PMID: 16603397 DOI: 10.1016/j.molcel.2006.03.029]

21 **Wang C**, Cigliano A, Jiang L, Li X, Fan B, Pilo MG, Liu Y, Gui B, Sini M, Smith JW, Dombrowski F, Calvisi DF, Evert M, Chen X. 4EBP1/eIF4E and p70S6K/RPS6 axes play critical and distinct roles in hepatocarcinogenesis driven by AKT and N-Ras proto-oncogenes in mice. *Hepatology* 2015; **61**: 200-213 [PMID: 25145583 DOI: 10.1002/hep.27396]

22 **Salmond RJ**, Zamoyska R. How does the mammalian target of rapamycin (mTOR) influence CD8 T cell differentiation? *Cell Cycle* 2010; **9**: 2952-2957 [PMID: 20699663 DOI: 10.4161/cc.9.15.12358]

23 **Yoo YJ**, Kim H, Park SR, Yoon YJ. An overview of rapamycin: from discovery to future perspectives. *J Ind Microbiol Biotechnol* 2017; **44**: 537-553 [PMID: 27613310 DOI: 10.1007/s10295-016-1834-7]

24 **Augustine JJ**, Bodziak KA, Hricik DDE. Use of Sirolimus in Solid Organ Transplantation. *Drugs* 2007; **67**: 369-391 [PMID: 17335296 DOI: 10.2165/00003495-200767030-00004]

25 **Schildknecht A**, Brauer S, Brenner C, Lahl K, Schild H, Sparwasser T, Probst HC, van den Broek M. FoxP3+ regulatory T cells essentially contribute to peripheral CD8+ T-cell tolerance induced by steady-state dendritic cells. *Proc Natl Acad Sci U S A* 2010; **107**: 199-203 [PMID: 20018763 DOI: 10.1073/pnas.0910620107]

26 **Fu BM**, He XS, Yu S, Hu AB, Zhang J, Ma Y, Tam NL, Huang JF. A tolerogenic semimature dendritic cells induce effector T-cell hyporesponsiveness by activation of antigen-specific CD4+CD25+ T regulatory cells that promotes skin allograft survival in mice. *Cell Immunol* 2010; **261**: 69-76 [PMID: 20038461 DOI: 10.1016/j.cellimm.2009.11.003]

27 **Matter MS**, Decaens T, Andersen JB, Thorgeirsson SS. Targeting the mTOR pathway in hepatocellular carcinoma: current state and future trends. *J Hepatol* 2014; **60**: 855-865 [PMID: 24308993 DOI: 10.1016/j.jhep.2013.11.031]

28 **Villanueva A**, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, Roayaie S, Minguez B, Sole M, Battiston C, Van Laarhoven S, Fiel MI, Di Feo A, Hoshida Y, Yea S, Toffanin S, Ramos A, Martignetti JA, Mazzaferro V, Bruix J, Waxman S, Schwartz M, Meyerson M, Friedman SL, Llovet JM. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1972-1983, 1983.e1 [PMID: 18929564 DOI: 10.1053/j.gastro.2008.08.008]

29 **Kim SH**, Lee JE, Yang SH, Lee SW. Induction of cytokines and growth factors by rapamycin in the microenvironment of brain metastases of lung cancer. *Oncol Lett* 2013; **5**: 953-958 [PMID: 23426399 DOI: 10.3892/ol.2013.1135]

30 **Wu L**, Feng Z, Cui S, Hou K, Tang L, Zhou J, Cai G, Xie Y, Hong Q, Fu B, Chen X. Rapamycin upregulates autophagy by inhibiting the mTOR-ULK1 pathway, resulting in reduced podocyte injury. *PLoS One* 2013; **8**: e63799 [PMID: 23667674 DOI: 10.1371/journal.pone.0063799]

31 **Nakamura K**, Zhang M, Kageyama S, Ke B, Fujii T, Sosa RA, Reed EF, Datta N, Zarrinpar A, Busuttil RW, Araujo JA, Kupiec-Weglinski JW. Macrophage heme oxygenase-1-SIRT1-p53 axis regulates sterile inflammation in liver ischemia-reperfusion injury. *J Hepatol* 2017; **67**: 1232-1242 [PMID: 28842295 DOI: 10.1016/j.jhep.2017.08.010]

32 **Afroz F**, Kist A, Hua J, Zhou Y, Sokoya EM, Padbury R, Nieuwenhuijs V, Barritt G. Rapamycin induces the expression of heme oxygenase-1 and peroxyredoxin-1 in normal hepatocytes but not in tumorigenic liver cells. *Exp Mol Pathol* 2018; **105**: 334-344 [PMID: 30290159 DOI: 10.1016/j.yexmp.2018.09.006]

33 **Martínez-Cisuelo V**, Gómez J, García-Junceda I, Naudí A, Cabré R, Mota-Martorell N, López-Torres M, González-Sánchez M, Pamplona R, Barja G. Rapamycin reverses age-related increases in mitochondrial ROS production at complex I, oxidative stress, accumulation of mtDNA fragments inside nuclear DNA, and lipofuscin level, and increases autophagy, in the liver of middle-aged mice. *Exp Gerontol* 2016; **83**: 130-138 [PMID: 27498120 DOI: 10.1016/j.exger.2016.08.002]

34 **Cabré N**, Camps J, Joven J. Inflammation, mitochondrial metabolism and nutrition: the multi-faceted progression of non-alcoholic fatty liver disease to hepatocellular carcinoma. *Hepatobiliary Surg Nutr* 2016; **5**: 438-443 [PMID: 27826560 DOI: 10.21037/hbsn.2016.09.11]

35 **Font-Burgada J**, Sun B, Karin M. Obesity and Cancer: The Oil that Feeds the Flame. *Cell Metab* 2016; **23**: 48-62 [PMID: 26771116 DOI: 10.1016/j.cmet.2015.12.015]

36 **Wong MM**, Winkler B, Karamariti E, Wang X, Yu B, Simpson R, Chen T, Margariti A, Xu Q. Sirolimus stimulates vascular stem/progenitor cell migration and differentiation into smooth muscle cells *via* epidermal growth factor receptor/extracellular signal-regulated kinase/β-catenin signaling pathway. *Arterioscler Thromb Vasc Biol* 2013; **33**: 2397-2406 [PMID: 23928863 DOI: 10.1161/ATVBAHA.113.301595]

37 **Malagelada C**, Jin ZH, Jackson-Lewis V, Przedborski S, Greene LA. Rapamycin protects against neuron death in in vitro and in vivo models of Parkinson's disease. *J Neurosci* 2010; **30**: 1166-1175 [PMID: 20089925 DOI: 10.1523/JNEUROSCI.3944-09.2010]

38 **Vivarelli M**, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, Pinna AD. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. *Liver Transpl* 2005; **11**: 497-503 [PMID: 15838913 DOI: 10.1002/lt.20391]

39 **Vivarelli M**, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008; **248**: 857-862 [PMID: 18948815 DOI: 10.1097/SLA.0b013e3181896278]

40 **Toso C**, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010; **51**: 1237-1243 [PMID: 20187107 DOI: 10.1002/hep.23437]

41 **Ling S**, Feng T, Zhan Q, Duan X, Jiang G, Shen T, Shan Q, Xu S, Ye Q, Liu P, Cen B, Zheng S, Xu X. Sirolimus-based immunosuppression improves outcomes in liver transplantation recipients with hepatocellular carcinoma beyond the Hangzhou criteria. *Ann Transl Med* 2020; **8**: 80 [PMID: 32175373 DOI: 10.21037/atm.2020.01.10]

42 **Menon KV**, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 411-419 [PMID: 23278125 DOI: 10.1111/apt.12185]

43 **Liang W**, Wang D, Ling X, Kao AA, Kong Y, Shang Y, Guo Z, He X. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. *Liver Transpl* 2012; **18**: 62-69 [PMID: 21964956 DOI: 10.1002/lt.22441]

44 **Yanik EL**, Chinnakotla S, Gustafson SK, Snyder JJ, Israni AK, Segev DL, Engels EA. Effects of maintenance immunosuppression with sirolimus after liver transplant for hepatocellular carcinoma. *Liver Transpl* 2016; **22**: 627-634 [PMID: 26784951 DOI: 10.1002/lt.24395]

45 **Guerrero M**, Ferrín G, Rodríguez-Perálvarez M, González-Rubio S, Sánchez-Frías M, Amado V, Pozo JC, Poyato A, Ciria R, Ayllón MD, Barrera P, Montero JL, de la Mata M. mTOR Expression in Liver Transplant Candidates with Hepatocellular Carcinoma: Impact on Histological Features and Tumour Recurrence. *Int J Mol Sci* 2019; **20** [PMID: 30650598 DOI: 10.3390/ijms20020336]

46 **Zhou L**, Pan LC, Zheng YG, Zhang XX, Liu ZJ, Meng X, Shi HD, Du GS, He Q. Reduction of FoxP3$^+$ Tregs by an immunosuppressive protocol of rapamycin plus Thymalfasin and Huaier extract predicts positive survival benefits in a rat model of hepatocellular carcinoma. *Ann Transl Med* 2020; **8**: 472 [PMID: 32395516 DOI: 10.21037/atm.2020.03.129]

47 **Geissler EK**, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, Duvoux C, Burra P, Jauch KW, Rentsch M, Ganten TM, Schmidt J, Settmacher U, Heise M, Rossi G, Cillo U, Kneteman N, Adam R, van Hoek B, Bachellier P, Wolf P, Rostaing L, Bechstein WO, Rizell M, Powell J, Hidalgo E, Gugenheim J, Wolters H, Brockmann J, Roy A, Mutzbauer I, Schlitt A, Beckebaum S, Graeb C, Nadalin S, Valente U, Turrión VS, Jamieson N, Scholz T, Colledan M, Fändrich F, Becker T, Söderdahl G, Chazouillères O, Mäkisalo H, Pageaux GP, Steininger R, Soliman T, de Jong KP, Pirenne J, Margreiter R, Pratschke J, Pinna AD, Hauss J, Schreiber S, Strasser S, Klempnauer J, Troisi RI, Bhoori S, Lerut J, Bilbao I, Klein CG, Königsrainer A, Mirza DF, Otto G, Mazzaferro V, Neuhaus P, Schlitt HJ. Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial. *Transplantation* 2016; **100**: 116-125 [PMID: 26555945 DOI: 10.1097/TP.0000000000000965]

48 **Schnitzbauer AA**, Filmann N, Adam R, Bachellier P, Bechstein WO, Becker T, Bhoori S, Bilbao I, Brockmann J, Burra P, Chazoullières O, Cillo U, Colledan M, Duvoux C, Ganten TM, Gugenheim J, Heise M, van Hoek B, Jamieson N, de Jong KP, Klein CG, Klempnauer J, Kneteman N, Lerut J, Mäkisalo H, Mazzaferro V, Mirza DF, Nadalin S, Neuhaus P, Pageaux GP, Pinna AD, Pirenne J, Pratschke J, Powel J, Rentsch M, Rizell M, Rossi G, Rostaing L, Roy A, Scholz T, Settmacher U,

Soliman T, Strasser S, Söderdahl G, Troisi RI, Turrión VS, Schlitt HJ, Geissler EK. mTOR Inhibition Is Most Beneficial After Liver Transplantation for Hepatocellular Carcinoma in Patients With Active Tumors. *Ann Surg* 2020; **272**: 855-862 [PMID: 32889867 DOI: 10.1097/SLA.0000000000004280]

49 **Xu SL**, Zhang YC, Wang GY, Yang Q, Liu B, Zhang J, Li H, Wang GS, Yang Y, Chen GH. Survival analysis of sirolimus-based immunosuppression in liver transplantation in patients with hepatocellular carcinoma. *Clin Res Hepatol Gastroenterol* 2016; **40**: 674-681 [PMID: 27825633 DOI: 10.1016/j.clinre.2016.03.006]

50 **Zhou L**, Du GS, Pan LC, Zheng YG, Liu ZJ, Shi HD, Yang SZ, Shi XJ, Xuan M, Feng LK, Zhu ZD. Sirolimus treatment for cirrhosis or hepatocellular carcinoma patients accompanied by psoriasis after liver transplantation: A single center experience. *Oncol Lett* 2017; **14**: 7817-7824 [PMID: 29344227 DOI: 10.3892/ol.2017.7217]

51 **Rodríguez-Perálvarez M**, Guerrero-Misas M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database Syst Rev* 2017; **3**: CD011639 [PMID: 28362060 DOI: 10.1002/14651858.CD011639.pub2]

52 **Hu AB**, Wu LW, Tai Q, Zhu XF, He XS. Safety and efficacy of four steroid-minimization protocols in liver transplant recipients: 3-year follow-up in a single center. *J Dig Dis* 2013; **14**: 38-44 [PMID: 23134408 DOI: 10.1111/1751-2980.12008]

53 **Balcan B**, Simsek E, Ugurlu AO, Demiralay E, Sahin S. Sirolimus-Induced Diffuse Alveolar Hemorrhage: A Case Report. *Am J Ther* 2016; **23**: e1938-e1941 [PMID: 26849007 DOI: 10.1097/MJT.0000000000000427]

54 **Sadowski K**, Kotulska K, Jóźwiak S. Management of side effects of mTOR inhibitors in tuberous sclerosis patients. *Pharmacol Rep* 2016; **68**: 536-542 [PMID: 26891243 DOI: 10.1016/j.pharep.2016.01.005]

55 **Klawitter J**, Nashan B, Christians U. Everolimus and sirolimus in transplantation-related but different. *Expert Opin Drug Saf* 2015; **14**: 1055-1070 [PMID: 25912929 DOI: 10.1517/14740338.2015.1040388]

56 **Dumortier J**, Dharancy S, Calmus Y, Duvoux C, Durand F, Salamé E, Saliba F. Use of everolimus in liver transplantation: The French experience. *Transplant Rev (Orlando)* 2016; **30**: 161-170 [PMID: 27083870 DOI: 10.1016/j.trre.2015.12.003]

57 **Arena C**, Troiano G, Zhurakivska K, Nocini R, Lo Muzio L. Stomatitis And Everolimus: A Review Of Current Literature On 8,201 Patients. *Onco Targets Ther* 2019; **12**: 9669-9683 [PMID: 31814732 DOI: 10.2147/OTT.S195121]

58 **Wasilewicz MP**, Moczydłowska D, Janik M, Grąt M, Zieniewicz K, Raszeja-Wyszomirska J. Immunosuppressive treatment with everolimus in patients after liver transplant: 4 years of single-center experience. *Pol Arch Intern Med* 2019; **129**: 686-691 [PMID: 31502586 DOI: 10.20452/pamw.14968]

59 **Huynh H**, Ngo VC, Koong HN, Poon D, Choo SP, Thng CH, Chow P, Ong HS, Chung A, Soo KC. Sorafenib and rapamycin induce growth suppression in mouse models of hepatocellular carcinoma. *J Cell Mol Med* 2009; **13**: 2673-2683 [PMID: 19220580 DOI: 10.1111/j.1582-4934.2009.00692.x]

60 **Gomez-Martin C**, Bustamante J, Castroagudin JF, Salcedo M, Garralda E, Testillano M, Herrero I, Matilla A, Sangro B. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. *Liver Transpl* 2012; **18**: 45-52 [PMID: 21932373 DOI: 10.1002/lt.22434]

61 **Na GH**, Hong TH, You YK, Kim DG. Clinical analysis of patients with hepatocellular carcinoma recurrence after living-donor liver transplantation. *World J Gastroenterol* 2016; **22**: 5790-5799 [PMID: 27433092 DOI: 10.3748/wjg.v22.i25.5790]

62 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [DOI: 10.1016/s0140-6736(18)30207-1]

63 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

64 **Yamamoto Y**, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014; **6**: 18 [PMID: 25197551 DOI: 10.1186/2045-824X-6-18]

65 **Yang Z**, Wang S, Tian XY, Xie QF, Zhuang L, Li QY, Chen CZ, Zheng SS. Impact of treatment modalities on patients with recurrent hepatocellular carcinoma after liver transplantation: Preliminary experience. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 365-370 [PMID: 32553774 DOI: 10.1016/j.hbpd.2020.06.002]

66 **Baumeister SH**, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory Pathways in Immunotherapy for Cancer. *Annu Rev Immunol* 2016; **34**: 539-573 [PMID: 26927206 DOI: 10.1146/annurev-immunol-032414-112049]

67 **Butte MJ**, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts

specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity* 2007; **27**: 111-122 [PMID: 17629517 DOI: 10.1016/j.immuni.2007.05.016]

68 **Topalian SL**, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer* 2016; **16**: 275-287 [PMID: 27079802 DOI: 10.1038/nrc.2016.36]

69 **Velu V**, Titanji K, Zhu B, Husain S, Pladevega A, Lai L, Vanderford TH, Chennareddi L, Silvestri G, Freeman GJ, Ahmed R, Amara RR. Enhancing SIV-specific immunity in vivo by PD-1 blockade. *Nature* 2009; **458**: 206-210 [PMID: 19078956 DOI: 10.1038/nature07662]

70 **Li H**, Li X, Liu S, Guo L, Zhang B, Zhang J, Ye Q. Programmed cell death-1 (PD-1) checkpoint blockade in combination with a mammalian target of rapamycin inhibitor restrains hepatocellular carcinoma growth induced by hepatoma cell-intrinsic PD-1. *Hepatology* 2017; **66**: 1920-1933 [PMID: 28732118 DOI: 10.1002/hep.29360]

71 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

72 **Zhu AX**, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

73 **Kittai AS**, Oldham H, Cetnar J, Taylor M. Immune Checkpoint Inhibitors in Organ Transplant Patients. *J Immunother* 2017; **40**: 277-281 [PMID: 28719552 DOI: 10.1097/CJI.0000000000000180]

74 **Zhang N**, Kong X, Yan S, Yuan C, Yang Q. Huaier aqueous extract inhibits proliferation of breast cancer cells by inducing apoptosis. *Cancer Sci* 2010; **101**: 2375-2383 [PMID: 20718753 DOI: 10.1111/j.1349-7006.2010.01680.x]

75 **Wang CY**, Bai XY, Wang CH. Traditional Chinese medicine: a treasured natural resource of anticancer drug research and development. *Am J Chin Med* 2014; **42**: 543-559 [PMID: 24871650 DOI: 10.1142/S0192415X14500359]

76 **Hu Z**, Yang A, Fan H, Wang Y, Zhao Y, Zha X, Zhang H, Tu P. Huaier aqueous extract sensitizes cells to rapamycin and cisplatin through activating mTOR signaling. *J Ethnopharmacol* 2016; **186**: 143-150 [PMID: 27045863 DOI: 10.1016/j.jep.2016.03.069]

77 **Yang AL**, Hu ZD, Tu PF. [Research progress on anti-tumor effect of Huaier]. *Zhongguo Zhong Yao Za Zhi* 2015; **40**: 4805-4810 [PMID: 27245026]

78 **Li C**, Wu X, Zhang H, Yang G, Hao M, Sheng S, Sun Y, Long J, Hu C, Sun X, Li L, Zheng J. A Huaier polysaccharide restrains hepatocellular carcinoma growth and metastasis by suppression angiogenesis. *Int J Biol Macromol* 2015; **75**: 115-120 [PMID: 25597429 DOI: 10.1016/j.ijbiomac.2015.01.016]

79 **Lei JY**, Yan LN, Zhu JQ, Wang WT. Hepatocellular Carcinoma Patients May Benefit From Postoperative Huaier Aqueous Extract After Liver Transplantation. *Transplant Proc* 2015; **47**: 2920-2924 [PMID: 26707314 DOI: 10.1016/j.transproceed.2015.10.045]

World Journal of Gastrointestinal Surgery

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*World J Gastrointest Surg* 2021 September 27; 13(9): 967-978

DOI: 10.4240/wjgs.v13.i9.967

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Finding the seed of recurrence: Hepatocellular carcinoma circulating tumor cells and their potential to drive the surgical treatment

Francesca Carissimi, Matteo Nazzareno Barbaglia, Livia Salmi, Cristina Ciulli, Linda Roccamatisi, Giuseppe Cordaro, Venkata Ramana Mallela, Rosalba Minisini, Biagio Eugenio Leone, Matteo Donadon, Guido Torzilli, Mario Pirisi, Fabrizio Romano, Simone Famularo

**ORCID number:** Francesca Carissimi 0000-0002-1647-8397; Matteo Nazzareno Barbaglia 0000-0001-9271-7508; Livia Salmi 0000-0002-8638-0897; Cristina Ciulli 0000-0003-0911-5114; Linda Roccamatisi 0000-0002-0306-1277; Giuseppe Cordaro 0000-0002-3414-4948; Venkata Ramana Mallela 0000-0001-9664-481X; Rosalba Minisini 0000-0002-7548-9731; Biagio Eugenio Leone 0000-0002-6978-2405; Matteo Donadon 0000-0003-0296-7648; Guido Torzilli 0000-0001-5798-5021; Mario Pirisi 0000-0001-9740-0155; Fabrizio Romano 0000-0001-5341-0706; Simone Famularo 0000-0002-9721-6304.

**Author contributions:** Carissimi F, Famularo S, Barbaglia MN, and Salmi L wrote the manuscript; Carissimi F, Famularo S, Barbaglia MN, Salmi L, Roccamatisi L, Cordaro G, Ciulli C, and Mallela VR collected and analyzed data; Carissimi F, Famularo S, Barbaglia MN, Salmi L, Roccamatisi L, Cordaro G, Ciulli C, Mallela VR, and Minisini R reviewed the literature; Salmi L, and Barbaglia MN realized figures; Famularo S, Carissimi F, Minisini R, Leone BE, Donadon M, Torzilli G, Pirisi M, and Romano F designed the study.

**Conflict-of-interest statement:** The authors declare that they have no

**Francesca Carissimi, Cristina Ciulli, Linda Roccamatisi, Giuseppe Cordaro, Biagio Eugenio Leone, Fabrizio Romano, Simone Famularo,** School of Medicine and Surgery, University of Milano-Bicocca, Monza 20900, Italy

**Matteo Nazzareno Barbaglia, Livia Salmi, Venkata Ramana Mallela, Rosalba Minisini, Mario Pirisi,** Department of Translational Medicine, Università del Piemonte Orientale, Novara 28100, Italy

**Biagio Eugenio Leone,** Unit of Pathology, San Gerardo Hospital, Monza 20900, Italy

**Matteo Donadon, Guido Torzilli, Simone Famularo,** Department of Hepatobiliary and General Surgery, IRCCS Humanitas Clinical and Research Hospital-Department of Biomedical Science, Humanitas University, Pieve Emanuele 20090, Italy

**Fabrizio Romano,** Department of Medicine and Surgery, University of Milan-Bicocca, Monza 20900, Italy

**Corresponding author:** Fabrizio Romano, MD, Professor, Surgeon, Surgical Oncologist, Department of Medicine and Surgery, University of Milan-Bicocca, *via* pergolesi 33, Monza 20900, Italy. fabrizio.romano@unimib.it

## Abstract

The treatment for hepatocellular carcinoma (HCC) relies on liver resection, which is, however, burdened by a high rate of recurrence after surgery, up to 60% at 5 years. No pre-operative tools are currently available to assess the recurrence risk tailored to every single patient. Recently liquid biopsy has shown interesting results in diagnosis, prognosis and treatment allocation strategies in other types of cancers, since its ability to identify circulating tumor cells (CTCs) derived from the primary tumor. Those cells were advocated to be responsible for the majority of cases of recurrence and cancer-related deaths for HCC. In fact, after being modified by the epithelial-mesenchymal transition, CTCs circulate as "seeds" in peripheral blood, then reach the target organ as dormant cells which could be subsequently "awakened" and activated, and then initiate metastasis. Their presence may justify the disagreement registered in terms of efficacy of anatomic *vs* non-anatomic resections, particularly in the case of microvascular invasion, which has been recently pointed as a histological sign of the spread of those cells. Thus, their presence, also in the early stages, may justify the recurrence event also

**Manuscript source:** Invited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Italy

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 21, 2021
**Peer-review started:** March 21, 2021
**First decision:** April 29, 2021
**Revised:** May 25, 2021
**Accepted:** August 10, 2021
**Article in press:** August 10, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Fernandes SA
**S-Editor:** Ma YJ
**L-Editor:** A
**P-Editor:** Wu RR

in the contest of liver transplant. Understanding the mechanism behind the tumor progression may allow improving the treatment selection according to the biological patient-based characteristics. Moreover, it may drive the development of novel biological tailored tests which could address a specific patient to neoadjuvant or adjuvant strategies, and in perspective, it could also become a new method to allocate organs for transplantation, according to the risk of relapse after liver transplant. The present paper will describe the most recent evidence on the role of CTCs in determining the relapse of HCC, highlighting their potential clinical implication as novel tumor behavior biomarkers able to influence the surgical choice.

**Key Words:** Hepatocellular carcinoma; Liquid biopsy; Circulating tumor cells; Liver surgery; Microvascular invasion; Hepatocellular carcinoma recurrence



**Core Tip:** In recent years many studies have shown that surgery is the first choice treatment for hepatocellular carcinoma (HCC) patients; although undergoing surgery at early stage many patients develop relapse during follow-up. Currently, there are no tools sensitive enough to identify recurrence risk factors. Recent studies have identified liquid biopsy as a valid method for diagnosis, prognosis and treatment allocation in HCC patients thanks to its effectiveness in identification of circulating tumor cells (CTCs), advocated to be responsible for relapse. In this manuscript we describe the main markers expressed by CTCs and how their presence in blood sample may be implied in the progression mechanism, and how they can modify the surgical strategy.

**Citation:** Carissimi F, Barbaglia MN, Salmi L, Ciulli C, Roccamatisi L, Cordaro G, Mallela VR, Minisini R, Leone BE, Donadon M, Torzilli G, Pirisi M, Romano F, Famularo S. Finding the seed of recurrence: Hepatocellular carcinoma circulating tumor cells and their potential to drive the surgical treatment. *World J Gastrointest Surg* 2021; 13(9): 967-978
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/967.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.967

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer by diagnosis and the fourth highest cause of cancer-related death worldwide[1]. Surgical resection or liver transplantation are curative options, but unfortunately less than 40% of patients are eligible due to advanced stage at diagnosis[2].

Liver resection remains the mainstay among the curative treatments, but it is affected by a recurrence rate of up to 60% at 5 years, even for early stage tumours[3]. The route of recurrence is still a matter of debate. The relapse of HCC may be driven by precancerous status of the remaining diseased liver: namely "multicentric de-novo occurrence", these tumours are always primitive[4].

However, the majority of recurrence is attributed to intra-hepatic metastasisation, driven by the acquisition of the cancer hallmark of invasiveness[5]. Clinically speaking, no tools have been developed to recognise the two different patterns before treatment, although basic and pre-clinical studies have identified several genetic signatures[6,7]. While multicentric occurrence cannot be controlled by liver resection alone, intra-hepatic metastasisation could be avoided by an appropriate resection: almost thirty years ago, Makuuchi *et al*[8] stasisation could be avoided by an appropriate resection: almost thirty years ago, Makuuchi *et al*[8] reported a high rate of recurrence after surgery when microvascular invasion and satellitosis were present in the histological specimen. This evidence and that from other experiments[8-10], ed portal vein dissemination to be considered to be the main route of intra-hepatic metastasis, developing the notion of anatomical resection that relies on the complete removal of the whole segmental portal-flow area of the liver segment hosting the tumour. This technical approach was expected to allow better control of the area with the highest risk of tumour spread, reducing recurrence rates. However, several authors

compared recurrence rates among anatomical and non-anatomical resections, without a clear conclusion[11]. In recent years, the challenge of recurrence even after liver transplantation, a better knowledge of the tumour blood flow area[12], and the modern knowledge derived from molecular studies, have forced us to rethink the portal theory of HCC recurrence. In fact, intra-hepatic metastasis seems to be caused by local dissemination among the tumour blood flow, or by the systemic dissemination of tumour cells. These circulating tumour cells (CTCs) have also been identified in other types of tumours[13], and may have the ability to rehome themselves in the liver[14], and consequently could explain cases of relapse even after organ transplantation. In the present paper, we aimed to critically review the literature regarding HCC recurrence and CTC identification, and their role in surgery. We inter-pret our previous data in light of results from other studies, aiming to suggest a possible general picture to inform future research in the field.

## RECONSIDERING THE ROUTE OF RECURRENCE: EVIDENCE-DRIVEN HYPOTHESIS

Nakashima *et al*[15] have proposed that the portal vein (PV) may act as the efferent vessel during the oncoprogression of HCC, particularly in the setting of cirrhotic patients, where the hepatic veins are compromised. In this theory, the hepatic artery is the feeding vessel, and the PV, as an efferent vessel, penetrates the tumour capsule, and becomes the path of minor resistance for tumour infiltration or expansion[9] and the drainage pathway of the neoplasm. This mechanism was described to explain the high rate of tumour thrombi observed, and the presence of satellitosis near the primitive tumour. Those considerations led to the proposal of the anatomic resection (AR) to completely remove the parenchymal area fed by the portal branch (namely, the liver segment), in which there may be an increased risk of recurrence. However, the superiority of AR has been never proven, and several reports are available in favour or against this hypothesis[11,16]. More importantly, according to the theory, AR should completely eliminate the risk of local recurrence (relapse at the surgical edge), by eliminating the area where the tumour may have spread. However, our and others data[17,18] have reported a comparable rate of local recurrence among AR and non-anatomical resections, questioning the ability of a radical segment resection to control the oncological burden. Thus, the highest rate of intra-hepatic recurrence occurred in other liver segments than the one carrying the primitive nodule, suggesting a different or at least a concomitant route of the tumour cells. More recently, we tried to identify the risk factors for either local or intra-hepatic distant recurrence in a large European series[19], observing that local relapse occurred frequently in cases of positive surgical margin (and consequently as a kind of surgical failure), while the presence of microvascular invasion and satellitosis were hallmarks of increased risk of intra-hepatic distant relapse. These data suggest that, when those histological features occurred, the tumour may have already invaded the blood circulation, with a metastasisation potential in other locations that may not be explained by the local portal flow, and that cannot be controlled by modifying the extent of surgery. In this sense, the tumour micro-thrombi assessed by histology near the primitive nodule could not be considered only a local extension of the disease (as supposed by the portal flow theory), but a sign of systemic dissemination. Another 'brick in the wall' was suggested by the clinical data: recently, Hidaka *et al*[20] reported that the complete removal of the portal-bearing area did not modify the risk of recurrence in cases of microvascular invasion, and this data was confirmed in our recent meta-analysis [11].

Sakon *et al*[12,21] studied the tumour blood flow (TBF) area, discovering that this coincided with the segmental portal area only in 18% of their cohort. In up to 75% of cases, the TBF was independent of the PV area, and the rate of recurrence was reduced only in cases where the TBF was completely included in the resection area, regardless of the removal of the liver segment. The authors proposed a subclassification of HCC recurrence based on two different mechanisms: local recurrence, which is driven by the invasion of the local tumour blood flow with a peritumoural dissemination, and a systemic dissemination driven by the spread of CTCs derived from the primitive nodule, which may be able to "rehome" after passing through the systemic circulation. While the first mechanism could be controlled by an effective radical resection, the second relies on the oncological progression of the tumour, and could explain cases of intra-hepatic relapse at a distance from the original site, but also recurrence after transplantation. In 2018, a very interesting study was conducted by Sun *et al*[22], who

tested the spatial heterogeneity of phenotypic and molecular characteristics of CTCs within the circulatory system, discovering that a higher number of CTCs were detected in sites other than the PV. In particular, the percentages of CTCs detected in blood sampled from a peripheral vein, peripheral artery, hepatic veins, infrahepatic inferior vena cava, and PV before HCC resection were 68.5%, 45.2%, 80.8%, 39.7%, and 58.9%, respectively. Moreover, CTC and circulating tumour microemboli burden detected in hepatic veins and peripheral circulation, but not in the PV, were associated with postoperative lung metastasis and intrahepatic recurrence, respectively. These pieces of evidence suggest that the classical recurrence theory for HCC cannot explain many real-scenario observations. A novel approach, integrating the discovery of CTCs and their role in tumour biology with clinical experience, will allow a novel and tailored approach to select the best candidates for curative strategies, but will also be able to provide a novel biomarker with the ability to summarise the biological data of the tumour, using a very simple blood sample analysis (Figure 1). The detection of these cells and their possible role in surgery will be further explored in the following sections.

## CTCS MOLECULAR CHARACTERISTICS

In the context of cancer pathogenesis, and especially for carcinomas, the "epithelial-mesenchymal transition" (EMT) is a fundamental mechanism playing a key role in the metastatic proces[23]. Several authors agree that this rearrangement of cell status is neither stable nor binary, and neoplastic epithelial cells that have activated an EMT program very rarely advance to a fully mesenchymal state[24]. Also, the reverse process known as mesenchymal-epithelial transition (MET) is required for metastatic colonisation in the same or other tissues[25]. Both of the above-mentioned mechanisms can actively operate in the generation of CTCs. Since CTCs are a phenotypically distinct subpopulation that originate from the tumour microenvironment, the idea behind the identification of CTCs is to discover characteristic markers of both EMT/MET transition and of the primary tumour.

CTC identification is technically difficult due to the low concentration of these cells in blood[26]. In recent years, research has focused on improving the specificity and sensitivity of CTC detection and facilitating accurate molecular characterisation[14]. Based on physical and/or biological properties of the cells, several strategies and systems have been developed to improve CTC enrichment. Filter membranes, such as the CanPatrol™ system, and microfluidic devices, such as CTC-iChip and Labyrinth-chip, allow separation of cells based on their sizes[14,27]. Alternatively, Ficoll-type density gradient methods make it easier to separate blood cells, exploiting their different density[28].

One of the most used methods is the Cell Search® system, which is based on immunomagnetic enrichment[29]. This CTC isolation strategy exploits the expression on the cell surface of the protein EpCAM, which is the most accredited marker for positive affinity-selection of CTCs. The Cell Search® system is the only system appro-ved by the Food and Drug Administration (FDA) to predict the outcome of patients affected by breast cancer[30]. Nevertheless, enumeration of $EpCAM^+$ CTCs alone has demonstrated modest clinical sensitivity and, for instance, in cancers with low EpCAM expression, the Cell Search® system showed a lower CTC recovery rate compared to microfluidic devices[31]. In 2018, Pang *et al*[32] developed a method which exploits the surface-enhanced Raman scattering (SERS) technology and nanoparticles linked to antibodies directed against the specific hepatic proteins asialoglycoprotein receptor (ASGPR) and glypican-3 (GPC3), allowing isolation of $EpCAM^-$ CTCs. Moreover, not all CTCs have metastatic or relapsing potential, so sim-ple quantification without better molecular characterisation could lead to incorrect clinical conclusions. The use of isolation and enrichment devices is supported by other laboratory techniques such as immunofluorescence staining of different markers [fluorescence-activated cell sorting (FACS) and fluorescent in situ hybridization (FISH)] and/or gene expression analysis [real time PCR (qPCR) and single cell RNA sequencing (scRNA-seq)] in order to obtain in depth CTC characterisation[33]. Considering all of these biological /phenotypic and experimental issues, the application of this method in common clinical practice has proved to be difficult. Making this strategy even harder is the heterogeneity of the tumour itself and, among protein markers, cytokeratins (CKs), vimentin, CD44, CD133 and CD90 are the most used so far[34]. CKs, like EpCAM, are epithelial markers, but unlike the latter, they are intracellular proteins, thus they are identified mainly using immunocytochemistry. Cells are usually stained for CK8, 18

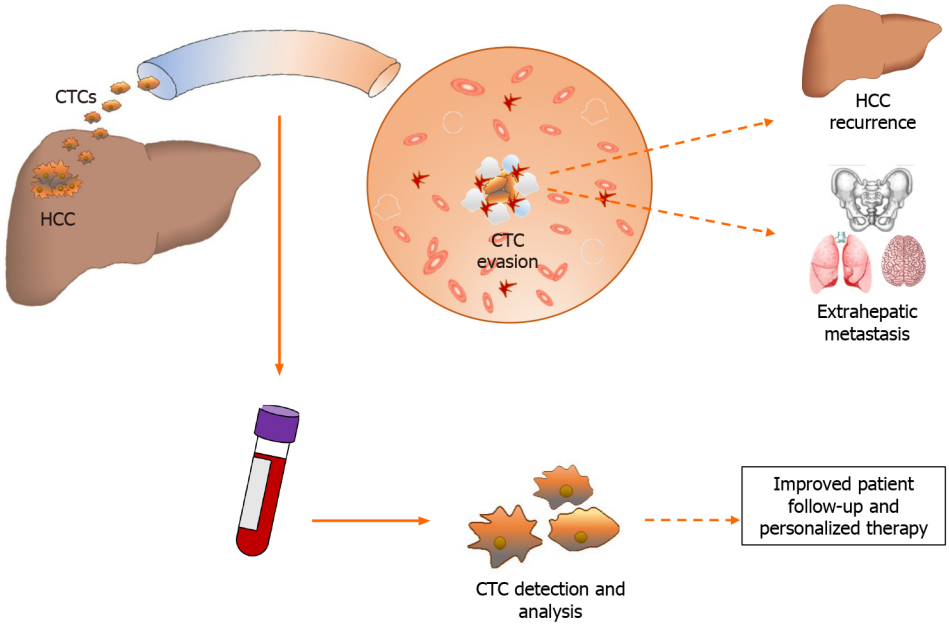


**Figure 1 Hepatocellular carcinoma releases tumor cells into circulation where they become circulating tumor cells.** Circulating tumor cells after evading the immune system can cause hepatocellular carcinoma recurrence or distant metastasis. The liquid biopsy intercepts these cells into the bloodstream and allows to study the tumor characteristics and guarantee personalized therapy. CTCs: Circulating tumor cells; HCC: Hepatocellular carcinoma.

and 19, but recently other markers such as human epidermal growth factor receptor 2 (HER2) and the estrogen receptor (ER) have been examined to facilitate detection of CTCs with metastatic potential[35].

As mentioned above, the major drawback of using epithelial markers is their inability to detect CTCs that no longer express them after undergoing EMT, a process which is strongly associated with overexpression of vimentin and CD44[36,37]. CD44 is often used as a marker in combination with the stem-like markers CD133 and CD90 [38]. However, plasma membrane and cytoplasmic proteins are not the only markers used to detect potential CTCs; complex studies have tried to generate the mRNA expression profiles of CTCs in different diseases[39]. In particular, D'Avola *et al*[33] recently developed a new method that sequentially combines image flow cytometry and high density scRNA-seq in order to identify CTCs in patients with HCC. The authors suggest the advantages of genome-wide transcriptome profiling to confidently detect CTCs and its potential role in monitoring HCC heterogeneity and detecting HCC driver genes, which could ultimately help customize therapeutic interventions in these patients.

## CTCS IDENTIFICATION IN HCC PATIENTS

To date, there are no specific or accredited CTC-related protocols for detection of HCC that are agreed upon by the scientific community. Several studies have been performed to deeply investigate and introduce the use of CTC enumeration/characterisation in HCC monitoring in clinical practice. Most of these studies are primarily based on the previously validated EpCAM/CK markers, with secondary examination of other markers or features (Figure 2). In recent years, several authors in the HCC field have taken advantage of combining the markers vimentin and twist; as mentioned above, these mesenchymal markers have followed the common epithelial markers EpCAM/CKs. Ou *et al*[40] observed that the presence of mesenchymal CTCs tended to occur in advanced stage patients and was associated with earlier recurrence in a large cohort of HCC patients. ASGPR and carbamoyl-phosphate synthetase 1 (CPS1) are interesting in the context of HCC. Liu *et al*[41] demonstrated that CTC enrichment, combined with identification using an antibody cocktail against ASGPR and CPS1, not only significantly improves sensitivity for CTC enrichment, but also provides high specificity for CTC detection in patients with HCC, thereby minimising false negative/positive results. The combination of ASGPR and CPS1 was used also by Li *et al*[42], confirming the increased sensitivity for HCC CTC detection.

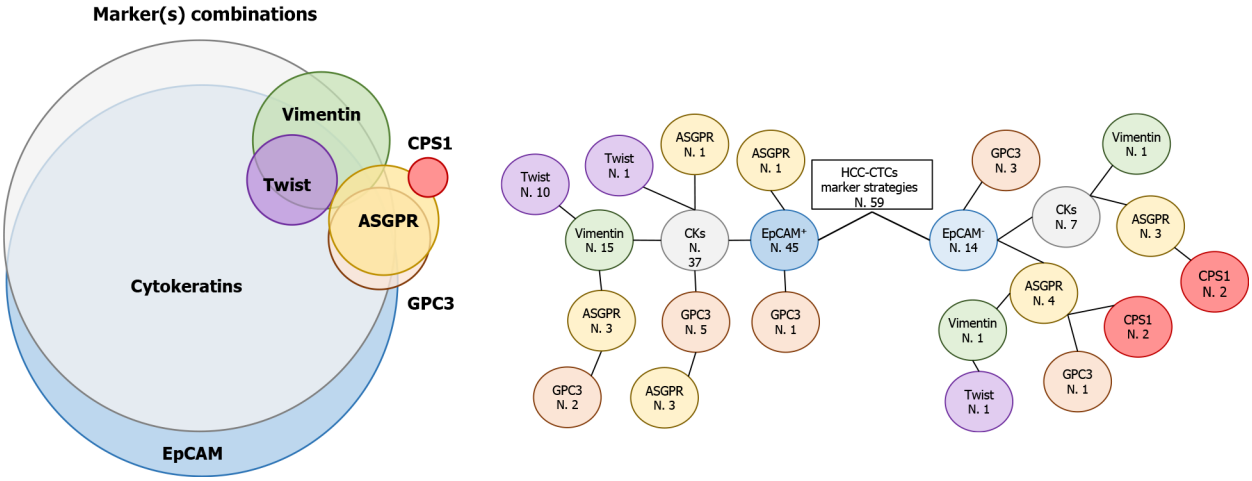


**Figure 2 Frequently used markers for circulating tumor cell detection hepatocellular carcinoma-related.** Epithelial cell adhesion molecule$^+$ circulating tumor cell identification is often combined with cytokeratins, vimentin, twist, Glypican-3 and asialoglycoprotein receptor (ASGPR). In some cases, ASGPR is also used with the hepatocellular marker carbamoyl-phosphate synthetase 1 (Venn diagram). Tree diagram show the number of articles (N.) that use different marker combinations for circulating tumor cell isolation. Bibliography counts articles related to hepatocellular carcinoma field and published from 2009 to 2020. EpCAM: Epithelial cell adhesion molecule; CKs: Cytokeratins; ASGPR: Asialoglycoprotein receptor; GPC3: Glypican-3; CPS1: Carbamoyl-phosphate synthetase 1.

In 2016, Zhang *et al*[43] isolated ASGPR$^+$/CPS1$^+$ CTCs from HCC patients, which were then cultured and expanded to form spheroid-like structures in a 3D cell culture assay. They suggested that this method could aid physicians in the selection of appropriate drug therapies for HCC patients. The role of CTCs expressing mesenchymal features in predicting HCC early recurrence was confirmed in the same year by Qi *et al*[44], in a monocentric study with 112 enrolled patients. However, mesenchymal CTC use in clinical practice is controversial, since their analysis in a different cohort of HCC patients who underwent liver transplantation was not able to predict HCC recurrence[45]. Conversely, in liver transplantation, the entire organ is replaced with a healthy liver deriving from a donor. Thus, the HCC recurrence is likely due to circulating and/or dormant tumour cells, which have acquired the ability to escape from the host's immune system. Clusters of CTCs were first predicted and then observed as intravascular tumour microemboli, represented by multicellular epithelial tumour cells. In a mouse model experiment, in which human-derived CTCs were used, it was observed that CTC clusters are not derived from intravascular aggregation of single CTCs or from the progeny of a single primary tumour cell that proliferates in the vascular space, but instead, evidence showed that CTC clusters derive from groupings of primary tumour cells that enter the bloodstream together [46].

## CTCS AS A MOLECULAR SIGNATURE OF THE HISTOLOGICAL CHARACTERISTICS OF THE PRIMITIVE HCC

Recently it has been reported that CTCs positive for EpCAM, N-Cadherin and CD90 expression (triple positive CTCs) are more frequently associated with microvascular invasion (MVI), as detected in a histological specimen after liver resection[47]. The histopathological finding of MVI is a feature of advanced HCC, associated with a higher probability of recurrence and metastasis[48]; however, with the imaging tests and biomarkers currently available, the preoperative identification of MVI remains difficult[49]. Rodríguez-Perálvarez *et al*[50] showed that MVI incidence was between 15.0% and 57.1% at histopathological examination after liver resection and transplantation, in a systematic review. Thus, different tumour stages and HCC invasive characteristics affect MVI incidence. The possibility given by the triple positive CTCs, associated with the actual diagnostics tool, to pre-operatively identify MVI may play a role in the use of preoperative predictive models in therapeutic decision-making in patients with HCC.

## CTCS VARIATIONS AFTER LIVER RESECTION

After surgical tumor excision, CTC levels drop dramatically and post-operative CTC levels can be used as tools to verify surgical resection as a monitor for tumor burden [14]. Yu *et al*[51] evaluated the effect of surgical liver resection on CTCs in patients with HCC, demonstrating that a lower CTC level after surgical resection is an independent prognostic factor for better disease-free-survival (HR 0.620; 95%CI: 0.479–0.803; $P < 0.001$) and overall-survival (HR 0.608; 95%CI: 0.443–0.834; $P = 0.002$). Ou *et al*[40] demonstrated that increased CTC numbers were observed in patients with high levels (> 400 mcg/L) of alpha fetoprotein (AFP), advanced TNM and BCLC stage, and the presence of embolus or microembolus. They also investigated CTC heterogeneity, noting a significant correlation between mesenchymal CTCs and high AFP levels, multiple tumours, advanced TNM and BCLC stage, presence of embolus or microembolus, and earlier recurrence.

These CTCs could be considered as a very early sign of tumour migration: invisible micro-metastasis, impossible to detect with standard methods but playing a fundamental role in patients' clinical evolution[52]. Sun *et al*[53] analysed the diagnostic value of CTCs in HCC patients, performing a meta-analysis on 20 studies of a total of 998 HCC patients. From their work, it emerges that CTC positivity is associated with a lower overall survival (HR 2.417; 95%CI: 1.421–3.250; $P < 0.001$) and disease free survival (HR 3.59; 95%CI: 1.984–6.495; $P < 0.001$). CTC analysis determines the tumour molecular characteristics before any treatment, evaluating cancer differentiation and identifying markers as possible molecular therapy targets or mechanisms of resistance to therapy[54]. The selective pressure that develops over time since starting the treatment leads to increased cellular heterogeneity of the tumour, production of drug resistant subclones, and the selection of rare mutants[55], essentially the tumour is characterised by different genetic backgrounds at different times. Therefore, the tumour genome during follow-up could differ significantly from its initial state, and this difference cannot be assessed unless repeated sampling is performed. However, repeat biopsy is rarely feasible and, without knowledge of the genetic changes, complete treatment personalisation and targeted therapy is impossible[56]. In comparison, liquid biopsy is easily repeatable during follow-up, making knowledge of all tumour genome changes possible. In the future, it will be desirable to use quantitative and qualitative analysis of CTCs to develop personalised therapy for each patient. The phenotyping of those cells, and their quantification in the peripheral blood, may allow identification of patients with a more severe and more aggressive disease, who could be the target population in which adjuvant therapies as Sorafenib may play a role. Currently, it is not evident what features are associated with response to such treatments[57]. The presence and characteristics of the CTCs identified in peripheral blood may become a molecular marker to decide the follow-up schedule, and estimations of risk could be updated at each visit by repeating the test. In other words, CTCs could become a new predictive marker to better stratify patients and assign them to the best individual treatment plan, improving long-term cancer outcomes.

## CTCS AND LIVER TRANSPLANT FOR HCC

Orthotopic liver transplantation (OLT) is the most favourable option for the treatment of HCC, with a 5-year overall survival rate of 75% and disease-free survival rate of 83%[58]. Despite stringent criteria in patient selection for transplantation, HCC recurrence still remains a significant problem, with a rate of 15%–20%[59,60]. Due to organ shortage and recurrence risk even after transplantation, it is important to be able to select patients for LT in order not to misallocate a limited resource.

Tumour size, AFP levels, and micro- and macro-vascular invasion are the main prognostic factors for recurrence risk after transplantation[61]. The aim of patient selection criteria should be to prevent transplantation in those patients with an expected HCC recurrence and to improve transplantation for those patients who have a high likelihood of being cured. The present parameters are based on morphology, but in the modern molecular era, new information could be available to better understand the patient's tumour biology in a tailored fashion.

Xu *et al*[62] highlighted how the CTC-positive rate and number of CTCs present is higher in patients beyond the Milan criteria than in patients within the criteria (91% *vs* 69%, $P = 0.009$; and 27 ± 27 *vs* 6 ± 9, $P < 0.001$; respectively). This suggests that including the CTC count in pre-transplant evaluation could revolutionise the eligi-

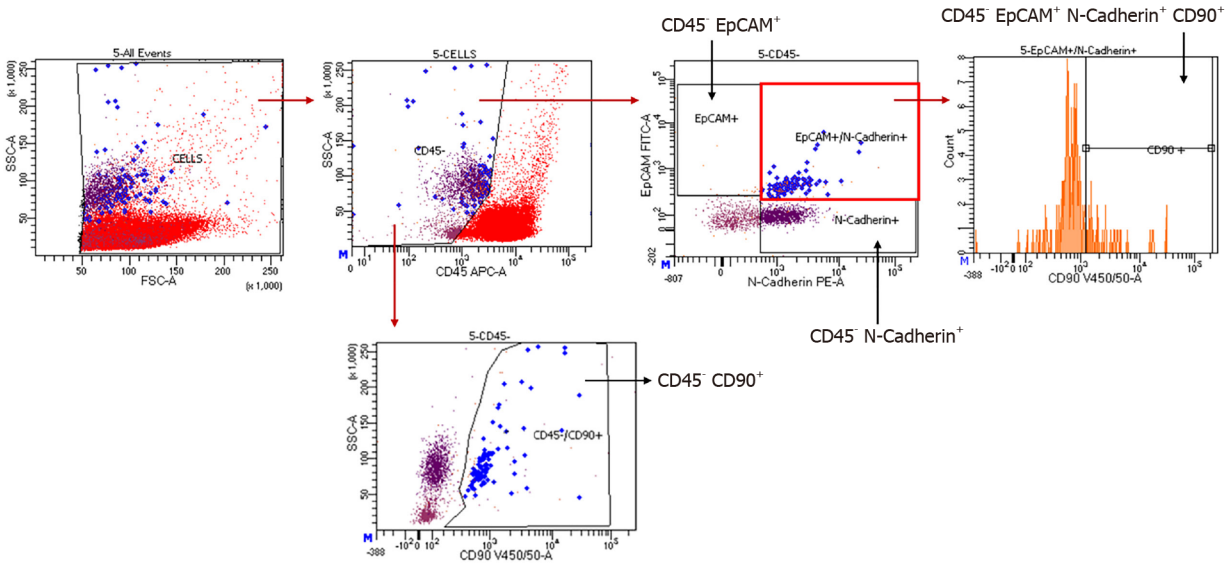


**Figure 3 Representative example of a patient's PBMC analysis within the FINDINGBIOREC protocol.**

bility criteria for transplantation. Chen *et al*[63] analysed preoperative CTCs in HCC patients who underwent LT and followed them up for at least one year, or until relapse or death occurred. They found that recurrence is associated with presence of preoperative CTCs ($P$ = 0.013); multivariate analysis confirmed that CTCs are an independent risk factor for the onset of recurrence after LT (HR: 5.411; 95%CI: 1.132–25,874; $P$ = 0.034). These data reflect the 1-year DFS rate, which is 91.6% for the CTC-negative and 61.5% for the CTC-positive group ($P$ = 0.020). On the other hand, the 1-year overall survival rate for the CTC-negative and CTC-positive group is 91.7% and 88.5%, respectively, with no significant difference. Very few data are available about the potential role of CTCs as preoperative predictors of HCC recurrence after LT, and it is still a controversial issue. However, their application could drastically change the allocation protocols, enabling a more tailored algorithm with potentially better ability to predict the risk of relapse and, consequently, differentiate the cases that could benefit from transplant from the ones that could not.

## CTCS IDENTIFICATION IN A REAL-CLINICAL SCENARIO: THE FINDINGBIOREC PROTOCOL

In light of the previously mentioned data, the University of Milano-Bicocca, the University of Piemonte Orientale and Humanitas University have decided to collaborate by creating a study with the aim of "finding the seeds of recurrence", using liquid biopsy to detect CTCs as markers of disease and prognosis in HCC.

Our hypothesis is that CTCs may spread from the original tumours as a hallmark of advanced cancer, which has already developed the characteristic of invasiveness. It is our opinion that early stage tumours do not release CTCs into the bloodstream at the same rate or quality as advanced tumours. Patients with a positive CTC liquid biopsy may have a worse prognosis, due to an increased relapse rate. Finally, from a patho-physiological point of view, we want to demonstrate that recurrence is due to CTC seeding, in order to gain a better understanding of HCC carcinogenesis. The "FINDINGIBIOREC" study (clinicaltrial.gov ID: NCT04800497) was developed: a prospective, observational cohort study, conducted in two tertiary referral centres for liver cancer, in which each enrolled patient is submitted to liquid biopsy prior to surgery and then every 3 mo during the follow-up schedules, for 3 years. Patients with a first diagnosis of HCC, no previous treatment for this condition, no other oncological history, and BCLC stage 0-A-B are prospectively enrolled. The samples are processed and the CTCs are detected using FACSymphony™ with subsequent identification of the following markers: EpCAM, N-cadherin (N-cad) and CD90 (Figure 3). Patients are followed up with clinical assessments; CT or, where necessary, MRI and AFP level, together with liquid biopsy. With this protocol, we aim to better highlight the trends of CTCs at different time-points and their correlation with the oncologic prognosis in very early

and early HCC. The study is currently enrolling, and it will be closed in 2023.

## CONCLUSION

HCC may produce early CTCs, which seem to be the seed of the recurrence. Their presence in the blood stream has been correlated with the presence of MVI, suggesting that the latter is a surrogate sign of a systemic disease that cannot be controlled by classical liver segment resection alone. Those cells could be detected and studied by liquid biopsy, which is a safe method to obtain information on the patient's disease status. This allows tumour molecular characterisation during different disease phases, and could become a new method for patient stratification. The study of CTCs allows selection of patients and the type of treatment they will receive in order to optimize HCC therapy. During the follow-up, an increase in CTCs makes it possible to identify tumour recurrence and implement further therapy early. In future, liquid biopsy could be implemented in the pre- and post-operative routine of HCC patients in order to gain more accurate information on tumour type and stage, and guarantee the most personalised therapy possible for the patients.

## REFERENCES


1 **Lin L**, Yan L, Liu Y, Qu C, Ni J, Li H. The Burden and Trends of Primary Liver Cancer Caused by Specific Etiologies from 1990 to 2017 at the Global, Regional, National, Age, and Sex Level Results from the Global Burden of Disease Study 2017. *Liver Cancer* 2020; **9**: 563-582 [PMID: 33083281 DOI: 10.1159/000508568]

2 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0]

3 **Tabrizian P**, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Ann Surg* 2015; **261**: 947-955 [PMID: 25010665 DOI: 10.1097/SLA.0000000000000710]

4 **Abdelaziz AO**, Nabil MM, Abdelmaksoud AH, Shousha HI, Cordie AA, Hassan EM, Omran DA, Leithy R, Elbaz TM. De-novo *vs* recurrent hepatocellular carcinoma following direct-acting antiviral therapy for hepatitis C virus. *Eur J Gastroenterol Hepatol* 2018; **30**: 39-43 [PMID: 29064851 DOI: 10.1097/MEG.0000000000001004]

5 **Yamamoto S**, Midorikawa Y, Nagae G, Tatsuno K, Ueda H, Moriyama M, Takayama T, Aburatani H. Spatial and temporal expansion of intrahepatic metastasis by molecularly-defined clonality in multiple liver cancers. *Cancer Sci* 2020; **111**: 601-609 [PMID: 31845427 DOI: 10.1111/cas.14282]

6 **Wang B**, Xia CY, Lau WY, Lu XY, Dong H, Yu WL, Jin GZ, Cong WM, Wu MC. Determination of clonal origin of recurrent hepatocellular carcinoma for personalized therapy and outcomes evaluation: a new strategy for hepatic surgery. *J Am Coll Surg* 2013; **217**: 1054-1062 [PMID: 24246620 DOI: 10.1016/j.jamcollsurg.2013.07.402]

7 **Carone C**, Olivani A, Dalla Valle R, Manuguerra R, Silini EM, Trenti T, Missale G, Cariani E. Immune Gene Expression Profile in Hepatocellular Carcinoma and Surrounding Tissue Predicts Time to Tumor Recurrence. *Liver Cancer* 2018; **7**: 277-294 [PMID: 30319985 DOI: 10.1159/000486764]

8 **Makuuchi M**, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346-350 [PMID: 2996162 DOI: 10.1055/s-2007-1022639]

9 **Mitsunobu M**, Toyosaka A, Oriyama T, Okamoto E, Nakao N. Intrahepatic metastases in hepatocellular carcinoma: the role of the portal vein as an efferent vessel. *Clin Exp Metastasis* 1996; **14**: 520-529 [PMID: 8970582 DOI: 10.1007/BF00115112]

10 **Yamanaka N**, Okamoto E, Fujihara S, Kato T, Fujimoto J, Oriyama T, Mitsunobu M, Toyosaka A, Uematsu K, Yamamoto K. Do the tumor cells of hepatocellular carcinomas dislodge into the portal venous stream during hepatic resection? *Cancer* 1992; **70**: 2263-2267 [PMID: 1327495 DOI: 10.1002/1097-0142(19921101)70:9<2263::aid-cncr2820700909>3.0.co;2-m]

11 **Famularo S**, Ceresoli M, Giani A, Ciulli C, Pinotti E, Romano F, Braga M, De Carlis L, Gianotti L. Is It Just a Matter of Surgical Extension to Achieve the Cure of Hepatocarcinoma? *J Gastrointest Surg* 2021; **25**: 94-103 [PMID: 31898106 DOI: 10.1007/s11605-019-04494-5]

12 **Sakon M**, Ogawa H, Fujita M, Nagano H. Hepatic resection for hepatocellular carcinoma based on tumor hemodynamics. *Hepatol Res* 2013; **43**: 155-164 [PMID: 23194466 DOI: 10.1111/hepr.12001]

13 **Ye Q**, Ling S, Zheng S, Xu X. Liquid biopsy in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. *Mol Cancer* 2019; **18**: 114 [PMID: 31269959 DOI: 10.1186/s12943-019-1043-x]

14 **Okajima W**, Komatsu S, Ichikawa D, Miyamae M, Ohashi T, Imamura T, Kiuchi J, Nishibeppu K, Arita T, Konishi H, Shiozaki A, Morimura R, Ikoma H, Okamoto K, Otsuji E. Liquid biopsy in patients with hepatocellular carcinoma: Circulating tumor cells and cell-free nucleic acids. *World J Gastroenterol* 2017; **23**: 5650-5668 [PMID: 28883691 DOI: 10.3748/wjg.v23.i31.5650]

15 **Okuda K**, Peters RL. Hepatocellular Carcinoma. John Wiley & Sons. Available from:

https://books.google.com/books/about/Hepatocellular_Carcinoma.html?hl=&id=YX9rAAAAMAAJ

16 **Shindoh J**, Kobayashi Y, Umino R, Kojima K, Okubo S, Hashimoto M. Successful Anatomic Resection of Tumor-Bearing Portal Territory Delays Long-Term Stage Progression of Hepatocellular Carcinoma. *Ann Surg Oncol* 2021; **28**: 844-853 [PMID: 32712886 DOI: 10.1245/s10434-020-08927-3]

17 **Famularo S**, Di Sandro S, Giani A, Lauterio A, Sandini M, De Carlis R, Buscemi V, Uggeri F, Romano F, Gianotti L, De Carlis L. Recurrence Patterns After Anatomic or Parenchyma-Sparing Liver Resection for Hepatocarcinoma in a Western Population of Cirrhotic Patients. *Ann Surg Oncol* 2018; **25**: 3974-3981 [PMID: 30244421 DOI: 10.1245/s10434-018-6730-0]

18 **Marubashi S**, Gotoh K, Akita H, Takahashi H, Sugimura K, Miyoshi N, Motoori M, Kishi K, Noura S, Fujiwara Y, Ohue M, Nakazawa T, Nakanishi K, Ito Y, Yano M, Ishikawa O, Sakon M. Analysis of Recurrence Patterns After Anatomical or Non-anatomical Resection for Hepatocellular Carcinoma. *Ann Surg Oncol* 2015; **22**: 2243-2252 [PMID: 25373536 DOI: 10.1245/s10434-014-4214-4]

19 **Famularo S**, Piardi T, Molfino S, Di Martino M, Ferrari C, Ielpo B, Diago MV, Giani A, Griseri G, Terés LB, Gianotti L, Baiocchi GL, Sommacale D, Romano F. Factors Affecting Local and Intra Hepatic Distant Recurrence After Surgery for Hcc: An Alternative Perspective on Microvascular Invasion and Satellitosis - A Western European Multicentre Study. *J Gastrointest Surg* 2021; **25**: 104-111 [PMID: 31965441 DOI: 10.1007/s11605-019-04503-7]

20 **Hidaka M**, Eguchi S, Okuda K, Beppu T, Shirabe K, Kondo K, Takami Y, Ohta M, Shiraishi M, Ueno S, Nanashima A, Noritomi T, Kitahara K, Fujioka H. Impact of Anatomical Resection for Hepatocellular Carcinoma With Microportal Invasion (vp1): A Multi-institutional Study by the Kyushu Study Group of Liver Surgery. *Ann Surg* 2020; **271**: 339-346 [PMID: 30048313 DOI: 10.1097/SLA.0000000000002981]

21 **Sakon M**, Kobayashi S, Wada H, Eguchi H, Marubashi S, Takahashi H, Akita H, Gotoh K, Yamada D, Asukai K, Hasegawa S, Ohue M, Yano M, Nagano H. "Logic-Based Medicine" Is More Feasible than "Evidence-Based Medicine" in the Local Treatment for Hepatocellular Carcinoma. *Oncology* 2020; **98**: 259-266 [PMID: 32045926 DOI: 10.1159/000505554]

22 **Sun YF**, Guo W, Xu Y, Shi YH, Gong ZJ, Ji Y, Du M, Zhang X, Hu B, Huang A, Chen GG, Lai PBS, Cao Y, Qiu SJ, Zhou J, Yang XR, Fan J. Circulating Tumor Cells from Different Vascular Sites Exhibit Spatial Heterogeneity in Epithelial and Mesenchymal Composition and Distinct Clinical Significance in Hepatocellular Carcinoma. *Clin Cancer Res* 2018; **24**: 547-559 [PMID: 29070526 DOI: 10.1158/1078-0432.CCR-17-1063]

23 **van Zijl F**, Zulehner G, Petz M, Schneller D, Kornauth C, Hau M, Machat G, Grubinger M, Huber H, Mikulits W. Epithelial-mesenchymal transition in hepatocellular carcinoma. *Future Oncol* 2009; **5**: 1169-1179 [PMID: 19852728 DOI: 10.2217/fon.09.91]

24 **Dongre A**, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol* 2019; **20**: 69-84 [PMID: 30459476 DOI: 10.1038/s41580-018-0080-4]

25 **Gunasinghe NP**, Wells A, Thompson EW, Hugo HJ. Mesenchymal-epithelial transition (MET) as a mechanism for metastatic colonisation in breast cancer. *Cancer Metastasis Rev* 2012; **31**: 469-478 [PMID: 22729277 DOI: 10.1007/s10555-012-9377-5]

26 **Edd JF**, Mishra A, Dubash TD, Herrera S, Mohammad R, Williams EK, Hong X, Mutlu BR, Walsh JR, Machado de Carvalho F, Aldikacti B, Nieman LT, Stott SL, Kapur R, Maheswaran S, Haber DA, Toner M. Microfluidic concentration and separation of circulating tumor cell clusters from large blood volumes. *Lab Chip* 2020; **20**: 558-567 [PMID: 31934715 DOI: 10.1039/c9lc01122f]

27 **Wan S**, Kim TH, Smith KJ, Delaney R, Park GS, Guo H, Lin E, Plegue T, Kuo N, Steffes J, Leu C, Simeone DM, Razimulava N, Parikh ND, Nagrath S, Welling TH. New Labyrinth Microfluidic Device Detects Circulating Tumor Cells Expressing Cancer Stem Cell Marker and Circulating Tumor Microemboli in Hepatocellular Carcinoma. *Sci Rep* 2019; **9**: 18575 [PMID: 31819089 DOI: 10.1038/s41598-019-54960-y]

28 **Gertler R**, Rosenberg R, Fuehrer K, Dahm M, Nekarda H, Siewert JR. Detection of circulating tumor cells in blood using an optimized density gradient centrifugation. *Recent Results Cancer Res* 2003; **162**: 149-155 [PMID: 12790329 DOI: 10.1007/978-3-642-59349-9_13]

29 **Wang PX**, Sun YF, Zhou KQ, Cheng JW, Hu B, Guo W, Yin Y, Huang JF, Zhou J, Fan J, Cheung TT, Qu XD, Yang XR. Circulating tumor cells are an indicator for the administration of adjuvant transarterial chemoembolization in hepatocellular carcinoma: A single-center, retrospective, propensity-matched study. *Clin Transl Med* 2020; **10**: e137 [PMID: 32702202 DOI: 10.1002/ctm2.137]

30 **Cristofanilli M**, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004; **351**: 781-791 [PMID: 15317891 DOI: 10.1056/NEJMoa040766]

31 **Sánchez-Lorencio MI**, Ramirez P, Saenz L, Martínez Sánchez MV, De La Orden V, Mediero-Valeros B, Veganzones-De-Castro S, Baroja-Mazo A, Revilla Nuin B, Gonzalez MR, Cascales-Campos PA, Noguera-Velasco JA, Minguela A, Díaz-Rubio E, Pons JA, Parrilla P. Comparison of Two Types of Liquid Biopsies in Patients With Hepatocellular Carcinoma Awaiting Orthotopic Liver Transplantation. *Transplant Proc* 2015; **47**: 2639-2642 [PMID: 26680058 DOI: 10.1016/j.transproceed.2015.10.003]

32 **Pang Y**, Wang C, Xiao R, Sun Z. Dual-Selective and Dual-Enhanced SERS Nanoprobes Strategy for

Circulating Hepatocellular Carcinoma Cells Detection. *Chemistry* 2018; **24**: 7060-7067 [PMID: 29521467 DOI: 10.1002/chem.201801133]

33 **D'Avola D**, Villacorta-Martin C, Martins-Filho SN, Craig A, Labgaa I, von Felden J, Kimaada A, Bonaccorso A, Tabrizian P, Hartmann BM, Sebra R, Schwartz M, Villanueva A. High-density single cell mRNA sequencing to characterize circulating tumor cells in hepatocellular carcinoma. *Sci Rep* 2018; **8**: 11570 [PMID: 30068984 DOI: 10.1038/s41598-018-30047-y]

34 **Yagci T**, Cetin M, Ercin PB. Cancer Stem Cells in Hepatocellular Carcinoma. *J Gastrointest Cancer* 2017; **48**: 241-245 [PMID: 28643126 DOI: 10.1007/s12029-017-9960-7]

35 **Masuda T**, Hayashi N, Iguchi T, Ito S, Eguchi H, Mimori K. Clinical and biological significance of circulating tumor cells in cancer. *Mol Oncol* 2016; **10**: 408-417 [PMID: 26899533 DOI: 10.1016/j.molonc.2016.01.010]

36 **Chen C**, Zhao S, Karnad A, Freeman JW. The biology and role of CD44 in cancer progression: therapeutic implications. *J Hematol Oncol* 2018; **11**: 64 [PMID: 29747682 DOI: 10.1186/s13045-018-0605-5]

37 **Satelli A**, Li S. Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cell Mol Life Sci* 2011; **68**: 3033-3046 [PMID: 21637948 DOI: 10.1007/s00018-011-0735-1]

38 **Guo W**, Sun YF, Shen MN, Ma XL, Wu J, Zhang CY, Zhou Y, Xu Y, Hu B, Zhang M, Wang G, Chen WQ, Guo L, Lu RQ, Zhou CH, Zhang X, Shi YH, Qiu SJ, Pan BS, Cao Y, Zhou J, Yang XR, Fan J. Circulating Tumor Cells with Stem-Like Phenotypes for Diagnosis, Prognosis, and Therapeutic Response Evaluation in Hepatocellular Carcinoma. *Clin Cancer Res* 2018; **24**: 2203-2213 [PMID: 29374055 DOI: 10.1158/1078-0432.CCR-17-1753]

39 **Mostert B**, Sieuwerts AM, Bolt-de Vries J, Kraan J, Lalmahomed Z, van Galen A, van der Spoel P, de Weerd V, Ramírez-Moreno R, Smid M, Verhoef C, IJzermans JN, Gratama JW, Sleijfer S, Foekens JA, Martens JW. mRNA expression profiles in circulating tumor cells of metastatic colorectal cancer patients. *Mol Oncol* 2015; **9**: 920-932 [PMID: 25655581 DOI: 10.1016/j.molonc.2015.01.001]

40 **Ou H**, Huang Y, Xiang L, Chen Z, Fang Y, Lin Y, Cui Z, Yu S, Li X, Yang D. Circulating Tumor Cell Phenotype Indicates Poor Survival and Recurrence After Surgery for Hepatocellular Carcinoma. *Dig Dis Sci* 2018; **63**: 2373-2380 [PMID: 29926241 DOI: 10.1007/s10620-018-5124-2]

41 **Liu HY**, Qian HH, Zhang XF, Li J, Yang X, Sun B, Ma JY, Chen L, Yin ZF. Improved method increases sensitivity for circulating hepatocellular carcinoma cells. *World J Gastroenterol* 2015; **21**: 2918-2925 [PMID: 25780289 DOI: 10.3748/wjg.v21.i10.2918]

42 **Li J**, Chen L, Zhang X, Zhang Y, Liu H, Sun B, Zhao L, Ge N, Qian H, Yang Y, Wu M, Yin Z. Detection of circulating tumor cells in hepatocellular carcinoma using antibodies against asialoglycoprotein receptor, carbamoyl phosphate synthetase 1 and pan-cytokeratin. *PLoS One* 2014; **9**: e96185 [PMID: 24763545 DOI: 10.1371/journal.pone.0096185]

43 **Zhang Y**, Zhang X, Zhang J, Sun B, Zheng L, Li J, Liu S, Sui G, Yin Z. Microfluidic chip for isolation of viable circulating tumor cells of hepatocellular carcinoma for their culture and drug sensitivity assay. *Cancer Biol Ther* 2016; **17**: 1177-1187 [PMID: 27662377 DOI: 10.1080/15384047.2016.1235665]

44 **Qi LN**, Xiang BD, Wu FX, Ye JZ, Zhong JH, Wang YY, Chen YY, Chen ZS, Ma L, Chen J, Gong WF, Han ZG, Lu Y, Shang JJ, Li LQ. Circulating Tumor Cells Undergoing EMT Provide a Metric for Diagnosis and Prognosis of Patients with Hepatocellular Carcinoma. *Cancer Res* 2018; **78**: 4731-4744 [PMID: 29915159 DOI: 10.1158/0008-5472.CAN-17-2459]

45 **Wang S**, Zheng Y, Liu J, Huo F, Zhou J. Analysis of circulating tumor cells in patients with hepatocellular carcinoma recurrence following liver transplantation. *J Investig Med* 2018; **66**: 1-6 [PMID: 29632031 DOI: 10.1136/jim-2017-000655]

46 **Aceto N**, Bardia A, Miyamoto DT, Donaldson MC, Wittner BS, Spencer JA, Yu M, Pely A, Engstrom A, Zhu H, Brannigan BW, Kapur R, Stott SL, Shioda T, Ramaswamy S, Ting DT, Lin CP, Toner M, Haber DA, Maheswaran S. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell* 2014; **158**: 1110-1122 [PMID: 25171411 DOI: 10.1016/j.cell.2014.07.013]

47 **Nam SJ**, Yeo HY, Chang HJ, Kim BH, Hong EK, Park JW. A New Cell Block Method for Multiple Immunohistochemical Analysis of Circulating Tumor Cells in Patients with Liver Cancer. *Cancer Res Treat* 2016; **48**: 1229-1242 [PMID: 27034142 DOI: 10.4143/crt.2015.500]

48 **Hirokawa F**, Hayashi M, Asakuma M, Shimizu T, Inoue Y, Uchiyama K. Risk factors and patterns of early recurrence after curative hepatectomy for hepatocellular carcinoma. *Surg Oncol* 2016; **25**: 24-29 [PMID: 26979637 DOI: 10.1016/j.suronc.2015.12.002]

49 **Xu X**, Zhang HL, Liu QP, Sun SW, Zhang J, Zhu FP, Yang G, Yan X, Zhang YD, Liu XS. Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. *J Hepatol* 2019; **70**: 1133-1144 [PMID: 30876945 DOI: 10.1016/j.jhep.2019.02.023]

50 **Rodríguez-Perálvarez M**, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol* 2013; **20**: 325-339 [PMID: 23149850 DOI: 10.1245/s10434-012-2513-1]

51 **Yu JJ**, Xiao W, Dong SL, Liang HF, Zhang ZW, Zhang BX, Huang ZY, Chen YF, Zhang WG, Luo HP, Chen Q, Chen XP. Effect of surgical liver resection on circulating tumor cells in patients with hepatocellular carcinoma. *BMC Cancer* 2018; **18**: 835 [PMID: 30126375 DOI: 10.1186/s12885-018-4744-4]

52 **Schulze K**, Gasch C, Staufer K, Nashan B, Lohse AW, Pantel K, Riethdorf S, Wege H. Presence of

EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *Int J Cancer* 2013; **133**: 2165-2171 [PMID: 23616258 DOI: 10.1002/ijc.28230]

53 **Sun C**, Liao W, Deng Z, Li E, Feng Q, Lei J, Yuan R, Zou S, Mao Y, Shao J, Wu L, Zhang C. The diagnostic value of assays for circulating tumor cells in hepatocellular carcinoma: A meta-analysis. *Medicine (Baltimore)* 2017; **96**: e7513 [PMID: 28723763 DOI: 10.1097/MD.0000000000007513]

54 **Micalizzi DS**, Maheswaran S, Haber DA. A conduit to metastasis: circulating tumor cell biology. *Genes Dev* 2017; **31**: 1827-1840 [PMID: 29051388 DOI: 10.1101/gad.305805.117]

55 **McGranahan N**, Swanton C. Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. *Cancer Cell* 2015; **27**: 15-26 [PMID: 25584892 DOI: 10.1016/j.ccell.2014.12.001]

56 **Zhou J**, Huang A, Yang XR. Liquid Biopsy and its Potential for Management of Hepatocellular Carcinoma. *J Gastrointest Cancer* 2016; **47**: 157-167 [PMID: 26969471 DOI: 10.1007/s12029-016-9801-0]

57 **Pinyol R**, Montal R, Bassaganyas L, Sia D, Takayama T, Chau GY, Mazzaferro V, Roayaie S, Lee HC, Kokudo N, Zhang Z, Torrecilla S, Moeini A, Rodriguez-Carunchio L, Gane E, Verslype C, Croitoru AE, Cillo U, de la Mata M, Lupo L, Strasser S, Park JW, Camps J, Solé M, Thung SN, Villanueva A, Pena C, Meinhardt G, Bruix J, Llovet JM. Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. *Gut* 2019; **68**: 1065-1075 [PMID: 30108162 DOI: 10.1136/gutjnl-2018-316408]

58 **Ramirez P**, Sáenz L, Cascales-Campos PA, González Sánchez MR, Llàcer-Millán E, Sánchez-Lorencio MI, Díaz-Rubio E, De La Orden V, Mediero-Valeros B, Navarro JL, Revilla Nuin B, Baroja-Mazo A, Noguera-Velasco JA, Sánchez BF, de la Peña J, Pons-Miñano JA, Sánchez-Bueno F, Robles-Campos R, Parrilla P. Oncological Evaluation by Positron-emission Tomography, Circulating Tumor Cells and Alpha Fetoprotein in Patients With Hepatocellular Carcinoma on the Waiting List for Liver Transplantation. *Transplant Proc* 2016; **48**: 2962-2965 [PMID: 27932119 DOI: 10.1016/j.transproceed.2016.07.035]

59 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

60 **Mazzola A**, Costantino A, Petta S, Bartolotta TV, Raineri M, Sacco R, Brancatelli G, Cammà C, Cabibbo G. Recurrence of hepatocellular carcinoma after liver transplantation: an update. *Future Oncol* 2015; **11**: 2923-2936 [PMID: 26414336 DOI: 10.2217/fon.15.239]

61 **Bertuzzo VR**, Cescon M, Ravaioli M, Grazi GL, Ercolani G, Del Gaudio M, Cucchetti A, D'Errico-Grigioni A, Golfieri R, Pinna AD. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. *Transplantation* 2011; **91**: 1279-1285 [PMID: 21617590 DOI: 10.1097/TP.0b013e3182187cf0]

62 **Xu W**, Cao L, Chen L, Li J, Zhang XF, Qian HH, Kang XY, Zhang Y, Liao J, Shi LH, Yang YF, Wu MC, Yin ZF. Isolation of circulating tumor cells in patients with hepatocellular carcinoma using a novel cell separation strategy. *Clin Cancer Res* 2011; **17**: 3783-3793 [PMID: 21527564 DOI: 10.1158/1078-0432.CCR-10-0498]

63 **Chen Z**, Lin X, Chen C, Chen Y, Zhao Q, Wu L, Wang D, Ma Y, Ju W, Chen M, He X. Analysis of preoperative circulating tumor cells for recurrence in patients with hepatocellular carcinoma after liver transplantation. *Ann Transl Med* 2020; **8**: 1067 [PMID: 33145286 DOI: 10.21037/atm-20-2751]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 979-987

DOI: 10.4240/wjgs.v13.i9.979

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

**Retrospective Cohort Study**

# Comparison of perioperative outcomes between laparoscopic and open partial splenectomy in children and adolescents

Mohamed Makansi, Martin Hutter, Till-Martin Theilen, Henning C Fiegel, Udo Rolle, Stefan Gfroerer

**ORCID number:** Mohamed Makansi 0000-0002-4300-8702; Martin Hutter 0000-0002-7455-8037; Till-Martin Theilen 0000-0003-4912-6547; Henning C Fiegel 0000-0001-5411-4335; Udo Rolle 0000-0002-1268-6092; Stefan Gfroerer 0000-0002-7273-6055.

**Author contributions:** Makansi M performed the acquisition, analysis and interpretation of data, drafted the paper and gave final approval of the version of the article to be published; Hutter M contributed substantially to the conception and design of the study, made critical revisions to important content of the manuscript and gave final approval of the version to be published; Theilen TM, Fiegel HC and Rolle U contributed substantially to analysis and interpretation of data, provided critical revisions related to important intellectual content of the manuscript and gave final approval of the manuscript version to be published; Gfroerer S designed the research study and provided substantial contribution to acquisition, analysis and interpretation of data, contributed substantially to drafting the manuscript and gave final approval of the version to be published.

**Institutional review board**

**Mohamed Makansi, Martin Hutter, Till-Martin Theilen, Henning C Fiegel, Udo Rolle,** Department of Pediatric Surgery and Pediatric Urology, University Hospital Frankfurt, Frankfurt am Main 60590, Germany

**Stefan Gfroerer,** Department of Pediatric Surgery and Pediatric Urology, Helios Clinic Berlin-Buch, Berlin 13125, Germany

**Corresponding author:** Stefan Gfroerer, MD, PhD, Director, Department of Pediatric Surgery and Pediatric Urology, Helios Clinic Berlin-Buch, Schwanebecker Chaussee 50, Berlin 13125, Germany. stefan.gfroerer@helios-gesundheit.de

## Abstract

***BACKGROUND***

In order to avoid consequences of total splenectomy, partial splenectomy (PS) is increasingly reported. The purpose of this study was to compare perioperative outcomes of laparoscopic PS (LPS) and open PS (OPS) in children and adolescents.

***AIM***

To compare perioperative outcomes of patients with LPS and OPS.

***METHODS***

After institutional review board approval, a total of 26 patients that underwent LPS or OPS between January 2008 and July 2018 were identified from the database of our tertiary referral center. In total, 10 patients had LPS, and 16 patients underwent OPS. Blood loss was calculated by Mercuriali's formula. Pain scores, analgesic requirements and complications were assessed. The Wilcoxon rank sum test was used for comparison. To compare categorical variables, Fisher's exact test was applied.

***RESULTS***

LPS was performed in 10 patients; 16 patients had OPS. Demographics (except for body mass index and duration of follow-up), indicating primary disease, preoperative spleen size and postoperative spleen volume, perioperative hematological parameters, postoperative pain scores, analgesic requirements, adverse events according to the Clavien-Dindo classification and the comprehensive complication index, median time from operation to initiation of feeds, median time from operation to full feeds, median time from operation to mobilization and

**statement:** The study protocols were reviewed and approved by the Ethics Committee of the University Hospital Frankfurt (339/18).

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written informed consent.

**Conflict-of-interest statement:** Makansi M, Hutter M and Drs. Gfroerer S, Fiegel HC, Theilen TM and Rolle U have no conflicts of interest or financial ties to disclose in relation to this manuscript.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.



**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Germany

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B

median length of hospital stay did not differ between LPS and OPS. Median (range) operative time (min) was longer in LPS compared to the OPS group [185 (135-298) *vs* 144 (112-270), respectively; $P = 0.048$]. Calculated perioperative blood loss (mL of red blood cell count) was higher in the LPS group compared to OPS [87 (-45-777) *vs* -37 (-114-553), respectively; $P = 0.039$].

*CONCLUSION*

This is the first study that compared outcomes of LPS and OPS. Both operative approaches had comparable perioperative outcomes. LPS appears to be a viable alternative to OPS.

**Key Words:** Laparoscopic *vs* open; Laparoscopy; Partial splenectomy; Perioperative outcome; Children; Adolescents



**Core Tip:** In this retrospective study, perioperative outcomes of children and adolescents that underwent laparoscopic or open partial splenectomy were analyzed. Postoperative outcomes including initiation of feeds and mobilization, adverse events assessed according to the Clavien-Dindo classification and the comprehensive complication index, postoperative pain scores and analgesic requirements were similar between both groups. Operative time and intraoperative blood loss were higher in the laparoscopic group. Results indicate that laparoscopic partial splenectomy is a safe alternative to open partial splenectomy. Future research needs to focus on a larger patient cohort and a prospective study design.

**Citation:** Makansi M, Hutter M, Theilen TM, Fiegel HC, Rolle U, Gfroerer S. Comparison of perioperative outcomes between laparoscopic and open partial splenectomy in children and adolescents. *World J Gastrointest Surg* 2021; 13(9): 979-987
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/979.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.979

## INTRODUCTION

The urge to implement minimally invasive approaches for traditionally open surgical procedures has occupied all surgical specialties for several decades[1], especially for an open procedure that inevitably requires a large abdominal incision such as a partial splenectomy (PS) in patients with splenomegaly. A reduction of transabdominal invasiveness appears desirable. Frequent reasoning advocating a minimally invasive approach in PS comprises a better cosmesis, less pain and less complications (*i.e.* adhesions)[2,3]. However, data comprising both techniques are rare[4]. Laparoscopic PS (LPS) has first been described by Poulin *et al*[5] in 1995. Several benefits resulting from a minimal invasive approach of this procedure have been described[6,7]. However, to date there are no data available stating which approach can be regarded as superior over the other. The aim of this study was to review perioperative outcomes of children and adolescent patients that had undergone either laparoscopic or open PS (OPS) and to compare their outcomes.

## MATERIALS AND METHODS

### *Study design*

In this retrospective study, we analyzed a series of 26 consecutive patients who underwent either LPS or OPS between January 2008 and July 2018 at the University Hospital Frankfurt. Patients who experienced an unplanned conversion to the open approach were allocated to the laparoscopic group. The study protocols were reviewed and approved by the Ethics Committee of the University Hospital Frankfurt (339/18). Analysis of clinical data included demographics, spleen characteristics,

Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 9, 2021
**Peer-review started:** February 9, 2021
**First decision:** March 30, 2021
**Revised:** April 10, 2021
**Accepted:** July 29, 2021
**Article in press:** July 29, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Zhang L
**S-Editor:** Gao CC
**L-Editor:** Filipodia
**P-Editor:** Ma YJ

operative and hematological variables, postoperative outcomes and postoperative adverse events. Demographics included gender, age at operation, weight and height of the patient, the body mass index at operation, the indicating primary disease and the duration of follow-up. Spleen characteristics included the longitudinal diameter of the spleen prior to operation measured by ultrasound and the postoperative residual spleen volume. Operative parameters included operative time and the frequency of a simultaneous cholecystectomy. The operative time included the time for simultaneous cholecystectomy. The procedures were classified into primary or secondary operation. Primary operation indicated that the patient underwent a PS for the first time, whereas secondary operation indicated that the patient was operated a second time (redo PS).

### Outcome measures

Postoperative outcome variables included time from operation to initiation of feeds (day on which feeding was initiated orally), time from operation to full feeds (day on which the parenteral nutrition was ceased), time from operation to mobilization of the patients and length of the postoperative hospital stay. The length of hospital stay did not include the day of operation but did include the day of discharge. For evaluation of individual postoperative adverse events we applied the Clavien-Dindo classification [8]. The Clavien-Dindo classification consists of seven grades (I, II, IIIa, IIIb, IVa, IVb, V). We categorized into minor morbidity (Clavien-Dindo grade I and II) and major morbidity (Clavien-Dindo grade III-V). Minor morbidity displayed non-invasive treatment including the need of red blood cell transfusions. Major morbidity comprised the need of surgical, endoscopic or radiological intervention. Additionally, we calculated the comprehensive complication index[9]. This index reflects the overall postoperative morbidity and its severity, ranging from 0 (no complication) to 100 (death). To calculate the comprehensive complication index we used the calculator available online (http://www.assessurgery.com).

For assessment of the perioperative blood loss we used the Mercuriali's formula[10]: estimated blood loss [mL of red blood cell count (RBC)] = Blood volume (mL) × [hematocrit (Hct)$_{preop}$ - Hct$_{postop}$] + RBC transfusion volume (mL).

The formula uses the difference between the preoperative hematocrit (Hct$_{preop}$) and the hematocrit of the fifth postoperative day (Hct$_{postop}$). A negative value of the estimated blood loss (mL of RBC) occurs when the volume of perioperatively transfused RBC exceeds the RBC loss.

Patient blood volume can be calculated through the Nadler formula[11]: blood volume (mL) = Weight (kg) × estimated blood volume (mL/kg).

For the different age groups and sexes, we used the following blood volumes per kilogram body weight: children < 10 years 75 mL/kg, males between 10-19 years 70 mL/kg and females between 10-19 years 65 mL/kg.

Furthermore, we analyzed how many patients received RBC, fresh frozen plasma and thrombocyte concentrate intra- and postoperatively. Transfusions of blood products were counted from operation to discharge of the patient.

Postoperative pain was assessed by a numerical rating scale ranging from 0 (no pain at all) to 10 (worst possible pain)[12,13]. The clinical pain scores were measured repeatedly daily by healthcare professionals. For a nuanced assessment of the patients' postoperative analgesic requirements, we categorized the pain medication into opioids and non-opioids and calculated the cumulative doses during the hospital stay. Three patients in the open group were excluded from pain assessment due to peridural anesthesia treatment.

### Statistical analysis

Continuous data were presented as median with range. For comparison, the Wilcoxon rank sum test was used. Pain assessment was measured longitudinally in F1-LD-F1 design, and the Wald-Test was used. Furthermore, we applied Fisher's exact test to compare categorical variables. Testing was based on a 5% significance level. We used statistical software R version 3.4.0 for analysis [R Foundation for Statistical Computing, Vienna, Austria (www.R-project.org)].

The statistical methods of this study were reviewed by Mr. Hutter M, biomedical statistician from the Department of Pediatric Surgery and Pediatric Urology, University Hospital Frankfurt.

## RESULTS

### Baseline characteristics

A total of 26 patients underwent a PS. The patient cohort consisted of 16 patients with OPS and 10 patients with LPS. OPS were performed by Gfroerer S, Theilen TM and Fiegel HC. Gfroerer S and Theilen TM performed LPS.

Table 1 compares the demographic data of both groups. Patients with LPS had a higher body mass index at time of operation [median (range), 21.3 (14.9-25.7) *vs* 16.6 (12.7-24.2) kg/m$^2$, $P = 0.036$] and a shorter follow-up period [median (range), 4.1 (2.1-5.2) *vs* 6.6 (4.4-11.4) years, $P < 0.001$]. The mean age was 13.1 (7.7-20.3) and 10.7 (5.0-18.2), respectively, for the LPS and OPS group. Table 2 displays the pre- and postoperative spleen characteristics of the laparoscopic group in comparison to the open group. Spleen characteristics did not differ in both groups.

Table 3 shows the operative variables. The operative time was higher in the LPS cohort compared to the OPS cohort [median (range), 185 (135-298) *vs* 144 (112-270) min, $P = 0.048$]. There were 1/10 (10%) conversions to laparotomy in the LPS group.

### Treatment outcomes

Table 4 compares postoperative outcomes in the LPS *vs* the OPS group. Both postoperative reconvalescence variables during hospital stay and scores of adverse events were comparable between both groups.

Table 5 lists all individual postoperative adverse events recorded within hospital stay. Neither post-splenectomy sepsis nor death occurred perioperatively.

Table 6 shows the hematological variables. The estimated blood loss was higher in the LPS group [median (range), 87 (-45-777) *vs* -37 (-114-553) mL, $P = 0.039$]. Individual frequency of perioperative blood product transfusions (RBC, fresh frozen plasma or thrombocyte concentrate) did not differ between groups.

Table 7 displays the results of the pain assessment and pain management in both groups. There was no difference between LPS and OPS groups.

## DISCUSSION

This is a retrospective analysis comparing perioperative outcomes of children and adolescents that underwent either LPS or OPS. To the best of our knowledge, this is the only study comparing both operative approaches to date.

In our study postoperative time from operation to initiation of feeds and to full feeds, time from operation until patient's mobilization, postoperative adverse events, pain assessment and analgesic requirements did not differ between LPS and OPS. Operative time in the LPS group was longer, and the estimated blood loss was higher reflecting the technical challenges of the minimally invasive surgery. In both groups, only intraoperative (not postoperative) transfusions of blood products were performed.

We assessed adverse events using the Clavien-Dindo classification and by calculating the comprehensive complication index. Both scores did not reveal differences between the LPS and OPS group.

Laparoscopic handling of the spleen was noticeably more difficult in spleens measuring ≥ 25 cm in cranio-caudal diameter due to the restricted view. As a reflection of our early learning curve, a patient's spleen sized > 25 cm led to a conversion to open splenectomy. This case taught us the need to consider a timely intraoperative laparoscopic multiple dissection of a large spleen in order to facilitate a controlled removal of the splenic parenchyma from the abdominal cavity without conversion to open surgery. The conversion rate in a larger cohort reported by Liu and Fan[14] was 3.6%.

There are a number of studies that examine the feasibility and safety of the LPS for different indications, such as splenic benign lesions[15,16], traumata that require emergency surgery[17] or patients with hereditary spherocytosis[16]. All these studies come to the result that LPS is safe and feasible; however, none of the studies compared perioperative outcomes of both approaches.

Our study has several limitations. One limitation is that our study was restricted to children and adolescents. The median age of all patients in our cohort was 11.9 years. Generally, there is very little data available on children and young adults undergoing PS. Costi *et al*[18] carried out a systematic review of 2130 published cases of PS published between 1960 and December 2017. Patient average age was 18.4 years. Because older patients undergoing a PS were suffering from severe comorbidities like portal hypertension (patient mean age 27.6 years) or neoplastic lesions such as

**Table 1 Demographic data for 26 patients undergoing laparoscopic partial splenectomy or open partial splenectomy**

| | Laparoscopic, *n* = 10 | Open, *n* = 16 | *P* value |
|---|---|---|---|
| Gender (male:female) | 2:8 | 7:9 | 0.399 |
| Age at operation (yr) | 13.1 (7.7-20.3) | 10.7 (5.0-18.2) | 0.220 |
| Weight at operation (kg) | 50.5 (25.0-70.0) | 32.6 (18.0-70.0) | 0.120 |
| Height at operation (m) | 1.54 (1.28-1.67) | 1.41 (1.10-1.85) | 0.316 |
| BMI at operation (kg/m$^2$) | 21.30 (14.92-25.71) | 16.58 (12.71-24.22) | 0.036 |
| Indicating primary disease | | | 0.292 |
| Hereditary spherocytosis (%) | 9 (90) | 14 (88) | |
| DiGeorge syndrome (%) | 0 (0) | 2 (13) | |
| Splenic cyst (%) | 1 (10) | 0 (0) | |
| Duration of follow-up (yr) | 4.1 (2.1-5.2) | 6.6 (4.4-11.4) | < 0.001 |

Data are median (range) or frequency (%). BMI: Body mass index.

**Table 2 Spleen characteristics**

| | Laparoscopic, *n* = 10 | Open, *n* = 16 | *P* value |
|---|---|---|---|
| Preoperative longitudinal spleen diameter (cm) | 15.8 (12.2-29.0) | 14.0 (9.9-28.9) | 0.523 |
| Postoperative spleen volume (cm$^3$) | 24 (16-48) | 31 (11-210) | 0.244 |
| Total splenectomy leaving the accessory spleen (%) | 2 (20) | 0 (0) | 0.138 |
| Splenic US visibility in follow-up sonography (%) | 4 (57) – *n* = 7 | 11 (79) – *n* = 14 | 0.354 |

Data are median (range) or frequency (%). US: Ultrasonography.

**Table 3 Operative variables**

| | Laparoscopic, *n* = 10 | Open, *n* = 16 | *P* value |
|---|---|---|---|
| Operative time (min) | 185 (135-298) | 144 (112-270) | **0.048** |
| Simultaneous cholecystectomy (%) | 6 (60) | 13 (81) | 0.369 |
| Primary (first PS) operation (%) | 10 (100) | 15 (94) | 1 |
| Secondary (redo PS) operation | 0 | 1 (6) | |
| Conversion to open (%) | 1 (10) | | |

Data are median (range) or frequency (%). PS: Partial splenectomy.

metastases (patient mean age 40 years) results from this study cannot easily be transferred to younger age groups. Further, patients in the review by Costi *et al*[18] undergoing a PS due to hematological issues represented 48% of all indications; 42% of the patients underwent the procedure due to nonhematological and nontraumatic condition and 9% as a result of a trauma. In contrast, 90% (LPS group) and 88% (OPS group) of our patients underwent PS due to hypersplenism caused by hereditary spherocytosis. No patient in our study underwent PS resulting from an acute trauma. All patients were electively admitted to hospital. The elective process guaranteed the presence of a senior surgeon with a long-term surgical experience.

According to the findings of our study when comparing both approaches, LPS and OPS are both feasible and safe procedures despite differences in operative time and intraoperative blood loss. LPS is a technically demanding minimally invasive procedure, resulting in a longer operative time compared to the open approach.

**Table 4 Postoperative outcomes**

| | Laparoscopic, *n* = 10 | Open, *n* = 16 | *P* value |
|---|---|---|---|
| Time from OP to initiation of feeds (h) | 37 (4-62) | 28 (16-63) | 0.580 |
| Time from OP to full feeds (d) | 3.5 (2.0-7.0) | 4.0 (3.0-6.0) | 0.313 |
| Time from OP to mobilization (h) | 46 (22-92) | 47 (19-98) | 0.812 |
| Length of postoperative hospital stay (d) | 5 (3-8) | 5 (3-8) | 0.602 |
| Morbidity (Clavien-Dindo grade I-V) (%) | 3 (30) | 9 (56) | 0.248 |
| Minor morbidity (Clavien-Dindo grade I-II) (%) | 3 (30) | 8 (50) | 0.428 |
| Major morbidity (Clavien-Dindo grade III-V) (%) | 0 (0) | 2 (13) | 0.508 |
| Comprehensive complication index | 0 (0-24.20) | 8.66 (0-39.70) | 0.387 |

Data are median (range) or frequency (%). OP: Operation.

**Table 5 Individual profile of postoperative adverse events graded according to Clavien-Dindo and with calculated comprehensive complication index**

| | Postoperative adverse events | Clavien-Dindo grade | CCI |
|---|---|---|---|
| **Laparoscopic** | | | |
| Patient 17 | Urticaria | II | 20.9 |
| Patient 18 | Pruritus | II | 20.9 |
| Patient 24 | Pleural effusion | I | |
| | External genital edema | I | |
| | Blood transfusion | II | 24.2 |
| **Open** | | | |
| Patient 1 | Lid edema | I | 8.7 |
| Patient 3 | Urticaria | II | 20.9 |
| Patient 4 | Pleural effusion | I | 8.7 |
| Patient 6 | Pleural effusion | I | 8.7 |
| Patient 7 | Wound dehiscence | I | 8.7 |
| Patient 9 | Exanthema | II | 20.9 |
| Patient 11 | Urine retention. bladder catheterization | IIIa | 26.2 |
| Patient 13 | Wound infection | II | |
| | Redo partial splenectomy | IIIb | 39.7 |
| Patient 20 | Pleural effusion | I | 8.7 |

CCI: Comprehensive complication index.

The small size of our retrospective case series does not enable us to draw representative conclusions. However, our analysis allows us to view the laparoscopic operation as a viable alternative compared to the open approach and warrants future research comprising prospective multicentric study designs.

## CONCLUSION

This is the first study that compared outcomes of LPS and OPS. LPS is a viable alternative to the open operation with a broadly similar perioperative outcome providing superior cosmesis of the ventral abdominal wall. However, a longer

**Table 6 Perioperative hematological variables**

| | Laparoscopic, *n* = 10 | Open, *n* = 16 | *P* value |
|---|---|---|---|
| Latest hematocrit prior to operation (%) | 31.6 (18.7-33.4) | 28.1 (24.1-35.7) | 0.633 |
| Latest hemoglobin prior to operation (g/L) | 114 (65-122) | 97 (78-133) | 0.221 |
| Lowest hematocrit postoperative (%) | 28.0 (26.0-31.0) | 30.0 (23.0-35.0) | 0.131 |
| Lowest hemoglobin postoperative (g/L) | 93 (79-104) | 99 (67-126) | 0.118 |
| Estimated blood loss (mL of RBC) | 87 (-45-777) | -37 (-114-553) | **0.039** |
| Patients receiving intra- or postoperative RBC (%) | 2 (20) | 1 (6) | 0.538 |
| Patients receiving intra- or postoperative FFP and TC (%) | 0 (0) | 2 (13) | 0.508 |

Data are median (range) or frequency (%). RBC: Red blood cell count; FFP: Fresh frozen plasma; TC: Thrombocyte concentrate.

**Table 7 Pain assessment and analgesics**

| | Laparoscopic, *n* = 10 | Open, *n* = 13 | *P* value |
|---|---|---|---|
| Pain assessment[1] (0-10 NRS) | | | 0.152[2] |
| Day 1 | 4 (2-6) | 4 (2-9) | |
| Day 2 | 2 (0-4) | 4 (1-7) | |
| Day 3 | 1.0 (0-2.5) | 2.0 (1.0-4.0) | |
| Day 4 | 0 (0-1) | 1 (0-2) | |
| Day 5 | 0 (0-3) | 0 (0-5) | |
| Day 6 | 0 (0-4) | 0 (0-0) | |
| Day 7 | 0 (0-0) | 0 (0-0) | |
| Non-opioids — cumulative doses (mg/kg body weight) | | | |
| Day 1 | 33.5 (10.0-48.4) | 37.7 (19.2-50.0) | |
| Day 2 | 35.3 (10.0-60.5) | 31.6 (10.0-68.2) | |
| Day 3 | 22.5 (0-37.0) | 30.3 (9.3-54.6) | |
| Day 4 | 5.0 (0-36.3) | 18.2 (0-39.9) | |
| Day 5 | 0 (0-36.3) | 0 (0-18.8) | |
| Day 6 | 0 (0-65.3) | 0 (0-0) | |
| Day 7 | 0 (0-36.3) | 0 (0-0) | |
| Overall dose | 113.0 (20.1-308.0) | 134.8 (50.5-172.7) | 0.232 |
| Opioids — cumulative doses (mg/kg body weight) | | | |
| Day 1 | 0.44 (0-0.69) | 0.32 (0-0.51) | |
| Day 2 | 0.42 (0-0.93) | 0.28 (0-0.55) | |
| Day 3 | 0.25 (0-0.71) | 0.09 (0-0.55) | |
| Day 4 | 0.08 (0-0.65) | 0 (0-0.31) | |
| Day 5 | 0 (0-0.53) | 0 (0-0.08) | |
| Day 6 | 0 (0-0.31) | 0 (0-0) | |
| Day 7 | 0 (0-0.26) | 0 (0-0) | |
| Overall dose | 1.06 (0.09-3.58) | 0.72 (0-1.75) | 0.343 |

[1]Median of all Numerical Rating Scale scores within 24 h.

[2]Comparison whether the pain scores of each day differed between the groups over time. Data are median (range) or frequency (%). Three patients in the open group were excluded from comparison due to peridural anesthesia treatment. NRS: Numerical Rating Scale.

operative time and higher intraoperative blood loss necessitates further laparoscopic refinement to adequately balance the superior cosmesis of the minimally invasive approach.

## ARTICLE HIGHLIGHTS

### *Research background*

Partial splenectomy for the treatment of hypersplenism is increasingly reported. To date no data stating which approach can be regarded as superior over the other are available.

### *Research motivation*

The purpose of this study was to compare perioperative outcomes of laparoscopic partial splenectomy (LPS) and open partial splenectomy (OPS) in children and adolescents.

### *Research objectives*

The objective of this study was to analyze and compare LPS and OPS with perioperative outcome parameters.

### *Research methods*

We retrospectively reviewed all patients ($n$ = 26) that underwent LPS ($n$ = 10) or OPS ( $n$ = 16) between January 2008 and July 2018. Clinical data including demographics, spleen characteristics, operative and hematological variables, postoperative outcomes including pain scores and analgesic requirements as well as postoperative adverse events were analyzed.

### *Research results*

Perioperative hematological parameters, postoperative pain scores, analgesic requirements, adverse events according to the Clavien-Dindo classification and the comprehensive complication index, median time from operation to initiation of feeds, median time from operation to full feeds, median time from operation to mobilization and median length of hospital stay did not differ between LPS and OPS. Median operative time was longer in LPS compared to the OPS group. Calculated perioperative blood loss (mL of red blood cells) was higher in the LPS group compared to OPS.

### *Research conclusions*

This is the first study that compared outcomes of LPS and OPS. LPS appears to be a viable alternative to the open operation with a broadly similar perioperative outcome providing superior cosmesis of the ventral abdominal wall.

### *Research perspectives*

Our study results warrant a prospective multicentric clinical trial to compare outcomes in a larger group.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of all professional colleagues, which helped to perform this research.

## REFERENCES

1 **Carr BM**, Lyon JA, Romeiser J, Talamini M, Shroyer ALW. Laparoscopic *vs* open surgery: a

systematic review evaluating Cochrane systematic reviews. *Surg Endosc* 2019; **33**: 1693-1709 [PMID: 30357523 DOI: 10.1007/s00464-018-6532-2]

2 **Winslow ER**, Brunt LM. Perioperative outcomes of laparoscopic *vs* open splenectomy: a meta-analysis with an emphasis on complications. *Surgery* 2003; **134**: 647-53; discussion 654 [PMID: 14605626 DOI: 10.1016/s0039-6060(03)00312-x]

3 **Minkes RK**, Lagzdins M, Langer JC. Laparoscopic *vs* open splenectomy in children. *J Pediatr Surg* 2000; **35**: 699-701 [PMID: 10813328 DOI: 10.1053/jpsu.2000.6010]

4 **Esposito F**, Noviello A, Moles N, Cantore N, Baiamonte M, Coppola Bottazzi E, Miro A, Crafa F. Partial splenectomy: A case series and systematic review of the literature. *Ann Hepatobiliary Pancreat Surg* 2018; **22**: 116-127 [PMID: 29896572 DOI: 10.14701/ahbps.2018.22.2.116]

5 **Poulin EC**, Thibault C, DesCôteaux JG, Côté G. Partial laparoscopic splenectomy for trauma: technique and case report. *Surg Laparosc Endosc* 1995; **5**: 306-310 [PMID: 7551284]

6 **Dutta S**, Price VE, Blanchette V, Langer JC. A laparoscopic approach to partial splenectomy for children with hereditary spherocytosis. *Surg Endosc* 2006; **20**: 1719-1724 [PMID: 17024531 DOI: 10.1007/s00464-006-0131-3]

7 **Slater BJ**, Chan FP, Davis K, Dutta S. Institutional experience with laparoscopic partial splenectomy for hereditary spherocytosis. *J Pediatr Surg* 2010; **45**: 1682-1686 [PMID: 20713220 DOI: 10.1016/j.jpedsurg.2010.01.037]

8 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

9 **Slankamenac K**, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013; **258**: 1-7 [PMID: 23728278 DOI: 10.1097/SLA.0b013e318296c732]

10 **Mercuriali F**, Inghilleri G. Proposal of an algorithm to help the choice of the best transfusion strategy. *Curr Med Res Opin* 1996; **13**: 465-478 [PMID: 9010613 DOI: 10.1185/03007999609115227]

11 **Nadler SB**, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; **51**: 224-232 [PMID: 21936146]

12 **Haefeli M**, Elfering A. Pain assessment. *Eur Spine J* 2006; **15** Suppl 1: S17-S24 [PMID: 16320034 DOI: 10.1007/s00586-005-1044-x]

13 **Ruskin D**, Lalloo C, Amaria K, Stinson JN, Kewley E, Campbell F, Brown SC, Jeavons M, McGrath PA. Assessing pain intensity in children with chronic pain: convergent and discriminant validity of the 0 to 10 numerical rating scale in clinical practice. *Pain Res Manag* 2014; **19**: 141-148 [PMID: 24712019 DOI: 10.1155/2014/856513]

14 **Liu G**, Fan Y. Feasibility and Safety of Laparoscopic Partial Splenectomy: A Systematic Review. *World J Surg* 2019; **43**: 1505-1518 [PMID: 30767061 DOI: 10.1007/s00268-019-04946-8]

15 **Chen J**, Yu S, Xu L. Laparoscopic Partial Splenectomy: A Safe and Feasible Treatment for Splenic Benign Lesions. *Surg Laparosc Endosc Percutan Tech* 2018; **28**: 287-290 [PMID: 30180141 DOI: 10.1097/SLE.0000000000000568]

16 **Wang X**, Wang M, Zhang H, Peng B. Laparoscopic partial splenectomy is safe and effective in patients with focal benign splenic lesion. *Surg Endosc* 2014; **28**: 3273-3278 [PMID: 24939157 DOI: 10.1007/s00464-014-3600-0]

17 **Li H**, Wei Y, Peng B, Li B, Liu F. Feasibility and safety of emergency laparoscopic partial splenectomy: A retrospective analysis. *Medicine (Baltimore)* 2017; **96**: e6450 [PMID: 28422834 DOI: 10.1097/MD.0000000000006450]

18 **Costi R**, Castro Ruiz C, Romboli A, Wind P, Violi V, Zarzavadjian Le Bian A. Partial splenectomy: Who, when and how. A systematic review of the 2130 published cases. *J Pediatr Surg* 2019; **54**: 1527-1538 [PMID: 30665627 DOI: 10.1016/j.jpedsurg.2018.11.010]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 988-999

DOI: 10.4240/wjgs.v13.i9.988

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

**Retrospective Cohort Study**

# Suture ligation for submucosal hemostasis during hand-sewn side-to-side duodeno-ileostomy in simultaneous pancreas and kidney transplantation

Hui Wang, Ying-Xin Fu, Wen-Li Song, Chun-Bai Mo, Gang Feng, Jie Zhao, Guang-Hui Pei, Xiao-Feng Shi, Zhen Wang, Yu Cao, Ye-Qi Nian, Zhong-Yang Shen

**ORCID number:** Hui Wang 0000-0002-6081-3834; Ying-Xin Fu 0000-0001-8010-224X; Wen-Li Song 0000-0001-6286-2704; Chun-Bai Mo 0000-0002-4226-9636; Gang Feng 0000-0002-1627-372X; Jie Zhao 0000-0002-6450-5046; Guang-Hui Pei 0000-0001-7691-3306; Xiao-Feng Shi 0000-0003-4052-4223; Zhen Wang 0000-0002-7746-8408; Yu Cao 0000-0002-1864-1784; Ye-Qi Nian 0000-0002-7479-5307; Zhong-Yang Shen 0000-0003-0045-4355.

**Author contributions:** Wang H contributed to acquisition of data and wrote the manuscript; Fu YX and Shen ZY provided substantial contribution to the conception and design of the study and corrected the manuscript; Song WL, Mo CB, Feng G, Zhao J, Pei GH, Shi XF and Wang Z performed operations and provided study materials of the patients; Cao Y and Nian YQ contributed to acquisition of data, analysis, and interpretation of data.

**Supported by** National Natural Science Foundation of China, No. 81970654.

**Institutional review board statement:** The study was approved by the clinical research ethics committee of the Tianjin

**Hui Wang, Ying-Xin Fu, Wen-Li Song, Chun-Bai Mo, Gang Feng, Jie Zhao, Guang-Hui Pei, Xiao-Feng Shi, Zhen Wang, Yu Cao, Ye-Qi Nian, Zhong-Yang Shen,** Department of Kidney and Pancreas Transplant, Tianjin First Central Hospital, School of Medicine, Nankai University, Tianjin 300192, China

**Corresponding author:** Ying-Xin Fu, MD, Chief Doctor, Department of Kidney and Pancreas Transplant, Tianjin First Central Hospital, School of Medicine, Nankai University, No. 24 Fukang Road, Nankai District, Tianjin 300192, China. yingxinfu@nankai.edu.cn

## Abstract

### *BACKGROUND*

Enteric anastomotic (EA) bleeding is a potentially life-threatening surgical complication associated with enteric anastomosis during simultaneous pancreas and kidney transplantation (SPKT).

### *AIM*

To investigate whether suture ligation (SL) for submucosal hemostasis during hand-sewn enteric anastomosis could decrease the morbidity of early EA bleeding in SPKT.

### *METHODS*

We compared the outcomes of 134 patients classified into SL ($n$ = 44) and no SL (NSL) groups ($n$ = 90). This study adheres to the declarations of Istanbul and Helsinki and all donors were neither paid nor coerced.

### *RESULTS*

During the first postoperative week, the EA bleeding rate in the SL group was lower than that in the NSL group (2.27% *vs* 15.56%; $P$ = 0.021); no relationship was found between EA bleeding and donor age, mean pancreatic cold ischemia time, platelet count, prothrombin time international normalized rate, activated partial thromboplastin time, and thrombin time. Anastomotic leakage was observed in one case in the SL group at postoperative day (POD) 14 and in one case at POD 16 in the NSL group ($P$ = 0.754). No significant difference was found between the two groups in the patient survival, pancreas graft survival, or kidney graft

First Central Hospital.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** All the authors have no conflict of interest related to the manuscript.

**Data sharing statement:** The anonymous dataset is available on request from the corresponding author at yingxinfu@nankai.edu.cn.

**STROBE statement:** The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.



**Manuscript source:** Unsolicited manuscript

**Specialty type:** Transplantation

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 22, 2021
**Peer-review started:** March 22, 2021
**First decision:** May 13, 2021
**Revised:** May 17, 2021
**Accepted:** August 10, 2021
**Article in press:** August 10, 2021

survival.

*CONCLUSION*

SL for submucosal hemostasis during hand-sewn enteric anastomosis in SPKT can decrease the morbidity of early EA bleeding without increasing the anastomotic leakage rate.

**Key Words:** Anastomosis; Gastrointestinal bleeding; Hemostasis; Ligation; Pancreas; Transplantation



**Core Tip:** Enteric anastomotic (EA) bleeding is a potentially life-threatening complication of simultaneous pancreas and kidney transplantation (SPKT) and can result in graft loss; therefore, it is essential to lower the incidence of EA bleeding. This study aimed to investigate whether suture ligation for submucosal hemostasis during enteric anastomosis could decrease the morbidity of early EA bleeding in SPKT. By comparing the outcomes of patients of suture ligation and no suture ligation groups, we found that suture ligation for submucosal hemostasis during enteric anastomosis in SPKT can decrease the morbidity of early EA bleeding without concurrently increasing the anastomotic leakage rate.

**Citation:** Wang H, Fu YX, Song WL, Mo CB, Feng G, Zhao J, Pei GH, Shi XF, Wang Z, Cao Y, Nian YQ, Shen ZY. Suture ligation for submucosal hemostasis during hand-sewn side-to-side duodeno-ileostomy in simultaneous pancreas and kidney transplantation. *World J Gastrointest Surg* 2021; 13(9): 988-999
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/988.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.988

## INTRODUCTION

Pancreas transplantation is the treatment of choice for patients with type 1 insulin-dependent diabetes mellitus; recently, more patients with type 2 diabetes mellitus have undergone pancreas transplantation[1]. In the United States, simultaneous pancreas and kidney transplantation (SPKT) was the most common type of pancreas transplantation in 2018[1]. More than 80% of pancreas transplantations are performed with enteric drainage (ED), and systemic venous drainage is used for more than 90% of pancreas transplantations[2]. The site of enteric anastomosis can range from the stomach to the distal ileum of the recipient[3-6]; most often, the site of anastomosis is at the jejunum[2]. Direct side-to-side anastomosis between the transplanted duodenal segment and the recipient small bowel is the most common technique. Gastrointestinal (GI) bleeding and anastomotic leak are the most common surgical complications associated with enteric anastomosis[7]. GI bleeding may occur early and late after transplantation, and the morbidity of GI bleeding could be as high as approximately 11% according to previous reports[5,8]; it can result in graft loss and can be a life-threatening condition[7,9]. The sites of GI bleeding are mainly at the level of the enteric anastomosis[8,9]. Suture ligation (SL) techniques have been used during hemostasis for larger blood vessels throughout gastrectomy. The intestinal wall has abundant microvessels. For ordinary small intestinal anastomosis, sufficient suture pitch and the adequate strength of knotting can ensure adequate hemostasis during the anastomosis between the small intestine, and an SL technique is not needed usually. Enteric anastomosis during SPKT is different from ordinary small intestinal anastomosis: The transplanted duodenal segment is edematous after blood reperfusion, and the anastomotic stoma is corroded by constant exocrine outputs of the pancreas graft. There have been no reports on whether the SL technique is beneficial for submucosal hemostasis during hand-sewn enteric anastomosis in pancreas transplantation. To investigate the advantages and disadvantages of this novel technique on early EA bleeding and anastomotic leakage, we retrospectively analyzed the clinical data of patients who underwent SPKT at our center. This study

**Published online:** September 27, 2021

**P-Reviewer:** De Carlis R
**S-Editor:** Liu M
**L-Editor:** A
**P-Editor:** Li JH

adheres to the declarations of Istanbul and Helsinki, and none of the organs used were from executed prisoners. All donors were neither paid nor coerced.

## MATERIALS AND METHODS

### Study subjects

From January 2016 to December 2019, 138 SKPT were performed in our center, and 134 patients were included in this study. All graft organs came from deceased donors, including 9 cases of anoxia, 45 cases of cerebrovascular accident/stroke, 73 cases of head trauma, 4 cases of central nervous system tumor, and 3 cases of organophosphorus poisoning. The indications for transplantation were type 1 or type 2 diabetes with end-stage renal disease. During the transplant evaluation process, all patients underwent gastroscopy and colonoscopy. Exploration of all the small intestines during operation was performed for every patient. Patients with one or more of the below diseases were excluded from the study: Gastroduodenal ulcer, severe gastritis and duodenitis, colitis, digestive tract tumor, diverticulum, digestive tract polyp, and GI bleeding history. Patients with graft pancreasectomy due to thrombosis or severe infection within the first postoperative week were excluded from the study. According the above criteria, two patients with graft pancreasectomy due to thrombosis within the first postoperative week were excluded from the study. One patient diagnosed with ascending colonic diverticulum by colonoscope before transplantation and experienced hemorrhage of diverticulum after SPKT was excluded. Another patient was excluded from the study because of a history of duodenal ulcer bleeding. Cytomegalovirus (CMV) DNA tests performed before SPKT were negative for all included patients. The characteristics of the recipients and donors included in the study are shown in Table 1.

### Surgical techniques

The liver, pancreas, and kidney were recovered using an *en bloc* technique for organ procurement. For the duodenal decontamination, lavage technique *via* the nasogastric tube was performed routinely with normal saline (500 mL), and then metronidazole solution (200 mL) was instilled during pancreas procurement. The proximal gastroduodenal artery (GDA) and distal common hepatic artery were distributed to the liver, leaving the aortic patch with the superior mesenteric artery and celiac trunk for the pancreas. Subsequently, the distal splenic artery and vein were ligated, and the spleen was removed. After the proximal and distal donor duodenum were closed using a linear cutting stapler, the stump was strengthened by interrupted seromuscular sutures. As reported in the literature[10], we reconstructed the GDA by end-to-end anastomosis with the common hepatic artery or left gastric artery and interposed a donor mesentery artery, if necessary.

Both kidney and pancreas transplantations were performed using a single right incision through the rectus abdominis. As reported by Tso[11], we anastomosed the renal artery to the internal iliac artery limb of the donor conduit and anastomosed the aortic patch of the graft to the external iliac artery limb of the donor conduit and the common iliac artery of the donor conduit to the right external iliac artery of the recipient in an end-to-side fashion, so both organs could be vascularized by utilizing a single Y arterial conduit (Figure 1). Both organs were transplanted on the right side of the patient's abdominal cavity. The renal vein was anastomosed to the right external iliac vein. The venous outflow of the pancreas graft was arranged *via* the systemic venous system by anastomosing the portal vein end-to-side to the distal vena cava. The head of the pancreas and duodenum were oriented superiorly, and the donor duodenal segment was anastomosed side-to-side to the distal ileum. The distance from the anastomotic stoma to the ileocecal valve was 60 cm. The operation process is illustrated in Figure 1.

According to the pattern of enteric anastomosis, patients were divided into two groups: SL or no SL (NSL) groups. From the first outpatient visit, during preoperative evaluation, operation, and follow-up after SPKT, a patient will be under constant supervision by the same doctor in our center. If a patient was supervised by the doctor who is the corresponding author of this paper, then the patient was allocated into the SL group. If a patient was not supervised by the doctor who is the corresponding author of this paper, then the patient was allocated into the NSL group. There were no other criteria for grouping. A total of 44 and 90 patients were classified into the SL group and NSL group, respectively. The transplanted duodenal segment and the distal ileum of the recipient were incised 3-4 cm longitudinally at the site of the anastomotic

**Table 1 Donor and simultaneous pancreas and kidney transplantation recipient clinical characteristics, *n* (%)**

| Characteristics | SL group (*n* = 44) | NSL group (*n* = 90) | *P* value |
|---|---|---|---|
| Donor age, yr | 34.00 ± 8.82 | 32.32 ± 10.65 | 0.367 |
| Donor gender (male/female, *n*) | 36/8 | 75/15 | 0.827 |
| Recipient age, yr | 46.52 ± 9.50 | 47.41 ± 10.79 | 0.643 |
| Recipient gender (male/female, *n*) | 37/7 | 75/15 | 0.911 |
| Duration of diabetes, yr | 16.73 ± 6.2 | 15.88 ± 5.9 | 0.449 |
| Diabetes type (1/2) | 7/37 | 18/72 | 0.568 |
| BMI | 24.66 ± 3.68 | 23.60 ± 3.18 | 0.089 |
| Blood type, *n* | | | |
| A+/B+/AB+/O+ | 10/10/4/20 | 17/35/10/28 | 0.169 |
| Duration of dialysis, months, median (IQR) | 12.00 (6.25, 36.00) | 10.00 (5.00, 20.75) | 0.037 |
| Pancreas ischemia time, minutes | 446.71 ± 104.11 | 400.94 ± 89.79 | 0.010 |
| HLA-A, -B, -DR mismatch | | | |
| 0-3 | 8 (18.18) | 19 (21.11) | 0.691 |
| 4-6 | 36 (81.82) | 71 (78.89) | 0.691 |
| Maintenance Immunosupression | | | |
| TAC | 40 (90.91) | 72 (80.00) | 0.109 |
| CsA | 4 (9.09) | 18 (20.00) | 0.109 |
| DIC indicators | | | |
| PT-INR | 1.50 ± 0.37 | 1.55 ± 0.35 | 0.463 |
| APTT (s) | 60.15 ± 35.18 | 56.35 ± 38.39 | 0.582 |
| TT (s) | 60.07 ± 37.90 | 66.34 ± 37.03 | 0.362 |
| PLT ($10^9$/L) | 106.41 ± 45.35 | 108.94 ± 50.87 | 0.780 |

SPKT: Simultaneous pancreas and kidney transplantation; SL: Suture ligation; NSL: No suture ligation; TAC: Tacrolimus; CsA: Cyclosporine A; PT-INR: Prothrombin time-international normalized rate; APTT: Activated partial thromboplastin time; TT: Thrombin time; PLT: Platelets.

stoma by using a scalpel after pancreas graft blood reperfusion. Then, mucosal aneriodine cotton balls were used for decontamination of the duodenal segment and the distal ileum. In the SL group, bleeding spots at the cut edge of the bowel (ileum of the recipient and duodenum of the transplanted organ) were staunched by transmural figure-of-eight SL at the mucosal points of the bleeding with a silk thread (Figure 2). A penetration of all layers from the serosa to the lumen was made, and the needle position on the serosa and mucosa was 1-2 mm apart from the cut edge. In the NSL group, SL was not performed, and electric coagulation using an argon knife was performed if necessary. After submucosal hemostasis, side-to-side duodeno-ileostomy was performed using a two-layer hand-sewn running anastomosis: A running unabsorbable suture for the transmural inner layer and an outer inverted seromuscular layer in both groups. The needle position was 4-5 mm from the cut edge when suturing the inner layer. Enteric anastomoses in the NSL group were performed by an experienced surgical team member who had performed more than 100 SPKT operations before this study, while enteric anastomoses in the SL group were performed by a relative younger surgical team member who had performed less than 10 SPKT operations before this study. To decrease the EA bleeding rate in SPKT, the doctors in the SL group proposed the conception of SL for submucosal hemostasis during hand-sewn side-to-side duodeno-ileostomy and applied this technique from January 2016. Cases before January 2016 in our center were excluded from this study.

### *Immunosuppressive agents*

Anti-thymocyte globulin was administered for induction at 1.5 mg/kg during surgery and 1.5 mg/kg per day for 3 d after transplantation. The maintenance immunosup-

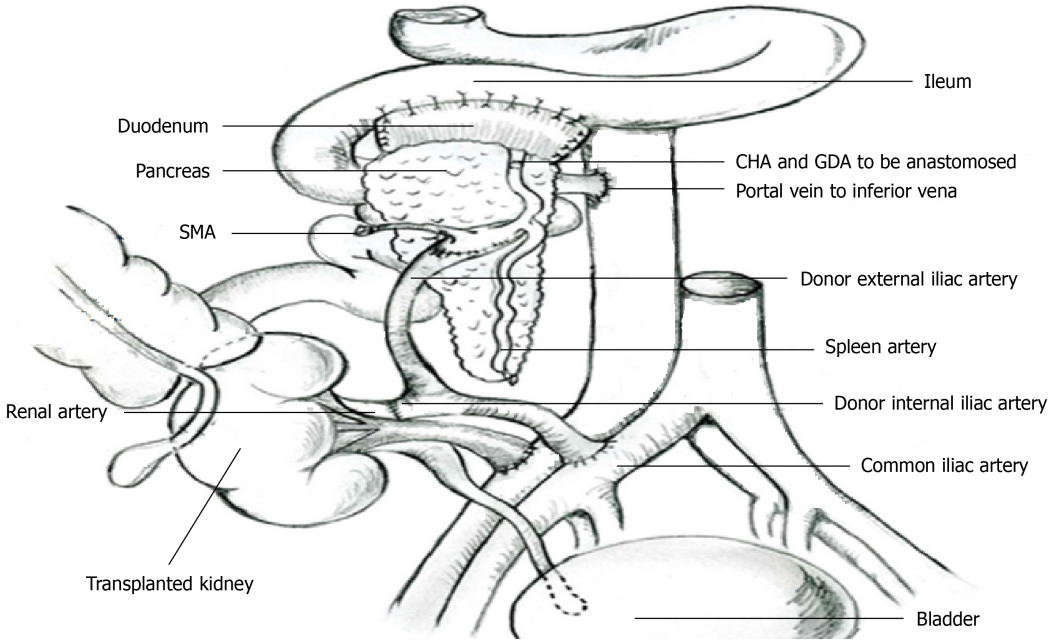


**Figure 1 Revascularization of the pancreas and kidney with a single arterial conduit. The donor duodenum segment was anastomosed side-to-side to the recipient's distal ileum.** CHA: Common hepatic artery; GDA: Gastroduodenal arterial; SMA: Superior mesenteric artery.

pression regimen included tacrolimus or cyclosporine, mycophenolate mofetil, and prednisolone (Table 1). The target trough level of tacrolimus was 8-12 ng/mL within 3 mo of transplantation, the target trough level of cyclosporine was 150-200 ng/mL, and the target level of cyclosporine 2 h after administering the medicine was 800-1200 ng/mL.

### *Prophylactic anticoagulation therapy*

To prevent pancreatic graft thrombosis, low-molecular-weight heparin was administered for 6 d (50 IU/kg/d) by subcutaneous injection for all patients, followed by the oral administration of aspirin (100 mg/d) for 3 mo. If GI bleeding occurred, prophylactic anticoagulation therapy was withdrawn. Patients of the two groups received the same anticoagulation prophylaxis. Routine monitoring of the platelet count and disseminated intravascular coagulation (DIC) indicators was performed during anticoagulation therapy.

### *Defining EA bleeding and anastomotic leak*

The diagnostic criteria of EA bleeding were as follows: (1) Patient experienced melena or hematochezia with obvious hemoglobin decline, and anastomotic bleeding was identified by angiography or relaparotomy; and (2) If the patient experienced melena or hematochezia with obvious hemoglobin decline, but relaparotomy was not performed and angiography results was negative and could not show the site of GI bleeding, then the following criteria must be met: No blood fluid was drained from nasogastric tubes and colonoscopy revealed that the end ileal lumen next to the ileocecal valve contained blood fluid. Anastomotic leak was diagnosed based on clinical symptoms, imaging study results, laboratory findings, or a combination thereof, as previously reported[12].

### *CMV DNA tests*

The results of CMV DNA blood tests of all EA bleeding recipients at the time of EA bleeding were collected.

### *Statistical analysis*

Continuous variables were reported as mean ± SD or medians [interquartile range (IQR)] depending on the distribution of the data. If data were normally distributed and had variance homogeneity, an analysis of variance was used for comparisons between groups. If the distribution was not normal, a Kruskal-Wallis rank-sum test was used for comparisons between groups. Categorical variables were analyzed using a chi-square test. Cumulative graft and patient survival rates were computed by a

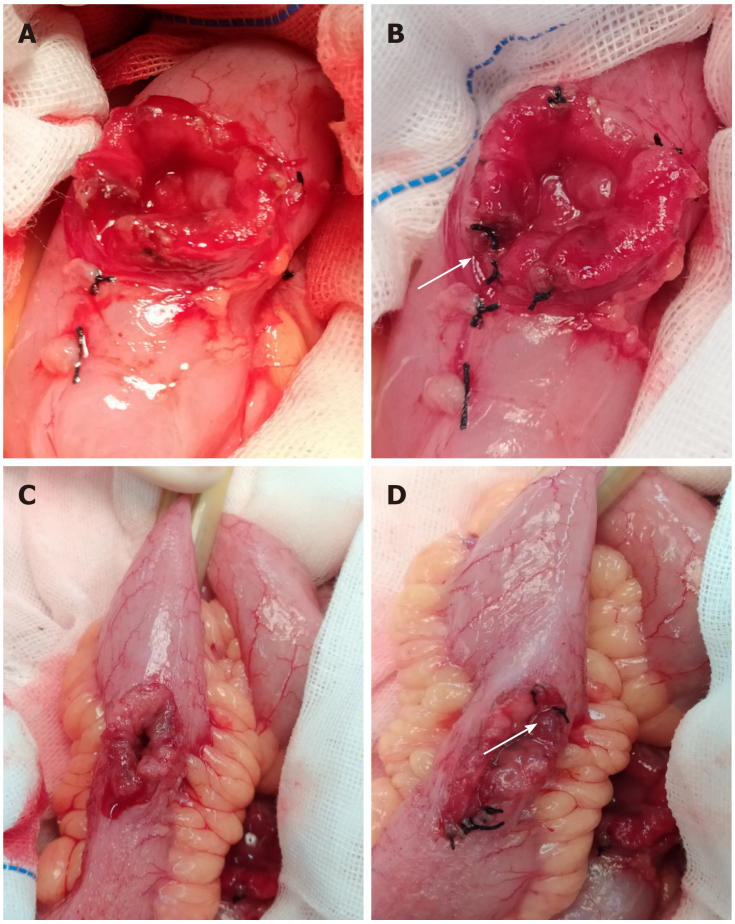


**Figure 2 Suture ligation for submucosal hemostasis.** A: Bleeding at the cut edge of the duodenum; B: Bleeding spots of the duodenum were staunched by transmural suture ligation; C: Bleeding at the cut edge of the ileum; D: Bleeding spots of the ileum were staunched by transmural suture ligation. White arrow: Knot of suture thread.

Kaplan-Meier survival analysis. Data analyses were performed using R 3.6.2 statistical software. The study was reviewed by our expert biomedical statistician Cao Y, MD.

## RESULTS

### *Patient characteristics*

The characteristics of the donors and recipients in the SL and NSL groups are displayed in Table 1. There were 44 and 90 patients in the SL group and NSL group, respectively. The two groups were matched for the following: Age of the donor; donor sex; age of the recipient; diabetes duration; diabetes type; body mass index; blood type; human leukocyte antigen (HLA) -A, HLA-B, and HLA-DR mismatch; immunosuppression; DIC indicators; and platelet count. The duration of dialysis was slightly longer in the SL group than in the NSL group [12.00 mo (IQR, 6.25, 36.00) *vs* 10.00 mo (IQR, 5.00, 20.75); $P = 0.037$]. The pancreas ischemia time was longer in the SL group than in the NSL group (446.71 ± 104.11 min *vs* 400.94 ± 89.79 min; $P = 0.010$).

### *EA bleeding and anastomotic leakage during the first 3 mo after transplantation*

In the first postoperative week, the EA bleeding rate was less in the SL group (1/44; 2.27%) than in the NSL group (14/90; 15.56%; $P = 0.021$) (Table 2), respectively. Patients from both groups received immediate anticoagulant treatment. The transfusion rate for EA bleeding in the first postoperative week was lower in the SL group than in the NSL group [2.27% (1/44) *vs* 14.44% (13/90); $P = 0.035$].

If medical treatment exceeded more than 48 h and hematochezia was not relieved and was accompanied by unstable blood pressure, relaparotomy was considered. Owing to the failure of conservative therapy, three patients in the NSL group underwent relaparotomy (Tables 2 and 3), and EA bleeding was identified, and the

**Table 2 Enteric anastomotic bleeding within 1 wk posttransplantation and anastomotic leakage, *n* (%)**

| Characteristics | SL group (*n* = 44) | NSL group (*n* = 90) | *P* value |
|---|---|---|---|
| EA bleeding | 1 (2.27) | 14 (15.56) | 0.021 |
| Transfusion rates due to EA bleeding | 1 (2.27) | 13 (14.44) | 0.035 |
| Relaparotomy due to EA bleeding | 0 (0.00) | 3 (3.33) | 0.551 |
| Anastomotic leakage | 1 (2.27) | 1 (1.11) | 0.754 |

EA: Enteric anastomotic; SL: Suture ligation; NSL: No suture ligation.

**Table 3 Cases of relaparotomy due to enteric anastomotic bleeding in no suture ligation group**

| Case | Age | Sex | Transplant time | Bleeding start time[1] |
|---|---|---|---|---|
| 1 | 47 | M | October 2016 | 5 |
| 2 | 29 | M | October 2016 | 7 |
| 3 | 40 | M | October 2017 | 6 |

[1]Days after operation.
The reconstruction of the anastomosis was performed for these patients and no recurrence of bleeding occurred. M: Male.

reconstruction of the anastomosis was performed in these three patients. There were no pancreas graft loss and no recurrence of GI bleeding after relaparotomy. The rate of relaparotomy due to EA bleeding was lower in the SL group than in the NSL group; however, no differences were found between the two groups [0% (0/44) *vs* 3.33% (3/90); $P = 0.551$].

Anastomotic leakage was observed in 1 (2.27%) of 44 patients in the SL group at postoperative day (POD) 14 and was healed by conservative treatment. One patient in the NSL group (1/90; 1.11%) experienced anastomotic leakage at POD 16; subsequently, the pancreas graft was lost.

### *CMV DNA test results of patients with GI bleeding*

CMV DNA blood testing was performed for all EA bleeding patients within 1 wk post-operation, and results were all negative. Three patients in the NSL group underwent relaparotomy; unfortunately, the biopsy of the transplanted duodenal segment was not performed during relaparotomy. Therefore, the results of the immunohisto-chemistry staining of the transplanted duodenal segment for CMV were not available.

### *Donor age, mean pancreatic cold ischemia time, and DIC indicators of patients with and without GI bleeding*

A comparison of patients with EA bleeding ($n = 15$) and those without EA bleeding ($n = 119$) within the first week after transplantation showed no differences in donor age (Figure 3A), mean pancreatic cold ischemia time (Figure 3B), platelet count (Figure 3C), prothrombin time international normalized rate (Figure 3D), activated partial thromboplastin time (Figure 3E), and thrombin time (Figure 3F).

### *Survival analysis*

The median follow-up durations were 2.11 years and 2.12 years for patients of the SL group and NSL group, respectively. The Kaplan–Meier curves plotted for comparisons between the SL and NSL groups after transplantation are shown in Figure 4. No significant difference was found between the two groups in terms of the survival curves for patients, pancreas graft, and kidney graft. The study was reviewed by our expert Biostatistic Cao Y, MD.

## DISCUSSION

In 1967, the first SPKT was performed by Kelly *et al*[13] at the University of Minnesota.

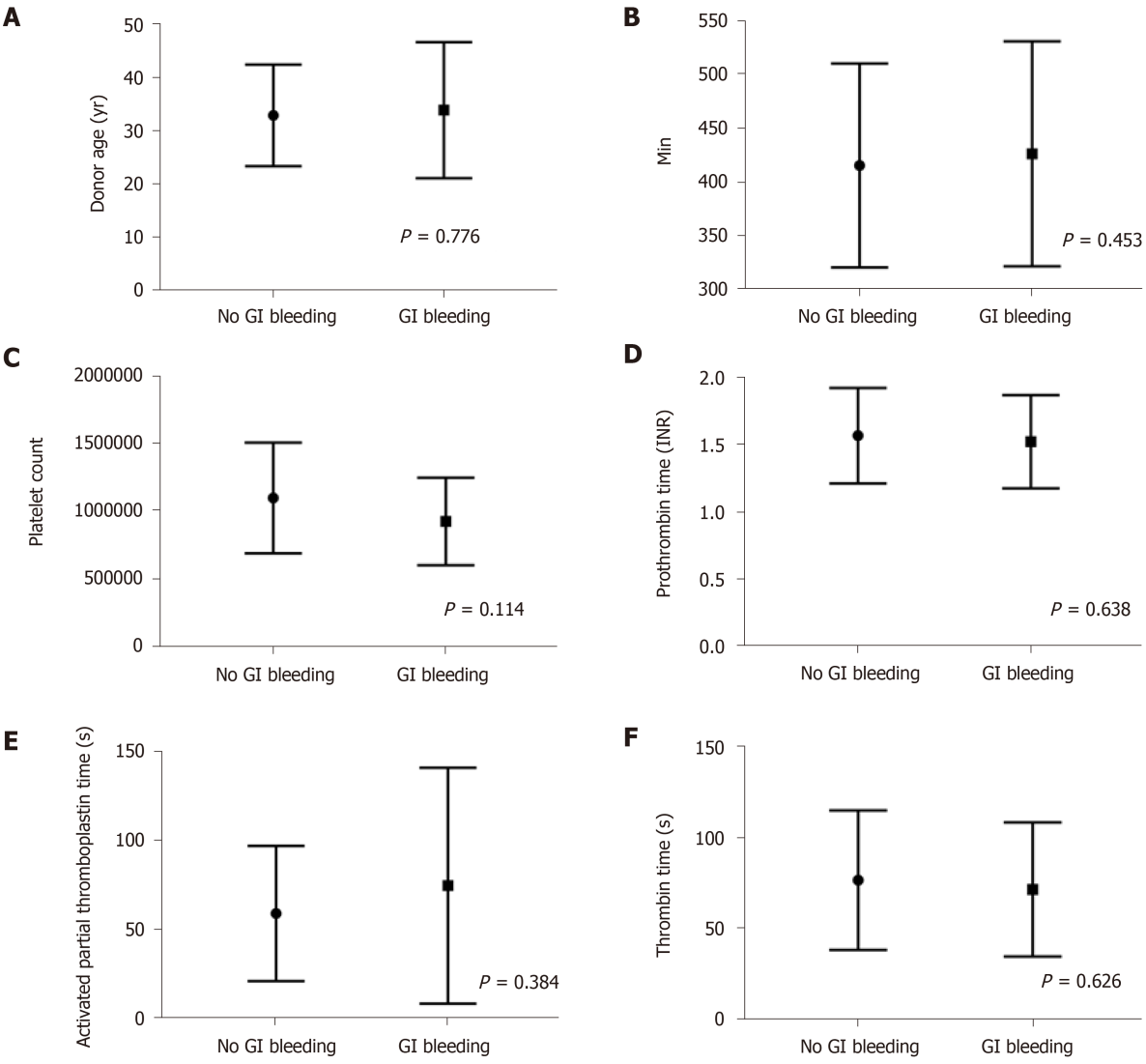


**Figure 3 Comparison of clinical features within 1 wk postoperatively in gastrointestinal bleeding and no gastrointestinal bleeding group.**
A: Donor age; B: Mean pancreatic graft cold ischemia time; C: Platelet count; D: Prothrombin time international normalized rate; E: Activated partial thromboplastin time; F: Thrombin time. GI: Gastrointestinal; INR: International normalized rate.

Since then, several pancreas transplantation techniques have been developed. From the mid-1970s to the mid-1980s, segmental pancreas transplantation was the prevalent technique. Subsequently, whole pancreaticoduodenal graft transplantation with ED became the gold standard for SPKT[6]. In the majority of cases involving ED, systemic venous drainage was used[14]. Inferior vena cava drainage and duodeno-ileostomy without a Roux-en-Y loop have been used in our center.

ED can be justified based on physiological conditions; however, the complications associated with a simultaneously transplanted duodenum, such as GI bleeding and anastomotic leakage, may be potentially life-threatening. The accurate morbidity rate associated with GI bleeding after ED pancreas transplantation is unknown. In the literature, the data on GI bleeding following pancreas transplantation are under-reported. Large case series reports are insufficient and the criteria for GI bleeding were not elucidated from these reports. Orsenigo *et al*[8] reported that 11% (7/61) of recipients experienced GI bleeding complications during the first postoperative week, and six patients (85.71%) required relaparotomy and EA bleeding was identified in five patients. In a study of 11 cases, one patient required endoscopy for the luminal bleeding of the duodenal anastomosis site[4]. A report in Austria showed that in 379 pancreas transplants, GI bleeding occurred in 28 (7.38%) patients, of which 23 (82.14%) patients experienced GI bleeding at the level of the enteric anastomosis, and surgery was required in 25% of GI bleeding cases[9]. In our study, 20.0% (3/15) of the patients with EA bleeding underwent relaparotomy.

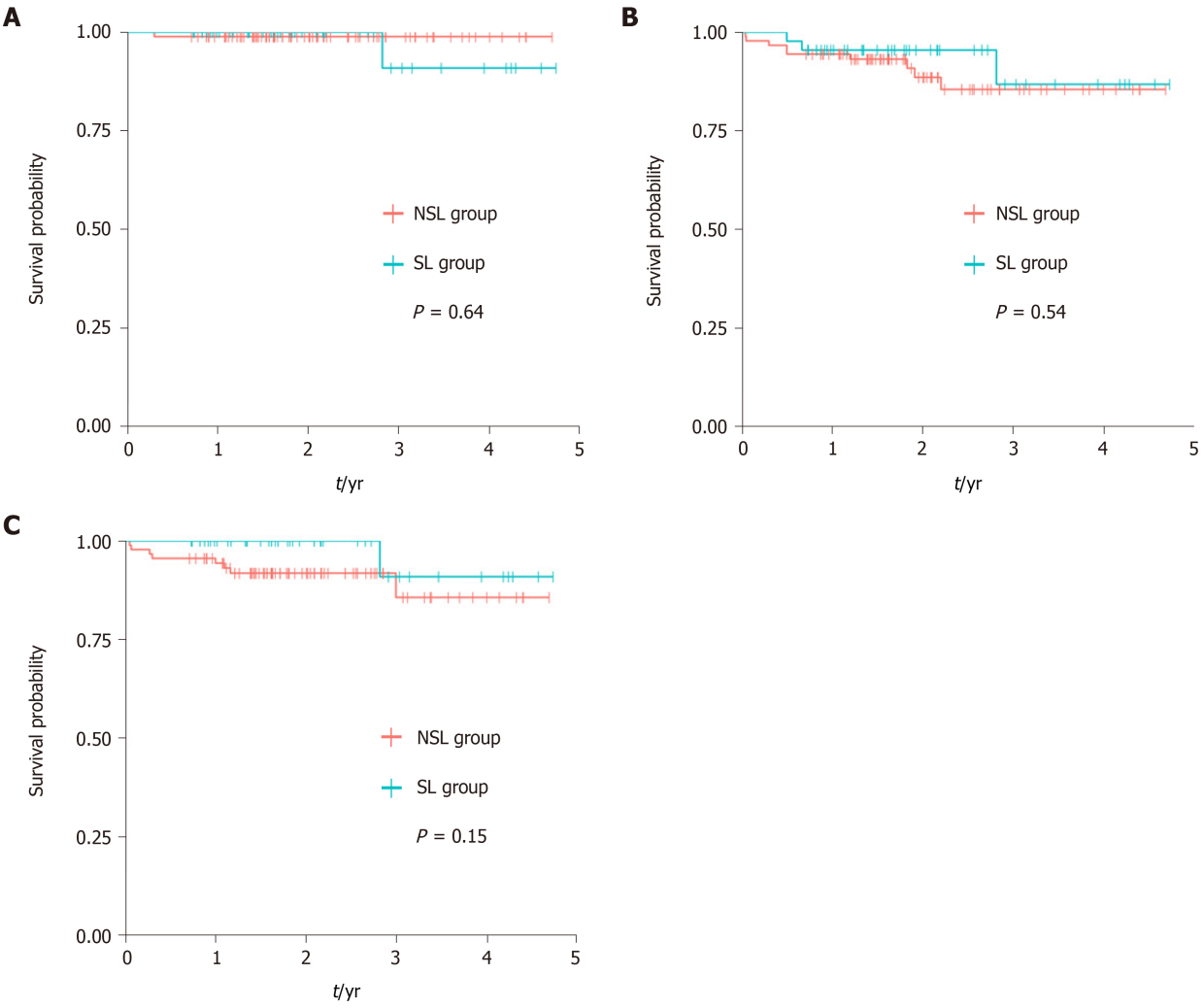


**Figure 4 The Kaplan–Meier curves for patient, kidney graft, and pancreas graft in suture ligation and no suture ligation group.** A: Patient survival curves; B: Kidney graft survival curves; C: Pancreas graft survival curves. SL: Suture ligation; NSL: No suture ligation.

With the dramatic improvements in staplers, stapled anastomoses are being used for digestive tract reconstruction in ordinary small intestinal surgery and for pancreas transplantation[15,16]. When using a linear cutting stapler for enteric anastomosis, bleeding along the staple line could be controlled by interrupted sutures[16]. Because the transplanted duodenal segment is usually edematous after blood reperfusion, stapled anastomoses may be unsuitable for the intestinal tract in severe edematous cases. Besides, stapled anastomoses are more expensive than hand-sewn technique especially in developing countries[17]. Compared with duodeno-duodenostomy, duodeno-ileostomy combined with postcava drainage in our study could decrease the surgical difficulty significantly but made it difficult to perform hemostasis by endoscopy in cases of EA bleeding. Therefore, improvements in the hand-sewn technique for ED are still required to decrease morbidity associated with complications related to the transplanted duodenal segment.

There are abundant vessels in the submucosal plexus of the intestinal wall[18]. In one report, ligation or electric coagulation was performed for hemostasis in 46 cases involving anastomoses of the small bowel to the small bowel in the control group[17]; however, there is no report involving SPKT cases. GI bleeding that occurs within 7 d of pancreas transplantation with ED usually initiates from the anastomotic suture line[8-9,19]. Our study demonstrated that the incidence of EA bleeding within the first postoperative week could be minimized by using a careful plication technique during SPKT. Pancreas transplantation is a complicated transplant procedure, and the surgical experience for pancreas transplantation may influence the success and complication rates of such a complicated transplant procedure. The surgical team in the NSL group possessed much more surgical experience and should achieve lower EA bleeding rate than the relative younger surgical team in the SL group, but our data showed the opposite result: The EA bleeding rate was lower in the SL group. We think that the

plication technique affected the EA bleeding rate more than surgical experience, leading to the decreasing EA bleeding rate in the SL group. Non-crushing bowel clamps should be applied to the ileum only, and the mesentery of the ileum should not be clamped, so that bleeding spots at the cut edge of the ileum of the patient could be thoroughly staunched. The blood vessels in the submucous layers might be destroyed by ligation, which may affect the anastomotic stoma healing rate, and cause anastomotic leakage. Compared with no SL, our data showed that plication techniques did not increase the morbidity of anastomotic leakage.

Several factors may account for the anastomotic stoma's propensity for EA bleeding. The transplanted duodenal segment is edematous after blood reperfusion. When edema subsides postoperatively, an onset of anastomotic stoma bleeding might occur at the anastomotic suture line due to the weakening compressive strength of the suture thread. Another factor is the exocrine output of the pancreas graft. Trypsinogen enters the small intestine and is stimulated as active trypsin by enterokinase in the small intestine. The introrsus cut edges of the bowel at the anastomotic site are directly exposed to the intestinal cavity and corroded by the active trypsin, thus increasing the susceptibility of the anastomotic stoma to bleeding. In 1982, Groth *et al*[20] inserted a catheter in the pancreatic duct to protect the anastomosis sutures during the segmental pancreas transplantation. Because of a propensity for thrombosis, most centers use some types of empiric thromboprophylaxis[21,22]. Poor coagulation function may be a risk factor for EA bleeding in SPKT. Our data showed no relationship between coagulation indicators and EA bleeding (Figure 3). Ulceration with bleeding due to CMV infections has been reported in the duodenal cuff of the transplanted pancreas [23], but CMV infection did not correlate with EA bleeding in our study.

The first limitation in this study is its retrospective approach. Another limitation of this study is the relatively small number of patients in the SL group; more cases are needed to confirm the benefit of SL technique in SPKT.

## CONCLUSION

Compared with no SL, a two-layer running hand-sewn anastomosis with hemostasis by SL at the cut edge of the bowel (ileum of the recipient and duodenum of the donor organ) may help decrease the morbidity of early EA bleeding and the transfusion rate, without increasing the anastomotic leakage rate.

## ARTICLE HIGHLIGHTS

### *Research background*

As a potentially life-threatening complication of simultaneous pancreas and kidney transplantation (SPKT), enteric anastomotic (EA) bleeding frequently results in surgical relaparotomy and graft loss; therefore, it is essential to decrease the incidence of EA bleeding.

### *Research motivation*

An effort was made for submucosal hemostasis during enteric anastomosis in SPKT with a lower EA bleeding rate.

### *Research objectives*

To investigate the advantages and disadvantages of suture ligation (SL) for submucosal hemostasis during enteric anastomosis on early EA bleeding and anastomotic leakage in SPKT.

### *Research methods*

We compared the outcomes of 134 patients classified into SL ($n$ = 44) and no SL (NSL) groups ($n$ = 90).

### *Research results*

During the first postoperative week, the EA bleeding rate in the SL group was lower than that in the NSL group during the first postoperative week. No relationship was found between EA bleeding and donor age, mean pancreatic cold ischemia time, platelet count, prothrombin time international normalized rate, activated partial

thromboplastin time, and thrombin time. No significant difference was noted between the two groups in terms of the anastomotic leakage rate, patient survival curve, pancreas graft survival curve, or kidney graft survival curve.

### Research conclusions

Compared with no SL, SL for submucosal hemostasis during enteric anastomosis in SPKT can decrease the EA bleeding rate and do not increase the anastomotic leakage rate.

### Research perspectives

Further clinical randomized controlled studies with a large sample size are needed to confirm the effect of plication techniques on submucosal hemostasis during enteric anastomosis in SPKT in the future.

## REFERENCES


1 **Kandaswamy R**, Stock PG, Gustafson SK, Skeans MA, Urban R, Fox A, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Pancreas. *Am J Transplant* 2020; **20** Suppl s1: 131-192 [PMID: 31898415 DOI: 10.1111/ajt.15673]

2 **Kerr HR**, Hatipoglu B, Krishnamurthi V. Pancreas transplant for diabetes mellitus. *Cleve Clin J Med* 2015; **82**: 738-744 [PMID: 26540324 DOI: 10.3949/ccjm.82a.14090]

3 **Linhares MM**, Beron RI, Gonzalez AM, Tarazona C, Salzedas A, Rangel EB, Sá JR, Melaragno C, Goldman SM, Souza MG, Sato NY, Matos D, Lopes-Filho GJ, Medina JO. Duodenum-stomach anastomosis: a new technique for exocrine drainage in pancreas transplantation. *J Gastrointest Surg* 2012; **16**: 1072-1075 [PMID: 22258867 DOI: 10.1007/s11605-011-1806-1]

4 **Ryu JH**, Lee TB, Park YM, Yang KH, Chu CW, Lee JH, Kim T, Choi BH. Pancreas transplant with duodeno-duodenostomy and caval drainage using a diamond patch graft: a single-center experience. *Ann Transplant* 2017; **22**: 24-34 [PMID: 28100901 DOI: 10.12659/aot.901469]

5 **Walter M**, Jazra M, Kykalos S, Kuehn P, Michalski S, Klein T, Wunsch A, Viebahn R, Schenker P. 125 cases of duodenoduodenostomy in pancreas transplantation: a single-centre experience of an alternative enteric drainage. *Transpl Int* 2014; **27**: 805-815 [PMID: 24750305 DOI: 10.1111/tri.12337]

6 **Squifflet JP**, Gruessner RW, Sutherland DE. The history of pancreas transplantation: past, present and future. *Acta Chir Belg* 2008; **108**: 367-378 [PMID: 18710120 DOI: 10.1080/00015458.2008.11680243]

7 **Boggi U**, Vistoli F, Del Chiaro M, Moretto C, Croce C, Signori S, D'Imporzano S, Amorese G, Campani D, Calabrese F, Capocasale E, Marchetti P. Total duodenectomy with enteric duct drainage: a rescue operation for duodenal complications occurring after pancreas transplantation. *Am J Transplant* 2010; **10**: 692-697 [PMID: 20121744 DOI: 10.1111/j.1600-6143.2009.02981.x]

8 **Orsenigo E**, Fiorina P, Dell'Antonio G, Cristallo M, Socci C, Invernizzi L, Maffi P, Secchi A, Di Carlo V. Gastrointestinal bleeding from enterically drained transplanted pancreas. *Transpl Int* 2005; **18**: 296-302 [PMID: 15730489 DOI: 10.1111/j.1432-2277.2004.00023.x]

9 **Messner F**, Bösmüller C, Oberhuber R, Maglione M, Cardini B, Resch T, Scheidl S, Öfner D, Schneeberger S, Margreiter C. Late recurrent bleeding episodes from duodenojejunostomy after pancreas transplantation. *Clin Transplant* 2018; **32**: e13350 [PMID: 30007083 DOI: 10.1111/ctr.13350]

10 **Li JQ**, He ZJ, Si ZZ, Hu W, Li YN, Qi HZ. Gastroduodenal arterial reconstruction of the pancreaticoduodenal allograft. *Transplant Proc* 2011; **43**: 3905-3907 [PMID: 22172870 DOI: 10.1016/j.transproceed.2011.10.043]

11 **Tso PL**, Cash MP, Pearson TC, Larsen CP, Newell KA. Simultaneous pancreas-kidney transplantation utilizing a common arterial conduit: early experience and potential applications. *Am J Transplant* 2003; **3**: 1440-1443 [PMID: 14525607 DOI: 10.1046/j.1600-6135.2003.00236.x]

12 **Humar A**, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg* 2000; **231**: 269-275 [PMID: 10674620 DOI: 10.1097/00000658-200002000-00017]

13 **Kelly WD**, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery* 1967; **61**: 827-837 [PMID: 5338113]

14 **Gruessner AC**. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2011; **8**: 6-16 [PMID: 21720668 DOI: 10.1900/RDS.2011.8.6]

15 **Verzaro R**, de Simone P. Use of circular stapler for enteric drainage of the pancreatic graft. *J Am Coll Surg* 2004; **199**: 518 [PMID: 15325628 DOI: 10.1016/j.jamcollsurg.2004.05.261]

16 **Lam VW**, Wong K, Hawthorne W, Ryan B, Lau H, Robertson P, Allen RD, Pleass H. The linear cutting stapler for enteric anastomosis: a new technique in pancreas transplantation. *Transpl Int* 2006; **19**: 915-918 [PMID: 17018127 DOI: 10.1111/j.1432-2277.2006.00368.x]

17 **Zhang Q**, Zeng Q, Lin W, Chen Y, Yu Z, Zhou M, Han S, You J. Single-layer anastomosis without hemostasis in the submucosa layer by electric coagulation or ligation: a novel technique of anastomosis for all gastrointestinal tracts. *Hepatogastroenterology* 2011; **58**: 96-98 [PMID: 21510293]

18 **BOULTER PS**, PARKS AG. Submucosal vascular patterns of the alimentary tract and their significance. *Br J Surg* 1960; **47**: 546-550 [PMID: 13803264 DOI: 10.1002/bjs.18004720518]

19 **Dhanireddy KK**. Pancreas transplantation. *Gastroenterol Clin North Am* 2012; **41**: 133-142 [PMID: 22341254 DOI: 10.1016/j.gtc.2011.12.002]

20 **Groth CG**, Collste H, Lundgren G, Wilczek H, Klintmalm G, Ringdén O, Gunnarsson R, Ostman J. Successful outcome of segmental human pancreatic transplantation with enteric exocrine diversion after modifications in technique. *Lancet* 1982; **2**: 522-524 [PMID: 6125680 DOI: 10.1016/s0140-6736(82)90601-8]

21 **Muthusamy AS**, Giangrande PL, Friend PJ. Pancreas allograft thrombosis. *Transplantation* 2010; **90**: 705-707 [PMID: 20616765 DOI: 10.1097/TP.0b013e3181eb2ea0]

22 **Raveh Y**, Ciancio G, Burke GW, Figueiro J, Chen L, Morsi M, Namias N, Singh BP, Lindsay M, Alfahel W, Sleem MS, Nicolau-Raducu R. Susceptibility-directed anticoagulation after pancreas transplantation: a single-center retrospective study. *Clin Transplant* 2019; **33**: e13619 [PMID: 31152563 DOI: 10.1111/ctr.13619]

23 **Barone GW**, Webb JW, Hudec WA. The enteric drained pancreas transplant: another potential source of gastrointestinal bleeding. *Am J Gastroenterol* 1998; **93**: 1369-1371 [PMID: 9707069 DOI: 10.1111/j.1572-0241.1998.420_a.x]

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*World J Gastrointest Surg* 2021 September 27; 13(9): 1000-1011

DOI: 10.4240/wjgs.v13.i9.1000

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Evaluating the benefit of adjuvant chemotherapy in patients with ypT0–1 rectal cancer treated with preoperative chemoradiotherapy

Ye Won Jeon, In Ja Park, Jeong Eun Kim, Jin-Hong Park, Seok-Byung Lim, Chan Wook Kim, Yong Sik Yoon, Jong Lyul Lee, Chang Sik Yu, Jin Cheon Kim

**ORCID number:** Ye Won Jeon 0000-0002-4434-4855; In Ja Park 0000-0001-5355-3969; Jeong Eun Kim 0000-0001-9766-1531; Jin-Hong Park 0000-0002-1088-0174; Seok-Byung Lim 0000-0001-8824-4808; Chan Wook Kim 0000-0002-2382-0939; Yong Sik Yoon 0000-0002-3196-8423; Jong Lyul Lee 0000-0002-5878-8000; Chang Sik Yu 0000-0001-9401-9981; Jin Cheon Kim 0000-0003-4823-8619.

**Author contributions:** Jeon YW and Park IJ conceptualized and designed the study and wrote the manuscript; Jeon YW provided data analysis and literature review; Kim JE and Park JH provided clinical data and critical revision; Lim SB, Lee JL, Yoon YS, Kim CW, Yu CS, and Kim JC critical revision and editing, and all authors approved of the final version.

**Institutional review board statement:** This study was approved by the Institutional Review Board of the Asan Medical Center, No. 2017-1114.

**Informed consent statement:** The requirement for obtaining an informed consent was waived.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Ye Won Jeon,** Department of Surgery, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

**In Ja Park, Seok-Byung Lim, Chan Wook Kim, Yong Sik Yoon, Jong Lyul Lee, Chang Sik Yu, Jin Cheon Kim,** Department of Colon and Rectal Surgery, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

**Jeong Eun Kim,** Department of Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

**Jin-Hong Park,** Department of Radiation Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

**Corresponding author:** In Ja Park, MD, PhD, Doctor, Professor, Surgeon, Department of Colon and Rectal Surgery, Asan Medical Center and University of Ulsan College of Medicine, No. 88 Olympic-ro, Songpa-gu, Seoul 05505, South Korea. ipark@amc.seoul.kr

## Abstract

***BACKGROUND***

Adjuvant chemotherapy (ACTx) is recommended in rectal cancer patients after preoperative chemoradiotherapy (PCRT), but its efficacy in patients in the early post-surgical stage who have a favorable prognosis is controversial.

***AIM***

To evaluate the long-term survival benefit of ACTx in patients with ypT0–1 rectal cancer after PCRT and surgical resection.

***METHODS***

We identified rectal cancer patients who underwent PCRT followed by surgical resection at the Asan Medical Center from 2005 to 2014. Patients with ypT0–1 disease and those who received ACTx were included. The 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) were analyzed according to the status of the ACTx.

***RESULTS***

Of 520 included patients, 413 received ACTx (ACTx group) and 107 did not (no ACTx group). No significant difference was observed in 5-year RFS (ACTx group,

**Data sharing statement:** Data are available upon reasonable request. We may be able to share de-identified participant data with researchers following the publication of this manuscript. Requests for data should be directed to the corresponding author. Data sharing will need to be approved by third-party data providers.



**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** South Korea

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 21, 2021
**Peer-review started:** February 21, 2021
**First decision:** May 13, 2021
**Revised:** May 22, 2021
**Accepted:** August 2, 2021
**Article in press:** August 2, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Macedo F
**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Guo X

87.9% *vs* no ACTx group, 91.4%, $P = 0.457$) and 5-year OS (ACTx group, 90.5% *vs* no ACTx group, 86.2%, $P = 0.304$) between the groups. cT stage was associated with RFS and OS in multivariate analysis [hazard ratio (HR): 2.57, 95% confidence interval (CI): 1.07–6.16, $P = 0.04$ and HR: 2.27, 95%CI: 1.09–4.74, $P = 0.03$, respectively]. Furthermore, ypN stage was associated with RFS and OS (HR: 4.74, 95%CI: 2.39–9.42, $P < 0.00$ and HR: 4.33, 95%CI: 2.20–8.53, $P < 0.00$, respectively), but only in the radical resection group.

*CONCLUSION*

Oncological outcomes of patients with ypT0–1 rectal cancer who received ACTx after PCRT showed no improvement, regardless of the radicality of resection. Further trials are needed to evaluate the efficacy of ACTx in these group of patients.

**Key Words:** Rectal neoplasm; Adjuvant chemotherapy; ypT0-1; Radical resection; Local excision



**Core Tip:** Adjuvant chemotherapy (ACTx) is administered based on the clinical stage of rectal cancer after preoperative chemoradiotherapy (PCRT), regardless of post-treatment pathologic stage. Prognosis differs according to post-treatment pathologic stage or regression grade. Adjuvant treatment may be administered based on prognostic influence. Patients with ypT0-1 rectal cancer with favorable oncologic outcomes were included. Since local excision (LE) frequency has increased, ACTx effects in these patients need to be studied. We included patients who underwent LE. ACTx in patients with ypT0-1 rectal cancer after PCRT and LE did not exert benefits in terms of overall survival and recurrence-free survival.

**Citation:** Jeon YW, Park IJ, Kim JE, Park JH, Lim SB, Kim CW, Yoon YS, Lee JL, Yu CS, Kim JC. Evaluating the benefit of adjuvant chemotherapy in patients with ypT0–1 rectal cancer treated with preoperative chemoradiotherapy. *World J Gastrointest Surg* 2021; 13(9): 1000-1011
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1000.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1000

## INTRODUCTION

The current guidelines recommend the use of adjuvant chemotherapy (ACTx) in patients who have undergone preoperative chemoradiotherapy (PCRT) and surgical resection based on the clinical stage before PCRT[1]. However, the efficacy of ACTx, regardless of the patients' pathological findings, is controversial[2]. Previous studies have reported an improvement in the oncological outcomes of rectal cancer patients who underwent PCRT, total mesorectal excision (TME), and ACTx[3-5]; the outcomes differed according to the postoperative pathological stage or the tumor regression grade[6,7] rather than the pre-PCRT clinical stage. Therefore, tumor regression grade and post-surgical stage have been considered predictors of oncological outcomes of ACTx[8].

Patients with good response to PCRT have a favorable prognosis, and the 5-year recurrence-free survival (RFS) of patients with yp stage 0 and 1 disease after PCRT is > 90%[9,10]. Considering the risks of ACTx such as toxicity and financial burden[11,12], limited information is available regarding the oncological benefit of ACTx in patients with early yp stage 0 and 1 diseases[13]. Recent studies analyzing the oncological benefit of ACTx in patients who achieved a pathological complete response have reported inconsistent results[14-18]. Therefore, it is imperative to analyze the survival benefit of ACTx in patients in the early post-surgical stage who have a good prognosis. Hence, this study aimed to evaluate the long-term survival benefit of ACTx in patients with ypT0–1 disease after PCRT and surgical resection.

## MATERIALS AND METHODS

### Patients

We initially identified 5207 rectal cancer patients who underwent PCRT followed by surgical resection [radical resection or local excision (LE)] between January 2005 and December 2014 at the Asan Medical Center, Seoul, South Korea. Of the patients who underwent PCRT, 42 who were lost to follow-up and 1341 with ypT2–4 or ypTx disease were excluded. Patients who received ACTx postoperatively were categorized into the ACTx group, while those who did not receive ACTx postoperatively were categorized into the no ACTx group (Figure 1). This study was approved by the Institutional Review Board of (registration No. 2017-1114), which waived the requirement for obtaining an informed consent due to the retrospective nature of the study.

### PCRT and surgery

For patients who opted to receive PCRT, a radiation dose of 45–50.4 Gy was delivered in 20–28 fractions (1.8–2.0 *per* fraction) to a target volume including the primary tumor, perirectal adipose tissue, lateral pelvis, and presacral lymph node (LN) during the PCRT treatment period. Concurrent chemotherapy consisted of either two cycles of intravenous bolus injection of 5-fluorouracil (5-FU, 375 mg/m$^2$/d) and leucovorin (20 mg/m$^2$/d) (FL) or oral administration of capecitabine (825 mg/m$^2$) twice daily. Other agents such as oxaliplatin, TS-1, and temozolomide were used as a combination therapy in some patients.

Surgical resection was performed 6–12 wk after the completion of radiation therapy. Radical surgical resection was performed according to the principles of TME. For the LE of the tumor, transanal LE, transanal minimally invasive surgery, or full thickness excision was performed.

ACTx was recommended in all medically fit patients who underwent PCRT. The recommended adjuvant regimen consisted of four cycles of 5-FU and leucovorin (FL) monthly or six cycles of capecitabine.

### Surveillance and oncological outcomes

All patients underwent postoperative follow-up, which consisted of physical examination, serum carcinoembryonic antigen measurement, chest radiography, and abdominal, pelvic, and chest computed tomography (CT) every 3–6 mo. Most patients underwent colonoscopy between 6 mo and 1 year postoperatively and every 2–3 years thereafter. Recurrence was determined according to the radiological or histopathological findings. Local recurrence was defined as the presence of a suspicious lesion in the areas contiguous to the bed of the primary rectal resection or the site of anastomosis, while distant metastasis was defined as the presence of any recurrence in a distant organ or dissemination to the peritoneal surface. RFS was measured from the date of surgery to the date of detection of the first recurrence or death.

Patients who underwent LE were followed up every 3 mo for the first 1–2 years postoperatively and every 6 mo thereafter. Physical assessment with digital rectal examination and laboratory tests including sigmoidoscopy were performed every 3 mo for the first 1–2 years and every 6 mo for the next 3–4 years for a total of 5 years. Full colonoscopy was performed within 1 year after surgery and every 2–3 years thereafter. Abdominopelvic and chest CT was performed every 6 mo for 5 years.

### Statistical analysis

Categorical variables were compared using the chi-square test, while normally distributed continuous data were analyzed using the Student's *t*-test. Survival curves were constructed using the Kaplan–Meier method and compared using log-rank tests according to the status of ACTx. The associations between the clinical factors and RFS were determined using the Cox proportional hazard regression analysis. Statistical significance was assumed at a level of 5%. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, United States).

## RESULTS

### Clinicopathological characteristics of patients

A total of 520 patients were enrolled. The mean (± SD) age was 59.1 ± 10.5) years.

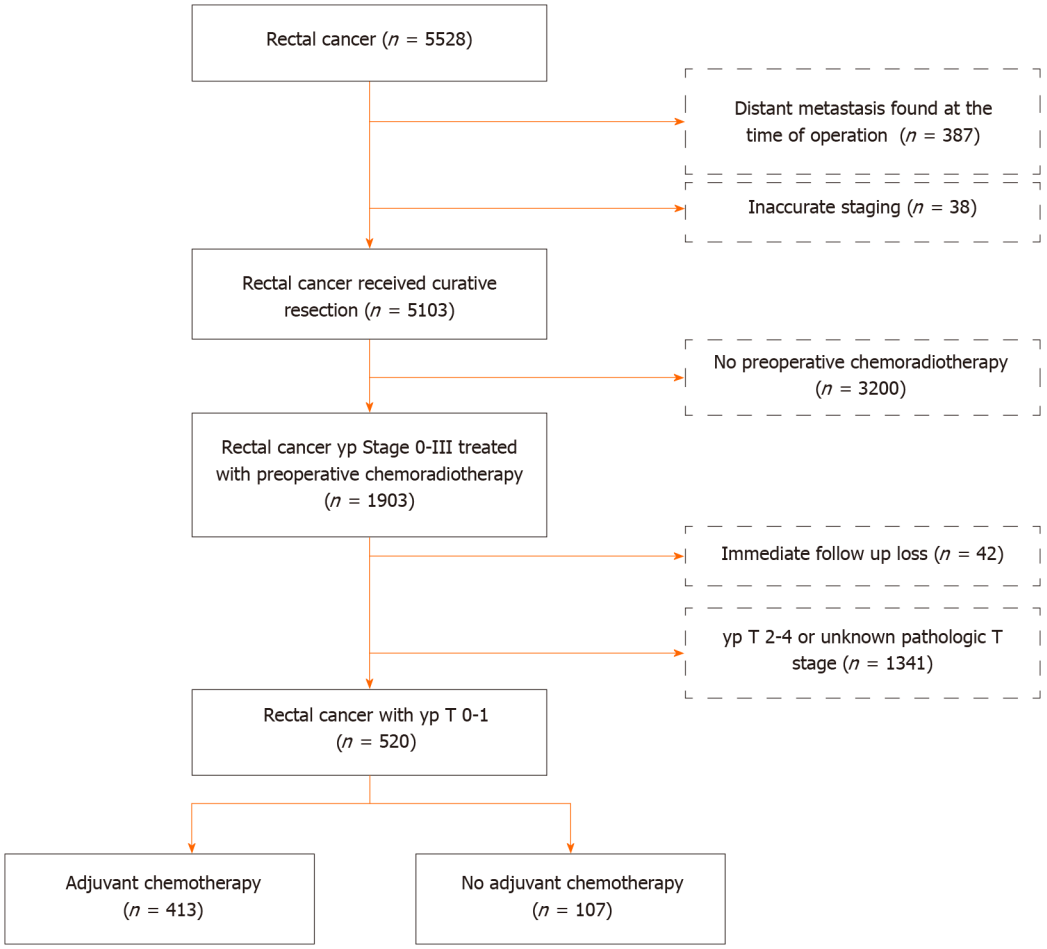



**Figure 1 CONSORT diagram.** Inclusion of patients.

Approximately 59.4% patients were men, and 85% patients underwent radical resection. The mean follow-up duration was 71.0 ± 32.6 mo. In the ACTx and no ACTx groups, the proportion of patients with cT3–4 and cN+ disease was higher than that of patients with cT1–2 and cN− disease. The ACTx group had a higher proportion of patients with advanced cT and cN disease compared with the no ACTx group. There was no significant difference in ypT stage between both groups. LN retrievals were evaluated in patients who underwent radical resection. The mean number of examined LNs and proportion of patients with ypN stage were similar in both groups (Table 1).

### *Oncological outcome according to ACTx*

The recurrence rates were significantly different according to the status of ACTx ($P$ = 0.009). The ACTx group had a recurrence rate of 10.4% (43/413), and most patients had distant metastasis (9.7%, 40/43). The most common site of metastasis in the ACTx group was the lung (57.5%). The no ACTx group had a recurrence rate of 7.4%, which was significantly lower than that of the ACTx group ($P$ = 0.009). Distant LNs were the most common site of metastasis in the no ACTx group (Table 2). The 5-year RFS rates in the ACTx and no ACTx groups were 87.9% and 91.4%, respectively ($P$ = 0.457), while the overall survival (OS) rates were 90.5% and 86.2%, respectively ($P$ = 0.304). No significant difference was observed in the RFS and OS between the groups (Figure 2).

When the RFS and OS were analyzed by the type of surgery (radical resection or LE) according to the status of ACTx, no significant difference was observed with regard to the 5-year RFS in patients who underwent radical resection and LE between the ACTx group and the no ACTx group (radical resection: 90.3% *vs* 92.9%, $P$ = 0.363; LE: 90.4% *vs* 89.6%, $P$ = 0.996). Similarly, no significant difference was found regarding the 5-year OS in patients who underwent radical resection and LE between the ACTx group and the no ACTx group (radical resection: 93.7% *vs* 90.6%, $P$ = 0.167; LE: 91.4% *vs* 90.7%, $P$ = 0.945; Figure 3).

**Table 1 Clinicopathological characteristics of the study patients**

| Variables | | ACTx (*n* = 413) | No ACTx (*n* = 107) | *P* value |
|---|---|---|---|---|
| Age, mean ± SD, yr | | 58 ± 10.1 | 63.4 ± 11.0 | < 0.001 |
| Sex, *n* (%) | | | | 0.659 |
| | Male | 243 (58.8) | 66 (61.7) | |
| | Female | 170 (41.2) | 41 (38.3) | |
| cT category, *n* (%) | | | | < 0.001 |
| | cT1–2 | 83 (20.1) | 48 (44.9) | |
| | cT3–4 | 330 (79.9) | 59 (55.1) | |
| cN category, *n* (%) | | | | < 0.001 |
| | cN- | 65 (15.7) | 34 (31.8) | |
| | cN+ | 348 (84.3) | 73 (68.2) | |
| Type of surgery, *n* (%) | | | | < 0.001 |
| | Radical resection | 378 (91.5) | 64 (59.8) | |
| | Local excision | 35 (8.5) | 43 (40.2) | |
| Number of examined LNs, mean ± SD[1] | | 14.7 ± 6.9 | 14.6 ± 6.3 | 0.892 |
| pT category, *n* (%) | | | | 0.099 |
| | ypT0 | 294 (71.2) | 67 (62.6) | |
| | ypTis–1 | 119 (28.8) | 40 (37.4) | |
| pN category[1], *n* (%) | | | | 0.201 |
| | ypN0 | 347 (91.8) | 62 (96.9) | |
| | ypN+ | 31 (8.2) | 2 (3.1) | |
| Lymphovascular invasion, *n* (%) | | 4 (1) | - | 0.339 |
| Follow-up duration mean ± SD, months | | 72.1 ± 33.0 | 66.4 ± 30.3 | 0.105 |

[1]Only for radical resection.
SD: Standard deviation; ACTx: Adjuvant chemotherapy; LN: Lymph node.

### *Risk factor associated with RFS and overall survival*

In the univariate analysis, none of the risk factors were associated with RFS, including the administration of ACTx. In the multivariate analysis, cT3–4 stage was the only risk factor associated with RFS [hazard ratio (HR): 2.57; 95% confidence interval (CI): 1.07–6.16, $P = 0.04$]. Even in the subgroup analysis of patients with cT3–4 stage disease, ACTx was not associated with RFS (HR: 1.358, $P = 0.521$; Table 3). Apart from age, none of the risk factors were associated with OS in the univariate analysis. In contrast, cT stage was a significant risk factor for OS in the multivariate analysis (HR: 2.268, 95%CI: 1.09–4.74, $P = 0.03$). However, in the multivariate Cox regression analysis of the cT3–4 group, administration of ACTx was not a significant risk factor for OS (Table 4).

In patients undergoing radical surgical resection, ypN stage was a risk factor associated with RFS and OS. ypN+ stage was a risk factor for RFS in both the univariate and multivariate analyses (HR: 4.86, $P < 0.00$ and HR: 4.74, 95%CI: 2.39–9.42, $P < 0.00$, respectively). It was also confirmed as a risk factor for OS in the multivariate analysis (HR: 4.33, 95%CI: 2.20–8.53, $P < 0.00$). However, administration of ACTx was not associated with both RFS and OS in patients who underwent radical resection.

## DISCUSSION

In this study, it was found that the ACTx did not improve the RFS and OS of patients with ypT0–1 rectal cancer who underwent PCRT and resection. In the subgroup

**Table 2 Sites of initial recurrence according to the status of adjuvant chemotherapy**

| Variables | ACTx (*n* = 413) | No ACTx (*n* = 107) | *P* value |
|---|---|---|---|
| Recurrence, *n* (%) | 43 (10.4) | 8 (7.4) | |
| Type of recurrence, *n* (%) | | | 0.009 |
| Local recurrence | 3 (0.7) | 4 (3.7) | |
| Distant metastasis | 40 (9.7) | 4 (3.7) | |
| Sites of distant metastasis[1], *n* (%) | | | |
| Liver | 8 (20) | 1 (12.5) | |
| Lung | 23 (57.5) | 2 (25) | |
| Distant lymph nodes | 6 (15) | 1 (12.5) | |
| Bone | 4 (10) | - | |
| Brain | 1 (2.5) | - | |
| Ovary | 1 (2.5) | - | |

[1]Among patients with distant metastasis.
ACTx: Adjuvant chemotherapy.

**Table 3 Risk factors associated with recurrence-free survival**

| | Univariate | | Multivariate | | |
|---|---|---|---|---|---|
| | HR | *P* value | HR | 95%CI | *P* value |
| Adjuvant chemotherapy | | 0.459 | | | 0.608 |
| No | 1 | | 1 | | |
| Yes | 1.331 | | 1.226 | 0.563–2.671 | |
| Sex | | 0.582 | | | |
| Male | 1 | | | | |
| Female | 1.77 | | | 0 | |
| cT category | | 0.082 | | | 0.035 |
| cT1–2 | 1 | | 1 | | |
| cT3–4 | 2.031 | | 2.565 | 1.06–6.156 | |
| cN category | | 0.399 | | | |
| cN− | 1 | | | | |
| cN+ | 0.756 | | | | |
| Type of surgery | | 0.927 | | | |
| Local excision | 1 | | | | |
| Radical resection | 1.038 | | | | |
| ypT stage | | 0.389 | | | |
| ypT0 | 1 | | | | |
| ypTis–1 | 0.757 | | | | |

HR: Hazard ratio; CI: Confidence interval.

analysis according to the type of resection, administration of ACTx was not associated with RFS and OS in patients who underwent LE and those who underwent radical resection. The significant risk factors for RFS and OS were cT stage and ypN stage in patients who underwent radical resection.

**Table 4 Risk factors associated with overall survival**

| | Univariate | | Multivariate | | |
|---|---|---|---|---|---|
| | HR | *P* value | HR | 95% CI | *P* value |
| Adjuvant chemotherapy | | 0.306 | | | 0.484 |
| No | 1 | | 1 | | |
| Yes | 0.729 | | 0.797 | 0.422–1.504 | |
| Age | 1.047 | 0.001 | 1.052 | 1.022–1.084 | 0.001 |
| Sex | | 0.156 | | | 0.213 |
| Male | 1 | | 1 | | |
| Female | 0.668 | | 0.701 | 0.400–1.227 | |
| cT category | | 0.122 | | | 0.029 |
| cT1–2 | 1 | | 1 | | |
| cT3–4 | 1.757 | | 2.268 | 1.085–4.741 | |
| cN category | | 0.475 | | | |
| cN− | 1 | | | | |
| cN+ | 1.296 | | | | |
| Type of surgery | | 0.692 | | | |
| Local excision | 1 | | | | |
| Radical resection | 1.174 | | | | |
| ypT stage | | 0.612 | | | |
| ypT0 | 1 | | | | |
| ypTis–1 | 0.861 | | | | |

HR: Hazard ratio; CI: Confidence interval.

The present study included patients who underwent LE and those who underwent radical resection, while previous studies included patients who underwent either radical surgical resection or TME[14-18]. Tumor regression after neoadjuvant chemoradiotherapy has made it possible to perform LE according to the principles of TME for rectal cancer. The rate of LE after PCRT for rectal cancer has gradually increased over time[19]. Therefore, enrollment of patients who underwent LE after PCRT in this study may have a more practical importance in the clinical decision making, especially in patients with pathological downstaging. Furthermore, patients in this study had good adherence to ACTx; hence, the efficacy of ACTx was evaluated more precisely.

Previous studies have demonstrated that patients who achieve a pathological complete response after chemoradiation have a better prognosis than those who do not achieve a pathological complete response[20-22]. However, there was a lack of consensus in the efficacy of ACTx for good responders. Four randomized control trials in patients treated with PCRT followed by surgical resection failed to show an improvement in the oncological outcomes after ACTx and reported low accrual rates [4,23-25]. Despite the heterogeneity of the inclusion criteria, several retrospective studies have also reported that there is no significant oncological benefit of ACTx in low-risk patients with good response to PCRT[17,18,26-31]. Even in the long-term analysis of the 10-year cumulative cancer-specific survival, ACTx had no significant impact on patients with ypTis-2N0M0 stage in our previous report[32]. The possible risk factors associated with oncological outcomes are tumor regression grade[33], yp stage[27], cT stage and resection margin status[28], tumor grade[18], and residual tumor of ypT1–4[31].

Recent studies based on the National Cancer Database have shown contradictory results. One study showed that ACTx was associated with improved OS in patients who achieved a pathological complete response, and while another showed that ACTx was more beneficial in patients with pretreatment node-positive cancer than those without metastatic nodes[14,15]. Although these studies analyzed a large sample of

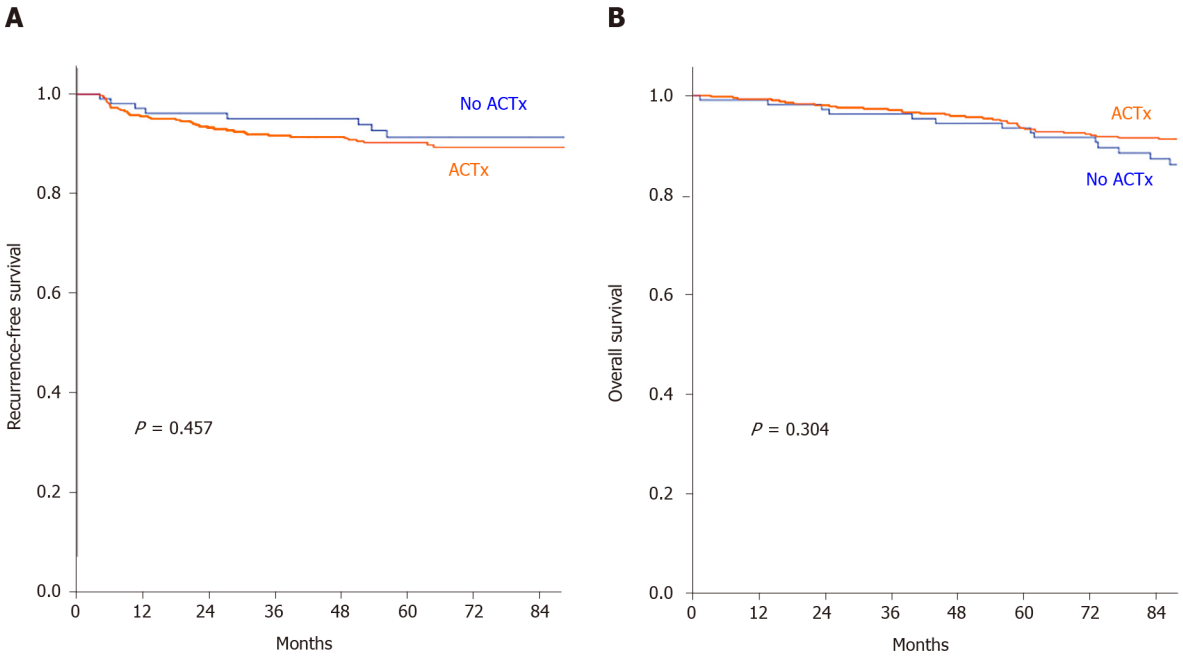



**Figure 2 Oncological outcomes according to the status of adjuvant chemotherapy in patients with ypT0–1 rectal cancer after preoperative chemoradiotherapy.** A: Recurrence-free survival; B: Overall survival. ACTx: Adjuvant chemotherapy.

patients, limited data on patient characteristics and clinical outcomes such as local recurrence and cancer-related death could obscure the results as an unmeasured confounding factor, worsened with the statistical features of propensity score matching[34]. Another large-scale study showed an association between the administration of ACTx and lower risk of death[35]; however, this study included all patients with stage II–III disease without analyzing the benefit of ACTx in each subgroup according to the ypT stage. A previous study showed additional benefit of ACTx; however, there was possible selection bias since younger and healthier patients were more likely to receive ACTx than older adults with comorbidities[16].

Hence, the results of the current study should be carefully interpreted as the analysis was performed in patients with ypN0 and ypN+ status. Although the LN status is one of the most important prognostic factors[36,37], we could not analyze the extent of nodal involvement as LN evaluation was limited during LE. In our study, the proportion of patients with ypT0–1N+ stage in the radical resection subgroup was 7.4% (33/442), which was similar to that reported in the previous study[36]; most of the patients with ypT0–1N+ stage received ACTx (93.9%, 31/33). Therefore, the influence of ACTx in patients with ypT0–1N+ could not be sufficiently evaluated in this study. Although the accuracy of the imaging diagnosis of LN metastasis is limited in current clinical practice, the rate of LE in rectal cancer patients who achieve complete or near complete regression of the primary tumor after PCRT has increased gradually[19]. Therefore, future studies should include not only patients who have undergone LE, but also those who have undergone radical resection considering the current clinical practice. In our study, among patients who had LE, 55.1% (43/78) did not receive ACTx, and the benefit of ACTx in ypT0–1 rectal cancer patients who underwent LE could be sufficiently evaluated.

The most common ACTx regimen administered in our study was 5-FU/Leucovorin or capecitabine. Long-term results of recent studies comparing the outcome of ACTx using different agents showed that patients with ypN1b and ypN2 disease benefited from FOLFOX rather than FL[8]. Patients enrolled in our study with early ypT stage who showed good response to PCRT seemed to have a lesser oncological benefit than those included in the abovementioned trial. LN metastasis remained a risk factor for RFS and OS even in patients with ypT0–1 disease. Therefore, further studies are needed to determine whether the same conclusion can be established when a more intense chemotherapy regimen is used.

This study has some limitations, which include the retrospective review of data from a single center and the small sample size. Selection bias resulted from the inclusion of patients who either underwent radical resection or LE. As current guidelines recommend ACTx to patients after PCRT and surgical resection regardless

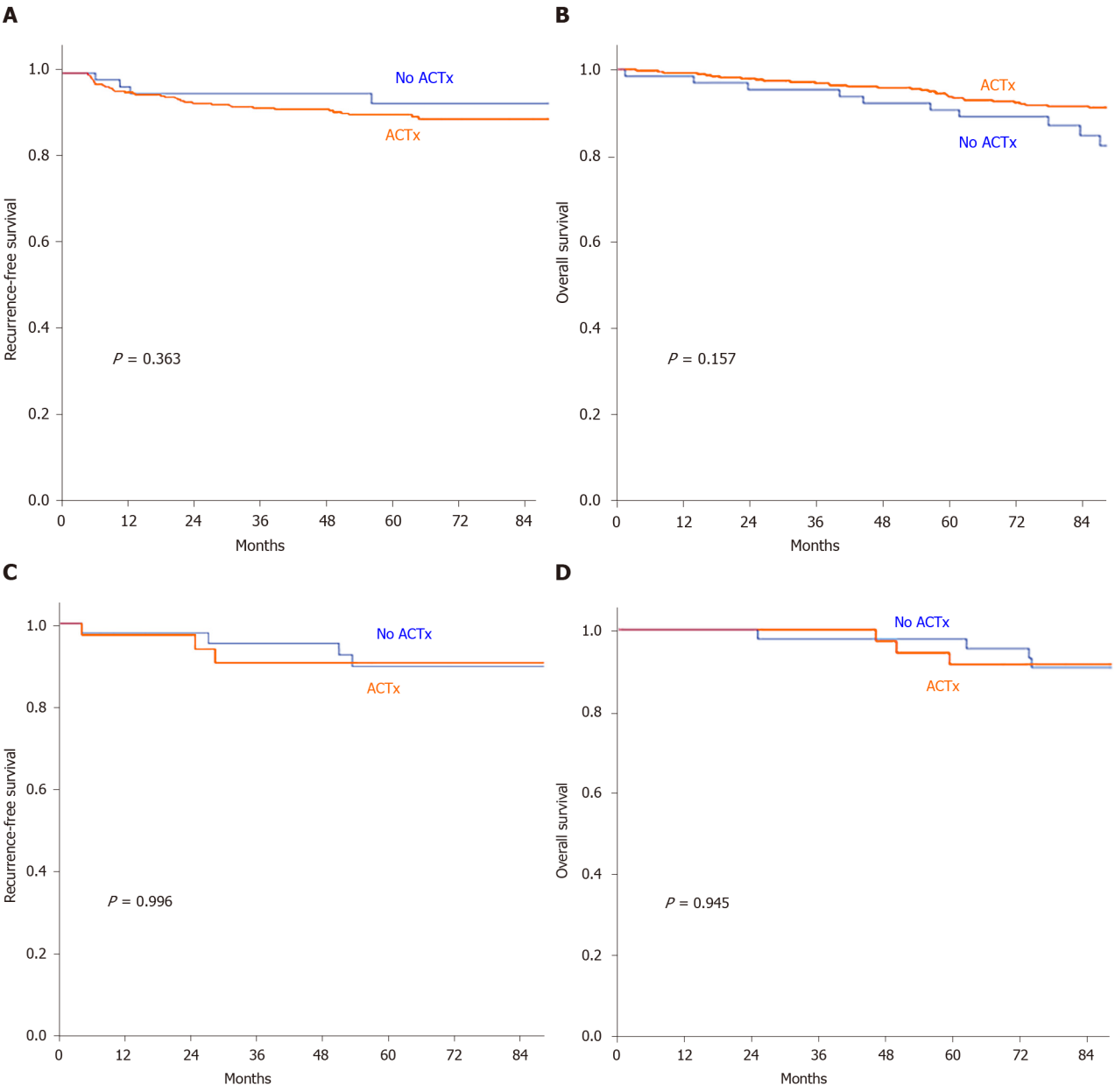



**Figure 3 Oncological outcomes according to the status of adjuvant chemotherapy by the type of surgery.** A: Recurrence-free survival (RFS) in patients treated with radical resection; B: Overall survival (OS) in patients who underwent radical resection; C: RFS in local excision (LE); D: OS in patients who underwent LE. ACTx: Adjuvant chemotherapy.

of post-treatment stage, few patients with ypT0–1N+ disease did not receive ACTx; hence, the comparison of patients with ypN+ disease who underwent radical resection between the ACTx group and the no ACTx group may not be sufficient. These limitations may influence the reliability of the results, which should be interpreted carefully.

Despite the study limitations, we demonstrated that there was no long-term survival benefit of ACTx in patients with ypT0–1 disease after PCRT regardless of the radicality of the surgery. Hence, the necessity of ACTx in patients with cT stage disease, a risk factor associated with RFS and OS, should be carefully reviewed in future studies.

## CONCLUSION

In conclusion, ACTx in patients with ypT0–1 disease who had a good response to PCRT followed by surgical resection may not be beneficial in improving the oncological outcome. Routine ACTx based on the pretreatment clinical stage should be

carefully applied in the clinical setting considering the heterogenous oncological outcomes of patients at post-surgical stage.

## ARTICLE HIGHLIGHTS

### *Research background*

In rectal cancer patients after preoperative chemoradiotherapy (PCRT), adjuvant chemotherapy (ACTx) is recommended regardless of post-surgical stage.

### *Research motivation*

It is controversial that ACTx improves the oncologic outcome in patients in the early yp stage expected to have a good prognosis.

### *Research objectives*

This study is a retrospective study that aims to evaluate the survival benefit of ACTx in patients with ypT0–1 who underwent PCRT and surgical resection, including local excision.

### *Research methods*

After identification of patients who received PCRT followed by surgical resection, analysis of the 5-yr recurrence-free survival (RFS) and overall survival (OS) of patients with ypT0–1 rectal cancer was performed according to the status of ACTx.

### *Research results*

There was no significant difference in the 5-year RFS and 5-year OS between the two groups. In the multivariate analysis, cT stage was associated with RFS and OS. Also, ypN stage only analyzed in the radical resection group was associated with RFS and OS.

### *Research conclusions*

Our study demonstrated no oncologic benefit of ACTx in patients with ypT0–1 rectal cancer after PCRT and surgical treatment regardless of the radicality of resection.

### *Research perspectives*

In rectal cancer treated with PCRT, ACTx use, regardless of the final pathologic stage, needs to be carefully reconsidered. For ypT0-1 rectal cancer, ACTx did not show any oncologic benefit. Therefore, risk-stratified risk-benefit consideration is important for rectal cancer patients with good pathologic results after PCRT. Further studies with prospective, large-scale, and randomized trials are needed to evaluate the efficacy of ACTx in patients with early post-treatment stage rectal cancer who have a favorable prognosis.

## REFERENCES


1 **NCCN**. National Clinical Practice Guidelines in Oncology (NCCN Guidelines). Rectal cancer version 6. 2020. [cited 25 June 2020]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

2 **Petersen SH**, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; CD004078 [PMID: 22419291 DOI: 10.1002/14651858.CD004078.pub2]

3 **Kapiteijn E**, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**: 638-646 [PMID: 11547717 DOI: 10.1056/NEJMoa010580]

4 **Bosset JF**, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, Bardet E, Beny A, Ollier JC, Bolla M, Marchal D, Van Laethem JL, Klein V, Giralt J, Clavère P, Glanzmann C, Cellier P, Collette L; EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**: 184-190 [PMID: 24440473 DOI: 10.1016/S1470-2045(13)70599-0]

5 **Sauer R**, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rödel C. Preoperative *vs* postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94

randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; **30**: 1926-1933 [PMID: 22529255 DOI: 10.1200/JCO.2011.40.1836]

6 **Kim MJ**, Jeong SY, Park JW, Ryoo SB, Cho SS, Lee KY, Park KJ. Oncologic Outcomes in Patients Who Undergo Neoadjuvant Chemoradiotherapy and Total Mesorectal Excision for Locally Advanced Rectal Cancer: A 14-Year Experience in a Single Institution. *Ann Coloproctol* 2019; **35**: 83-93 [PMID: 31113173 DOI: 10.3393/ac.2019.04.22.1]

7 **Fokas E**, Fietkau R, Hartmann A, Hohenberger W, Grützmann R, Ghadimi M, Liersch T, Ströbel P, Grabenbauer GG, Graeven U, Hofheinz RD, Köhne CH, Wittekind C, Sauer R, Kaufmann M, Hothorn T, Rödel C; German Rectal Cancer Study Group. Neoadjuvant rectal score as individual-level surrogate for disease-free survival in rectal cancer in the CAO/ARO/AIO-04 randomized phase III trial. *Ann Oncol* 2018; **29**: 1521-1527 [PMID: 29718095 DOI: 10.1093/annonc/mdy143]

8 **Hong YS**, Kim SY, Lee JS, Nam BH, Kim KP, Kim JE, Park YS, Park JO, Baek JY, Kim TY, Lee KW, Ahn JB, Lim SB, Yu CS, Kim JC, Yun SH, Kim JH, Park JH, Park HC, Jung KH, Kim TW. Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE): Long-Term Results of a Randomized Controlled Trial. *J Clin Oncol* 2019; **37**: 3111-3123 [PMID: 31593484 DOI: 10.1200/JCO.19.00016]

9 **Benzoni E**, Intersimone D, Terrosu G, Bresadola V, Cojutti A, Cerato F, Avellini C. Prognostic value of tumour regression grading and depth of neoplastic infiltration within the perirectal fat after combined neoadjuvant chemo-radiotherapy and surgery for rectal cancer. *J Clin Pathol* 2006; **59**: 505-512 [PMID: 16522747 DOI: 10.1136/jcp.2005.031609]

10 **Yoo RN**, Kim HJ. Organ Preservation Strategies After Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. *Ann Coloproctol* 2019; **35**: 53-64 [PMID: 31113170 DOI: 10.3393/ac.2019.04.15.1]

11 **Shah R**, Botteman M, Solem CT, Luo L, Doan J, Cella D, Motzer RJ. A Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) Analysis of Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma (aRCC). *Clin Genitourin Cancer* 2019; **17**: 356-365.e1 [PMID: 31272883 DOI: 10.1016/j.clgc.2019.05.010]

12 **Hisashige A**, Yoshida S, Kodaira S. Cost-effectiveness of adjuvant chemotherapy with uracil-tegafur for curatively resected stage III rectal cancer. *Br J Cancer* 2008; **99**: 1232-1238 [PMID: 18797469 DOI: 10.1038/sj.bjc.6604666]

13 **Carvalho C**, Glynne-Jones R. Challenges behind proving efficacy of adjuvant chemotherapy after preoperative chemoradiation for rectal cancer. *Lancet Oncol* 2017; **18**: e354-e363 [PMID: 28593861 DOI: 10.1016/S1470-2045(17)30346-7]

14 **Dossa F**, Acuna SA, Rickles AS, Berho M, Wexner SD, Quereshy FA, Baxter NN, Chadi SA. Association Between Adjuvant Chemotherapy and Overall Survival in Patients With Rectal Cancer and Pathological Complete Response After Neoadjuvant Chemotherapy and Resection. *JAMA Oncol* 2018; **4**: 930-937 [PMID: 29710274 DOI: 10.1001/jamaoncol.2017.5597]

15 **Polanco PM**, Mokdad AA, Zhu H, Choti MA, Huerta S. Association of Adjuvant Chemotherapy With Overall Survival in Patients With Rectal Cancer and Pathologic Complete Response Following Neoadjuvant Chemotherapy and Resection. *JAMA Oncol* 2018; **4**: 938-943 [PMID: 29710272 DOI: 10.1001/jamaoncol.2018.0231]

16 **Shahab D**, Gabriel E, Attwood K, Ma WW, Francescutti V, Nurkin S, Boland PM. Adjuvant Chemotherapy Is Associated With Improved Overall Survival in Locally Advanced Rectal Cancer After Achievement of a Pathologic Complete Response to Chemoradiation. *Clin Colorectal Cancer* 2017; **16**: 300-307 [PMID: 28420585 DOI: 10.1016/j.clcc.2017.03.005]

17 **Gamaleldin M**, Church JM, Stocchi L, Kalady M, Liska D, Gorgun E. Is routine use of adjuvant chemotherapy for rectal cancer with complete pathological response justified? *Am J Surg* 2017; **213**: 478-483 [PMID: 27939008 DOI: 10.1016/j.amjsurg.2016.11.028]

18 **Zhou J**, Qiu H, Lin G, Xiao Y, Wu B, Wu W, Sun X, Lu J, Zhang G, Xu L, Liu Y. Is adjuvant chemotherapy necessary for patients with pathological complete response after neoadjuvant chemoradiotherapy and radical surgery in locally advanced rectal cancer? *Int J Colorectal Dis* 2016; **31**: 1163-1168 [PMID: 27044403 DOI: 10.1007/s00384-016-2579-5]

19 **You YN**, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified? *Ann Surg* 2007; **245**: 726-733 [PMID: 17457165 DOI: 10.1097/01.sla.0000252590.95116.4f]

20 **Maas M**, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, Calvo FA, García-Aguilar J, Glynne-Jones R, Haustermans K, Mohiuddin M, Pucciarelli S, Small W Jr, Suárez J, Theodoropoulos G, Biondo S, Beets-Tan RG, Beets GL. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11**: 835-844 [PMID: 20692872 DOI: 10.1016/S1470-2045(10)70172-8]

21 **Capirci C**, Valentini V, Cionini L, De Paoli A, Rodel C, Glynne-Jones R, Coco C, Romano M, Mantello G, Palazzi S, Mattia FO, Friso ML, Genovesi D, Vidali C, Gambacorta MA, Buffoli A, Lupattelli M, Favretto MS, La Torre G. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008; **72**: 99-107 [PMID: 18407433 DOI: 10.1016/j.ijrobp.2007.12.019]

22 **Zorcolo L**, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A, Melis M. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. *Ann Surg Oncol* 2012; **19**: 2822-2832 [PMID: 22434243 DOI: 10.1245/s10434-011-2209-y]

23 **Breugom AJ**, van Gijn W, Muller EW, Berglund Å, van den Broek CBM, Fokstuen T, Gelderblom

H, Kapiteijn E, Leer JWH, Marijnen CAM, Martijn H, Meershoek-Klein Kranenbarg E, Nagtegaal ID, Påhlman L, Punt CJA, Putter H, Roodvoets AGH, Rutten HJT, Steup WH, Glimelius B, van de Velde CJH. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015; **26**: 696-701 [PMID: 25480874 DOI: 10.1093/annonc/mdu560]

24 **Sainato A**, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, Aristei C, Vidali C, Conti M, Galardi A, Ponticelli P, Friso ML, Iannone T, Osti FM, Manfredi B, Coppola M, Orlandini C, Cionini L. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**: 223-229 [PMID: 25454175 DOI: 10.1016/j.radonc.2014.10.006]

25 **Glynne-Jones R**, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, Ledermann J, Sebag-Montefiore D. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) *vs* control. *Ann Oncol* 2014; **25**: 1356-1362 [PMID: 24718885 DOI: 10.1093/annonc/mdu147]

26 **Lim YJ**, Kim Y, Kong M. Adjuvant chemotherapy in rectal cancer patients who achieved a pathological complete response after preoperative chemoradiotherapy: a systematic review and meta-analysis. *Sci Rep* 2019; **9**: 10008 [PMID: 31292517 DOI: 10.1038/s41598-019-46457-5]

27 **Voss RK**, Lin JC, Roper MT, Al-Temimi MH, Ruan JH, Tseng WH, Tam M, Sherman MJ, Klaristenfeld DD, Tomassi MJ. Adjuvant Chemotherapy Does Not Improve Recurrence-Free Survival in Patients With Stage 2 or Stage 3 Rectal Cancer After Neoadjuvant Chemoradiotherapy and Total Mesorectal Excision. *Dis Colon Rectum* 2020; **63**: 427-440 [PMID: 31996583 DOI: 10.1097/DCR.0000000000001558]

28 **Kim CG**, Ahn JB, Shin SJ, Beom SH, Heo SJ, Park HS, Kim JH, Choe EA, Koom WS, Hur H, Min BS, Kim NK, Kim H, Kim C, Jung I, Jung M. Role of adjuvant chemotherapy in locally advanced rectal cancer with ypT0-3N0 after preoperative chemoradiation therapy and surgery. *BMC Cancer* 2017; **17**: 615 [PMID: 28865435 DOI: 10.1186/s12885-017-3624-7]

29 **Geva R**, Itzkovich E, Shamai S, Shacham-Shmueli E, Soyfer V, Klausner JM, Tulchinsky H. Is there a role for adjuvant chemotherapy in pathological complete response rectal cancer tumors following neoadjuvant chemoradiotherapy? *J Cancer Res Clin Oncol* 2014; **140**: 1489-1494 [PMID: 24849731 DOI: 10.1007/s00432-014-1712-5]

30 **You KY**, Huang R, Ding PR, Qiu B, Zhou GQ, Chang H, Xiao WW, Zeng ZF, Pan ZZ, Gao YH. Selective use of adjuvant chemotherapy for rectal cancer patients with ypN0. *Int J Colorectal Dis* 2014; **29**: 529-538 [PMID: 24474499 DOI: 10.1007/s00384-014-1831-0]

31 **Maas M**, Nelemans PJ, Valentini V, Crane CH, Capirci C, Rödel C, Nash GM, Kuo LJ, Glynne-Jones R, García-Aguilar J, Suárez J, Calvo FA, Pucciarelli S, Biondo S, Theodoropoulos G, Lambregts DM, Beets-Tan RG, Beets GL. Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection: a pooled analysis of 3,313 patients. *Int J Cancer* 2015; **137**: 212-220 [PMID: 25418551 DOI: 10.1002/ijc.29355]

32 **Gahagan JV**, Whealon MD, Phelan MJ, Mills S, Jafari MD, Carmichael JC, Stamos MJ, Zell JA, Pigazzi A. Improved survival with adjuvant chemotherapy in locally advanced rectal cancer patients treated with preoperative chemoradiation regardless of pathologic response. *Surg Oncol* 2020; **32**: 35-40 [PMID: 31726418 DOI: 10.1016/j.suronc.2019.10.021]

33 **Park IJ**, Kim DY, Kim HC, Kim NK, Kim HR, Kang SB, Choi GS, Lee KY, Kim SH, Oh ST, Lim SB, Kim JC, Oh JH, Kim SY, Lee WY, Lee JB, Yu CS. Role of Adjuvant Chemotherapy in ypT0-2N0 Patients Treated with Preoperative Chemoradiation Therapy and Radical Resection for Rectal Cancer. *Int J Radiat Oncol Biol Phys* 2015; **92**: 540-547 [PMID: 26068489 DOI: 10.1016/j.ijrobp.2015.02.020]

34 **Chang GJ**. Is There Validity in Propensity Score-Matched Estimates of Adjuvant Chemotherapy Effects for Patients With Rectal Cancer? *JAMA Oncol* 2018; **4**: 921-923 [PMID: 29710090 DOI: 10.1001/jamaoncol.2018.0227]

35 **Turner MC**, Keenan JE, Rushing CN, Gulack BC, Nussbaum DP, Benrashid E, Hyslop T, Strickler JH, Mantyh CR, Migaly J. Adjuvant Chemotherapy Improves Survival Following Resection of Locally Advanced Rectal Cancer with Pathologic Complete Response. *J Gastrointest Surg* 2019; **23**: 1614-1622 [PMID: 30635829 DOI: 10.1007/s11605-018-04079-8]

36 **García-Flórez LJ**, Gómez-Álvarez G, Frunza AM, Barneo-Serra L, Fresno-Forcelledo MF. Response to chemoradiotherapy and lymph node involvement in locally advanced rectal cancer. *World J Gastrointest Surg* 2015; **7**: 196-202 [PMID: 26425268 DOI: 10.4240/wjgs.v7.i9.196]

37 **Lee HG**, Kim SJ, Park IJ, Hong SM, Lim SB, Lee JB, Yu CS, Kim JC. Effect of Responsiveness of Lymph Nodes to Preoperative Chemoradiotherapy in Patients With Rectal Cancer on Prognosis After Radical Resection. *Clin Colorectal Cancer* 2019; **18**: e191-e199 [PMID: 31014994 DOI: 10.1016/j.clcc.2019.03.001]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 1012-1024

DOI: 10.4240/wjgs.v13.i9.1012

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Optimal postoperative surveillance strategies for stage III colorectal cancer

Min Young Park, In Ja Park, Hyo Seon Ryu, Jay Jung, Minsung Kim, Seok-Byung Lim, Chang Sik Yu, Jin Cheon Kim

**ORCID number:** Min Young Park 0000-0002-7444-5075; In Ja Park 0000-0001-5355-3969; Hyo Seon Ryu 0000-0003-2606-9973; Jay Jung 0000-0003-1680-9704; Minsung Kim 0000-0002-1984-5084; Seok-Byung Lim 0000-0001-8824-4808; Chang Sik Yu 0000-0001-9401-9981; Jin Cheon Kim 0000-0003-4823-8619.

**Author contributions:** Kim JC, Yu CS, and Lim SB guaranted the integrity of the study; Park IJ conceptualized the study; Park IJ and Park MY collected the data, edited the manuscript; Park MY did statistical analysis and prepared manuscript; Park IJ, Park MY, Ryu HS, Jung J, and Kim MS reviewed manuscript; all authors have read and approve the final manuscript.

**Institutional review board statement:** This study was approved by the Institutional Review Board of Asan Medical Center, No: 2017-0955.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment.

**Conflict-of-interest statement:** We

**Min Young Park,** Colon and Rectal Surgery, Asan Medical Center, Seoul 05505, South Korea

**In Ja Park, Hyo Seon Ryu, Jay Jung, Minsung Kim, Seok-Byung Lim, Chang Sik Yu, Jin Cheon Kim,** Colon and Rectal Surgery, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

**Corresponding author:** In Ja Park, MD, PhD, Doctor, Professor, Surgeon, Colon and Rectal Surgery, Asan Medical Center and University of Ulsan College of Medicine, No. 88 Olympic-ro, Songpa-gu, Seoul 05505, South Korea. ipark@amc.seoul.kr

## Abstract

### *BACKGROUND*

Optimal surveillance strategies for stage III colorectal cancer (CRC) are lacking, and intensive surveillance has not conferred a significant survival benefit.

### *AIM*

To examine the association between surveillance intensity and recurrence and survival rates in patients with stage III CRC.

### *METHODS*

Data from patients with pathologic stage III CRC who underwent radical surgery between January 2005 and December 2012 at Asan Medical Center, Seoul, Korea were retrospectively reviewed. Surveillance consisted of abdominopelvic computed tomography (CT) every 6 mo and chest CT annually during the 5 year follow-up period, resulting in an average of three imaging studies per year. Patients who underwent more than the average number of imaging studies annually were categorized as high intensity (HI), and those with less than the average were categorized as low intensity (LI).

### *RESULTS*

Among 1888 patients, 864 (45.8%) were in HI group. Age, sex, and location were not different between groups. HI group had more advanced T and N stage ($P$ = 0.002, 0.010, each). Perineural invasion (PNI) was more identified in the HI group (21.4% *vs* 30.3%, $P < 0.001$). The mean overall survival (OS) and recurrence-free interval (RFI) was longer in the LI group ($P < 0.001$, each). Multivariate analysis indicated that surveillance intensity [odds ratio (OR) = 1.999; 95% confidence interval (CI): 1.680–2.377; $P < 0.001$], pathologic T stage (OR = 1.596; 95%CI:

have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.



**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** South Korea

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 24, 2021
**Peer-review started:** February 24, 2021
**First decision:** May 13, 2021
**Revised:** June 3, 2021
**Accepted:** August 2, 2021
**Article in press:** August 2, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Hazafa A
**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Wu RR

1.197–2.127; $P$ = 0.001), PNI (OR = 1.431; 95%CI: 1.192–1.719; $P$ < 0.001), and circumferential resection margin (OR = 1.565; 95%CI: 1.083–2.262; $P$ = 0.017) in rectal cancer were significantly associated with RFI. The mean post-recurrence survival (PRS) was longer in patients who received curative resection ($P$ < 0.001). Curative resection rate of recurrence was not different between HI (29.3%) and LI (23.8%) groups ($P$ = 0.160). PRS did not differ according to surveillance intensity ( $P$ = 0.802).

*CONCLUSION*

Frequent surveillance with CT scan do not improve OS in stage III CRC patients. We need to evaluate role of other surveillance method rather than frequent CT scans to detect recurrence for which curative treatment was possible because curative resection is the important to improve post-recurrence survival.

**Key Words:** Colorectal cancer; Surveillance intensity; Survival; Recurrence



**Core Tip:** This is a retrospective study to evaluate the association between surveillance intensity and recurrence and survival rates in patients with stage III colorectal cancer (CRC). The overall survival (OS) and recurrence-free interval (RFI) was longer in the low intensity group. Post-recurrence survival (PRS) did not change according to surveillance intensity. Therefore, frequent postoperative imaging studies do not improve OS or RFI in patients with stage III CRC. However, in high-risk patients, early detection of recurrence improves the chance of curative resection, which may improve PRS.

**Citation:** Park MY, Park IJ, Ryu HS, Jung J, Kim M, Lim SB, Yu CS, Kim JC. Optimal postoperative surveillance strategies for stage III colorectal cancer. *World J Gastrointest Surg* 2021; 13(9): 1012-1024
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1012.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1012

## INTRODUCTION

In patients who undergo surgery for colorectal cancer (CRC), ongoing surveillance is recommended to detect and treat recurrences early, which improves the chances of curative treatment and thus overall survival (OS)[1]. Surveillance also provides an opportunity to assess the quality of the primary surgery and detect metachronous tumors at an earlier stage.

CRC is the second most common cancer among Korean males and the fourth most common among females, and the third leading cause of cancer-related death in South Korea[2]. The 5 year trend from 2013 to 2017 indicates that approximately 78% of CRC patients in Korea have resectable tumors with localized or regional disease is similar with that in United States[3]. Despite high prevalence and mortality rates, patients with CRC represent the second largest group of 5 year cancer survivors. More than 90% of local recurrences appear within the first 5 years after surgery, and the most of them appear within 3 years after surgery[4,5]. After radical surgery with curative intent, surveillance is recommended with the goal of improving OS and disease-specific survival by detecting recurrence or metachronous cancer at an early stage. Hypothetically intensive surveillance during recurrence-prone period could be useful to detect recurrence in early phase and thus improve the prognosis of these patients[6-8] especially in patients with high risk of recurrence by early onset of proper treatment.

Although many clinical guidelines recommended surveillance method and schedule, optimal surveillance strategies have not been established to date, and systemic reviews and a randomized trial have provided inconclusive results regarding the survival benefits related to surveillance[9-11]. Recent studies indicate that intensive surveillance does not significantly increase survival rates[12-14]. However, studies

examining recurrence rates report that intensive surveillance increases the frequency of curative surgery for the recurred lesion[15-18]. Survival rates are higher for patients examined by computed tomography (CT) and detection of carcinoembryonic antigen [9,15]. The lack of consistency between reports underscores the need to evaluate the survival benefits associated with intensive surveillance. In contrary, intensive surveillance without benefit in oncologic outcomes need to be carefully reconsidered because it would be burden of medical expense as well as for patients. In addition, previous study reported the false positive rates of the CT scan which is most commonly used in CRC surveillance[19]. According to the study, CT scan showed false positive rate up to 28% for a patient with no actual recurrence. Therefore, CRC surveillance based on imaging studies requires not only a CT machine with sufficient performance but also well-trained radiologists who can make accurate readings. Furthermore, frequent CT scan resulted in sequelae of CT radiation exposure. Given these risks of intensive surveillance, unnecessary intensive surveillance should be avoided if the risk of recurrence is low or there is no survival benefit.

The purpose of the current study was to determine the association between surveillance intensity, the detection of recurrence, and survival rates. Additionally, this study investigated the effect of intensive surveillance on the outcome of curative treatment in patients with recurrent disease.

## MATERIALS AND METHODS

### *Participants and clinical variables*

Data from patients with pathologic stage III CRC who underwent radical surgery between January 2005 and December 2012 at Asan Medical Center, Seoul, Korea were retrospectively reviewed. Patients who underwent radical resection and elective surgery for primary CRC, as well as those treated with preoperative chemoradiotherapy (PCRT) followed by radical resection, were included. Patients with synchronous distant metastasis, synchronous cancer in another organ, cancer diagnosed within 5 years, inflammatory disease associated CRC, those who under-went local excision, and those with unknown staging status were excluded. Patients who were lost to follow-up surveillance were excluded from analyses as well. As a result, 1888 patients who met the criteria were included in the final analysis.

Patient characteristics analyzed included age, sex, pathologic differentiation, lymphovascular invasion (LVI), perineural invasion (PNI), circumferential resection margin (CRM) of rectal cancer (involving < 1 mm), PCRT, recurrence, treatment after recurrence, and survival. Postoperative surveillance included abdomino-pelvic CT (APCT) and chest CT (CCT).

This study was approved by the Institutional Review Board of Asan Medical Center, No. 2017-0955.

### *Surgical procedures and postoperative surveillance*

The objectives of surgical treatment for colon cancer were ligation of feeding vessels at their roots, principal node removal, and achieving a sufficient resection margin for both proximal and distal margins. Surgery was performed according to the principle of total mesorectal excision for rectal cancer. Patients who received PCRT underwent surgical resection at 6–10 wk after completion of the chemoradiotherapy course. The majority of surgical procedures were carried out by one of seven experienced colomajority of surgical procedures were carried out by one of seven experiencedrectal surgeons, and the remaining procedures were performed by colorectal fellows.

Adjuvant chemotherapy was recommended for pathologic stage III colon cancer patients and for stage II patients with risk factors such as preoperative obstruction, LVI, PNI, high tumor budding, and < 12 resected lymph nodes. In patients with rectal cancer, adjuvant chemotherapy was recommended for pathologic stage II and III patients or for those treated with PCRT regardless of pathologic stage. PCRT was indicated for patients who had clinical stage II or III cancer and for those with clinical stage I who were eligible for sphincter-saving surgery due to low lying rectal cancer and those who were not candidates for major surgery because of medical comorbidities.

All patients received postoperative follow-up examination consisting of a physical examination and serum carcinoembryonic antigen measurements every 3–6 mo. Abdominal, pelvic, and chest CT scans were performed every 6–12 mo. Patients with obstructive lesions underwent colonoscopy within 6 mo after surgical resection and every 2–3 years thereafter.

### Definition of surveillance intensity

All patients were followed-up for approximately 5 years after surgery with APCT and CCT. Patients underwent surveillance every 6 mo at the outpatient clinic, including APCT every 6 mo and CCT every 12 mo on average. The number of expected imaging studies was two for APCT and one for CCT, with a total of three studies per year.

The average number of studies for each patient was calculated as the number of examinations during 5 years/60 mo of follow-up without recurrence, or the number of examinations until the first recurrence for patients who experienced recurrence. Patients who underwent more than the average number of studies per year (3) were categorized as high intensity (HI), whereas those who underwent less than three annual studies were categorized as low intensity (LI). Patients were categorized based on intensity of imaging studies to account for differences in risk-related surveillance.

### Statistical analysis

Continuous variables were compared using a *t*-test and expressed as the mean and range. Categorical variables were compared using Pearson's $\chi^2$ test or Fisher's exact test and expressed as numbers and percentages. Univariate analyses were performed to identify factors associated with survival. Factors with $P < 0.1$ on univariate analysis were included in a multivariate binary logistic regression analysis. OS, recurrence-free interval (RFI), and post-recurrence survival (PRS) were calculated using the Kaplan–Meier method[20] and compared with the Cox-regression model[21]. All statistical analyses were performed using SPSS for Windows, ver. 25.0 (SPSS Inc., Chicago, IL, United States), with $P < 0.05$ defined as statistically significant.

## RESULTS

### Patient characteristics

Of 1888 patients, 1024 were included in the LI group and 864 were included in the HI group. The demographic characteristics of the patients and the clinicopathological features of the tumors are shown in Table 1. Demographic characteristics did not differ between the LI group and the HI group. In terms of pathologic features, patients in the HI group had a higher T and N stage and included more risk factors such as a high degree of malignant differentiation, PNI, or positive CRM. The average number of APCT studies performed per year was 1.8-fold higher in the HI group than in the LI group, and CCT was performed at a 2.4-fold higher rate in the HI group than in the LI group ($P < 0.001$) (Table 1). In patients with rectal cancer, positive CRM was higher in the HI group than in the LI group (Supplementary Table 1).

### Oncologic outcomes according to surveillance intensity

The number of APCT and CCT studies was significantly higher in patients who experienced recurrence than in those who did not ($P < 0.001$). Patients with recurrence were categorized into intra-abdominal and intra-thoracic according to site of recurrence. The number of APCT studies was higher in patients who experienced intra-abdominal recurrence, and the number of CCT studies was higher in patients who experienced intra-thoracic recurrence ($P < 0.001$) (Figure 1). Among patients with rectal cancer, 50 patients showed local recurrence, of which 21 (42%) were in the LI group and 29 (58%) were in the HI group. Analysis of APCT intensity in patients with rectal cancer showed no difference in the incidence of local recurrence according to APCT intensity ($P = 0.860$). Distant metastasis was confirmed in 509 patients, of which 193 were in the LI group and 316 were in the HI group. Curative treatment was possible in 143 patients, of which 48 were in the LI group and 95 were in the HI group. The curative resection rate according to surveillance intensity was higher in the HI group, although the difference was not statistically significant (25% *vs* 30%, $P = 0.206$).

The RFI was longer in the LI group than in the HI group (61 ± 33.95 mo *vs* 45 ± 28.35 mo, $P < 0.001$). In patients who experienced recurrence, the mean RFI remained longer in the LI group than in the HI group (23 ± 16.09 mo *vs* 19 ± 11.86 mo, $P = 0.001$). Both intra-abdominal RFI according to APCT intensity and intra-thoracic RFI according to CCT intensity were longer in the LI group than in the HI group (abdomen, 23 ± 16.38 mo *vs* 17 ± 11.39 mo, $P < 0.001$; chest, 26 ± 15.36 mo *vs* 20 ± 13.79 mo, $P = 0.004$) (Figure 2). The mean RFI in recurred patients did not differ significantly according to tumor location (colon, 22 ± 11.21 mo *vs* rectum, 20 ± 14.41 mo, $P = 0.059$).

Among patients who experienced recurrence, the mean PRS time did not differ according to surveillance intensity (35 ± 31.94 mo in the LI group and 34 ± 29.28 mo in

**Table 1 Demographic and clinical characteristics of participants according to surveillance intensity (*n* = 1888)**

| Variables | Surveillance intensity | | *P* value |
|---|---|---|---|
| | Lower intensity (*n* = 1024) | Higher intensity (*n* = 864) | |
| Age, mean (IQR) | 60.0 (52.0–68.0) | 58.0 (50.3–67.0) | 0.178 |
| Gender, *n* (%) | | | 0.502 |
| Male | 607 (59.3) | 528 (61.1) | |
| Female | 417 (40.7) | 336 (38.9) | |
| Cancer site, *n* (%) | | | 0.795 |
| Colon | 365 (35.6) | 303 (35.1) | |
| Rectum | 659 (64.4) | 561 (64.9) | |
| Differentiation, *n* (%) | | | 0.027 |
| WD/MD | 945 (92.3) | 781 (90.4) | |
| PD/SRC/MUC | 72 (7.0) | 82 (9.5) | |
| Unknown | 7 (0.7) | 1 (0.1) | |
| Total lymph nodes, *n* (%) | | | 0.001 |
| < 12 | 129 (12.6) | 49 (5.7) | |
| ≥ 12 | 895 (87.4) | 815 (94.3) | |
| (y) pT, *n* (%) | | | 0.002 |
| 0 | 12 (1.2) | 6 (0.7) | |
| 1 | 66 (6.4) | 36 (4.2) | |
| 2 | 126 (12.3) | 89 (10.3) | |
| 3 | 770 (75.2) | 660 (76.4) | |
| 4 | 50 (4.9) | 73 (8.4) | |
| (y) pN, *n* (%) | | | 0.010 |
| 1c | 14 (1.4) | 8 (0.9) | |
| 1 | 735 (71.8) | 570 (66.0) | |
| 2 | 275 (26.8) | 286 (33.1) | |
| Perineural invasion, *n* (%) | 219 (21.4) | 262 (30.3) | < 0.001 |
| Lymphovascular invasion, n (%) | 371 (36.2) | 344 (39.8) | 0.110 |
| Resection margin, *n* (%) | | | 0.004 |
| Positive | 18 (1.7) | 41 (4.7) | |
| Unknown | 7 (0.7) | 8 (0.9) | |
| APCT, mean ± SD | 1.49 ± 0.47 | 2.67 ± 1.31 | < 0.001 |
| CCT, mean ± SD | 0.62 ± 0.41 | 1.48 ± 0.91 | < 0.001 |
| Total imaging studies, mean ± SD | 2.11 ± 0.58 | 4.14 ± 1.64 | < 0.001 |

IQR: Inter-quartile range; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; SRC: Signet ring cell type; MUC: Mucinous carcinoma; APCT: Abdomino-pelvic computed tomography; SD: Standard deviation; CCT: Chest computed tomography.

the HI group; $P$ = 0.802) (Figure 3). There was no difference in the PRS according to tumor location (colon, 29 ± 29.65 mo *vs* 37 ± 30.08 mo, $P$ = 0.250; rectum, 36 ± 32.20 mo *vs* 33 ± 28.94 mo, $P$ = 0.415). Curative resection was possible in 152 of all recurred patients, of which 51 (23.8%) were in the LI group and 101 (29.3%) were in the HI group ($P$ = 0.160). Of the 51 patients in the LI group, seven (13.7%) had colon cancer and 44 (86.3%) had rectal cancer. In the HI group, 35 (34.6%) patients had colon cancer and 66 (55.4%) had rectal cancer. There was no difference in the rate of curative resection between surveillance intensity groups according to tumor location (colon, $P$

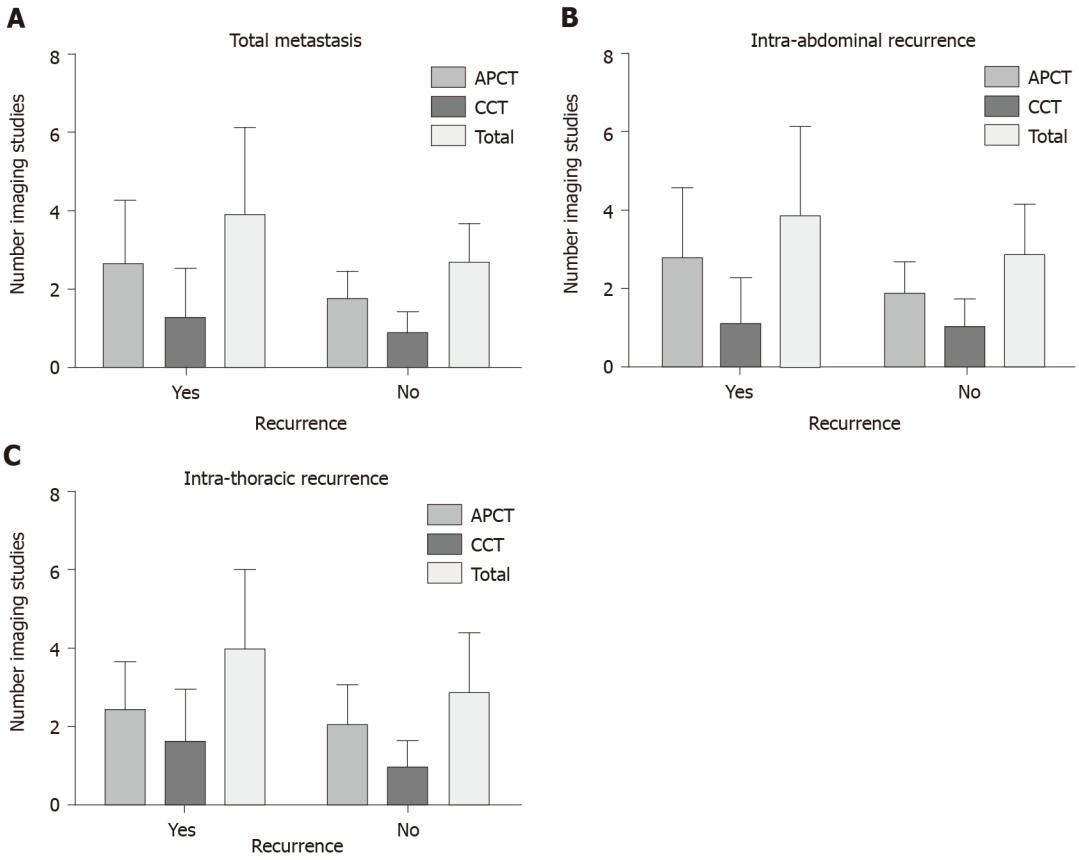



**Figure 1 Number of imaging studies during surveillance period based on the development of recurrence.** A: Mean number of abdomino-pelvic computed tomography (APCT) and chest computed tomography (CCT) studies were higher in the recurrence group (APCT, 2.63 ± 1.64 *vs* 1.77 ± 0.66; CCT, 1.27 ± 1.24 *vs* 0.91 ± 0.49; $P < 0.001$, each); B: In patients with intra-abdominal recurrence, mean number of APCT studies were higher in the recurrence group (APCT, 2.75 ± 1.79 *vs* 1.85 ± 0.79, $P < 0.001$; CCT, 1.09 ± 1.13 *vs* 1.00 ± 0.71, $P = 0.060$); C: In patients with intra-thoracic recurrence, mean number of APCT and CCT studies were higher in the recurrence group (APCT, 2.41 ± 1.21 *vs* 1.97 ± 1.09; CCT, 1.58 ± 1.34 *vs* 0.93 ± 0.66; $P < 0.001$, each). APCT: Abdomino-pelvic computed tomography; CCT: Chest computed tomography.

= 0.673; rectum, $P = 0.318$). PRS according to the curative intent after recurrence was significantly longer in patients who underwent curative resection (54 ± 30.96 mo *vs* 27 ± 26.82 mo, $P < 0.001$).

The mean OS was significantly longer in the LI group (68 ± 31.89 mo) than in the HI group (58 ± 27.35 mo, $P < 0.001$) (Figure 4). Analysis of survival according to tumor location showed that OS was longer in the LI group regardless of tumor location (colon, 74 ± 27.84 mo *vs* 56 ± 23.66 mo, $P < 0.001$; rectum, 65 ± 33.58 mo *vs* 59 ± 29.12 mo, $P = 0.001$).

### *Factors associated with oncologic outcomes*

Univariate analysis identified factors affecting OS. Age, sex, surveillance intensity, pathologic differentiation, pathologic T and N stages, LVI, PNI, and CRM in rectal cancer significantly affected OS ($P < 0.05$). In the multivariate analysis, age, sex, surveillance intensity, differentiation, pathologic T stage, LVI, PNI, and CRM in rectal cancer were significantly associated with OS (Table 2).

Univariate analysis of factors affecting RFI indicated that surveillance intensity, differentiation, pathologic T stage, pathologic N stage, LVI, PNI, and CRM in rectal cancer significantly affected RFI ($P < 0.05$). In the multivariate analysis, surveillance intensity, pathologic T stage, PNI, and CRM in rectal cancer were significantly associated with RFI. Among patients who experienced intra-abdominal recurrence, APCT intensity, differentiation, pathologic T stage, PNI, and CRM in rectal cancer were significantly associated with RFI. In patients with intra-thoracic recurrence, CCT intensity, differentiation, pathologic T stage, LVI, PNI, and CRM in rectal cancer were significantly associated with RFI (Table 3).

Univariate analysis of patients who experienced recurrence to identify factors affecting PRS showed that age, differentiation, LVI, PNI, and curative resection were significantly associated with PRS. Multivariate analysis showed that age, differentiation, PNI, and curative resection were significantly associated with PRS. In patients

**Table 2 Factors affecting overall survival of participants**

| Factors | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Age (yr) | 1.027 (1.019–1.035) | < 0.001 | 1.031 (1.023–1.039) | < 0.001 |
| Sex | 0.704 (0.592–0.836) | < 0.001 | 0.711 (0.598–0.845) | < 0.001 |
| Surveillance intensity | 1.650 (1.400–1.945) | < 0.001 | 1.531 (1.295–1.808) | < 0.001 |
| Differentiation | | | | |
| WD/MD | Ref. | | Ref. | |
| PD/SRC/MUC | 1.832 (1.424–2.356) | < 0.001 | 1.660 (1.285–2.143) | < 0.001 |
| (y) pT stage | | | | |
| 0–2 | Ref. | | Ref. | |
| 3–4 | 1.937 (1.491–2.516) | < 0.001 | 1.461 (1.111–1.921) | 0.007 |
| (y) pN stage | | | | |
| 1c | Ref. | | Ref. | |
| 1 | 5.136 (0.721–36.571) | 0.102 | 4.754 (0.667–33.906) | 0.12 |
| 2 | 9.322 (1.308–66.457) | 0.026 | 7.067 (0.988–50.556) | 0.051 |
| Lymphovascular invasion | 1.607 (1.365–1.891) | < 0.001 | 1.256 (1.057–1.491) | 0.01 |
| Perineural invasion | 1.818 (1.535–2.154) | < 0.001 | 1.466 (1.224–1.755) | < 0.001 |
| Resection margin[1] | 1.972 (1.360–2.860) | < 0.001 | 1.603 (1.097–2.341) | 0.015 |

[1]Resection margin indicated circumferential resection margin, and were calculated with rectal cancer patients. OR: Odds ratio; CI: Confidence interval; Ref: Reference; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; SRC: Signet ring cell type; MUC: Mucinous carcinoma.

with intra-abdominal recurrence, age, differentiation, PNI, and curative resection were associated with PRS, whereas in patients with intra-thoracic recurrence, only sex and curative resection affected PRS (Table 4). The results of univariate and multivariate analyses of patients with rectal cancer were comparable to the results for all patients (Supplementary Table 1).

## DISCUSSION

Existing guidelines recommend surveillance after primary surgery with a curative intent for CRC[22-26], although consistent guidelines are lacking. The European Society of Medical Oncology recommends abdominal and chest CT every 6 to 12 mo for 3 years, and then yearly for 2 years for patients with colon cancer; however, there are no imaging recommendations for patients with rectal cancer. The American Society of Clinical Oncology guidelines recommend abdominal and chest CT annually for 3 years, and every 6 to 12 mo for the first 3 years for high-risk patients. The National Comprehensive Cancer Network guidelines suggest an abdominal CT scan for high-risk patients with poorly differentiated cancer or those with perineural or venous invasion, although there are no guidelines regarding frequency. The American Society of Colorectal Surgeons guidelines recommend chest and abdominopelvic imaging annually for 5 years.

The Gruppo Italiano Lavoro per la Diagnosi Anticipata trial launched in 1998 found that an intensive surveillance program after curative treatment for CRC detects asymptomatic local or distant recurrences but does not affect OS[27]. Similarly, the Follow-up After Colorectal Surgery randomized trial, the results of which were recently publi-shed, changed the original endpoint of unmeasured OS to a practical endpoint of surgical treatment of recurrence with curative intent[16]. Several meta-analyses and prospective randomized trials showed no survival benefit associated with intensive surveillance[15,18]. However, other studies showed an association between intensive surveillance and a significant reduction in mortality and increased OS[28,29].

**Table 3 Factors affecting recurrence-free interval of participants**

| Factors | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Age (yr) | 0.995 (0.987–1.002) | 0.165 | 0.999 (0.991–1.006) | 0.715 |
| Sex | 0.907 (0.765–1.076) | 0.262 | | |
| Surveillance intensity | 2.218 (1.870–2.632) | < 0.001 | 1.999 (1.680–2.377) | < 0.001 |
| Differentiation | | | | |
| WD/MD | Ref. | | Ref. | |
| PD/SRC/MUC | 1.507 (1.151–1.974) | 0.003 | 1.287 (0.979–1.694) | 0.071 |
| (y) pT stage | | | | |
| 0–2 | Ref. | | Ref. | |
| 3–4 | 2.118 (1.610–2.785) | < 0.001 | 1.596 (1.197–2.127) | 0.001 |
| (y) pN stage | | | | |
| 1c | Ref. | | Ref. | |
| 1 | 2.737 (0.682–10.989) | 0.156 | 2.501 (0.621–10.063) | 0.197 |
| 2 | 5.260 (1.308–21.156) | 0.019 | 3.813 (0.943–15.413) | 0.060 |
| Lymphovascular invasion | 1.460 (1.236–1.724) | < 0.001 | 1.143 (0.957–1.364) | 0.140 |
| Perineural invasion | 1.949 (1.641–2.313) | < 0.001 | 1.431 (1.192–1.719) | < 0.001 |
| Resection margin[1] | 2.192 (1.529–3.144) | < 0.001 | 1.565 (1.083–2.262) | 0.017 |

[1]Resection margin indicated circumferential resection margin, and were calculated with rectal cancer patients. OR: Odds ratio; CI: Confidence interval; Ref: Reference; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; SRC: Signet ring cell type; MUC: Mucinous carcinoma.

In this study, patients were divided into LI and HI groups according to the number of imaging studies during the follow-up period. The average number of imaging studies was higher in patients with recurrence regardless of the location of recurrence. Patients in the HI group had higher pathologic T and N stages and were more likely to have risk factors such as LVI and PNI. This suggests a tendency to perform surveillance more frequently in patients with a high risk of recurrence. Among rectal cancer patients, 50 had local recurrence, most of which were lateral pelvic lymph node recurrence except in four patients with anastomosis recurrence. Among patients with local recurrence, 21 were in the LI group and 29 were in the HI group, and the detection rate of local recurrence did not differ between the two groups. Of the 50 patients with local resection, 16 underwent surgical resection, of which 10 achieved curative resection. Four patients (19%) in the LI group and six patients (21%) in the HI group were eligible for curative resection, and there was no difference according to surveillance intensity ($P$ = 0.886) even after stratifying patients according to APCT intensity ($P$ = 0.382). This result could be due to the small number of patients with local recurrence, of whom few underwent curative treatment. The remaining 17 patients received palliative treatment, such as chemotherapy or radiotherapy, and had a short-term follow-up because metastasis was unclear when first detected. In these patients, metastasis to distant lymph nodes or distant organs was found during follow-up, and the patients were not eligible for curative treatment. These results indicate that the current imaging surveillance guidelines, which is based on CT, may result in a missed local recurrence that can be treated with curative resection in approximately 35% of patients. The accuracy of CT scans for detecting recurrence is limited regardless of imaging frequency. Therefore, additional examinations or surgical treatment rather than short-term follow-up could improve the chances of curative resection in patients suspected of recurrence.

Survival analysis showed that OS and RFI were longer in the LI group than in the HI group, whereas PRS did not differ between the two groups. The shorter OS and RFI could be related to the higher aggressive biology of the HI group. Analysis of patients who did not experience recurrence showed that OS was approximately 10 mo shorter in the HI group than in the LI group. Although not statistically significant, the probability of curative resection of recurrent lesions was slightly higher in the HI group.

**Table 4 Factors affecting post-recurrence survival of participants**

| Factors | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Age (yr) | 1.015 (1.007–1.024) | < 0.001 | 1.015 (1.006–1.024) | 0.001 |
| Sex | 0.824 (0.676–1.004) | 0.054 | 0.842 (0.688–1.032) | 0.098 |
| Image intensity | 0.971 (0.799–1.179) | 0.767 | | |
| Differentiation | | | | |
| WD/MD | Ref. | | Ref. | |
| PD/SRC/MUC | 2.632 (1.779–3.137) | < 0.001 | 2.072 (1.553–2.766) | < 0.001 |
| (y) pT stage | | | | |
| 0–2 | Ref. | | | |
| 3–4 | 1.146 (0.833–1.576) | 0.401 | | |
| (y) pN stage | | | | |
| 1c | Ref. | | | |
| 1 | 2.139 (0.300–15.256) | 0.448 | | |
| 2 | 3.363 (0.471–24.009) | 0.226 | | |
| Lymphovascular invasion | 1.456 (1.204–1.760) | < 0.001 | 1.152 (0.940–1.412) | 0.174 |
| Perineural invasion | 1.384 (1.141–1.677) | 0.001 | 1.284 (1.045–1.579) | 0.018 |
| Resection margin[1] | 1.416 (0.966–2.075) | 0.075 | 1.266 (0.856–1.871) | 0.237 |
| Curative resection | 0.296 (0.229–0.381) | < 0.001 | 0.331 (0.255–0.428) | < 0.001 |

[1]Resection margin indicated circumferential resection margin, and were calculated with rectal cancer patients. OR: Odds ratio; CI: Confidence interval; Ref: Reference; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; SRC: Signet ring cell type; MUC: Mucinous carcinoma.

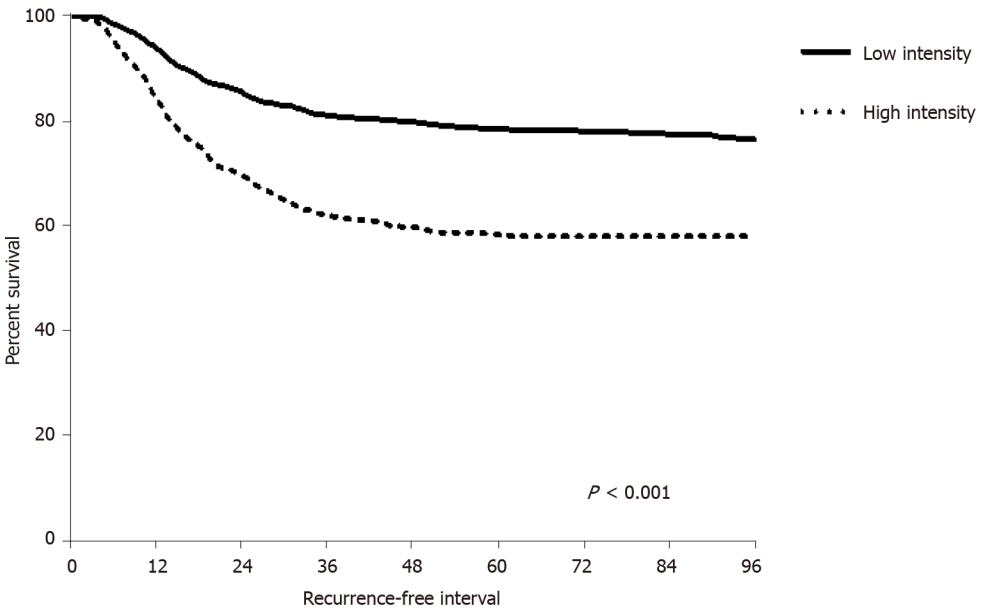



**Figure 2 Kaplan–Meier analyses of recurrence-free interval according to surveillance intensity.** Recurrence-free interval was significantly longer in low intensity group.

Analysis of survival according to surveillance intensity after dividing patients based on initial tumor location (colon and rectum) did not show statistically significant differences between the groups. Pathologic risk factors, such as degree of differentiation, PNI, and LVI, had a greater effect on OS, RFI, and PRS than surveillance

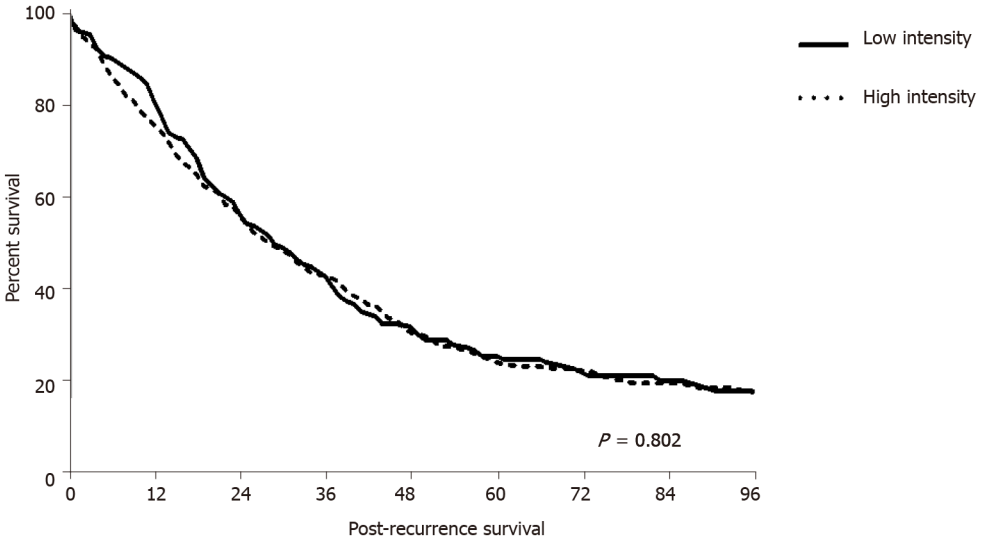



**Figure 3 Kaplan–Meier analyses of post-recurrence survival according to surveillance intensity.** Surveillance intensity did not show difference in post-recurrence survival.

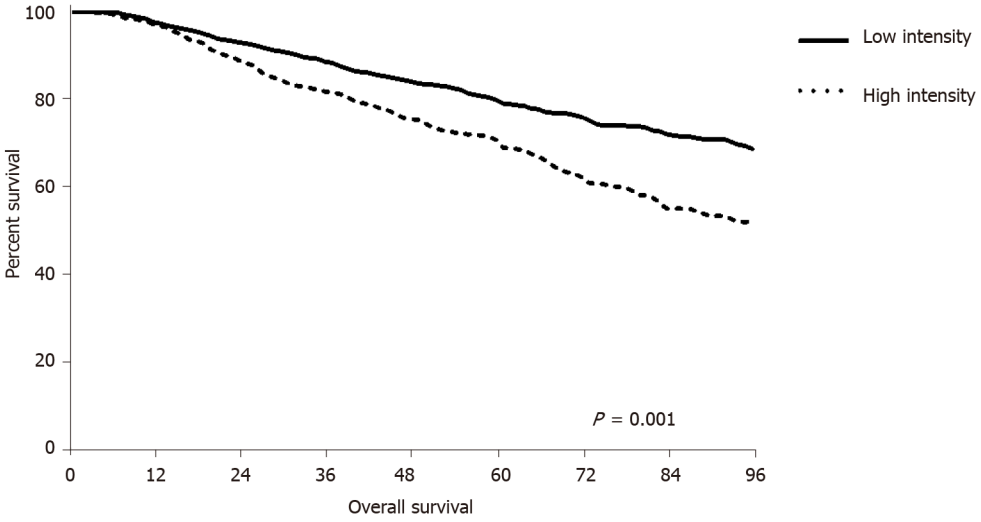



**Figure 4 Kaplan–Meier analyses of overall survival according to surveillance intensity.** High intensity group had lower overall survival rate than low intensity group.

intensity. In particular, curative resection had a greater effect on PRS than surveillance intensity. The PRS of recurred patients was 2-fold longer in those who received curative resection than in those who did not (54 mo *vs* 27 mo, respectively). The results of multivariate analysis confirmed that curative resection improves PRS. However, when analyzing only patients who underwent curative resection, there was no difference in OS or PRS according to imaging intensity. This suggests that although imaging intensity itself does not improve OS or PRS, intensive surveillance can increase the possibility of curative resection, thereby improving PRS. Furthermore, the aggressive biology of the HI group may mitigate the benefit of curative resection of recurrence. Assessment of the effect of surveillance intensity on PRS may have been affected by the small number of patients who underwent curative treatment for recurrence in this study.

This study has several limitations. First, it was a retrospective, observational cohort study, and patients were not randomized. Surveillance intensity can vary according to the patient's condition at the time of treatment, which may have resulted in selection bias. Second, the average surveillance schedule may have differed depending on the physician. Additional research is needed to determine the standard routine surveillance in our institution.

## CONCLUSION

In conclusion, in patients with stage III CRC, frequent postoperative image studies alone do not improve OS and RFI. Curative resection is the most important factors to improve PRS and we need to find a way to increase curative treatment of recurrent disease *via* optimal surveillance. Therefore, role of other imaging modalities according to risk of recurrence would be evaluated rather than increasing surveillance frequency to improve oncologic outcomes.

## ARTICLE HIGHLIGHTS

### *Research background*

Optimal surveillance strategies for stage III colorectal cancer (CRC) are lacking, and intensive surveillance has not conferred a significant survival benefit.

### *Research motivation*

Evaluating appropriate surveillance intensity would be helpful to improve oncologic outcomes or decrease un-necessary imaging studies during surveillance.

### *Research objectives*

We examined the association between surveillance intensity and recurrence and survival rates in patients with stage III CRC.

### *Research methods*

Data from patients with pathologic stage III CRC who underwent radical surgery between January 2005 and December 2012 at Asan Medical Center, Seoul, Korea were retrospectively reviewed. Surveillance consisted of abdominopelvic computed tomography (CT) every 6 mo and chest CT annually during the 5 year follow-up period, resulting in an average of three imaging studies per year. Patients who underwent more than the average number of imaging studies annually were categorized as high intensity (HI), and those with less than the average were categorized as low intensity (LI).

### *Research results*

Among 1888 patients, 864 (45.8%) were in HI group. The HI group had more advanced T and N stage ($P$ = 0.002, 0.010, each). A high degree of malignant differentiation was more common in the HI group than in the LI group ($P$ = 0.027). Perineural invasion (PNI) was significantly more identified in the HI group (21.4% *vs* 30.3%, $P$ < 0.001).

The mean overall survival (OS) and Recurrence-free interval (RFI) was longer in the LI group ($P$ < 0.001, each). Multivariate analysis indicated that surveillance intensity was negatively associated with RFI [odds ratio (OR) = 1.999; 95% confidence interval (CI): 1.680–2.377; $P$ < 0.001] and OS [OR = 1.531, 95%CI: 1.295–1.808; $P$ < 0.001]. The mean post-recurrence survival (PRS) was significantly longer in patients who received curative resection ($P$ < 0.001). Curative resection rate of recurrence was not different between HI (29.3%) and LI (23.8%) groups ($P$ = 0.160). PRS did not differ according to surveillance intensity ($P$ = 0.802).

### *Research conclusions*

Frequent postoperative surveillance with CT scan alone do not improve OS and RFI. Curative resection is the most important factors to improve PRS and we need to find a way to increase curative treatment of recurrent disease *via* optimal surveillance.

### *Research perspectives*

Role of other imaging modalities according to risk of recurrence would be evaluated rather than increasing surveillance frequency to improve oncologic outcomes.

## REFERENCES

1 **Taylor I**. Quality of follow-up of the cancer patient affecting outcome. *Surg Oncol Clin N Am* 2000; **9**: 21-25, vi [PMID: 10601521 DOI: 10.1016/S1055-3207(18)30165-0]

2 **Lee BI**, Hong SP, Kim SE, Kim SH, Kim HS, Hong SN, Yang DH, Shin SJ, Lee SH, Park DI, Kim

YH, Kim HJ, Yang SK, Jeon HJ; Multi-Society Task Force for Development of Guidelines for Colorectal Polyp Screening, Surveillance and Management. Korean guidelines for colorectal cancer screening and polyp detection. *Clin Endosc* 2012; **45**: 25-43 [PMID: 22741131 DOI: 10.5946/ce.2012.45.1.25]

3 **Miller KD**, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL, Siegel RL. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; **69**: 363-385 [PMID: 31184787 DOI: 10.3322/caac.21565]

4 **Böhm B**, Schwenk W, Hucke HP, Stock W. Does methodic long-term follow-up affect survival after curative resection of colorectal carcinoma? *Dis Colon Rectum* 1993; **36**: 280-286 [PMID: 8449134 DOI: 10.1007/BF02053511]

5 **Kjeldsen BJ**, Kronborg O, Fenger C, Jørgensen OD. The pattern of recurrent colorectal cancer in a prospective randomised study and the characteristics of diagnostic tests. *Int J Colorectal Dis* 1997; **12**: 329-334 [PMID: 9457525 DOI: 10.1007/s003840050118]

6 **Holm T**, Cedermark B, Rutqvist LE. Local recurrence of rectal adenocarcinoma after 'curative' surgery with and without preoperative radiotherapy. *Br J Surg* 1994; **81**: 452-455 [PMID: 8173929 DOI: 10.1002/bjs.1800810344]

7 **Secco G**, Fardelli R, Campora E, Rovida S, Martinoli C, Motta G. Results of postoperative follow-up *vs* no follow-up in colorectal cancer. *Coloproctology* 1990; **6**: 362-368

8 **Törnqvist A**, Ekelund G, Leandoer L. The value of intensive follow-up after curative resection for colorectal carcinoma. *Br J Surg* 1982; **69**: 725-728 [PMID: 7171973 DOI: 10.1002/bjs.1800691213]

9 **Renehan AG**, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002; **324**: 813 [PMID: 11934773 DOI: 10.1136/bmj.324.7341.813]

10 **Figueredo A**, Rumble RB, Maroun J, Earle CC, Cummings B, McLeod R, Zuraw L, Zwaal C; Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. *BMC Cancer* 2003; **3**: 26 [PMID: 14529575 DOI: 10.1186/1471-2407-3-26]

11 **Mant D**, Gray A, Pugh S, Campbell H, George S, Fuller A, Shinkins B, Corkhill A, Mellor J, Dixon E, Little L, Perera-Salazar R, Primrose J. A randomised controlled trial to assess the cost-effectiveness of intensive *vs* no scheduled follow-up in patients who have undergone resection for colorectal cancer with curative intent. *Health Technol Assess* 2017; **21**: 1-86 [PMID: 28641703 DOI: 10.3310/hta21320]

12 **Rosati G**, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G, Daniele B, Gaion F, Oliverio G, Duro M, Martignoni G, Pinna N, Sozzi P, Pancera G, Solina G, Pavia G, Pignata S, Johnson F, Labianca R, Apolone G, Zaniboni A, Monteforte M, Negri E, Torri V, Mosconi P, Fossati R; GILDA working group. A randomized trial of intensive *vs* minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma. *Ann Oncol* 2016; **27**: 274-280 [PMID: 26578734 DOI: 10.1093/annonc/mdv541]

13 **Wille-Jørgensen P**, Syk I, Smedh K, Laurberg S, Nielsen DT, Petersen SH, Renehan AG, Horváth-Puhó E, Påhlman L, Sørensen HT; COLOFOL Study Group. Effect of More *vs* Less Frequent Follow-up Testing on Overall and Colorectal Cancer-Specific Mortality in Patients With Stage II or III Colorectal Cancer: The COLOFOL Randomized Clinical Trial. *JAMA* 2018; **319**: 2095-2103 [PMID: 29800179 DOI: 10.1001/jama.2018.5623]

14 **Smoragiewicz M**, Lim H, Peixoto RD. Surveillance for asymptomatic recurrence in resected stage III colon cancer: does it result in a more favorable outcome? *J Gastrointest Oncol* 2015; **6**: 268-273 [PMID: 26029453 DOI: 10.3978/j.issn.2078-6891.2015.019]

15 **Jeffery M**, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2019; **9**: CD002200 [PMID: 31483854 DOI: 10.1002/14651858.CD002200.pub4]

16 **Primrose JN**, Perera R, Gray A, Rose P, Fuller A, Corkhill A, George S, Mant D; FACS Trial Investigators. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014; **311**: 263-270 [PMID: 24430319 DOI: 10.1001/jama.2013.285718]

17 **Wang T**, Cui Y, Huang WS, Deng YH, Gong W, Li CJ, Wang JP. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective, randomized clinical study. *Gastrointest Endosc* 2009; **69**: 609-615 [PMID: 19136105 DOI: 10.1016/j.gie.2008.05.017]

18 **Tjandra JJ**, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. *Dis Colon Rectum* 2007; **50**: 1783-1799 [PMID: 17874269 DOI: 10.1007/s10350-007-9030-5]

19 **Augestad KM**, Rose J, Crawshaw B, Cooper G, Delaney C. Do the benefits outweigh the side effects of colorectal cancer surveillance? *World J Gastrointest Oncol* 2014; **6**: 104-111 [PMID: 24834140 DOI: 10.4251/wjgo.v6.i5.104]

20 **Adams K**, Higgins L, Beazley S, Papagrigoriadis S. Intensive surveillance following curative treatment of colorectal cancer allows effective treatment of recurrence even if limited to 4 years. *Int J Colorectal Dis* 2015; **30**: 1677-1684 [PMID: 26320020 DOI: 10.1007/s00384-015-2356-x]

21 **Peto R**, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer* 1977; **35**: 1-39 [PMID: 831755 DOI: 10.1038/bjc.1977.1]

22 **Benson AB**, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Gregory KM, Gurski L, Freedman-Cass DA. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 874-901 [PMID: 30006429 DOI: 10.6004/jnccn.2018.0061]

23 **Benson AB 3rd**, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wu CS, Gregory KM, Freedman-Cass D. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 370-398 [PMID: 28275037 DOI: 10.6004/jnccn.2017.0036]

24 **Argilés G**, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, Laurent-Puig P, Quirke P, Yoshino T, Taieb J, Martinelli E, Arnold D; ESMO Guidelines Committee. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31**: 1291-1305 [PMID: 32702383 DOI: 10.1016/j.annonc.2020.06.022]

25 **Meyerhardt JA**, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, Petrelli NJ, Ryan K, Schrag DH, Wong SL, Benson AB 3rd; American Society of Clinical Oncology. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2013; **31**: 4465-4470 [PMID: 24220554 DOI: 10.1200/JCO.2013.50.7442]

26 **Steele SR**, Chang GJ, Hendren S, Weiser M, Irani J, Buie WD, Rafferty JF; Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. *Dis Colon Rectum* 2015; **58**: 713-725 [PMID: 26163950 DOI: 10.1097/DCR.0000000000000410]

27 **Johnson F**, Virgo K, Grossmann E, Longo W, Fossati R. Colorectal cancer patient follow-up following surgery with curative intent: the GILDA trial. *J Clin Oncol* 2004; **22**: 3645-3645 [DOI: 10.1200/jco.2004.22.90140.3645]

28 **Laubert T**, Bader FG, Oevermann E, Jungbluth T, Unger L, Roblick UJ, Bruch HP, Mirow L. Intensified surveillance after surgery for colorectal cancer significantly improves survival. *Eur J Med Res* 2010; **15**: 25-30 [PMID: 20159668 DOI: 10.1186/2047-783x-15-1-25]

29 **Rodríguez-Moranta F**, Saló J, Arcusa A, Boadas J, Piñol V, Bessa X, Batiste-Alentorn E, Lacy AM, Delgado S, Maurel J, Piqué JM, Castells A. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol* 2006; **24**: 386-393 [PMID: 16365182 DOI: 10.1200/JCO.2005.02.0826]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 1025-1038

DOI: 10.4240/wjgs.v13.i9.1025

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Carbohydrate antigen 19-9 as a novel prognostic biomarker in distal cholangiocarcinoma

Tao Jiang, Shao-Cheng Lyu, Lin Zhou, Jing Wang, Han Li, Qiang He, Ren Lang

**ORCID number:** Tao Jiang 0000-0003-2587-3521; Jing Wang 0000-0001-7199-4784; Shao-Cheng Lyu 0000-0002-2757-7868; Lin Zhou 0000-0001-8055-4203; Han Li 0000-0002-0286-3737; Qiang He 0000-0002-8900-1688; Ren Lang 0000-0001-9759-6725.

**Author contributions:** Jiang T and Lyu SC contributed to the conception and design; He Q and Lang R contributed to the administrative support; Zhou L and Lang R contributed to the provision of study materials or patients; Wang J and Li H contributed to the collection and assembly of data; Lyu SC, Wang J and Zhou L contributed to the data analysis and interpretation; All authors contributed to the manuscript writing and final approval of manuscript.

**Supported by** the Beijing Municipal Science & Technology Commission, No. Z181100001718164; and Capital's Funds for Health Improvement and Research, No. CFH 2020-2-2036.

**Institutional review board statement:** The study was approved by the Ethics Committee of Beijing Chaoyang Hospital, No. 2020-D.-301.

**Tao Jiang, Shao-Cheng Lyu, Lin Zhou, Jing Wang, Han Li, Qiang He, Ren Lang,** Department of Hepatobiliary Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

**Corresponding author:** Ren Lang, MD, PhD, Academic Fellow, Chief Doctor, Professor, Department of Hepatobiliary Surgery, Beijing Chaoyang Hospital, Capital Medical University, No. 8 Gongtinan Road, Chaoyang District, Beijing 100020, China. dr_langren@126.com

## Abstract

### *BACKGROUND*

Distal cholangiocarcinoma (DCC) presents as one of the relatively rare malignant tumors in the digestive system and has a poor long-term prognosis. Curative resection is currently the most appropriate therapy for patients with DCC because of the lack of effective adjuvant therapies. Therefore, it is important to accurately predict the prognosis for formulating a reasonable treatment plan and avoiding unnecessary surgical trauma.

### *AIM*

To minimize the interference of obstructive jaundice on carbohydrate antigen 19-9 (CA19-9) level by adapting CA19-9 to γ-glutamyltransferase (GGT) as an indicator, to determine the strong associations between CA19-9/GGT and postoperative neoplasm recurrence and long-term outcome of DCC.

### *METHODS*

We enrolled 186 patients who were diagnosed with DCC between January 2010 and December 2019 and performed radical excision with strict criteria as follows in our hospital. Receiver operating characteristic curves were drawn according to preoperative CA19-9/GGT and 1-year survival. Based on this, patients were divided into two groups (group 1, low-ratio, $n$ = 81; group 2, high-ratio, $n$ = 105). Afterwards, by the way of univariate and multivariate analysis, the risk factors influencing postoperative tumor recrudesce and long-term prognosis of patients with DCC were screened out.

### *RESULTS*

Optimum cut-off value of CA19-9/GGT was 0.12. Patients in group 2 represented higher CA19-9 and lymphatic metastasis rate accompanied by lower GGT, when compared with group 1 ($P$ < 0.05). The 1-, 3- and 5-year overall survival rates of patients in groups 1 and 2 were 88.3%, 59.2% and 48.1%, and 61.0%, 13.6% and

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Data sharing statement:** The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.



**Manuscript source:** Unsolicited manuscript

**Specialty type:** Oncology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 1, 2021
**Peer-review started:** March 1, 2021
**First decision:** June 3, 2021
**Revised:** June 18, 2021
**Accepted:** August 19, 2021
**Article in press:** August 19, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Han IW
**S-Editor:** Zhang H
**L-Editor:** Kerr C

13.6%, respectively ($P$ = 0.000). Multivariate analysis indicated that CA19-9/GGT, lymphatic metastasis and tumor differentiation were independent risk factors for tumor recurrence and long-term prognosis of DCC.

*CONCLUSION*

Elevation of CA19-9/GGT performed better as a biomarker of aggressive carcinoma and predictor of poor clinical outcomes by reducing the effect of obstruction of biliary tract on CA19-9 concentration in patients with DCC.

**Key Words:** Distal cholangiocarcinoma; Pancreaticoduodenectomy; Carbohydrate antigen 19-9; γ-Glutamyltransferase; Relapse; Prognosis



**Core Tip:** Distal cholangiocarcinoma (DCC) is a rare malignant tumor in the digestive system and has a poor long-term prognosis. Curative resection is currently the best treatment for patients with DCC because of the lack of effective adjuvant therapies. Therefore, it is important to accurately predict the prognosis for formulating a reasonable treatment plan and avoiding unnecessary surgical trauma. Carbohydrate antigen 19-9 to serum γ-glutamyltransferase (CA19-9/GGT) ratio was adapted as an indicator to minimize the interference of obstructive jaundice CA19-9 level, to determine the strong associations between CA19-9/GGT and postoperative neoplasm recurrence and long-term outcome of DCC.

**Citation:** Jiang T, Lyu SC, Zhou L, Wang J, Li H, He Q, Lang R. Carbohydrate antigen 19-9 as a novel prognostic biomarker in distal cholangiocarcinoma. *World J Gastrointest Surg* 2021; 13(9): 1025-1038
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1025.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1025

## INTRODUCTION

Cholangiocarcinoma is a primary biliary system malignant tumor that originates from bile duct epithelial cells and is one of the rare malignant tumors in the digestive system and has a poor long-term prognosis. The incidence of cholangiocarcinoma appears low, accounting for about 3% of malignant tumors of the digestive system[1]. Cholangiocarcinomas are usually classified as intrahepatic, hilar or distal, depending on their anatomical location. Treatment and long-term prognosis of cholangiocarcinoma differ according to location. Distal cholangiocarcinoma (DCC) refers to extrahepatic cholangiocarcinoma located outside the perihilar region, that is, the primary tumor originates from the bile duct malignant tumor in the middle and lower segments of the common bile duct. It accounts for about 20%–40% of cholangiocarcinoma and is relatively rare clinically[2,3]. Radical surgery remains the optimum therapy for curing DCC because of the lack of effective adjuvant therapies. However, the 5-year survival rate for postoperative patients remains poor at about 20%[4]. It is important to accurately predict the prognosis for formulating a reasonable treatment plan and avoiding unnecessary surgical trauma. At present, the differentiation of tumor, lymphatic metastasis and other related risk factors can only be obtained after surgery, and the information acquisition is delayed[5,6].

There is a strong association between carbohydrate antigen 19-9 (CA19-9) and the diagnosis, recurrence and prognosis of malignant tumors[7]. CA19-9 is not restricted to tumor cells; epithelial cells in the pancreas, bile duct, stomach and colon are also able to synthesize CA19-9[8]. Under the circumstance of biliary obstruction, CA19-9 originating from bile duct epithelial cells cannot be excreted into the intestinal tract normally, and CA19-9 from pancreatic epithelial cells may flow back into the biliary tract abnormally. Local inflammation secondary to biliary obstruction leads to the proliferation of bile duct epithelial cells. All of these will induce an abnormal increase in serum CA19-9[9]. In the absence of specific symptoms, most patients with DCC do not seek treatment until they have jaundice symptoms. At that time, biliary obstruction

**P-Editor:** Li JH

has already occurred; therefore, the concentration of CA19-9 would be inconsistent with the increase of tumor invasiveness, resulting in a decline in its predictive function for the prognosis of DCC.

γ-Glutamyltransferase (GGT) is widely distributed in the human body and located on the surface of cell membranes, and is a key enzyme involved in glutathione (GSH) metabolism. GGT participates in oxidative stress and plays a proinflammatory role, leading to the occurrence of various chronic metabolic diseases, and is closely related to the occurrence and development of tumors[10,11]. Serum GGT is mainly secreted from the hepatobiliary system and is excreted by bile[12]. After biliary obstruction leads to bile drainage obstruction, GGT produced by bile duct epithelial cells and hepatocytes increases, and, due to bile excretion obstruction, GGT enters the blood in reverse flow, and may result in an atypical increase in GGT. However, GGT is commonly used clinically as a diagnostic test; mainly as a biomarker of hepatobiliary disease and alcohol intake[13]. Although GGT is released in a variety of tumor types, its role in malignant tumor behavior and prognosis remains unclear.

In view of the above considerations, we adjusted CA19-9 by CA19-9/GGT, thereby eliminating or reducing the impact of biliary obstruction on the concentration of CA19-9. The aim of our study was to establish the role of CA19-9/GGT in DCC and its influence as a prognostic biomarker.

## MATERIALS AND METHODS

### *Ethics approval*

This study was approved by the Ethical Committee of Beijing Chao-Yang Hospital (No. 2020-D.-301) and in accordance with the Declaration of Helsinki of the World Medical Association. Since this was a retrospective study design, participants' informed consent was not required.

### *Inclusion and exclusion criteria*

The data of patients who underwent pancreaticoduodenectomy (pancreaticoduodenectomy, PD) for DCC between January 2010 and December 2019 at our hospital were collected and analyzed. We screened 186 patients with DCC who met the criteria (Figure 1). Inclusion criteria: (1) DCC patients who underwent PD from January 2010 to December 2019; (2) Age 20–85 years; (3) Preoperative imaging showed no invasion of celiac vessels; (4) Tumor was completely removed during the operation; (5) Postoperative pathology confirmed bile duct adenocarcinoma; and (6) Informed consent of the patients and their families was obtained for the surgical methods and treatment strategies. Exclusion criteria: (1) Tumor was not removed for various reasons during the operation; (2) Patients with complicated cancers of other systems; (3) Pathological diagnosis was nonconventional ductal adenocarcinoma; and (4) Incomplete follow-up data or loss to follow-up.

### *Patients' characteristics*

Of 186 patients who were screened out, there were 73 women, with a male: female ratio of 1.5:1, mean age 64.9 ± 8.6 years. The primary symptoms mainly included jaundice ($n$ = 156) and epigastric pain ($n$ = 17) and the other 10 patients were identified during physical examination. Among the included patients, 62 (33.3%) had a history of smoking and 53 had diabetes (28.5%). Ninety of 158 patients who had jaundice received preoperative biliary drainage (PBD), which included 23 cases of endoscopic retrograde cholangiopancreatography and 67 of percutaneous transhepatic biliary drainage.

### *Patients grouping and determination of receiver operating characteristic (ROC) threshold*

ROC curves were drawn based on preoperative CA19-9/GGT and 1-year survival. The best cut-off value of CA19-9/GGT was 0.12 [area under the curve, 0.695, 95%confidence interval (CI): 0.613–0.777] (Figure 2), and the patients were divided into two different groups (group 1, low-ratio, $n$ = 81; group 2, high-ratio, $n$ = 105). The CA19-9 and GGT assays were used to obtain the results from the last blood sample before surgery. For the patients who underwent PBD, our center rechecked the CA19-9 and GGT index the day before the surgery.

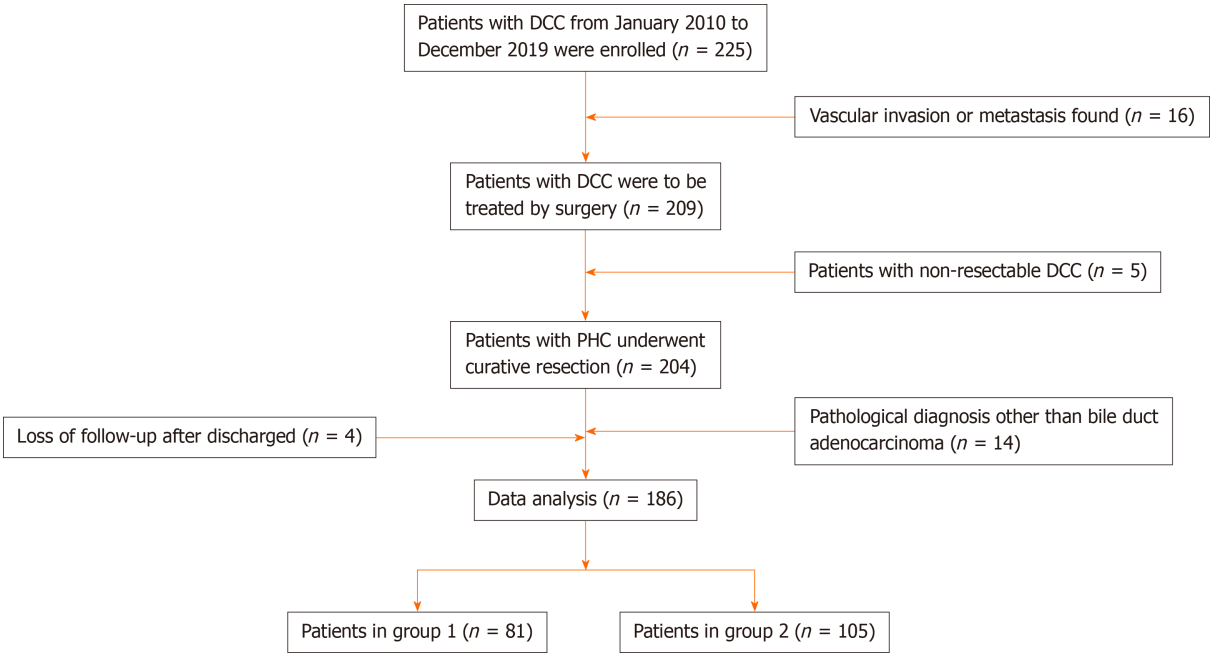



**Figure 1 Screening flow chart.** DCC: distal cholangiocarcinoma; PHC: primary hepatic carcinoma.

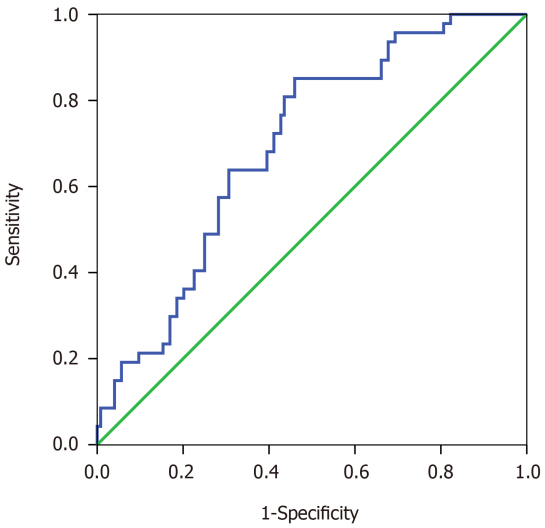


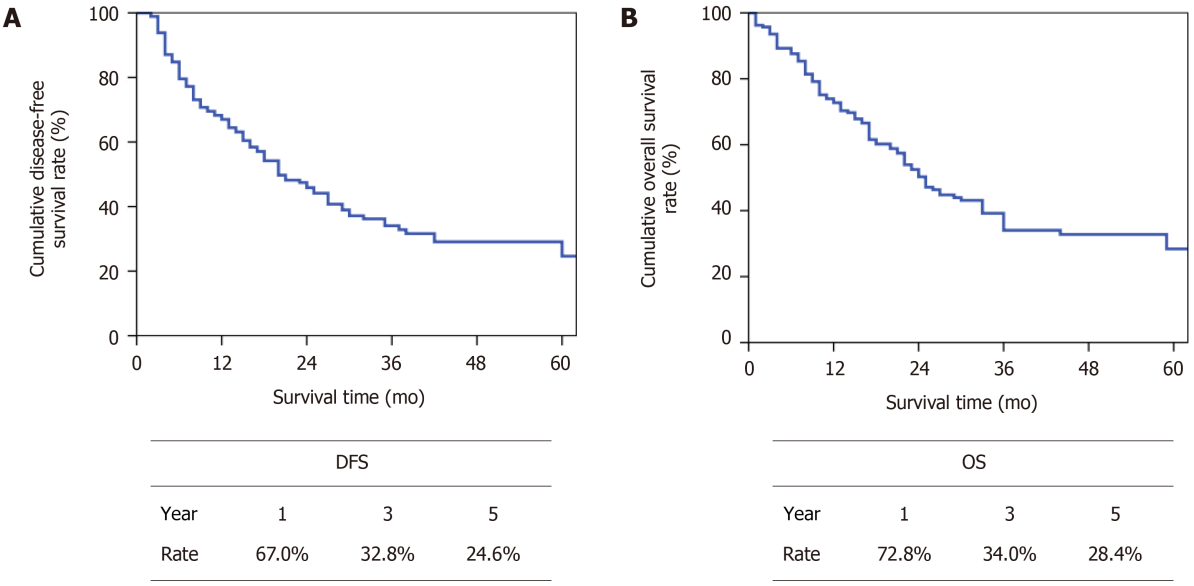

**Figure 2 Time-dependent receiver operating characteristic curve.** The area under curve of the carbohydrate antigen 19-9 to γ-glutamyltransferase ratio to predict the 1-year overall survival was 0.695.

### *Clinicopathological data and follow-up strategies*

The clinicopathological data during the perioperative period were extracted from the medical records. After surgery, routine laboratory tests were performed once every 3 mo within 2 years and once every 6 mo thereafter, as were imaging examinations including abdominal enhanced computed tomography (CT), pulmonary CT, electroconvulsive therapy, *etc.* and subsequent treatment regimens, tumor recurrence and survival were compared in different groups. The end points of follow-up were usually defined as tumor recurrence and death.

### *Statistical analysis*

All data analysis was carried out by SPSS version 22.0 software, and each index was expressed as mean ± SD. Survival rates, including overall survival (OS) and disease-free survival (DFS), were calculated using the Kaplan–Meier method and evaluated with the log-rank test. The Cox proportional model was used to analyze multivariate survival, and the independent risk factors affecting the survival time. Qualitative variables were compared using $\chi^2$ tests. Statistical significance was defined as $P < 0.05$.




| DFS | | | |
|---|---|---|---|
| Year | 1 | 3 | 5 |
| Rate | 67.0% | 32.8% | 24.6% |

| OS | | | |
|---|---|---|---|
| Year | 1 | 3 | 5 |
| Rate | 72.8% | 34.0% | 28.4% |

**Figure 3 Long-term prognosis of the patients with distal cholangiocarcinoma.** A: Overall DFS curve of patients; B: OS curve of patients. DFS: disease-free survival; OS: overall survival.

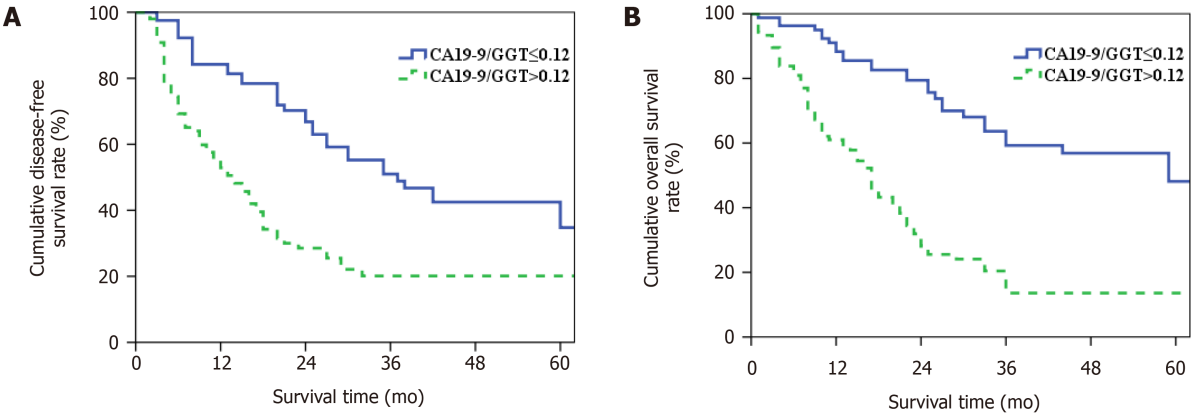



**Figure 4 Overall long-term prognosis between two groups in patients with distal cholangiocarcinoma.** A: Overall disease-free survival curve of two groups of patients; B: Overall survival curve of two groups of patients. CA19-9: carbohydrate antigen 19-9; GGT: γ-glutamyltransferase.

## RESULTS

### *Patients' background and surgical outcomes*

During the perioperative period, bleeding volume was 500 (400–600) mL, and 66 patients (35.5%) received blood transfusions. The duration of the operation was 9.8 ± 1.9 h. Pathology showed the degree of tumor differentiation was as follows: poor in 52 cases (28.0%), moderate in 109 (58.6%) and high in 25 (13.4%). Tumor size was 2.2 ± 1.0 cm, and positive lymph nodes was detected in 75 patients (40.3%). Radical resection (R0) was performed in 178 cases (95.7%).

Fifty-four patients (29.0%) had postoperative complications. Among them, 19 were accompanied with biochemical fistula (10.2%), six with grade B pancreatic fistula (3.2%), seven with grade C pancreatic fistula (3.8%), 16 with intra-abdominal infection (8.6%), 11 with hemorrhage (5.9%), eight with disturbance of gastric emptying (4.3%), two each with biliary fistula, gastrointestinal bleeding or myocardial infarction (1.1%). There was one case each with intracranial hemorrhage or pulmonary embolism (0.5%). Among them, perioperative mortality was 3.8% in seven cases. Four patients died of grade C pancreatic fistula with abdominal hemorrhage, and one each with myocardial infarction, pulmonary embolism or intracranial hemorrhage.

### *Overall prognosis in DCC*

The median follow-up period was 38 mo until March 2020. The median overall DFS

**Table 1 Demographic and pathological findings in patients with distal cholangiocarcinoma**

| Variables | Group 1 (*n* = 81) | Group 2 (*n* = 105) | *P* |
|---|---|---|---|
| Gender (M/F) | 50/31 | 63/42 | 0.811 |
| Age, mean ± SD, yr | 63.7 ± 9.1 | 65.8 ± 8.1 | 0.093 |
| Smoking (Y/N) | 24/57 | 38/67 | 0.347 |
| Diabetes (Y/N) | 18/63 | 35/70 | 0.096 |
| PBD (Y/N) | 35/46 | 55/50 | 0.215 |
| TB (μmol/L) | 76.7 (35.4–211.3) | 110.0 (24.1–203.4) | 0.78 |
| CA19-9 (U/mL) | 27.3 (11.7–45.6) | 139.8 (42.7–316.2) | 0 |
| γ-GGT (U/L) | 706 (395–1194) | 207 (80–446) | 0 |
| Tumor size, mean ± SD, cm | 2.1 ± 0.9 | 2.2 ± 1.1 | 0.82 |
| Tumor differentiation (poor/moderate & high) | 20/61 | 32/73 | 0.412 |
| Nerve invasion (Y/N) | 68/13 | Nov-94 | 0.261 |
| Intraoperative blood loss (mL) | 500 (400–600) | 500 (400–800) | 0.222 |
| Blood transfusion (Y/N) | 30/51 | 36/69 | 0.697 |
| OP time, mean ± SEM, h | 9.5 ± 1.4 | 10.0 ± 2.1 | 0.079 |
| LN metastasis (+/–) | 18/63 | 57/48 | 0 |
| Resection margin (R0/R1) | Jan-80 | Jul-98 | 0.141 |
| Postoperative chemotherapy (Y/N) | 20/61 | 19/86 | 0.273 |

PBD: preoperative biliary drainage; TB: total bilirubin; CA19-9: carbohydrate antigen 19-9; γ-GGT: γ-glutamyltransferase; OP: operation; LN: lymph node; R: resection margin.

was 20 mo (Figure 3A) and the median OS was 25 mo (Figure 3B).

### *Impact of CA19-9/GGT on survival of DCC in different groups*

Patients in group 2 had higher CA19-9 and lymph node metastasis, accompanied by lower GGT, when compared with group 1 ($P < 0.05$) (Table 1). Postoperative morbidity between the groups was compared (Table 2), and there was no significant difference in postoperative mortality and morbidity rate ($P > 0.05$, Table 3). Patients had a median DFS of 37 mo in group 1 and 14 mo in group 2. The 1-, 3- and 5-year DFS rates were 84.2%, 51.0% and 34.8% and 52.9%, 20.1% and 20.1% ($P = 0.000$, Figure 4A). The median OS of patients in groups 1 and 2 was 59 and 17 mo, respectively, and the 1-, 3- and 5-year OS rates were 88.3%, 59.2% and 48.1% and 61.0%, 13.6% and 13.6% ($P = 0.000$, Figure 4B).

### *Risk factors affecting tumor recurrence for DCC*

Postoperative tumor recurrence was taken as a dependent variable and preoperative data [gender, age, smoking history, diabetes, PBD, total bilirubin (TB), GGT, CA19-9, CA19-9/GGT], intraoperative data, pathological data, postoperative complications and chemotherapy as independent variables for univariate and multivariate analysis (Tables 3 and 4). CA19-9/GGT [relative risk (RR) = 2.134, 95% CI: 1.319–3.451), carcinoma differentiation (RR = 1.695, 95% CI: 1.115–2.576) and lymphatic node metastasis (RR = 2.145, 95% CI: 1.404–3.277) were independent risk factors for tumor recurrence in DCC. Patients with the smaller CA19-9/GGT, higher degree of tumor differentiation and the absence of lymphatic metastasis, the lower the risk of tumor recurrence.

### *Risk factors affecting long-term prognosis for DCC after surgery*

The long-term outcome of DCC after surgery was considered as the dependent variable and intraoperative, preoperative, pathological and postoperative data were used as independent variables for univariate and multivariate analysis (Tables 5 and 6). CA19-9/GGT (RR = 2.837, 95% CI: 1.727–4.660), carcinoma differentiation (RR = 1.725, 95% CI: 1.140–2.690) and lymphatic metastasis (RR = 2.050, 95% CI: 1.336–3.144)

**Table 2 Univariate analysis of risk factors for distal cholangiocarcinoma recurrence**

| Variable | *n* | 1-yr OS (%) | 3-yr OS (%) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender | | | | 2.434 | 0.119 |
| Male | 113 | 69.6 | 42.9 | | |
| Female | 73 | 63 | 23.3 | | |
| Age, yr | | | | 1.155 | 0.283 |
| ≤ 60 | 53 | 67.7 | 39.7 | | |
| > 60 | 133 | 66.8 | 31.8 | | |
| Smoking | | | | 0.883 | 0.347 |
| Yes | 62 | 69.3 | 32 | | |
| No | 124 | 65.9 | 35.5 | | |
| Diabetes | | | | 0.734 | 0.391 |
| Yes | 53 | 61.6 | 32.7 | | |
| No | 133 | 69.1 | 34.9 | | |
| PBD | | | | 0.519 | 0.471 |
| Yes | 90 | 67 | 31.3 | | |
| No | 96 | 67.1 | 36.8 | | |
| TB (μmol/L) | | | | 2.556 | 0.11 |
| ≤ 21 | 38 | 82.4 | 34.3 | | |
| > 21 | 148 | 63.3 | 32.4 | | |
| CA19-9 (U/mL) | | | | 5.688 | 0.017 |
| ≤ 37 | 69 | 83.5 | 43.7 | | |
| > 37 | 117 | 56.5 | 28 | | |
| γ-GGT (U/L) | | | | 0.06 | 0.806 |
| ≤ 45 | 11 | 51.1 | 51.1 | | |
| > 45 | 175 | 68 | 34 | | |
| CA19-9/GGT | | | | 26.824 | 0 |
| ≤ 0.12 | 81 | 84.2 | 51 | | |
| > 0.12 | 105 | 52.9 | 20.1 | | |
| OP time, h | | | | 0.299 | 0.585 |
| ≤ 9 | 83 | 65.4 | 36.3 | | |
| > 9 | 103 | 68.2 | 31.5 | | |
| Intraoperative blood loss (mL) | | | | 1.282 | 0.258 |
| ≤ 500 | 117 | 69.3 | 35.5 | | |
| > 500 | 69 | 62.6 | 30.7 | | |
| Blood transfusion | | | | 7.235 | 0.007 |
| Yes | 66 | 56.3 | 24.7 | | |
| No | 120 | 72.7 | 37.9 | | |
| Degree of differentiation | | | | 20.848 | 0 |
| Poor | 52 | 34.2 | 22.2 | | |
| Moderate & high | 134 | 79.9 | 39 | | |
| Tumor size, cm | | | | 3.313 | 0.069 |
| ≤ 2 | 114 | 72.7 | 39.6 | | |

| | | | | | |
|---|---|---|---|---|---|
| > 2 | 72 | 57.7 | 24.5 | | |
| LN metastasis | | | | 32.491 | 0 |
| Yes | 75 | 45.6 | 15.4 | | |
| No | 111 | 81.1 | 47.8 | | |
| Nerve invasion | | | | 4.963 | 0.026 |
| Yes | 162 | 65.4 | 31.8 | | |
| No | 24 | 80 | 60 | | |
| Resection margin | | | | 0.943 | 0.332 |
| R0 | 178 | 67 | 34.8 | | |
| R1 | 8 | 66.7 | 16.7 | | |
| Postoperative complication | | | | 0.197 | 0.657 |
| Yes | 54 | 75.2 | 30.1 | | |
| No | 132 | 64.3 | 34.9 | | |
| Postoperative chemotherapy | | | | 0.011 | 0.917 |
| Yes | 39 | 65.7 | 36.5 | | |
| No | 147 | 67.4 | 33.5 | | |

OS: overall survival; PBD: preoperative biliary drainage; TB: total bilirubin; CA19-9: carbohydrate antigen 19-9; γ-GGT: γ-glutamyltransferase; OP: operation; LN: lymph node; R: resection margin.

were independent risk factors for long-term outcome in DCC.

## DISCUSSION

DCC is mainly managed by surgical resection to achieve DFS; however, the long-term outcome of patients remained unsatisfactory. The data of 1490 patients who were diagnosed with DCC and received PD in the USA were retrospectively analyzed by Andrianello *et al*[14]. They included patients with median OS of 31 mo and at 1-, 3- and 5-year postoperative survival of 89%, 40% and 18%, respectively. Further analysis indicated the independent risk factors for long-term prognosis in patients with DCC, including lymph node metastasis and tumor differentiation. However, these predictive factors had their own limitations in optimizing treatment decisions preoperatively in clinical practice since most of them were not available before surgery and were influenced by human factors. Therefore, developing noninvasive blood-based biomarkers that can make accurate prognostic prediction of DCC preoperatively will be of importance clinically.

CA19-9 is a glycolipid tumor-associated antigen on the cell membrane. As a serological marker, CA19-9 is important in clinical diagnosis of cholangiocarcinoma [15]. It has also been proved to correlate with the long-term outcome of patients. Eighty-nine patients diagnosed with cholangiocarcinoma were reviewed by Coelho *et al*[16], from which they identified CA19-9 as an independent risk factor for long-term prognosis. Nevertheless, patients with DCC were not specifically distinguished. Tella *et al*[17] retrospectively analyzed the data from the National Cancer Database; 2100 patients with extrahepatic cholangiocarcinoma were included and 1474 (70.2%) had elevated CA19-9. They observed a particularly lower median survival time in patients with increasing level of CA19-9 compared to those with normal level of CA19-9 (8.5 *vs* 16.0 mo) and they confirmed CA19-9 as an independent risk factor for long-term prognosis in patients with extrahepatic cholangiocarcinoma. Nevertheless, some researchers have indicated that the efficacy of CA19-9 in the diagnosis and prognosis of biliary tract carcinoma is greatly reduced in the presence of biliary obstruction. Lin *et al*[18] showed that CA19-9 alone is not enough to distinguish malignant or benign biliary obstructive diseases, based on a group of patients with biliary obstruction. In their research 39 patients with benign biliary diseases were included whose level of CA19-9 was 401.9 U/mL on average, and the CA19-9 value of 10 patients was > 1000 U/mL. In a study conducted by Tan *et al*[19], clinical data of 84 patients diagnosed

**Table 3 Morbidity and mortality between two groups in patients with distal cholangiocarcinoma**

| Variables | Group 1 (*n* = 81) | Group 2 (*n* = 105) | *P* |
|---|---|---|---|
| Postoperative hospital stay (d) | 21 (16–24) | 20 (16–29) | 0.368 |
| In-hospital death | 1 | 6 | 0.229 |
| Complications | 20 | 34 | 0.252 |
| Biochemical fistula | 12 | 7 | 0.069 |
| Pancreatic fistula | | | |
| Grade B | 4 | 2 | 0.458 |
| Grade C | 3 | 4 | 0.726 |
| Delayed gastric emptying | 2 | 6 | 0.473 |
| Intra-abdominal infection | 7 | 9 | 0.986 |
| Abdominal hemorrhage | 4 | 7 | 0.856 |

**Table 4 Multivariate analysis of independent risk factors for distal cholangiocarcinoma recurrence**

| Variable | RR | 95%CI | *P* |
|---|---|---|---|
| CA19-9 | 0.921 | 0.578–1.468 | 0.728 |
| CA19-9/GGT | 2.134 | 1.319–3.451 | 0.002 |
| Blood transfusion | 0.74 | 0.497–1.103 | 0.139 |
| Degree of differentiation | 1.695 | 1.115–2.576 | 0.013 |
| LN metastasis | 2.145 | 1.404–3.277 | 0 |
| Nerve invasion | 1.238 | 0.520–2.951 | 0.63 |

RR: relative risk; CI: confidence interval; CA19-9: carbohydrate antigen 199; GGT: γ-glutamyltransferase; LN: lymph node.

with DCC were reviewed. A lower level of CA19-9 indicated better long-term prognosis, but multivariate analysis revealed that CA19-9 was not an independent risk factor for poor outcome. Bolm *et al*[20] also demonstrated that CA19-9 could not be a prognostic indicator for patients with DCC, which is in urgent need of confirmation. In our study, 62.9% of patients with DCC were accompanied by elevated CA19-9 (> 37 U/mL) and had worse long-term prognosis than those patients with normal level of CA19-9 (≤ 37 U/mL). Nevertheless, CA19-9 has been proved not to be an independent risk factor for poor long-term prognosis in multivariate analysis. We attribute it to the high proportion of patients (79.6%) who had combined biliary obstruction in this cohort. Due to bile excretion disorders resulting from biliary obstruction, these patients tended to have a higher overall level of CA19-9, making CA19-9 a less accurate indicator in evaluating the prognosis of DCC patients.

γ-GGT is a membrane-bound glycoprotein and a mitochondrial enzyme containing a sulfhydryl group. γ-GGT plays a key role in the metabolism of GSH and is mostly distributed in the liver, kidney, pancreas and other substantial organs[21]. GGT can be used in the diagnosis and prognosis of malignant tumors, kidney and cardiovascular diseases, and metabolic syndrome[22-25]. According to underlying biological mechanisms illustrating the relationship between GGT expression and cancer, GGT may facilitate the progression, invasion and drug resistance of tumor by modulating a series of vital redox-sensitive functions, including antioxidant/antitoxic defenses and the cellular proliferative/apoptotic balance[26-28]. GGT mainly originates from hepatic Kupffer cells and endothelial cells of the bile duct, and has a significantly higher expression level in hepatocellular carcinoma tissues and fetal liver[29]. However, no related research has been done to reveal the clinical value of GGT in patients diagnosed with DCC. Most patients with DCC are accompanied with various degrees of biliary obstruction, resulting in an abnormal increase in serum GGT, which accounts for up to 94.1% of the data in this group. Therefore, GGT can reflect the degree of biliary obstruction to some extent and is more sensitive than bilirubin. By aligning the ratio of CA19-9 to GGT, we corrected CA19-9 to minimize the effect of

**Table 5 Univariate analysis of long-term survival in patients with distal cholangiocarcinoma**

| Variable | *n* | 1-yr OS (%) | 3-yr OS (%) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender | | | | 1.351 | 0.245 |
| Male | 113 | 76.1 | 40.8 | | |
| Female | 73 | 67.9 | 25.9 | | |
| Age, yr | | | | 2.381 | 0.123 |
| ≤ 60 | 53 | 80.9 | 36.4 | | |
| > 60 | 133 | 69.5 | 32.3 | | |
| Smoking | | | | 0.822 | 0.364 |
| Yes | 62 | 78.2 | 27.3 | | |
| No | 124 | 70.2 | 36.1 | | |
| Diabetes | | | | 0.014 | 0.906 |
| Yes | 53 | 70.8 | 32.6 | | |
| No | 133 | 73.5 | 34.6 | | |
| PBD | | | | 1.217 | 0.27 |
| Yes | 90 | 70.2 | 27.7 | | |
| No | 96 | 75.1 | 39.9 | | |
| TB (μmol/L) | | | | 0.623 | 0.43 |
| ≤ 21 | 38 | 78.9 | 44.4 | | |
| > 21 | 148 | 70.9 | 32.3 | | |
| CA19-9 (U/ml) | | | | 8.239 | 0.004 |
| ≤ 37 | 69 | 85 | 49 | | |
| > 37 | 117 | 65.5 | 25.5 | | |
| γ-GGT (U/L) | | | | 0.169 | 0.681 |
| ≤ 45 | 11 | 71.6 | 43 | | |
| > 45 | 175 | 72.9 | 34.1 | | |
| CA19-9/GGT | | | | 38.091 | 0 |
| ≤ 0.12 | 81 | 88.3 | 59.2 | | |
| > 0.12 | 105 | 61 | 13.6 | | |
| OP time, h | | | | 0.008 | 0.929 |
| ≤ 9 | 83 | 68.8 | 38.4 | | |
| > 9 | 103 | 76 | 31.6 | | |
| Intraoperative blood loss (mL) | | | | 2.693 | 0.101 |
| ≤ 500 | 117 | 72.8 | 39.1 | | |
| > 500 | 69 | 72.5 | 26.2 | | |
| Blood transfusion | | | | 8.307 | 0.004 |
| Yes | 66 | 65.1 | 26.1 | | |
| No | 120 | 76.9 | 37.3 | | |
| Degree of differentiation | | | | 21.212 | 0 |
| Poor | 52 | 51.5 | 19.4 | | |
| Moderate & high | 134 | 80.9 | 40 | | |
| Tumor size, cm | | | | 1.544 | 0.214 |
| ≤ 2 | 114 | 78.4 | 35.7 | | |

| | | | | | |
|---|---|---|---|---|---|
| > 2 | 72 | 63.6 | 31.3 | | |
| LN metastasis | | | | 30.845 | 0 |
| Yes | 75 | 59.8 | 15.8 | | |
| No | 111 | 81.4 | 48.4 | | |
| Nerve invasion | | | | 1.861 | 0.173 |
| Yes | 162 | 73.7 | 30.3 | | |
| No | 24 | 66.2 | 66.2 | | |
| Resection margin | | | | 3.343 | 0.067 |
| R0 | 178 | 73.2 | 35.2 | | |
| R1 | 8 | 62.5 | 12.5 | | |
| Postoperative complication | | | | 2.357 | 0.125 |
| Yes | 54 | 67.8 | 28.8 | | |
| No | 132 | 74.9 | 36.3 | | |
| Postoperative chemotherapy | | | | 0.073 | 0.788 |
| Yes | 39 | 70.4 | 36.8 | | |
| No | 147 | 73.4 | 33.5 | | |

OS: overall survival; PBD: preoperative biliary drainage; TB: total bilirubin; CA19-9: carbohydrate antigen 19-9; γ-GGT: γ-glutamyltransferase; OP: operation; LN: lymph node; R: resection margin.

biliary obstruction on the level of serum CA19-9. As far as we know, no similar retrospective studies uncovering the relationship between CA19-9/GGT and DCC have been done. Moreover, CA19-9/GGT is identified as an independent risk factor for long-term outcome in patients with DCC according to our results, and its predictive value even exceeds that of differentiation degree and lymph node metastasis due to the highest RR. Patients with smaller CA19-9/TB have a lower rate of postoperative tumor recurrence and better prognosis in the long term.

Our results also revealed an association between CA19-9/GGT and lymphatic metastasis. A smaller CA19-9/GGT indicated a higher rate of lymphatic metastasis; nevertheless, no significant relation between CA19-9/GGT and tumor size and differentiation was observed in our research. Bergquist *et al*[30] asserted that, among patients with DCC, 28.7% whose CA19-9 was ≤ 37 U/mL presented with lymph node metastasis, which was significantly lower than 43.8% in patients whose CA19-9 was > 37 U/mL. In addition, by mediating extracellular GSH cleavage and intracellular GSH synthesis, overexpression of GGT may increase the metastatic activity in melanoma, and intertissue flow of GSH may have a growth-promoting effect on GGT-positive tumors[31] . This emphasizes the significant correlation between higher GGT level and lymph node involvement. The exact mechanism for the relation between GGT level and lymph node metastasis remains unknown and requires further study, to elucidate the role that GGT plays in tumor invasion. Nevertheless, most patients with DCC are accompanied with various degrees of biliary obstruction, resulting in abnormal increase of serum GGT. It has also been confirmed that lymphatic metastasis is an independent risk factor for long-term prognosis of patients with DCC, and it is considered to be an important factor in judging the degree of malignancy and local spread of malignant tumor. Therefore, it is reasonable to assume that CA19-9/GGT can function as a better biomarker in reflecting the malignancy and aggressiveness of DCC.

Our study had some limitations. First, as a single-center retrospective study, a certain degree of bias was inevitable. Second, the proportion relationship between CA19-9 and bilirubin remained unclear, as did whether CA19-9 decreased in proportion to bilirubin after relief of biliary obstruction. Therefore, for patients with different degrees of biliary obstruction, however, the effect of GGT correction may be biased to a certain extent of DCC after curative resection.

**Table 6 Multivariate analysis of long-term survival in patients with distal cholangiocarcinoma**

| Variable | RR | 95%CI | *P* |
|---|---|---|---|
| CA19-9 | 0.974 | 0.607–1.561 | 0.911 |
| CA19-9/GGT | 2.837 | 1.727–4.660 | 0 |
| Blood transfusion | 0.763 | 0.513–1.135 | 0.182 |
| Degree of differentiation | 1.725 | 1.140–2.609 | 0.01 |
| LN metastasis | 2.05 | 1.336–3.144 | 0.001 |

CA19-9: carbohydrate antigen 19-9; GGT: γ-glutamyltransferase; LN: lymph node.

## CONCLUSION

Elevation of CA19-9/GGT performed better as a biomarker of aggressiveness of DCC, as well as a predictor of poor clinical outcomes by reducing the effect of biliary tract obstruction of CA19-9 concentration. CA19-9/GGT might be a significant indicator for identifying DCC patients at high risk of early recurrence and unfavorable prognosis.

## ARTICLE HIGHLIGHTS

### *Research background*

Distal cholangiocarcinoma (DCC) is a rare malignant tumor in the digestive system and has a poor long-term prognosis. Curative excision is currently the most appropriate therapy for patients with DCC because of the lack of effective adjuvant therapies. Therefore, it is important to determine the long-term prognosis for formulating a reasonable treatment plan and avoiding unnecessary surgical trauma.

### *Research motivation*

At present, tumor differentiation, lymphatic metastasis and other pathological risk factors for DCC can only be obtained after surgery, and the information acquisition is delayed.

### *Research objectives*

We aimed to minimize the interference effect of obstructive jaundice on the concentration of carbohydrate antigen 19-9 (CA19-9), so as to determine the strong association between CA19-9/γ-glutamyltransferase (GGT) and postoperative tumor recurrence and long-term outcome of DCC.

### *Research methods*

We enrolled 186 patients. Receiver operating characteristic curves were drawn according to preoperative CA19-9/GGT and 1-year survival, and the patients were divided into two groups (group 1, low-ratio, $n$ = 81; group 2, high-ratio, $n$ = 105). By univariate and multivariate analyses, the risk factors influencing tumor recurrence and long-term outcome of patients with DCC were screened out.

### *Research results*

The optimum value of CA19-9/GGT was 0.12. Patients in group 2 had higher CA19-9 and lymphatic metastasis rate accompanied by lower GGT, when compared with group 1 ($P$ < 0.05). The 1-, 3- and 5-year overall survival rates of patients in group 1 and group 2 were 88.3%, 59.2% and 48.1% and 61.0%, 13.6% and 13.6%, respectively ($P$ = 0.000). Multivariate analysis indicated that CA19-9/GGT, lymphatic metastasis and tumor differentiation were independent risk factors for tumor recurrence and long-term prognosis of DCC.

### *Research conclusions*

Elevation of CA19-9/GGT performed better as an indicator of aggressive tumor behavior, as well as a predictor of poor clinical outcomes by reducing the effect of biliary obstruction on CA19-9 concentration in patients with DCC. CA19-9/GGT

might be a significant indicator for identifying DCC patients at high risk of early recurrence and unfavorable prognosis.

### *Research perspectives*

CA19-9/GGT is more valuable in judging DCC patients at high risk of early recurrence and unfavorable outcomes.

## REFERENCES


1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Razumilava N**, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; **383**: 2168-2179 [PMID: 24581682 DOI: 10.1016/S0140-6736(13)61903-0]

3 **Lad N**, Kooby DA. Distal cholangiocarcinoma. *Surg Oncol Clin N Am* 2014; **23**: 265-287 [PMID: 24560110 DOI: 10.1016/j.soc.2013.11.001]

4 **Lee RM**, Maithel SK. Approaches and Outcomes to Distal Cholangiocarcinoma. *Surg Oncol Clin N Am* 2019; **28**: 631-643 [PMID: 31472910 DOI: 10.1016/j.soc.2019.06.014]

5 **Strijker M**, Belkouz A, van der Geest LG, van Gulik TM, van Hooft JE, de Meijer VE, Haj Mohammad N, de Reuver PR, Verheij J, de Vos-Geelen J, Wilmink JW, Groot Koerkamp B, Klümpen HJ, Besselink MG; Dutch Pancreatic Cancer Group. Treatment and survival of resected and unresected distal cholangiocarcinoma: a nationwide study. *Acta Oncol* 2019; **58**: 1048-1055 [PMID: 30907207 DOI: 10.1080/0284186X.2019.1590634]

6 **Wellner UF**, Shen Y, Keck T, Jin W, Xu Z. The survival outcome and prognostic factors for distal cholangiocarcinoma following surgical resection: a meta-analysis for the 5-year survival. *Surg Today* 2017; **47**: 271-279 [PMID: 27236779 DOI: 10.1007/s00595-016-1362-0]

7 **Bergquist JR**, Puig CA, Shubert CR, Groeschl RT, Habermann EB, Kendrick ML, Nagorney DM, Smoot RL, Farnell MB, Truty MJ. Carbohydrate Antigen 19-9 Elevation in Anatomically Resectable, Early Stage Pancreatic Cancer Is Independently Associated with Decreased Overall Survival and an Indication for Neoadjuvant Therapy: A National Cancer Database Study. *J Am Coll Surg* 2016; **223**: 52-65 [PMID: 27049786 DOI: 10.1016/j.jamcollsurg.2016.02.009]

8 **Lee SP**, Sung IK, Kim JH, Lee SY, Park HS, Shim CS. Usefulness of Carbohydrate Antigen 19-9 Test in Healthy People and Necessity of Medical Follow-up in Individuals with Elevated Carbohydrate Antigen 19-9 Level. *Korean J Fam Med* 2019; **40**: 314-322 [PMID: 30959581 DOI: 10.4082/kjfm.18.0057]

9 **La Greca G**, Sofia M, Lombardo R, Latteri S, Ricotta A, Puleo S, Russello D. Adjusting CA19-9 values to predict malignancy in obstructive jaundice: influence of bilirubin and C-reactive protein. *World J Gastroenterol* 2012; **18**: 4150-4155 [PMID: 22919247 DOI: 10.3748/wjg.v18.i31.4150]

10 **Xiao Y**, Yang H, Lu J, Li D, Xu C, Risch HA. Serum gamma-glutamyltransferase and the overall survival of metastatic pancreatic cancer. *BMC Cancer* 2019; **19**: 1020 [PMID: 31664937 DOI: 10.1186/s12885-019-6250-8]

11 **Whitfield JB**. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001; **38**: 263-355 [PMID: 11563810 DOI: 10.1080/20014091084227]

12 **Mei Y**, Chen L, Zeng PF, Peng CJ, Wang J, Li WP, Du C, Xiong K, Leng K, Feng CL, Jia JH. Combination of serum gamma-glutamyltransferase and alkaline phosphatase in predicting the diagnosis of asymptomatic choledocholithiasis secondary to cholecystolithiasis. *World J Clin Cases* 2019; **7**: 137-144 [PMID: 30705891 DOI: 10.12998/wjcc.v7.i2.137]

13 **Griffith OW**, Bridges RJ, Meister A. Transport of gamma-glutamyl amino acids: role of glutathione and gamma-glutamyl transpeptidase. *Proc Natl Acad Sci U S A* 1979; **76**: 6319-6322 [PMID: 42913 DOI: 10.1073/pnas.76.12.6319]

14 **Andrianello S**, Paiella S, Allegrini V, Ramera M, Pulvirenti A, Malleo G, Salvia R, Bassi C. Pancreaticoduodenectomy for distal cholangiocarcinoma: surgical results, prognostic factors, and long-term follow-up. *Langenbecks Arch Surg* 2015; **400**: 623-628 [PMID: 26134446 DOI: 10.1007/s00423-015-1320-0]

15 **Grunnet M**, Mau-Sørensen M. Serum tumor markers in bile duct cancer--a review. *Biomarkers* 2014; **19**: 437-443 [PMID: 24857368 DOI: 10.3109/1354750X.2014.923048]

16 **Coelho R**, Silva M, Rodrigues-Pinto E, Cardoso H, Lopes S, Pereira P, Vilas-Boas F, Santos-Antunes J, Costa-Maia J, Macedo G. CA 19-9 as a Marker of Survival and a Predictor of Metastization in Cholangiocarcinoma. *GE Port J Gastroenterol* 2017; **24**: 114-121 [PMID: 28848795 DOI: 10.1159/000452691]

17 **Tella SH**, Kommalapati A, Yadav S, Bergquist JR, Goyal G, Durgin L, Borad M, Cleary SP, Truty MJ, Mahipal A. Novel staging system using carbohydrate antigen (CA) 19-9 in extra-hepatic cholangiocarcinoma and its implications on overall survival. *Eur J Surg Oncol* 2020; **46**: 789-795 [PMID: 31954549 DOI: 10.1016/j.ejso.2020.01.016]

18 **Lin MS**, Huang JX, Yu H. Elevated serum level of carbohydrate antigen 19-9 in benign biliary stricture diseases can reduce its value as a tumor marker. *Int J Clin Exp Med* 2014; **7**: 744-750 [PMID: 24753772]

19 **Tan X**, Xiao K, Liu W, Chang S, Zhang T, Tang H. Prognostic factors of distal cholangiocarcinoma after curative surgery: a series of 84 cases. *Hepatogastroenterology* 2013; **60**: 1892-1895 [PMID: 24719923]

20 **Bolm L**, Petrova E, Weitz J, Rückert F, Wittel UA, Makowiec F, Lapshyn H, Bronsert P, Rau BM, Khatkov IE, Bausch D, Keck T, Wellner UF, Distler M. Prognostic relevance of preoperative bilirubin-adjusted serum carbohydrate antigen 19-9 in a multicenter subset analysis of 179 patients with distal cholangiocarcinoma. *HPB (Oxford)* 2019; **21**: 1513-1519 [PMID: 30956162 DOI: 10.1016/j.hpb.2019.03.363]

21 **Hanigan MH**. Gamma-glutamyl transpeptidase: redox regulation and drug resistance. *Adv Cancer Res* 2014; **122**: 103-141 [PMID: 24974180 DOI: 10.1016/B978-0-12-420117-0.00003-7]

22 **Fu SJ**, Zhao Q, Ji F, Chen MG, Wu LW, Ren QQ, Guo ZY, He XS. Elevated Preoperative Serum Gamma-glutamyltranspeptidase Predicts Poor Prognosis for Hepatocellular Carcinoma after Liver Transplantation. *Sci Rep* 2016; **6**: 28835 [PMID: 27381639 DOI: 10.1038/srep28835]

23 **Kunutsor SK**, Laukkanen JA. Gamma-glutamyltransferase and risk of chronic kidney disease: A prospective cohort study. *Clin Chim Acta* 2017; **473**: 39-44 [PMID: 28811239 DOI: 10.1016/j.cca.2017.08.014]

24 **Dalos D**, Binder C, Duca F, Aschauer S, Kammerlander A, Hengstenberg C, Mascherbauer J, Reiberger T, Bonderman D. Serum levels of gamma-glutamyltransferase predict outcome in heart failure with preserved ejection fraction. *Sci Rep* 2019; **9**: 18541 [PMID: 31811258 DOI: 10.1038/s41598-019-55116-8]

25 **Coku V**, Shkembi X. Serum Gamma-glutamyltransferase and Obesity: is there a Link? *Med Arch* 2018; **72**: 112-115 [PMID: 29736099 DOI: 10.5455/medarh.2017.72.112-115]

26 **Pompella A**, De Tata V, Paolicchi A, Zunino F. Expression of gamma-glutamyltransferase in cancer cells and its significance in drug resistance. *Biochem Pharmacol* 2006; **71**: 231-238 [PMID: 16303117 DOI: 10.1016/j.bcp.2005.10.005]

27 **Franzini M**, Corti A, Lorenzini E, Paolicchi A, Pompella A, De Cesare M, Perego P, Gatti L, Leone R, Apostoli P, Zunino F. Modulation of cell growth and cisplatin sensitivity by membrane gamma-glutamyltransferase in melanoma cells. *Eur J Cancer* 2006; **42**: 2623-2630 [PMID: 16928443 DOI: 10.1016/j.ejca.2006.04.016]

28 **Dominici S**, Valentini M, Maellaro E, Del Bello B, Paolicchi A, Lorenzini E, Tongiani R, Comporti M, Pompella A. Redox modulation of cell surface protein thiols in U937 lymphoma cells: the role of gamma-glutamyl transpeptidase-dependent H2O2 production and S-thiolation. *Free Radic Biol Med* 1999; **27**: 623-635 [PMID: 10490284 DOI: 10.1016/s0891-5849(99)00111-2]

29 **Yao DF**, Dong ZZ. Hepatoma-related gamma-glutamyl transferase in laboratory or clinical diagnosis of hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 9-11 [PMID: 17287158]

30 **Bergquist JR**, Ivanics T, Storlie CB, Groeschl RT, Tee MC, Habermann EB, Smoot RL, Kendrick ML, Farnell MB, Roberts LR, Gores GJ, Nagorney DM, Truty MJ. Implications of CA19-9 elevation for survival, staging, and treatment sequencing in intrahepatic cholangiocarcinoma: A national cohort analysis. *J Surg Oncol* 2016; **114**: 475-482 [PMID: 27439662 DOI: 10.1002/jso.24381]

31 **Obrador E**, Carretero J, Ortega A, Medina I, Rodilla V, Pellicer JA, Estrela JM. gamma-Glutamyl transpeptidase overexpression increases metastatic growth of B16 melanoma cells in the mouse liver. *Hepatology* 2002; **35**: 74-81 [PMID: 11786961 DOI: 10.1053/jhep.2002.30277]

World Journal of Gastrointestinal Surgery

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*World J Gastrointest Surg* 2021 September 27; 13(9): 1039-1049

DOI: 10.4240/wjgs.v13.i9.1039

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

# Novel suturing technique, based on physical principles, achieves a breaking point double that obtained by conventional techniques

Francisco Javier Pérez Lara, Rogelio Zubizarreta Jimenez, Francisco Javier Moya Donoso, Jose Manuel Hernández Gonzalez, Tatiana Prieto-Puga Arjona, Ricardo Marín Moya, Maria Pitarch Martinez

**ORCID number:** Francisco Javier Pérez Lara 0000-0002-2942-5040; Rogelio Zubizarreta Jimenez 0000-0003-2703-9960; Francisco Javier Moya Donoso 0000-0001-8737-3691; Jose Manuel Hernández Gonzalez 0000-0001-5829-568X; Tatiana Prieto-Puga Arjona 0000-0001-6382-0338; Ricardo Marín Moya 0000-0003-1438-2233; Maria Pitarch Martinez 0000-0002-7808-9960.

**Author contributions:** Pérez Lara FJ made a substantial contribution to the concept and design, drafted the article or revised it critically for important intellectual content, and approved the version to be published; Zubizarreta Jimenez R drafted the article or revised it critically for important intellectual content and approved the version to be published; Moya Donoso F approved the version to be published; Hernández González JM approved the version to be published; Prieto-Puga T approved the version to be published; Marín Moya R approved the version to be published; Pitarch Martínez M approved the version to be published.

**Institutional review board statement:** This study didn't involve the human subjects.

**Conflict-of-interest statement:** The

**Francisco Javier Pérez Lara, Francisco Javier Moya Donoso, Jose Manuel Hernández Gonzalez, Tatiana Prieto-Puga Arjona, Ricardo Marín Moya, Maria Pitarch Martinez,** Department of Surgery, Hopital de Antequera, Malaga 29200, Spain

**Rogelio Zubizarreta Jimenez,** DOXA, Malaga 29730, Spain

**Corresponding author:** Francisco Javier Pérez Lara, PhD, Doctor, Department of Surgery, Hopital de Antequera, Avda. Poeta Muñoz Rojas sn, Antequera 29200, Malaga, Spain. javinewyork@hotmail.com

## Abstract

### *BACKGROUND*

Sutures have been used to repair wounds since ancient times. However, the basic suture technique has not significantly changed. In Phase I of our project, we proposed a "double diabolo" suture design, using a theoretical physical study to show that this suture receives 50% less tension than conventional sutures, and so a correspondingly greater force must be applied to break it.

### *AIM*

To determine whether these theoretical levels of resistance were met by the new type of suture.

### *METHODS*

An observational study was performed to compare three types of sutures, using a device that exerted force on the suture until the breaking point was reached. The tension produced by this traction was measured. The following variables were considered: Tearing stress on entry/exit points, edge separation stress, and suture break stress. The study sample consisted of 30 sutures with simple interrupted stitches (Group 1), 30 with continuous stitches (Group 2), and 30 with the "double diabolo" design (Group 3).

### *RESULTS*

The mean degree of force required to reach the breaking point for each of these variables (tearing, separation, and final breaking) was highest in Group 3 (14.56, 18.28, and 21.39 kg), followed by Group 1 (7.36, 10.38, and 12.81 kg) and Group 2 (5.77, 7.7, and 8.71 kg). These differences were statistically significant ($P < 0.001$) in all cases.

authors have no conflict of interest.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.



**Manuscript source:** Invited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Spain

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** January 29, 2021
**Peer-review started:** January 29, 2021
**First decision:** May 4, 2021
**Revised:** May 10, 2021
**Accepted:** August 4, 2021
**Article in press:** August 4, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Kelemen D
**S-Editor:** Ma YJ
**L-Editor:** Filipodia
**P-Editor:** Li JH

*CONCLUSION*

The experimental results show that with the "double diabolo" suture, compared with conventional sutures, greater force must be applied to reach the breaking point (almost twice as much as in the simple interrupted suture and more than double that required for the continuous suture). If these results are confirmed in Phase III (the clinical phase) of our study, we believe the double diabolo technique should be adopted as the standard approach, especially when the suture must withstand significant tension (*e.g.*, laparotomy closure, thoracotomy closure, diaphragm suture, or hernial orifice closure).

**Key Words:** Suture; Technique; Physical principles; Tension



**Core Tip:** The aim of this project was to design and validate a new technique that imposes the least possible tension on the suture threads and entry/exit points, thus creating a suture that is more stable and resistant. We manufactured a device to apply a progressively increasing separation force to the suture surfaces, and to measure the tension exerted until the breaking point is reached. With this device we compared three groups: Simple interrupted stitches, continuous stitches, and our proposed technique.

**Citation:** Pérez Lara FJ, Zubizarreta Jimenez R, Moya Donoso FJ, Hernández Gonzalez JM, Prieto-Puga Arjona T, Marín Moya R, Pitarch Martinez M. Novel suturing technique, based on physical principles, achieves a breaking point double that obtained by conventional techniques. *World J Gastrointest Surg* 2021; 13(9): 1039-1049
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1039.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1039

## INTRODUCTION

Sutures are a vital element of almost all surgical procedures. They join tissues, close and stabilise wound margins, and promote healing[1]. The desirable characteristics of sutures are well documented, and include aspects such as high and predictable tensile strength, ease of application, and secure knotting[2].

On a daily basis, surgeons must draw wound tissues closer together and maintain this state, but their choice of suture design is often empirical, based on experience alone. To date, no methodical investigation has been conducted to determine the ideal suture design from the perspective of theoretical physics.

Needles were first used between 50000 and 30000 BCE, and from 20000 BCE until the Renaissance, bone needles were the best available. It is reasonable to assume that these needles were also used to stitch wounds[3]. Throughout history, materials such as linen, cotton, horsehair, animal tendons and intestines, and precious metal filaments have been used to draw wound edges together and to act as ligatures. Preferences and technologies have evolved over time, resulting in the highly sophisticated products used in current practice. Nevertheless, despite these advances[4-7], little progress has been made in suturing, and most surgeons continue to use the two classical techniques: Continuous suture or simple interrupted suture.

The aim of this project was to design and validate a new technique that imposes the least possible tension on the suture threads and entry/exit points, thus creating a suture that is more stable and resistant. By examining the vector forces exerted on a suture, it can be seen that distribution of the tension on a thread that joins two diverging points will decrease according to the cosine of the angle between the thread and the perpendicular of the force applied to separate the points. In other words, the wider the angle of approach of the thread, the less tension it must support. For example, if the angle in question is expanded to 45º, the cosine will be 0.7; therefore, the tension on the thread is equal to 0.7 of the force exerted, that is, it is reduced by 30%. In this project, our initial consideration is that the sutures currently in use, whether interrupted or continuous, join the points in a straight line. Therefore, the angulation is zero and the sutures are subjected to maximum tension.

On the basis of this physical law, and as a proposal for an improved suture design, we recently published (in Phase 1 of our study[8]) details of the double diabolo suture, in which the suture point is supported by two central inverted double angles and by four lateral angles, thus creating eight 45º angles (Figure 1) and more widely distributing the stress exerted. In the earlier study, we showed theoretically that the tension on the thread was reduced by 65% compared to the interrupted suture and by 50% compared to the continuous suture. Moreover, the tension on the entry/exit points was reduced by 33% and 50%, respectively.

However, these theoretical physical postulates must be confirmed experimentally, showing that with the suture design that we describe, both the suture thread and the entry/exit points are indeed subjected to less tension (for a given separation force applied) than is the case with conventional sutures, and therefore that a greater force can be applied to our sutures before they break.

## MATERIALS AND METHODS

In this second phase of this project, an observational study was conducted to compare the two types of suture used in standard practice, the simple interrupted suture (Group 1) and the continuous suture (Group 2), with the proposed new design, the double diabolo (Group 3). To compare these three groups, we manufactured a device (Figure 2) to apply a progressively increasing separation force to the suture surfaces, and to measure the tension exerted until the breaking point is reached. These tests were performed on 90 sutures, 30 for each group, and the results obtained were compared.

### *Simple interrupted suture (Group 1)*

Sutures were inserted perpendicular to the two surfaces to be joined, and each suture was knotted in the centre.

### *Continuous suture (Group 2)*

The whole suture was created with a single thread *via* ligatures perpendicular to the two surfaces to be joined, knotting only the first and last points.

### *Double diabolo suture (Group 3)*

With this suture, each stitch was addressed by eight 45º angles. We started with a central stitch that was perpendicular to the surfaces to be joined (Figure 3A). Then we created an X-shaped stitch to the right (Figure 3B), returned with a second central stitch (Figure 3C), created another X-shaped stitch, this time to the left (Figure 3D), and finally returned with a third central stitch to complete the "central column" (Figure 3E). The stitch assembly was then knotted with the thread that was centrally located at the outset (Figure 3F).

**Measuring the force exerted:** The measuring device (Figure 2) was composed of a base to which a metal frame was fitted, with a dynamometer and two plates attached to a screw mechanism (like a small garrotte), applied to two fragments of sutured material. With this device, the tension exerted on the suture can be progressively increased until it breaks. The amount of force exerted was measured with the dynamometer.

In testing the three suture designs, three moments were taken as points of reference: First, when the entry/exit points began to tear (tearing force, TF); Second, when the edges of the sutured material began to separate (separation force, SF); and Third, when complete separation of the sutured elements occurred, either because of the thread breaks or due to complete rupture of the sutured material (breaking point, BP). The tension exerted at each moment was measured and compared for the three types of suture.

In order to avoid bias in our results, the same parameters were applied to each of the three groups. Thus, in every case the same material was used (PVC sheets, 6 cm long and 2 mm thick). In every case, three stitches were formed, at 1 cm from the edge, with the same separation between them. The thread used was always the same (monofilament gauge 0) and all knots were tied six times, and cut at 1 cm from the knot. The statistical study is shown in Table 1.

### *Statistical analyses*

A descriptive analysis was performed of the sample (90 elements). Summary statistics (mean, standard deviation, median, minimum and maximum) were calculated for each

**Table 1 The statistical study**

| | |
|---|---|
| Aim | To compare the force exerted at which the breaking point is reached, for the three types of suture (Groups 1, 2 and 3) according to the measurements of tearing (TF), separation (SF) and rupture (BP) |
| Method | The study sample was composed of 90 elements |
| Clinical variables | (1) Tearing (the force applied at which the suture points begin to tear); (2) Separation (the force applied at which the suture edges begin to separate); and (3) Break (the force applied at which the suture breaks) |
| Classification of the variables (suture type) | (1) Group 1 (simple interrupted suture); (2) Group 2 (continuous suture); and (3) Group 3 (double diabolo suture) |

BP: Breaking point; SF: Separation force; TF: Tearing force.

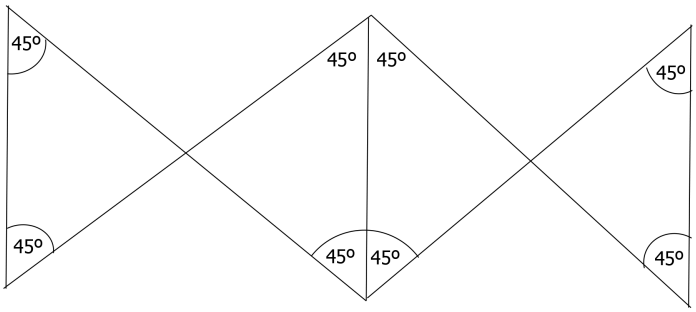



**Figure 1 Theoretical model to reduce tension *via* an 8-angle suture pattern.**

of the clinical variables. The Kolmogorov-Smirnov test of normality was performed to determine the most suitable means of comparing the suture types. This test considered the following hypotheses:

\ (H_0 = \text{The sample follows a normal distribution}\)

\ (H_1 = \text{The sample does not follow a normal distribution}\)

Therefore, if $P < 0.05$, the hypothesis that the sample had been drawn from a population with a normal distribution was rejected. The comparative analysis based on the suture-type classificatory variable was performed by analysis of variance when the variables followed a normal distribution and otherwise by the non-parametric Kruskal-Wallis test. The following hypotheses were considered:

\(H_0= \text{Groups 1, 2 and 3 react to exerted pressure in the same way}\)

\(H_1= \text{At least one of the groups reacts differently }\)

Therefore, if $P < 0.05$, the hypothesis that Groups 1, 2 and 3 react in the same way to the pressure exerted was rejected. In both of these evaluations, if intergroup differences were detected, two-by-two tests were performed, using the Bonferroni correction. The Student's *t*-test was used in the parametric case and the Mann-Whitney *U* test in the non-parametric case. In both cases, when $P < 0.05$, the hypothesis that the groups were equal was rejected.

## RESULTS

### *Descriptive analysis of the sample*

The 90 cases considered were divided equally among the three types of suture. For each case, the above-described device was used to apply a separation force to the two surfaces of the suture, and the resulting measurements were obtained for the study variables. The summary statistics (mean, standard deviation, median, minimum and maximum) obtained for the variables TF, SF, and BP are detailed in Table 2. For the overall sample of 90 sutures, the average TF of the entry/exit points was 9.23 ± 4.41 kg, the average SF of the suture edges was 12.12 ± 4.96 kg, and the average BP was 14.3 ± 5.82 kg. The variables TF, SF, and BP were not normally distributed, producing statistics of D = 0.12, 0.16 and 0.10 and *P* values of < 0.01, < 0.01 and < 0.05 respectively, according to the Kolmogorov-Smirnov test.

**Table 2 The summary statistics (mean, standard deviation, median, minimum and maximum) obtained for the variables tearing force, separation force and breaking point**

| | mean ± SD | Median | Min | Max |
|---|---|---|---|---|
| TF | 9.23 ± 4.41 | 7.9 | 2.4 | 19.5 |
| SF | 12.12 ± 4.96 | 10.7 | 2.6 | 21.7 |
| BP | 14.3 ± 5.82 | 12.98 | 2.85 | 25.2 |

BP: Breaking point; SF: Separation force; TF: Tearing force.

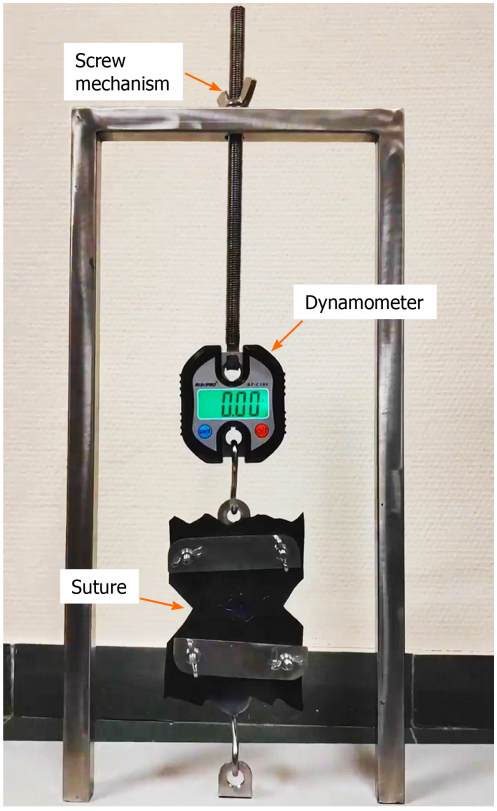



**Figure 2 Device to apply a progressively-increasing separation force to the suture surfaces, and to measure the tension exerted until the breaking point is reached.**

### *Comparative analysis*

The results of the comparative analysis are detailed in Figure 4. In brief, the mean values for TF, SF, and BP were highest in Group 3 (14.56, 18.28, and 21.39 kg), followed by Group 1 (7.36, 10.38, and 12.81 kg) and Group 2 (5.77, 7.7, and 8.71 kg). The differences among the three groups were statistically significant ($P < 0.001$). A two-by-two test was carried out to determine whether the pairs of suture types presented differences, showing that in every case (TF, SF, and BP), the differences between Groups 1 and 3, Groups 2 and 3, and Groups 1 and 2 were statistically significant ($P < 0.005$).

## DISCUSSION

Inserting sutures is one of the most challenging and time-consuming surgical tasks[9]. The limitations associated with the work of a human operator, together with the repetitive nature of this operation make it a suitable candidate for automation.

The purpose of sutures in general is to approximate wound tissues, without excess tension, minimising ischaemia and tissue injury. As the wound heals, the strength of the scar increases until the tissue approaches or regains its original tensile strength. For

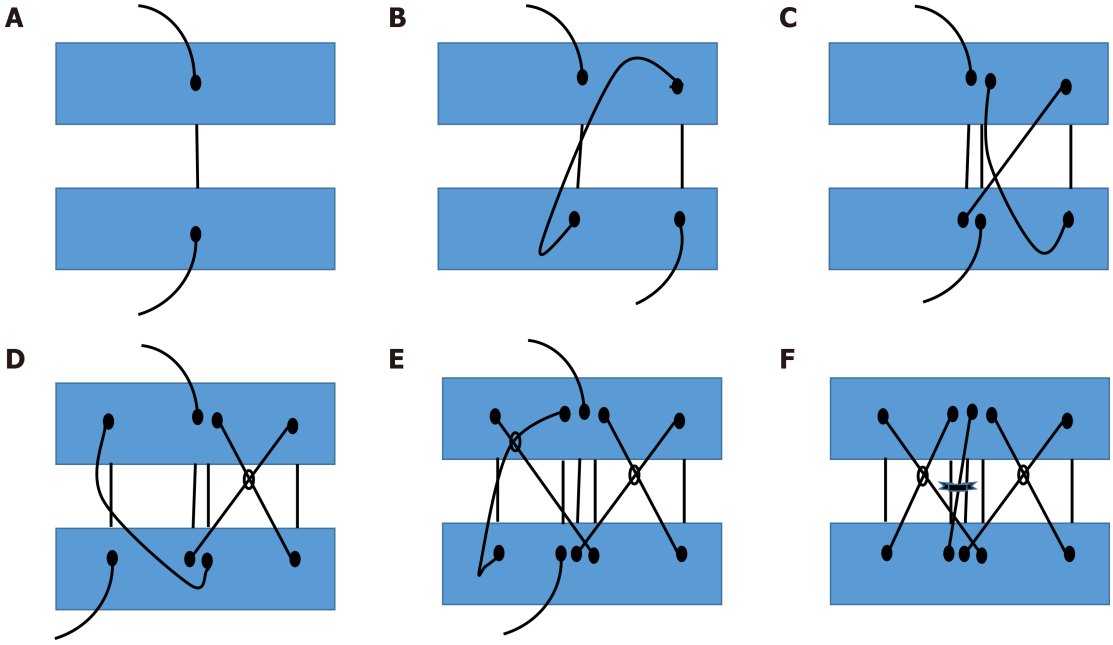



**Figure 3 Steps to create the proposed "double-diabolo" suture.** A: We started with a central stitch that was perpendicular to the surfaces to be joined; B: Then we created an X-shaped stitch to the right; C: We returned with a second central stitch; D: We created another X-shaped stitch, this time to the left; E: We finally returned with a third central stitch to complete the "central column"; F: Then the stitch assembly was knotted with the thread that was centrally located at the outset.

either single- or multi-layer wound closure, the suture size or diameter chosen should be the smallest for purpose, thus minimising both the tissue trauma with each needle pass and the amount of foreign material inserted. However, smaller-diameter sutures are associated with lower tensile strength, and so a balance must be struck between the size of the suture and the need to maintain the tissue approximation[2].

Since ancient times, mankind has used materials in one way or another to bond the edges of wounds and promote healing. However, despite much progress in the development of new suture materials and efforts to enhance techniques, little significant improvement has been achieved for decades[10,11] and indeed, concerns the distribution of stress angles for millennia.

On the other hand, numerous proposals have been made to improve the stability of the suture. Thus, Sen *et al*[12] proposed an algorithm to minimise the length of the suture and to maintain the needle at an orthogonal angle to the tissue entry point. Another study by Wieskötter *et al*[13] compared different types of suture and the biomechanical stability provided to the tendons in each case.

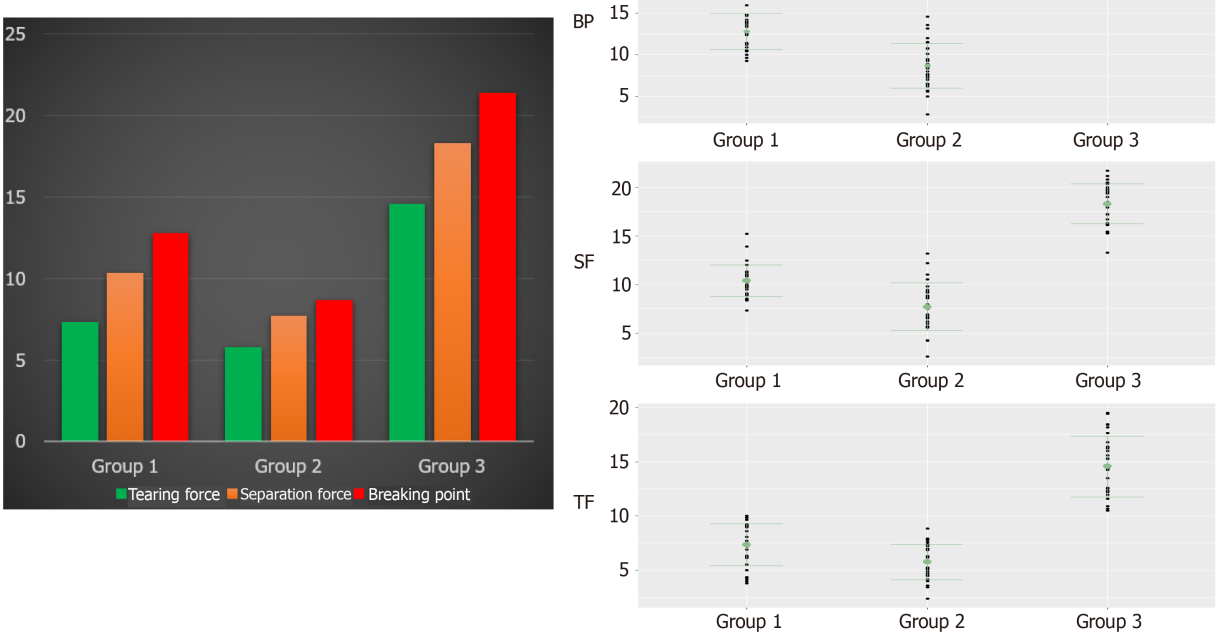
Israelsson *et al*[14-17] addressed the question of which technique should best be used to achieve continuous closure, and in accordance with their experimental and clinical data recommended the short stitch technique.

On the other hand, a meta-analysis by Henriksen *et al*[18] found no significant differences between the results obtained by the interrupted and the continuous suture techniques. This meta-analysis concluded that the best evidence was obtained for laparotomy incision closure by means of the "small bites" technique with a 2-0 slowly absorbable suture in which aponeurosis was only present in a suture: Wound length ratio of at least 4:1. Kubota *et al*[19] studied the mechanical properties of six types of circumferential sutures for the tendon, and reported that the suture termed "Lin-locking" supported the greatest tensile force. However, to the best of our knowledge, no high-quality evidence has been reported on the best suture material or technique to reduce, for example, the rate of incisional hernia after a laparotomy closure.

As Albert Einstein said, "The important thing is not to stop questioning," and this notion has been applied by Srivastava *et al*[20] and by Srivastava *et al*[21]. These authors highlight the fundamental importance of physical laws in the field of surgery, noting that the basic mechanisms by which living and non-living beings function are guided by the laws of the pure sciences, that is, physics, chemistry, and mathematics. In this respect, Srivastava *et al*[21] performed a systematic search in Medline (1960–2008) using keywords such as mechanics, Laplace's Law, Pascal's Law, the laws of vectors and suture techniques, *etc.* and discussed, among other topics, the laws of mechanics, thermodynamics and the vectors applied to soft tissue and bone and Laplace's Law, with respect to colon perforation, compression therapy, childbirth,

**A**

| | Group 1 | Group 2 | Group 3 | *P* value |
|---|---|---|---|---|
| Tearing force | Mean 7.360 (SD 1.924) | Mean 5.770 (SD 1.642) | Mean 14.560 (SD 2.801) | < 0.0011 |
| Separation force | Mean 10.380 (SD 1.611) | Mean 7.700 (SD 2.440) | Mean 18.292 (SD 2.060) | < 0.0011 |
| Breaking point | Mean 12.810 (SD 2.174) | Mean 8.710 (SD 2.694) | Mean 21.388 (SD 2.321) | < 0.0011 |




**B**

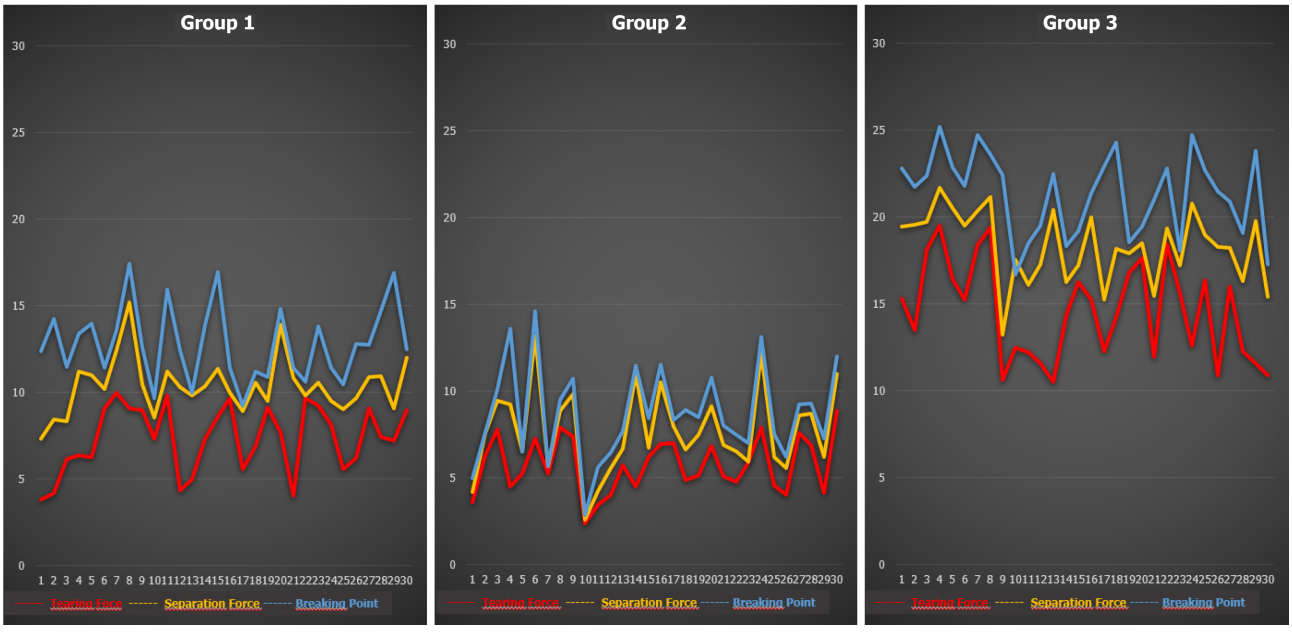



**Figure 4 Results of the comparative analysis (A and B).**

ruptured varicose veins, herniated discs, *etc*. Moreover, consideration of Pascal's Law is necessary when conducting hernia repair and the Heimlich manoeuvre. The components of the forces derived from trigonometry, which come into play when a suture is inserted, reveal how the wound may be closed. The thickness and the bite of the suture determine the extent of the tissue reaction, and the tension exerted may be reduced, according to the cosine of the angle. However, to date no suture design taking advantage of this physical law has been proposed.

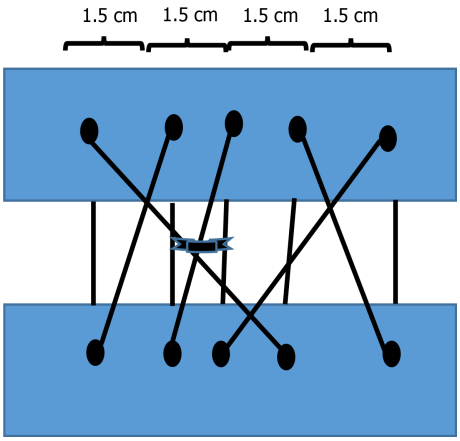



**Figure 5 Final model of "double-diabolo" suture with central points sited approximately 1-1.5 cm.**

Thus, our review of the literature did not reveal any prior in-depth study of the physical laws that govern the tensions generated in sutures, conducted in order to create a new, more effective suture design. The real-world situation continues unchanged, and so the use of continuous sutures and simple interrupted stitches (with minor variations) remains standard practice, with stitches perpendicular to the traction forces and therefore without achieving any reduction in the tension exerted on the thread.

Sutures, therefore, continue to fail, either due to the thread breaking or to tissue tearing, in both cases due to their inability to withstand the tension exerted. For this reason, and in view of our finding, after evaluating the physical formulations of many possible suture structures, that the greater the angle of the thread path with respect to the direction of the force exerted on it, the less tension will need to be withstood, we have designed a new type of suture. The design we propose obtained the best results in the theoretical model, and features four 45º angles on each part of the surfaces to be joined (forming eight angles in all), which rest upon a triple-column central structure.

The relatively poor performance of continuous sutures was highlighted both in our theoretical study and under experimental conditions. It is important to note that the tension generated in continuous sutures includes a lateral force at each entry/exit point which is equivalent to the force on the cosine of the angle, and that this force can provoke lateral tears, destabilising the suture even when relatively little force is applied. In the design we propose, however, although the lateral angles are also subjected to tension, the vertical force applied is only half that received by the continuous suture. Because it is multiplied by the cosine of the angle, the resulting lateral force on each entry/exit point is only half that exerted on the continuous suture. Therefore, the new suture design is twice as resistant to lateral tearing.

As observed in our earlier study on this question, the weakest version of the new suture design was that obtained when the central stitches were passed through the same entry/exit point, in which case the tension exerted was much greater. This variable was considered in our preliminary tests, which showed that even this weaker version of the new design withstood 30% more force than the continuous suture or the simple interrupted suture methods before reaching the breaking point.

Finally, we considered a suture design with separate central points. This reduced the tension on each of the entry/exit points, which meant that the suture was almost three times stronger than continuous sutures and almost twice as strong as the interrupted suture method.

In view of these considerations, and for maximum suture stability, for Phase 3 of our project (the clinical study) these central points will be sited approximately 1-1.5 cm apart, producing the suture model shown in Figure 5. It is also interesting to note that with this design each point of the double-diabolo suture can unite 6 cm of tissue, which makes it very useful in practical terms; for example, a 24 cm laparotomy could be closed with just four sutures, making the procedure much less laborious and time consuming.

In this context of clinical application, it is also important to note that the surgical closure of laparotomies is associated with a failure rate of approximately 15% and a corresponding occurrence of incisional hernias[4,14,22]. This incidence of incisional hernias has remained constant over the last decade despite numerous technical and material modifications[23]. While the early failure of laparotomy closure and the

development of an evisceration is almost always attributed to technical errors, the development of an incisional hernia is assumed to be of multifactorial origin[24,25].

Deerenberg *et al*[26] reported that the annual cost of incisional hernia repair in the United States was $3.2 billion. Therefore, if the results of our work are confirmed in the clinical study (Phase 3) and if the breaking point of our suture is proven to be almost twice that of conventional sutures, it would be possible to reduce the incidence of laparotomic hernias by half, producing an annual financial saving, in the United States alone, of $1.6 billion.

## CONCLUSION

In summary, the results obtained in this study experimentally confirm our hypothesis that the double diabolo suture design results in less tension being exerted on the thread and on the entry/exit points (for a given separation force) than is the case with conventional sutures. In consequence, the double diabolo design has a breaking point that is almost twice that of the simple interrupted suture and more than twice that of the continuous suture. As observed above, *in vivo* results have still to be obtained. For this purpose, Phase III of our study is now in progress, in which we will evaluate the results of laparotomy closure comparing the performance of the double diabolo suture with that of the two traditional techniques. We believe that if the theoretical and experimental findings are reproduced in the clinical phase, the technique we describe should enter into standard practice, especially in cases in which the suture must withstand significant tension, as is the case for example with laparotomy closure, thoracotomy closure, diaphragm suture and the closure of a hernial orifice.

## ARTICLE HIGHLIGHTS

### *Research background*

The basic suture technique has not changed significantly since ancient times.

### *Research motivation*

To find a suture more resistant than the usual ones.

### *Research objectives*

To compare the two types of suture used in standard practice with the proposed new design, the double diabolo.

### *Research methods*

The authors manufactured a device to apply a progressively-increasing separation force to the suture surfaces, and to measure the tension exerted until the breaking point is reached.

### *Research results*

With the "double diabolo" suture, in comparison with conventional sutures, greater force must be applied to reach the breaking point.

### *Research conclusions*

The results obtained in this study experimentally confirm our hypothesis that the double diabolo design has a breaking point that is almost twice that of the simple interrupted suture and more than twice that of the continuous suture.

### *Research perspectives*

Phase III of our study is now in progress, in which we will evaluate the results of laparotomy closure comparing the performance of the double diabolo suture with that of the two traditional techniques.

## REFERENCES

1 **Matalon S**, Kozlovsky A, Kfir A, Levartovsky S, Mazor Y, Slutzky H. The effect of commonly used

sutures on inflammation inducing pathogens - an *in vitro* study. *J Craniomaxillofac Surg* 2013; **41**: 593-597 [PMID: 23290271 DOI: 10.1016/j.jcms.2012.11.033]
2 **Ethicon Wound Closure Manual**. Somerville, NJ: Johnson & Johnson. February 2, 2019. Available from: https://www.ethicon.com/
3 **Kirkup J**. The Evolution of Surgical Instruments: An Illustrated History from Ancient Time to the Twentieth Century. Publisher: Novato, Calif.: Historyofscience.com. 2006: 449-465. Available from: https://librarysearch.ohsu.edu/permalink/f/t8l2fp/CP71132283300001451
4 **Högström H**, Haglund U, Zederfeldt B. Suture technique and early breaking strength of intestinal anastomoses and laparotomy wounds. *Acta Chir Scand* 1985; **151**: 441-443 [PMID: 3901638]
5 **Högström H**, Haglund U, Zederfeldt B. Tension leads to increased neutrophil accumulation and decreased laparotomy wound strength. *Surgery* 1990; **107**: 215-219 [PMID: 2154055]
6 **Israelsson LA**. The surgeon as a risk factor for complications of midline incisions. *Eur J Surg* 1998; **164**: 353-359 [PMID: 9667469 DOI: 10.1080/110241598750004382]
7 **Trimbos JB**, van Rooij J. Amount of suture material needed for continuous or interrupted wound closure: an experimental study. *Eur J Surg* 1993; **159**: 141-143 [PMID: 8102887]
8 **Pérez Lara FJ**, Zubizarreta Jimenez R, Hernández González JM, Prieto-Puga T, Moya Donoso F. A novel suturing technique, based on physical principles. *World J Adv Res Rev* 2020; **08**: 080-090 [DOI: 10.30574/wjarr.2020.8.3.0462]
9 **Fretz P**, Fischer R. Possible phycomycetes granuloma in the larynx of a horse. *Can Vet J* 1976; **17**: 293-297 [PMID: 974984 DOI: 10.1001/archsurg.133.9.957]
10 **Bloemen A**, van Dooren P, Huizinga BF, Hoofwijk AG. Randomized clinical trial comparing polypropylene or polydioxanone for midline abdominal wall closure. *Br J Surg* 2011; **98**: 633-639 [PMID: 21254041 DOI: 10.1002/bjs.7398]
11 **Fink C**, Baumann P, Wente MN, Knebel P, Bruckner T, Ulrich A, Werner J, Büchler MW, Diener MK. Incisional hernia rate 3 years after midline laparotomy. *Br J Surg* 2014; **101**: 51-54 [PMID: 24281948 DOI: 10.1002/bjs.9364]
12 **Sen S**, Garg A, Gealy D, McKinley S, Jen Y, Goldberg K. Automating multi-throw multilateral surgical suturing with a mechanical needle guide and sequential convex optim.ization. In IEEE International Conference on Robotics and Automation (ICRA), 2016. Available from: https://goldberg.berkeley.edu/pubs/icra2016-final-suturing.pdf
13 **Wieskötter B**, Herbort M, Langer M, Raschke MJ, Wähnert D. The impact of different peripheral suture techniques on the biomechanical stability in flexor tendon repair. *Arch Orthop Trauma Surg* 2018; **138**: 139-145 [PMID: 29134318 DOI: 10.1007/s00402-017-2836-2]
14 **Israelsson LA**, Jonsson T. Overweight and healing of midline incisions: the importance of suture technique. *Eur J Surg* 1997; **163**: 175-180 [PMID: 9085058]
15 **Israelsson LA**, Jonsson T. Suture length to wound length ratio and healing of midline laparotomy incisions. *Br J Surg* 1993; **80**: 1284-1286 [PMID: 8242299 DOI: 10.1002/bjs.1800801020]
16 **Millbourn D**, Cengiz Y, Israelsson LA. Effect of stitch length on wound complications after closure of midline incisions: a randomized controlled trial. *Arch Surg* 2009; **144**: 1056-1059 [PMID: 19917943 DOI: 10.1001/archsurg.2009.189]
17 **Cengiz Y**, Blomquist P, Israelsson LA. Small tissue bites and wound strength: an experimental study. *Arch Surg* 2001; **136**: 272-275 [PMID: 11231844 DOI: 10.1001/archsurg.136.3.272]
18 **Henriksen NA**, Deerenberg EB, Venclauskas L, Fortelny RH, Miserez M, Muysoms FE. Meta-analysis on Materials and Techniques for Laparotomy Closure: The MATCH Review. *World J Surg* 2018; **42**: 1666-1678 [PMID: 29322212 DOI: 10.1007/s00268-017-4393-9]
19 **Kubota H**, Aoki M, Pruitt DL, Manske PR. Mechanical properties of various circumferential tendon suture techniques. *J Hand Surg Br* 1996; **21**: 474-480 [PMID: 8856537 DOI: 10.1016/s0266-7681(96)80049-0]
20 **Srivastava A**, Sood A, Joy SP, Woodcock J. Principles of physics in surgery: the laws of flow dynamics physics for surgeons - Part 1. *Indian J Surg* 2009; **71**: 182-187 [PMID: 23133151 DOI: 10.1007/s12262-009-0064-x]
21 **Srivastava A**, Sood A, Joy PS, Mandal S, Panwar R, Ravichandran S, Sarangi S, Woodcock J. Principles of physics in surgery: the laws of mechanics and vectors physics for surgeons-part 2. *Indian J Surg* 2010; **72**: 355-361 [PMID: 21966132 DOI: 10.1007/s12262-010-0155-8]
22 **Schumpelick V**, Kingsnorth AN. Closure of laparotomy. In: Schumpelick V, Kingsnorth AN, (eds). Incisional Hernia. Part V. Berlin, Springer, 1999: 231-234
23 **Israelsson LA**, Jonsson T. Closure of midline laparotomy incisions with polydioxanone and nylon: the importance of suture technique. *Br J Surg* 1994; **81**: 1606-1608 [PMID: 7827883 DOI: 10.1002/bjs.1800811114]
24 **Wadström J**, Gerdin B. Closure of the abdominal wall; how and why? *Acta Chir Scand* 1990; **156**: 75-82 [PMID: 2181798]
25 **Petersen S**, Ludwig K. Comments on the publication of Korenkov M, Paul A, Sauerland S, Neugebauer E, Arndt M, Chevrel JP, Corcione F, Fingerhut A, Flament JB, Kux M, Matzinger A, Myrvold HE, Rath AM, Simmermacher RKJ (2001) Classification and surgical treatment of incisional hernia. Langenbeck's Arch Surg 386:65-73. *Langenbecks Arch Surg* 2001; **386**: 309 [PMID: 11466574 DOI: 10.1007/s004230100237]
26 **Deerenberg EB**, Harlaar JJ, Steyerberg EW, Lont HE, van Doorn HC, Heisterkamp J, Wijnhoven BP, Schouten WR, Cense HA, Stockmann HB, Berends FJ, Dijkhuizen FPH, Dwarkasing RS, Jairam AP,

van Ramshorst GH, Kleinrensink GJ, Jeekel J, Lange JF. Small bites *vs* large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial. *Lancet* 2015; **386**: 1254-1260 [PMID: 26188742]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 1050-1062

DOI: 10.4240/wjgs.v13.i9.1050

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

# Quality of life after colorectal surgery: A prospective study of patients compared with their spouses

Gökçe Aylaz, Cihangir Akyol, Akın Fırat Kocaay, Derya Gökmen, Ayşe Burcu Yavuzarslan, Ayhan Bülent Erkek, Mehmet Ayhan Kuzu

**ORCID number:** Gökçe Aylaz 0000-0002-9349-8359; Cihangir Akyol 0000-0002-3941-5268; Akın Fırat Kocaay 0000-0002-6985-910X; Derya Gökmen 0000-0001-6266-3035; Ayşe Burcu Yavuzarslan 0000-0001-7880-7910; Ayhan Bülent Erkek 0000-0002-9041-341X; Mehmet Ayhan Kuzu 0000-0003-1561-9060.

**Author contributions:** Aylaz G, Akyol C and Kuzu MA contributed to the study conception and design; Aylaz G, Kocaay AF, Yavuzarslan AB and Erkek AB contributed to the literature search and data extraction; Aylaz G, Gökmen D and Kuzu MA contributed to the acquisition, management, analysis and interpretation of data; Aylaz G, Kocaay AF and Akyol C drafted the manuscript; Kuzu MA and Akyol C critically revised the manuscript.

**Institutional review board statement:** The study was approved by the Ethics Committee of the Faculty of Medicine, Ankara University (21 September 2009, approval number: 06-82).

**Clinical trial registration statement:** This study is registered at ClinicalTrials.gov. The registration identification number is NCT04744792.

**Gökçe Aylaz,** Department of Surgery, Sisli Memorial Hospital, Istanbul 34385, Turkey

**Cihangir Akyol, Akın Fırat Kocaay, Ayşe Burcu Yavuzarslan, Ayhan Bülent Erkek, Mehmet Ayhan Kuzu,** Department of Surgery, Ankara University School of Medicine, Ankara 06100, Turkey

**Derya Gökmen,** Department of Biostatistics, Ankara University School of Medicine, Ankara 06100, Turkey

**Corresponding author:** Cihangir Akyol, FASCRS, FEBS, MD, Professor, Department of Surgery, Divison of Colorectal Surgery, Ankara University School of Medicine, Ankara 06100, Turkey. cihangirakyol@gmail.com

## Abstract

### *BACKGROUND*

Although radical surgery for colorectal cancer improves the oncological outcomes, a significant portion of patients suffer from alterations in their quality of life (QoL). There are many studies investigating the QoL of patients who have colorectal cancer but none of these focus on the QoL of spouses.

### *AIM*

To compare the QoL of patients after colorectal surgery to the QoL of spouses.

### *METHODS*

This prospective study consisted of patients who were married and who underwent surgery at the University of Ankara, Department of Surgery between March 2006 and November 2010. Patients' spouses were also enrolled. The study was approved by the Ethics Committee of the Faculty of Medicine, Ankara University, and all patients provided written informed consent. The study included patients who underwent curative surgery for colorectal carcinoma [$n$ = 100; abdominoperineal excision ($n$ = 33), low anterior resection ($n$ = 33), left hemicolectomy ($n$ = 34)] and their spouses ($n$ = 100). The patients and spouses completed the Medical Outcome Study 36-item Short Form Survey (SF-36) and the World Health Organization Disability Assessment Schedule II (WHODAS-II) preoperatively and at postoperative months 15 to 18.

### *RESULTS*

During this 4.5-year study period, 273 patients with sigmoid or rectal cancer were

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** None of the authors have a conflict of interest.

**Data sharing statement:** No additional data are available.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.



**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Turkey

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

**Received:** March 25, 2021
**Peer-review started:** March 25, 2021
**First decision:** June 14, 2021
**Revised:** June 30, 2021
**Accepted:** July 29, 2021
**Article in press:** July 29, 2021
**Published online:** September 27, 2021

admitted to the hospital. Of these patients, 119 were eligible and willing to participate. Eleven patients had either systemic or locally inoperable disease, three patients had a severe surgical complication, and five patients were lost to follow-up. Therefore, a total of 100 patients completed the follow-up period. There was a statistically significant positive correlation between the disability scores of patients and the scores of their spouses for some of the WHODAS-II subscales, such as "self-care," "life activities," and "participation in society," as well as for the total WHODAS-II score. There was also a positive correlation between the QoL of patients and the QoL of their spouses in most of the SF-36 subscales. Statistically significant correlations were observed for the "bodily pain," "general health," "vitality," "social function," "emotion," "mental health," and mental component summary score subscales of the SF-36. When gender differences were evaluated, the QoL of male patients' spouses changed more when compared with female patients' spouses for all of the WHODAS-II subscales. Colorectal cancer surgery has a significant effect on the QoL of both patients and their spouses, these effects were more significant among male patients' spouses.

*CONCLUSION*

Preoperative counseling regarding potential problems should therefore collectively address patient and their spouse as a couple rather than the patient alone, particularly for patients undergoing low anterior resection and abdominoperineal resection procedures.

**Key Words:** Quality of life; Colorectal surgery; Patients' spouses; Prospective study; Male spouses; Preoperative counseling



**Core Tip:** Although radical surgery for colorectal cancer improves the oncological outcomes, a significant portion of patients suffer from alterations in their quality of life (QoL). There are many studies investigating the QoL of patients who have colorectal cancer but none of these focus on the QoL of spouses. To the best of our knowledge, this is the first prospective and comparative study investigating the QoL following colorectal cancer surgery in both the patients and their spouses during the same time frame. The results of this study showed that patients as well as their spouses QoL was affected following colorectal cancer surgery.

**Citation:** Aylaz G, Akyol C, Kocaay AF, Gökmen D, Yavuzarslan AB, Erkek AB, Kuzu MA. Quality of life after colorectal surgery: A prospective study of patients compared with their spouses. *World J Gastrointest Surg* 2021; 13(9): 1050-1062
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1050.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1050

## INTRODUCTION

There is no doubt that radical colorectal surgery improves the oncological outcomes of patients with cancer. However, the literature has clearly documented that social, physical, sexual, and psychological aspects of life, as well as religious worship, are severely impaired after this treatment[1-5]. A significant portion of patients suffer from alterations in their quality of life (QoL), particularly after surgery on distal rectal tumors. Patients who require a stoma or who have low anterior resection (LAR) syndrome may face difficulty adapting to their new anatomy, managing the stoma, defecating, and continuing normal activities in their sociocultural environment. Patients pay an immense price following both sphincter-saving and sphincter-sacrificing surgery. Moreover, these psychological and social difficulties, as well as sexual dysfunction, may affect patients' relationships with their spouses, who are generally the primary informal caregivers for patients with cancer. In addition to caring for their sick partners, the spouses also have to deal with their own anxiety,

**P-Reviewer:** Nishizawa T, Zyoud SH
**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Li JH

fatigue, and depression. Previous studies on patients with breast and prostate cancer have also revealed such changes in spouses' QoL7[6-8]. Therefore, both patients' and spouses' QoL should be taken into consideration following surgery for colorectal cancer.

Although there are many studies investigating the QoL of patients who have colorectal cancer[1-5,9] none of these focus on the QoL of spouses. Therefore, we hypothesized that radical rectal cancer surgery affects not only patients' physical, social, and psychological wellbeing but also the QoL of their spouses. The aim of this prospective comparative study was to investigate the QoL of patients and their spouses. To the best of our knowledge, this is the first prospective comparative study to investigate QoL following colorectal cancer surgery in both patients and their spouses during the same time frame.

## MATERIALS AND METHODS

### Participant selection

This prospective study consisted of patients who were married and who underwent surgery at the University of Ankara, Department of Surgery between March 2006 and November 2010. Patients' spouses were also enrolled. The study was approved by the Ethics Committee of the Faculty of Medicine, Ankara University, and all patients provided written informed consent.

### Inclusion criteria

Patient demographics, surgical details, follow-up data, and disease-related data were recorded. To be eligible, patients had to meet the following inclusion criteria: (1) Curative surgery for colorectal adenocarcinoma; (2) Living with a spouse; (3) No other primary malignant tumors; (4) No additional complicating or disabling disease that necessitated nursing assistance (*e.g.*, mental illness); (5) No chemo-radiotherapy within 8 wk prior to the interview; (6) No admittance to a hospital except for stoma closure during the study period (no interview during stoma closure); (7) No major morbidity ( *e.g.*, anastomotic leakage, abdominal sepsis, stoma-related problems, and intensive care unit transfer); (8) No evidence of disease recurrence or metastasis, which was determined at the time of follow-up interviews; (9) Aged over 18 years; and (10) Muslim faith.

### Groups

Patients and their spouses were grouped by the type of surgery they received: Abdominoperineal resection (APR), sphincter-saving resection with an anastomosis within 6 cm of the anal verge on rigid sigmoidoscopy (LAR), or anterior resection with anastomosis at or above 7 cm, including sigmoid colectomy (AR).

### Scales and questionnaires

**Medical outcomes (36-item short form health survey):** The 36-item short form health survey (SF-36) was used as a measure of health-related QoL because it is an internationally recognized global measure[4,10]. It comprises 36 items that measure perceived health on eight scales (*i.e.*, physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health) with higher scores (range 0-100) reflecting better perceived health. Additionally, two summary scores can be obtained: The physical component summary score (PCS) and the mental component summary score (MCS). In addition, this tool has been validated in Turkish patients with chronic illnesses, with an internal consistency of 0.92 and a test-retest reliability of 0.94, which are consistent with published work[11]. Higher SF-36 scores indicate better health-related QoL.

### The World Health Organization disability assessment schedule II

The World Health Organization disability assessment schedule II (WHODAS-II) is an instrument developed by the World Health Organization to assess behavioral limitations and restrictions regarding participation in specific activity domains experienced by an individual independent of their medical diagnosis. The conceptual frame of reference of this instrument is the International Classification of Functioning, Disability, and Health (ICF). Specifically, the instrument is a 36-item, generic, multidimensional questionnaire designed to evaluate the functioning of the individual in six activity domains (*i.e.*, understanding and communicating, getting around, self-care,

getting along with people, life activities, and participation in society)[5]. This questionnaire has been validated in Turkish patients with chronic illnesses, with an internal consistency of 0.92 and a test–retest reliability of 0.94, which are consistent with published work[6,7]. A higher WHODAS-II score reflects a higher level of disability.

### Ankara university life standards questionnaire

To identify how surgery affected the life standards of patients and their spouses, a questionnaire was designed by the Department of Public Health, General Surgery and Psychology, Ankara University (Life Standards Questionnaire)[12,13]. It covers the following areas: (1) Employment, including changes in work capability and changes in household chores in daily practice for unemployed women; (2) Social activity; (3) Colostomy care (if applicable); and (4) Religious worship. Religious worship in Muslims was emphasized because their belief structure is particularly affected by the presence of both a stoma and fecal incontinence[13].

### Counseling

Surgical details, possible complications, and temporary or permanent stoma formation were explained preoperatively by the surgeon, and ostomy education was given by the stomatherapist. Religious education and counseling were also performed. Patients had direct access to doctors, the stomatherapist, appliance suppliers, and a religious leader (Imam) at the hospital during the study period.

### Interviews

Patients and spouses were interviewed at the Department of Surgery of Ibni Sina Hospital. The coauthors of the study were trained to administer the questionnaires in a standard fashion and practiced by using the questionnaires on healthy volunteers before the study began. Patients and spouses were interviewed in a private room by a person of the same gender. The same interviewer was used in the preoperative and postoperative period for each patient and spouse, but the interviewer was not blinded to the type of surgery that the patient had undergone. Patients were first asked to complete a demographic questionnaire designed to determine their age, gender, marital status, educational level, income level, and preoperative employment. The SF-36, WHODAS-II, and Ankara University Life Standards Questionnaire were administered together and consisted of a total of 92 items, which took approximately 35 min to 45 min to complete. Both patients and spouses completed the SF-36, WHODAS-II, and Ankara University Life Standards Questionnaire preoperatively and at postoperative months 15 to 18.

### Statistical analysis

Statistical analyses were performed with SPSS for Windows 11.5 (SPSS Inc., Chicago, IL, United States). Descriptive statistics were given as the mean ± SD [median (minimum-maximum)] for metric variables and frequency (percent) for categorical variables. Data from the questionnaires are expressed as the percent change [(postoperative months 15 to 18 – preoperative)/preoperative × 100]. To compare two (or more than two) independent groups in terms of metric variables, the Mann-Whitney *U* test (or Kruskal-Wallis analysis of variance) was used. When the Kruskal-Wallis test revealed a significant difference between the groups, a multiple comparison test was used to determine which groups differed from each other. Bonferroni correction was used for multiple testing. The Wilcoxon signed-rank test was used to evaluate within-group differences between ordinal variables. For categorical variables, independent groups were compared with the chi-squared test, and dependent groups were evaluated using the McNemar test. The degree of association between ordinal variables was evaluated by Spearman's correlation coefficient. A $P$ value of $< 0.05$ was considered statistically significant.

## RESULTS

During this 4.5-year study period, 273 patients with sigmoid or rectal cancer were admitted to the hospital. Of these patients, 119 were eligible and willing to participate. Eleven patients had either systemic or locally inoperable disease, three patients had a severe surgical complication, and five patients were lost to follow-up. Therefore, a total of 100 patients completed the follow-up period. The sociodemographic features of patients and their spouses are shown in Table 1. Correlation of the percentage

**Table 1 Sociodemographic features of patients and their spouses (*n* = 100)**

| Sociodemographic features | Number of patients (male/female) | Number of spouses (male/female) |
|---|---|---|
| Type of surgery | | |
| APR (male/female) | 33 (24/9) | 33 (9/24) |
| LAR (male/female) | 33 (17/16) | 33 (16/17) |
| AR (male/female) | 34 (15/19) | 34 (19/15) |
| Age (yr) | 57.4 ± 12.3 [57 (28-83)] | 56.7 ± 12.1 [58 (26-85)] |
| Gender (male/female) | 56/44 | 44/56 |
| Educational level | | |
| Illiterate | 6 | 12 |
| Primary education | 51 | 41 |
| High school | 26 | 32 |
| College | 17 | 15 |
| Preoperative employment | | |
| Government employee | 7 | 11 |
| Self-employed | 20 | 17 |
| Retired | 37 | 25 |
| Unemployed | 5 | 3 |
| Housewife | 31 | 44 |

Cells represent frequency except for age, mean ± SD [median (minimum-maximum)]. APR: Abdominoperineal resection; LAR: Low anterior resection; AR: Anterior resection.

change in quality of life scores between patients and their spouses are shown in Table 2. The surgery groups were comparable with respect to age, gender, preoperative employment status, tumor-node-metastasis stage, and length of postoperative follow-up.

For all the subscales of the WHODAS-II, there was an increase in postoperative disability across all surgery types. This increase in disability was minimal in patients who underwent AR compared with patients who underwent LAR or APR: The LAR group had a significantly greater increase in disability scores for the "getting around" and "life activities" subscales, whereas the AR group had significantly less change in disability scores for the "getting along with people" and "participation in society" subscales and the WHODAS-II total score compared with the other two groups. Similar changes were found for the disability levels of patients' spouses. The "life activities" and WHODAS-II total scores were the least changed in the AR group, whereas the increase in disability level for the "participation in society" subscale was highest in the LAR group (Table 3).

In all the subscales of the SF-36, there was a decrease in the QoL of patients with all surgery types from the preoperative to postoperative period. However, the change in patients' SF-36 scores was significantly lower in the AR group than in the LAR and APR groups. The most significant decrease in QoL scores was detected in the LAR group. Changes in spousal SF-36 scores echoed patients' scores (*i.e.*, they were significantly less changed in the LAR group than in the other groups for the "vitality," "social function," "emotional role," "mental health," "PCS," and "MCS" subscales) (Table 3).

### *Comparison of the disability and QoL changes in patients and their spouses by gender*

There were increases in the postoperative disability level for all subscales of the WHODAS-II in both genders, but these increases were not statistically significant, except for the "life activities" subscale, which showed a significant increase in female patients and male patients' spouses compared with males, and the "participation in society" subscale, which showed a significant increase in female patients' spouses

**Table 2 Correlation of the percentage change in quality of life scores between patients and their spouses**

| Scale | Subscale | Spearman's correlation coefficient |
|---|---|---|
| WHODAS-II | Understanding and communication | 0.183 |
| | Getting around | 0.037 |
| | Self-care | 0.349[b] |
| | Getting along with people | 0.189 |
| | Life activities | 0.323[b] |
| | Participation in society | 0.312[b] |
| | Total | 0.636[c] |
| SF-36 | Physical function | 0.071 |
| | Role physical | -0.170 |
| | Bodily pain | 0.246[a] |
| | General health | 0.233[a] |
| | PCS | -0.035 |
| | Vitality | 0.271[b] |
| | Social function | 0.487[c] |
| | Role emotional | 0.483[c] |
| | Mental health | 0.359[c] |
| | MCS | 0.536[c] |

Cells represent Spearman's correlation coefficients.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
WHODAS-II: World Health Organization Disability Assessment Schedule II; SF-36: 36-item Short Form Survey; PCS: Physical component score; MCS: Mental component score.

(Table 4).

There was a decrease in QoL scores between the preoperative and postoperative measurements for both genders as assessed by the subscales of the SF-36. Although these decreases tended to be greater in female patients, they were not significantly different when compared with the decreases observed among male patients. Regarding the spouses' QoL, similar changes were found in both genders (Table 4).

When the data were analyzed with respect to gender and type of surgery, no significant difference was detected in most of the WHODAS-II and SF-36 scores, with the exception of disability level, which showed higher scores on the "life activities" subscale for the female LAR patient group and on the "understanding and communicating" subscale for the female LAR patients' spouses group.

### *Ankara university life standards questionnaire*

A comparison of patients' and spouses' feelings regarding their own general health and their QoL preoperatively and 18 mo postoperatively revealed significant decreases in self-rated health and QoL following surgery ($P < 0.001$). This negative effect was observed across all types of surgery, but the most significant decrease was found in the LAR group when compared with the AR group (Table 5). However, there were no gender differences in either the patient group or spouse group for these measures (data not shown).

The time it takes to return to former activities of daily living and work capabilities was increased following APR and LAR, but these increases were not statistically significant (Table 5). Furthermore, no gender differences were detected (data not shown). Patients who underwent either LAR or APR spent more time together with their spouse and more time at home following surgery than patients in the AR group (Table 5). Moreover, male patients' spouses spent significantly more time with their husbands ($P = 0.009$; while 71.4% of male patients' spouses reported that they spent more time with their husbands, only 40.9% of female patients' spouses said the same)

**Table 3 Comparison of quality of life changes in patients and their spouses according to type of surgery**

| Scale | Subscale | Patient | | | | Spouse | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | APR | LAR | AR | *P* value | APR | LAR | AR | *P* value |
| WHODAS-II | Understanding and communication | 16 ± 29 [0 (-33; 100)] | 1 ± 27 [0 (-100; 50)] | 7 ± 19 [0 (0; 86)] | 0.103 | 14 ± 30 [0 (0; 100)] | 15 ± 53 [0 (-100; 151)] | 2 ± 7 [0 (0; 25)] | 0.241 |
| | Getting around | 24 ± 54 [0 (-100; 200)] | 77 ± 133 [46 (-100; 500)] | 10 ± 26 [0 (0; 100)] | 0.001[1] | 8 ± 27 [0 (-33; 100)] | 4 ± 26 [0 (-80; 100)] | -3 ± 17 [0 (-100; 11)] | 0.467 |
| | Self-care | 4 ± 19 [0 (0; 100)] | 1 ± 34 [0 (-100; 133)] | 2 ± 13 [0 (0; 75)] | 0.830 | 0 | -3 ± 18 [0 (-100; 0)] | 2 ± 9 [0 (0; 50)] | 0.226 |
| | Getting along with people | 107 ± 173 [50 (-100; 800)] | 64 ± 70 [88 (-33; 200)] | 3 ± 23 [0 (-100; 50)] | <0.001[2] | 25 ± 47 [0 (-100; 100)] | 53 ± 67 [58 (-80; 200)] | 15 ± 30 [0 (0; 150)] | 0.099 |
| | Life activities | 34 ± 86 [0 (-33; 400)] | 54 ± 86 [0 (-100; 300)] | 11 ± 71 [0 (-100; 300)] | 0.085 | 92 ± 128 [38 (0; 400)] | 128 ± 210 [0 (-100; 800)] | 10 ± 38 [0 (-100; 100)] | 0.013[2] |
| | Participation in society | 84 ± 66 [71 (-45; 300)] | 97 ± 123 [71 (-100; 550)] | 59 ± 70 [47 (-58; 300)] | 0.036[2] | 50 ± 52 [43 (-100; 200)] | 63 ± 185 [13 (-100; 799)] | 38 ± 36 [31 (-50; 114)] | 0.013[1] |
| | Total | 83 ± 61 [57 (-41; 218)] | 112 ± 150 [66 (-100; 635)] | 55 ± 76 [29 (-57; 301)] | 0.012[2] | 69 ± 67 [67 (-100; 349)] | 79 ± 89 [59 (-95; 301)] | 34 ± 40 [27 (-33; 200)] | 0.002[2] |
| SF-36 | Physical function | -6 ± 10 [-4 (-44; 12)] | -8 ± 7 [-8 (-30; 3)] | 0 ± 4 [0 (-11; 15)] | < 0.001[3] | 0 ± 1 [0 (-7; 0)] | 2 ± 12 [0 (-11; 65)] | -1 ± 4 [0 (-24; 0)] | 0.936 |
| | Physical role | -10 ± 20 [0 (-50; 14)] | -24 ± 32 [-29 (-50; 101)] | 9 ± 29 [0 (0; 101)] | < 0.001[3] | 0 ± 14 [0 (-50; 61)] | 3 ± 13 [0 (-25; 33)] | 1 ± 20 [0 (-50; 101)] | 0.389 |
| | Bodily pain | -16 ± 12 [-18 (-48; 12)] | -20 ± 15 [-19 (-53; 35)] | -8 ± 12 [-10 (-26; 24)] | < 0.001[3] | 0 ± 9 [0 (-19; 24)] | -1 ± 15 [0 (-27; 68)] | -2 ± 7 [0 (-31; 11)] | 0.690 |
| | General health | -17 ± 12 [-18 (-50; 0)] | -20 ± 12 [-22 (-48; 15)] | -10 ± 8 [-13 (-21; 16)] | 0.001[3] | -3 ± 4 [-2 (-18; 8)] | -5 ± 6 [-5 (-22; 7)] | -3 ± 5 [0 (-16; 0)] | 0.077 |
| | PCS | -10 ± 11 [-8 (-45; 13)] | -15 ± 11 [-19 (-35; 11)] | -3 ± 8 [-5 (-18; 32)] | < 0.001[3] | 2 ± 7 [0 (-12; 18)] | 8 ± 7 [9 (-4; 19)] | -0 ± 9 [0 (-30; 27)] | < 0.001[1] |
| | Vitality | -7 ± 10 [-5 (-43; 5)] | -8 ± 13 [-10 (-19; 54)] | -4 ± 8 [-4 (-18; 28)] | 0.019[1] | -4 ± 7 [-4 (-23; 12)] | -6 ± 16 [-5 (-21; 70)] | -3 ± 5 [0 (-16; 5)] | 0.029[4] |
| | Social function | -18 ± 14 [-19 (-37; 16)] | -22 ± 23 [-24 (-46; 61)] | -10 ± 17 [-13 (-47; 40)] | 0.003[3] | -11 ± 13 [-12 (-38; 0)] | -22 ± 24 [-24 (-59; 61)] | -9 ± 11 [-12 (-40; 13)] | < 0.001[1] |
| | Emotional role | -18 ± 38 [0 (-57; 133)] | -39 ± 39 [-57 (-57; 133)] | 11 ± 39 [0 (-31; 133)] | < 0.001[3] | -3 ± 36 [0 (-57; 133)] | -30 ± 39 [-47 (-57; 133)] | 3 ± 25 [0 (-47; 133)] | < 0.001[1] |
| | Mental health | -9 ± 10 -6 (-33; 19)] | -12 ± 21 [-11 (-33; 91)] | -6 ± 9 [-5 (-31; 16)] | 0.002[1] | -7 ± 11 [0 (-31; 13)] | -8 ± 25 [-10 (-36; 115)] | -3 ± 8 [0 (-31; 8)] | 0.007[1] |
| | MCS | -16 ± 19 [-14 (-51; 44)] | -24 ± 30 [-32 (-45; 123)] | -4 ± 12 [-5 (-23; 25)] | < 0.001[3] | -11 ± 18 [-5 (-55; 28)] | -29 ± 34 [-38 (-62; 124)] | -4 ± 10 [-3 (-33; 35)] | < 0.001[1] |

Cells represent the mean ± SD [median (minimum-maximum)].
[1]Low anterior resection (LAR) is different.
[2]Anterior resection (AR) is different from others.
[3]All are different.
[4]LAR is different from AR.
PCS: Physical component score; MCS: Mental component score; WHODAS-II: World Health Organization Disability Assessment Schedule II; SF-36: 36-item Short Form Survey; APR: Abdominoperineal resection; LAR: Low anterior resection; AR: Anterior resection.

and spent more time at home ($P < 0.001$) than female patients' spouses (the proportion of spouses who spent more time at home was 82.1% and 43.2% for male patients' spouses and female patients' spouses, respectively). Alterations to the patients' sex

**Table 4 Comparison of the changes in patients' and spouses' quality of life according to gender**

| | | Patient | | | Spouse | | |
|---|---|---|---|---|---|---|---|
| **Scale** | **Subscale** | **Male** | **Female** | ***P* value** | **Male** | **Female** | ***P* value** |
| WHODAS-II | Understanding andcommunication | 8 ± 28 [0 (-100; 100)] | 9 ± 24 [0 (-27; 86)] | 0.829 | 6 ± 30 [0 (-100; 100)] | 14 ± 37 [0 (-100; 150)] | 0.127 |
| | Getting around | 43 ± 103 [0 (-100; 500)] | 27 ± 57 [0 (-100; 300)] | 0.900 | 5 ± 29 [0 (-100; 100)] | 2 ± 20 [0 (-80; 100)] | 0.247 |
| | Self-care | 5 ± 24 [0 (0; 133)] | -1 ± 20 [0 (-100; 75)] | 0.343 | -1 ± 17 [0 (-100; 50) ] | 0 ± 0 [0 (0; 0)] | 1.000 |
| | Getting along withpeople | 69 ± 138 [25 (-100; 800)] | 38 ± 66 [0 (-100; 200)] | 0.317 | 37 ± 58 [17 (0; 200)] | 25 ± 47 [0 (-100; 100)] | 0.322 |
| | Life activities | 8 ± 47 [0 (-100; 150)] | 59 ± 104 [0 (-100; 400)] | *0.008* | 39 ± 96 [0 (-100; 350)] | 101 ± 174 [0 (-100; 800)] | *0.046* |
| | Participation insociety | 72 ± 66 [69 (-100; 240)] | 91 ± 112 [60 (-50; 550)] | 0.593 | 77 ± 156 [37 (-17; 799)] | 29 ± 51 [20 (-100; 200)] | *0.044* |
| | Total | 74 ± 85 [58 (-100; 400)] | 92 ± 123 [44 (-12; 635)] | 0.500 | 72 ± 74 [50 (-25; 301)] | 51 ± 66 [41 (-100; 349)] | 0.453 |
| SF-36 | Physical function | -4 ± 7 [-4 (-24; 15)] | -5 ± 9 [0 (-44; 3)] | 0.664 | -1 ± 4 [0 (-24; 7)] | 1 ± 9 [0 (-11; 65)] | 0.237 |
| | Physical role | -7 ± 34 [0 (-50; 101)] | -10 ± 26 [0 (-50; 101)] | 0.833 | 0 ± 13 [0 (-50; 33)] | 1 ± 19 [0 (-50; 101)] | 0.894 |
| | Bodily pain | -14 ± 15 [-18 (-40; 35)] | -15 ± 13 [-11 (-53; 11)] | 0.842 | -3 ± 9 [0 (-31; 22)] | 0 ± 12 [0 (-27; 68)] | 0.456 |
| | General health | -15 ± 12 [-14 (-36; 16)] | -16 ± 11 [-14 (-50; 0)] | 0.655 | -3 ± 5 [-0 (-22; 7)] | -4 ± 5 [0 (-18; 8)] | 0.766 |
| | PCS | -8 ± 11 [-6 (-27; 32)] | -11 ± 11 [-8 (-45; 7)] | 0.465 | 3 ± 9 [1 (-30; 18)] | 3 ± 8 [1 (-15; 27)] | 0.911 |
| | Vitality | -6 ± 11 [-7 (-22; 54)] | -7 ± 8 [-4 (-43; 5)] | 0.414 | -5 ± 7 [-4 (-21; 6)] | -4 ± 13 [-2 (-28; 70)] | 0.760 |
| | Social function | -13 ± 20 [-15 (-40; 61)] | -21 ± 16 [-19 (-47; 18)] | 0.090 | -14 ± 15 [-12 (-53; 18)] | -14 ± 19 -13 (-59; 61)] | 0.615 |
| | Emotional role | -15 ± 50 [0 (-57; 133)] | -15 ± 34 [0 (-57; 133)] | 0.447 | -14 ± 23 [0 (-57; 23)] | -7 ± 44 [0 (-57; 133)] | 0.832 |
| | Mental health | -8 ± 18 [-11 (-33; 91)] | -10 ± 10 [-7 (-33; 4)] | 0.613 | -8 ± 11 [-6 (-31; 7)] | -5 ± 19 [-5 (-36; 115)] | 0.674 |
| | MCS | -14 ± 27 [-16 (-44; 123)] | -15 ± 16 [-10 (-51; 25)] | 0.542 | -17 ± 18 [-6 (-61; 2)] | -14 ± 28 [-8 (-62; 124)] | 0.955 |

Cells represent the mean ± SD [median (minimum-maximum)] of the percentage change in score between the preoperative value and the postoperative value at 15-18 mo for each subject. WHODAS-II: World Health Organization Disability Assessment Schedule II; SF-36: 36-item Short Form Survey; PCS: Physical component score; MCS: Mental component score.

lives were significantly more common following LAR and APR than AR (Table 5). Regarding the religious worship of patients, praying and fasting activities were decreased after surgery; these decreases were significant in the LAR and APR groups compared with the AR group. There were no changes in the praying and fasting activities of spouses (Table 5). The fulfillment of religious activities decreased in male patients compared with female patients (data not shown).

## DISCUSSION

The evaluation of the consequences of diseases and treatments on patient-reported outcomes, such as QoL, has gained extensive attention[8,13-17]. In fact, the diagnosis of cancer and the associated treatment process have considerable social, physical, psychological, and sexual impacts for both patients and their spouses. Little information is available regarding spouses' QoL following colorectal cancer surgery.

**Table 5 Evaluation of the Ankara University Life Standards Questionnaire according to the type of surgery**

| | Patient | | | | Spouse | | | |
|---|---|---|---|---|---|---|---|---|
| **Questions** | **APR** | **LAR** | **AR** | ***P* value** | **APR** | **LAR** | **AR** | ***P* value** |
| General health status[1] | 0.58 ± 0.97 [1 (-2; 2)] | 0.75 ± 0.51 [1 (0; 2)] | 0.18 ± 0.72 [0 (-2; 2)] | *0.002* | 0.42 ± 0.66 [0 (0; 2)] | 0.66 ± 0.75 [1 (-1; 2)] | 0.15 ± 0.44 [0 (-1; 1)] | *0.006* |
| General quality of life[1] | 0.76 ± 0.71 [1 (-1; 2)] | 0.81 ± 0.59 [1 (0; 2)] | 0.50 ± 0.66 [0 (0; 2)] | *0.068* | 0.48 ± 0.71 [0 (-1; 2)] | 1.06 ± 0.84 [1 (0; 3)] | 0.32 ± 0.77 [0 (-2; 2)] | *0.001* |
| Time to return to old life and activity (mo)[2] | 4.17 ± 1.37 [5 (0; 5)] | 4.03 ± 1.52 [5 (0; 5)] | 3.70 ± 1.16 [4 (1; 5)] | *0.077* | 4.07 ± 1.14 [4 (0; 5)] | 3.57 ± 1.75 [4 (0; 5)] | 3 ± 1.53 [3 (0; 5)] | *0.018* |
| Amount of time spent with spouse[3] | | | | | | | | |
| Unchanged | 6 (18.2) | 10 (31.3) | 21 (61.8) | | 5 (15.2) | 5 (15.6) | 22 (64.7) | |
| Decreased | 8 (24.2) | - | 8 (23.5) | | 4 (12.1) | 1 (3.1) | 5 (14.7) | |
| Increased | 19 (57.6) | 22 (68.8) | 5 (14.7) | *< 0.001* | 24 (72.7) | 26 (81.3) | 7 (20.6) | *< 0.001* |
| Amount of time spent at home[3] | | | | | | | | |
| Unchanged | 5 (15.2) | 8 (25) | 26 (76.5) | | 4 (12.1) | 4 (12.5) | 21 (61.8) | |
| Decreased | 3 (9.1) | - | 3 (8.8) | *< 0.001* | 3 (9.1) | 1 (3.1) | 2 (5.9) | *< 0.001* |
| Increased | 25 (75.8) | 24 (75) | 5 (14.7) | | 26 (78.8%) | 27 (84.4) | 11 (32.4) | |
| Sex life[3] | | | | | | | | |
| Unchanged | 13 (39.4) | 18 (56.3) | 32 (94.1) | *< 0.001* | 20 (60.6) | 19 (59.4) | 31 (91.2) | *0.005* |
| Unavailable | 20 (60.6) | 14 (43.8) | 2 (5.9) | | 13 (39.4) | 13 (40.6) | 3 (8.8) | |
| Praying[3] | | | | | | | | |
| Unchanged | 13 (46.4) | 17 (68) | 26 (100) | *< 0.001* | 27 (96.4) | 25 (96.2) | 22 (100) | NA |
| Decreased | 15 (53.6) | 8 (32) | - | | 1 (3.6) | 1 (3.8) | - | |
| Fasting[3] | | | | | | | | |
| Unchanged | 10 (35.7) | 16 (64) | 24 (92.3) | *< 0.001* | 25 (89.3%) | 25 (96.2) | 22 (100) | NA |
| Decreased | 18 (64.3) | 79 (36) | 2 (7.7) | | 3 (10.7) | 1 (3.8) | - | |
| Purifying aims[3] | | | | | | | | |
| Unchanged | 22 (78.6) | 18 (72) | 25 (96.2) | 0.064 | 27 (96.4) | 25 (96.2) | 22 (100) | NA |
| Decreased | 6 (21.4) | 7 (28) | 1 (3.8) | | 1 (3.6) | 1 (3.8) | - | |

[1]Cells represent the mean ± SD [median (minimum-maximum)] of the percentage change in score between the preoperative value and the postoperative value at 15-18 mo- for each subject.
[2]mean ± SD [median (minimum-maximum)].
[3]Frequency (percent).
APR: Abdominoperineal resection; LAR: Low anterior resection; AR: Anterior resection.

Depending on the localization of the colorectal carcinoma, either sphincter-saving or sphincter-sacrificing radical surgery can be performed. All procedures have a significant impact on patients' QoL. The stoma itself can disrupt rectal function owing to the presence of a low anastomosis. Moreover, significant sexual and urological dysfunction has also been reported, mainly due to damage to the autonomic pelvic nerve plexus[1]. Colorectal cancer diagnosis and treatment are not isolated experiences [18]. Spouses are the most frequent providers of support to patients with colorectal cancer. Patients with cancer and their caregivers (*e.g.*, spouses) experience emotional distress, physical problems, psychological difficulties, and sexual problems related to changes in their life[19,20]. The present study aimed to evaluate the QoL following surgery for colorectal cancer, namely, AR, LAR, and APR, in both patients and their spouses during the same time frame.

The present study revealed a significant relationship between the disability levels of patients and their spouses in terms of both the total score and subscales (self-care, life

activities, and participation in society) of the WHODAS-II. There were also positive correlations between the QoL of patients and their spouses for most of the subscales (bodily pain, general health, vitality, social function, emotional role, mental health, and MCS) of the SF-36. When the evaluations were conducted separately for each surgical procedure, there was an increase in postoperative disability levels in patients for all surgery types; however, the level of disability was minimal in patients following AR when compared with patients who underwent LAR or APR. Similarly, there was a decrease in the patient QoL for all surgery types during the postoperative period as measured by all subscales of the SF-36. However, this deterioration was minimal in the AR group when compared with the LAR and APR groups.

As hypothesized, we found decreases in the QoL scores over time in the spouses of patients with colorectal cancer when measured with the SF-36, specifically in the "vitality," "social function," "emotional role," "mental health," and MCS subscales. Additionally, we found an increase in spousal disability over time for the "life activity" and "participation in society" subscales and the total score of the WHODAS-II. Similarly, Badger *et al*[21] showed that 25% of partners often suffer the same or higher levels of emotional distress compared with cancer survivors. In fact, cancer treatment, with its collateral side effects, produces physical and emotional disturbances that influence QoL. A study by Graça Pereira *et al*[3], which compared different modes of treatment (*i.e.*, surgery, surgery plus chemotherapy, or surgery followed by radiotherapy) in colorectal cancer, demonstrated that patients who received only surgery had lower levels of depression, anxiety, and traumatic stress symptoms when compared with patients who received surgery plus chemotherapy or surgery plus radiotherapy. Similar results were found for the spouses of patients undergoing these treatments.

Previous studies on changes in the QoL of spouses of patients with breast and prostate cancer have not explored gender-related differences in QoL, as doing a gender-based comparison is only meaningful in gender nonspecific cancers such as colorectal cancer[2,22,23]. In the present study, there was an increase in postoperative disability for all subscales of the WHODAS-II for both genders, but these increases were not statistically significant except for the "life activities" subscale, which showed a significant increase the score among female patients and male patients' spouses. The "participation in society" subscale also showed a significant increase among female patients' spouses.

The results of the Ankara University Life Standards Questionnaire show that patients' and spouses' perceptions of their own general health and general QoL significantly decreased following patients' surgeries. Many studies in the literature have compared patients who underwent LAR with patients who underwent APR, and the general consensus in these publications is that there exists a possibility of LAR syndrome in patients with very low-level anastomosis, which has a negative effect on QoL. In these patients, constipation, diarrhea, frequent stools, and the development of fecal incontinence is a major problem that decreases QoL[24-26]. In our study, when the types of surgery were compared, there was a distinct deterioration in the LAR group. However, there were no gender differences between the patients and spouses. We found that patients and their spouses tended to spend more time together and at home following surgery, especially in the LAR and APR groups. Interestingly, we found that male patients' spouses spent significantly more time with their husbands and spent more time at home than female patients' spouses. This situation significantly impacts the lifestyle of male patients' spouses. As mentioned previously by Cakmak *et al*[27], this may be because male patients are more willing to have their colostomy care managed by their wives. Changes in sex life were significantly more common following LAR and APR than in the AR group.

With regard to the religious attitudes of patients, the literature suggests that religion is an important factor in coping with cancer[28,29]. Shaheen Al Ahwal *et al*[28] found that religiosity is associated with fewer depressive symptoms and fewer suicidal thoughts in Muslim patients with colorectal cancer. We found that religious activities, such as praying and fasting, decreased significantly in the LAR and APR groups when compared with the AR group, whereas there were no changes in praying and fasting in spouses. This is probably because of the importance of cleanliness and the desire to be free of any fecal material, especially when praying in Islam. We also found that fulfillment of religious duties decreased more among male patients than among female patients.

Although the present study has shown valuable findings, its design is not without certain flaws. The main limitations could be counted as followed: The first concern is to include the patients who underwent AR for sigmoid colon cancer. AR is a different type of surgery compared to LAR and APR. It is already known that these patients

have better functional and sexual outcomes. Another limitation is about the exclusion criterias; patients with major morbidity were excluded from the study. Complications are an unavoidable aspect of colorectal surgery. It may be better to eveluate the effects of major complications in QoL scoring.

## CONCLUSION

Colorectal cancer surgery has a significant effect on the QoL of both patients and their spouses, with a greater impact on male patients' spouses. Preoperative counseling regarding potential problems should therefore collectively address the patient and their spouse as a couple rather than the patient alone, particularly for patients undergoing LAR and APR procedures.

## ARTICLE HIGHLIGHTS

### *Research background*

We hypothesized that colorectal cancer surgery affects not only the patient's physical, social, and psychological aspects of lifestyle, but also the quality of life (QoL) of the patient's spouse.

### *Research motivation*

Although there are many studies investigating the QoL in patients who have colorectal cancer none of these focus on the spousal QoL. To the best of our knowledge, this is the first prospective and comparative study investigating the QoL following colorectal cancer surgery in both the patients and their spouses during the same time frame.

### *Research objectives*

The aim of this prospective and comparative study was to investigate the QoL of patients and their spouses.

### *Research methods*

Patients who remained well a minimum of 5 years after curative surgery for colorectal carcinoma and their spouse's as well were included in this prospective study. Both patients ($n$: 100) and their spouses ($n$: 100) filled SF-36 (Medical Outcome Study 36-item Short Form Survey) and WHODAS-II (World Health Organization-Disability Assessment Schedule II) preoperatively (preop), and postop 15-18 mo.

### *Research results*

There were statistically significant positive correlations between the disability scores of both patients and their spouses for the "self-care", "life activities" and "participation in society" subscales of WHODAS II and the total score for WHODAS II ($P < 0.01$; for each). There were also positive correlations between the life quality of both patients and their spouses in most of the subscales of SF-36. Statistically significant correlations were found for "bodily pain", "general health", "vitality", "social function", "role emotional", "mental health" and MCS subscales of SF-36 ($P < 0.05$; for each). When the gender differences were evaluated, it was found that the QoL of female spouses changed more than male spouses for all subscales of WHODAS-II.

### *Research conclusions*

Patients as well as their spouses QoL was affected following colorectal cancer surgery. These changes detected more significantly in female spouses.

### *Research perspectives*

Randomized controlled trials are expected to be conducted to measure the effect of counseling of the patients with colorectal cancer and their spouses.

## REFERENCES

1 **Calpista A**, Lai S, Agostini A, Mancini M, Artibani W. Functional urological complications after

colo-rectal cancer surgery. *Pelviperineology* 2007; **26**: 38-40
2 **Duggleby W**, Doell H, Cooper D, Thomas R, Ghosh S. The quality of life of male spouses of women with breast cancer: hope, self-efficacy, and perceptions of guilt. *Cancer Nurs* 2014; **37**: E28-E35 [PMID: 23348665 DOI: 10.1097/NCC.0b013e31827ca807]
3 **Graça Pereira M**, Figueiredo AP, Fincham FD. Anxiety, depression, traumatic stress and quality of life in colorectal cancer after different treatments: A study with Portuguese patients and their partners. *Eur J Oncol Nurs* 2012; **16**: 227-232 [PMID: 21783416 DOI: 10.1016/j.ejon.2011.06.006]
4 **Ware JE Jr**, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-483 [PMID: 1593914]
5 **World Health Organization**. 2018 WHO disability assessment schedule II (WHODAS-II). [cited 15 March 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health/who-disability-assessment-schedule
6 **Kutlay S**, Küçükdeveci AA, Elhan AH, Oztuna D, Koç N, Tennant A. Validation of the World Health Organization disability assessment schedule II (WHODAS-II) in patients with osteoarthritis. *Rheumatol Int* 2011; **31**: 339-346 [PMID: 20020133 DOI: 10.1007/s00296-009-1306-8]
7 **Küçükdeveci AA**, Kutlay Ş, Yıldızlar D, Öztuna D, Elhan AH, Tennant A. The reliability and validity of the World Health Organization Disability Assessment Schedule (WHODAS-II) in stroke. *Disabil Rehabil* 2013; **35**: 214-220 [PMID: 22671861 DOI: 10.3109/09638288.2012.690817]
8 **Rubin GP**, Devlin HB. The quality of life with a stoma. *Br J Hosp Med* 1987; **38**: 300-303, 306 [PMID: 3315080]
9 **Pachler J**, Wille-Jørgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev* 2005; CD004323 [PMID: 15846707 DOI: 10.1002/14651858.CD004323.pub3]
10 **Brazier JE**, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305**: 160-164 [PMID: 1285753 DOI: 10.1136/bmj.305.6846.160]
11 **Pinar R**. Quality of life in diabetic patients, Doctoral Dissertation. Istanbul, Turkey: University of Istanbul, 1995
12 **Celasin H**, Karakoyun R, Yılmaz S, Elhan AH, Erkek B, Kuzu MA. Quality of life measures in Islamic rectal carcinoma patients receiving counselling. *Colorectal Dis* 2011; **13**: e170-e175 [PMID: 21651692 DOI: 10.1111/j.1463-1318.2011.02649.x]
13 **Kuzu MA**, Topçu O, Uçar K, Ulukent S, Unal E, Erverdi N, Elhan A, Demirci S. Effect of sphincter-sacrificing surgery for rectal carcinoma on quality of life in Muslim patients. *Dis Colon Rectum* 2002; **45**: 1359-1366 [PMID: 12394435 DOI: 10.1007/s10350-004-6425-4]
14 **Devlin HB**, Plant JA, Griffin M. Aftermath of surgery for anorectal cancer. *Br Med J* 1971; **3**: 413-418 [PMID: 5566622 DOI: 10.1136/bmj.3.5771.413]
15 **Engel J**, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Hölzel D. Quality of life in rectal cancer patients: a four-year prospective study. *Ann Surg* 2003; **238**: 203-213 [PMID: 12894013 DOI: 10.1097/01.sla.0000080823.38569.b0]
16 **Essink-Bot ML**. Health status as a measure of outcome of disease and treatment. Humanitas. Rotterdam, The Netherlands: Erasmus University Rotterdam, 1995
17 **Sprangers MA**, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. *Dis Colon Rectum* 1995; **38**: 361-369 [PMID: 7720441 DOI: 10.1007/bf02054222]
18 **Silva AL**, Monteiro PS, Sousa JB, Vianna AL, Oliveira PG. Partners of patients having a permanent colostomy should also receive attention from the healthcare team. *Colorectal Dis* 2014; **16**: O431-O434 [PMID: 25104405 DOI: 10.1111/codi.12737]
19 **Ozturk O**, Yalcin BM, Unal M, Yildirim K, Ozlem N. Sexual dysfunction among patients having undergone colostomy and its relationship with self-esteem. *J Family Med Com Health* 2015; **2**: 1028
20 **Traa MJ**, Braeken J, De Vries J, Roukema JA, Orsini RG, Den Oudsten BL. Evaluating quality of life and response shift from a couple-based perspective: a study among patients with colorectal cancer and their partners. *Qual Life Res* 2015; **24**: 1431-1441 [PMID: 25429822 DOI: 10.1007/s11136-014-0872-8]
21 **Badger T**, Segrin C, Dorros SM, Meek P, Lopez AM. Depression and anxiety in women with breast cancer and their partners. *Nurs Res* 2007; **56**: 44-53 [PMID: 17179873 DOI: 10.1097/00006199-200701000-00006]
22 **Alacacioglu A**, Yavuzsen T, Dirioz M, Yilmaz U. Quality of life, anxiety and depression in Turkish breast cancer patients and in their husbands. *Med Oncol* 2009; **26**: 415-419 [PMID: 19031014 DOI: 10.1007/s12032-008-9138-z]
23 **Kim Y**, Kashy DA, Wellisch DK, Spillers RL, Kaw CK, Smith TG. Quality of life of couples dealing with cancer: dyadic and individual adjustment among breast and prostate cancer survivors and their spousal caregivers. *Ann Behav Med* 2008; **35**: 230-238 [PMID: 18365297 DOI: 10.1007/s12160-008-9026-y]
24 **Bretagnol F**, Troubat H, Laurent C, Zerbib F, Saric J, Rullier E. Long-term functional results after sphincter-saving resection for rectal cancer. *Gastroenterol Clin Biol* 2004; **28**: 155-159 [PMID: 15060460 DOI: 10.1016/s0399-8320(04)94870-1]
25 **Kakodkar R**, Gupta S, Nundy S. Low anterior resection with total mesorectal excision for rectal cancer: functional assessment and factors affecting outcome. *Colorectal Dis* 2006; **8**: 650-656 [PMID:

16970574 DOI: 10.1111/j.1463-1318.2006.00992.x]

26 **Ortiz H**, Armendariz P. Anterior resection: do the patients perceive any clinical benefit? *Int J Colorectal Dis* 1996; **11**: 191-195 [PMID: 8876278 DOI: 10.1007/s003840050042]

27 **Cakmak A**, Aylaz G, Kuzu MA. Permanent stoma not only affects patients' quality of life but also that of their spouses. *World J Surg* 2010; **34**: 2872-2876 [PMID: 20706836 DOI: 10.1007/s00268-010-0758-z]

28 **Shaheen Al Ahwal M**, Al Zaben F, Sehlo MG, Khalifa DA, Koenig HG. Religious beliefs, practices, and health in colorectal cancer patients in Saudi Arabia. *Psychooncology* 2016; **25**: 292-299 [PMID: 25990540 DOI: 10.1002/pon.3845]

29 **Balboni TA**, Vanderwerker LC, Block SD, Paulk ME, Lathan CS, Peteet JR, Prigerson HG. Religiousness and spiritual support among advanced cancer patients and associations with end-of-life treatment preferences and quality of life. *J Clin Oncol* 2007; **25**: 555-560 [PMID: 17290065 DOI: 10.1200/JCO.2006.07.9046]

World Journal of Gastrointestinal Surgery

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*World J Gastrointest Surg* 2021 September 27; 13(9): 1063-1078

DOI: 10.4240/wjgs.v13.i9.1063

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

# Literature review of the outcome of and methods used to improve transperineal repair of rectocele

Mohammad Fathy, Ahmed Hossam Elfallal, Sameh Hany Emile

**ORCID number:** Mohammad Fathy 0000-0002-1177-7961; Ahmed Hossam Elfallal 0000-0002-7658-0596; Sameh Hany Emile 0000-0001-7854-5244.

**Author contributions:** Fathy M and Elfallal AH collected the data and wrote the manuscript; Emile SH designed and revised the manuscript.

**Conflict-of-interest statement:** No conflict of interest to be disclosed by the authors.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA guideline, and the manuscript was prepared and revised according to the PRISMA guideline.



**Mohammad Fathy, Ahmed Hossam Elfallal, Sameh Hany Emile,** General Surgery, Mansoura University Faculty of Medicine, Mansoura 35516, Egypt

**Corresponding author:** Sameh Hany Emile, FACS, MBChB, MD, Associate Professor, Surgeon, General Surgery, Mansoura University Faculty of Medicine, 60 ElGomhouria street, Mansoura 35516, Dakahlia, Egypt. sameh200@hotmail.com

## Abstract

### *BACKGROUND*

Rectocele is commonly seen in parous women and sometimes associated with symptoms of obstructed defecation syndrome (ODS).

### *AIM*

To assess the current literature in regard to the outcome of the classical transperineal repair (TPR) of rectocele and its technical modifications.

### *METHODS*

An organized literature search for studies that assessed the outcome of TPR of rectocele was performed. PubMed/Medline and Google Scholar were queried in the period of January 1991 through December 2020. The main outcome measures were improvement in ODS symptoms, improvement in sexual functions and continence, changes in manometric parameters, and quality of life.

### *RESULTS*

After screening of 306 studies, 24 articles were found eligible for inclusion to the review. Nine studies (301 patients) assessed the classical TPR of rectocele. The median rate of postoperative improvement in ODS symptoms was 72.7% (range, 45.8%-83.3%) and reduction in rectocele size ranged from 41.4%-95.0%. Modifications of the classical repair entailed omission of levatorplasty, addition of implant, concomitant lateral internal sphincterotomy, changing the direction of plication of rectovaginal septum, and site-specific repair.

### *CONCLUSION*

The transperineal repair of rectocele is associated with satisfactory, yet variable, improvement in ODS symptoms with parallel increase in quality-of-life score. Several modifications of the classical TPR were described. These modifications include omission of levatorplasty, insertion of implants, performing lateral sphincterotomy, changing the direction of classical plication, and site-specific repair. The indications for these modifications are not yet fully clear and need

**Manuscript source:** Invited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Egypt

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** January 25, 2021
**Peer-review started:** January 25, 2021
**First decision:** June 17, 2021
**Revised:** June 18, 2021
**Accepted:** July 22, 2021
**Article in press:** July 22, 2021
**Published online:** September 27, 2021

**P-Reviewer:** García-Flórez LJ
**S-Editor:** Liu M
**L-Editor:** Filipodia
**P-Editor:** Li JH

further prospective studies to help tailor the technique to rectocele patients.

**Key Words:** Transperineal repair; Rectocele; Review; Modifications; Outcome



**Core Tip:** An organized literature search for studies that assessed the outcome of transperineal repair of rectocele was performed. Out of 306 studies, 24 were found eligible for inclusion to this review. Nine studies (301 patients) assessed the classical transperineal repair of rectocele. The median rate of postoperative improvement in obstructed defecation syndrome symptoms was 72.7% (range, 45.8%-83.3%), whereas reduction in rectocele size ranged from 41.4%-95.0%. Modifications of the classical repair entailed omission of levatorplasty, addition of implant, concomitant lateral internal sphincterotomy, changing the direction of plication of rectovaginal septum, and site-specific repair.

**Citation:** Fathy M, Elfallal AH, Emile SH. Literature review of the outcome of and methods used to improve transperineal repair of rectocele. *World J Gastrointest Surg* 2021; 13(9): 1063-1078
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1063.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1063

## INTRODUCTION

### *Anatomic background*

Rectocele is a variant of pelvic organ prolapse (POP) that is defined as the herniation of the rectum into the posterior vaginal lumen through a weakness or defect of the rectovaginal septum (RVS)[1]. The RVS is the connective tissue fascia that separates the genital system from the digestive tract[2]. It is more firmly adherent and closely attached to the vagina than to the anorectum[3]. The thickness of the RVS varies from 0.1 mm to 2.6 mm, being thicker medially and looser and more adipose laterally[4].

### *Incidence and pathogenesis*

Rectocele affects nearly two-thirds of parous women at variable degrees that may or may not be associated with symptoms[3]. A recent study suggested a strong association between vaginal delivery, namely the first delivery, and the development of rectocele and its size[5]. However, it was reported that nearly 12% of nulliparous women may also develop rectocele secondary to congenital defects[6].

The pathogenesis of rectocele is multifactorial including a variety of modifiable and non-modifiable factors that result in loss of integrity of the RVS and the development of rectocele. Non-modifiable risk factors include advanced age and genetic susceptibility whereas the modifiable risk factors include greater parity, history of vaginal delivery, history of pelvic surgery, obesity, level of education, constipation, and chronic increase in the intra-abdominal pressure[4].

Basically, rectoceles are based on defects in the RVS. According to Diets and Steensma[7], vaginal delivery leads to increased prevalence and size of already present, asymptomatic defects in the RVS. Richardson[8] suggested that the etiology of rectocele may be related to discreet defects in the RVS. The most common form of these defects is a transverse break just above the perineal body.

Further factors that may contribute to the development of rectocele include the loss of natural fixation that impairs the ability of the posterior wall to resist pressures from behind[8]. In addition, long-standing denervation of the pelvic floor and widening of the genital hiatus during delivery may worsen the condition[9]. Also, the change in orientation of the levator ani muscles, which are important elements in vaginal support, in response to birth trauma can contribute to the pathogenesis of rectocele. It was observed that the levator ani muscles are stretched more than 200% beyond the threshold for stretch injuries during the second stage of labor[10].

### Clinical features

Rectocele usually presents with many symptoms that may not be constant and may vary from day to day. These symptoms include pelvic pain or feeling of pressure, feeling of the posterior vaginal bulge, manifestations of obstructed defecation syndrome (ODS), constipation, and dyspareunia[11]. Physical examination includes both rectal and vaginal assessment. Rectocele can be graded according to the Baden-Walker system, which measures the distance of the most distal point of the prolapsed wall from the hymen during Valsalva maneuver[12]. To ensure better accuracy and reliability, the POP quantification system is used to assess the rectocele with a two-point assessment method followed by grading[13].

### Assessment

Fluoroscopic defecography is usually used for the anatomical assessment of rectocele. It involves the introduction of a contrast medium into the rectum and the assessment of the anatomy and function at rest and during straining using an X-ray machine and a special commode[14]. It is worthy to note that up to 93% of healthy, asymptomatic women were found to have a radiologic evidence of rectocele in fluoroscopic defecography. Therefore, the indication for surgical treatment of rectocele should be predominantly based on clinical symptoms and not just the radiologic evidence of an anatomical rectocele.

More superior to X-ray defecography is the dynamic magnetic resonance imaging defecography that can confer more detailed diagnosis and can easily reconstruct the sequence of images into a video to assess the condition more precisely[15]. Also, endoanal ultrasonography dynamic scan (echodefecography) and transperineal ultrasonography are used successfully in the assessment of rectocele, perineal body, and anal sphincters[16,17].

### Management

Non-surgical management of rectocele involves eating a high-fiber diet, increasing water intake, and stool softeners. In addition, pelvic floor physiotherapy, such as Kegel exercises, is used to improve rectocele symptoms, but they appear to be more successful in anterior compartment prolapse[18]. Vaginal pessaries have been used with good results and succeed to avoid surgery in nearly two-third of patients[19].

Surgical management of rectocele is reserved for those who fail to improve after conservative treatment[20]. Surgery aims at correcting the anatomy and strengthening the rectal wall as well as correcting any coexisting pathology. Rectocele repair can be achieved through transvaginal, transperineal, transanal, or abdominal approaches. Transvaginal repair is the most common and preferable approach to gynecologists, while transanal and transperineal repairs are the preferable approaches to coloproctologists[3]. The transabdominal approach, namely ventral mesh rectopexy, is mainly indicated for high-level rectoceles, rectoceles associated with internal rectal prolapse, and/or descending perinium syndrome, associated genital prolapse, or when transperineal and transvaginal repairs are contraindicated[3,20].

The transperineal approach may have an advantage over the transvaginal and transanal approaches in that it does not involve the vaginal mucosa and does not induce stretching of the anal sphincter muscles and therefore does not compromise sexual functions or the continence mechanism[21].

### Classical technique of transperineal repair of rectocele

The procedure is usually done under spinal anesthesia. Patients are placed in the lithotomy position, and the buttocks are separated. A curvilinear incision is made between the anal verge and the posterior fourchette to allow for proper dissection of rectovaginal space anterior to the anal sphincter complex. Using a combination of blunt and sharp dissection, with the help of digital palpation, the separation of vaginal mucosa from the rectal wall is achieved taking care to avoid injury of the vagina and rectum. The dissection is continued until the rectocele bulge is fully exposed. Then, plication of the RVS is performed in a side-to-side manner with interrupted absorbable sutures. The transperineal approach is usually combined with levatorplasty to restore the normal vaginal hiatus. Anal sphincteroplasty can be also performed in case of sphincter defects. After adequate hemostasis, perineorrhaphy is performed, and the skin is closed with interrupted absorbable sutures[22].

## MATERIALS AND METHODS

### *Strategy of literature search*

This was a comprehensive literature review in which an organized literature search was completed using the following keywords "rectocele," "anterior rectocele," "perineal repair," "transperineal repair," "pelvic organ prolapse," "transperineal approach," and "rectocele repair." Eligible studies were identified by searching PubMed/Medline database and Google Scholar in addition to manual search of reference lists of retrieved studies. The search process started from January 1991 through December 2020.

The inclusion criteria comprised prospective or retrospective case series and cohort studies and randomized clinical trials that reported the outcome of classical transperineal rectocele repair and its technical modifications with at least 6 mo of follow-up. We excluded irrelevant studies, studies assessing techniques for rectocele repair other than the transperineal repair, studies that did not report the outcome of transperineal repair clearly, and articles without an English full text.

## RESULTS

### *Literature analysis*

The preliminary search yielded 306 articles. After duplicates subtraction, 264 articles were initially screened. After screening, we excluded irrelevant studies, other study types (review articles, case reports, letters, and conferences papers), and articles in languages other than English, and finally 24 studies were eligible for analysis. The studies included were 13 retrospective studies, 7 prospective studies, and 4 randomized trials. The literature search and study selection process are outlined in Figure 1.

The 24 studies included 1349 patients, 821 (60.9%) of whom underwent TPR of rectocele, either using the classic repair or modified repair techniques as shown in Figure 2.

### *Classical transperineal repair*

A total of 301 patients from nine studies underwent the classical TPR of rectocele. The average age of the patients ranged from 43.2-63.3 years, and the mean follow-up duration ranged from 6-48 mo (Table 1).

The median rate of postoperative improvement in ODS symptoms was 72.7% (range, 45.8%-83.3%)[23-31]. More specifically, a significant decline in the symptom score used to measure ODS symptoms ranged from 54.8%-78.0%[23,24,27,28]. The studies that used fluoroscopic defecography for assessment reported a reduction in rectocele depth ranging from 41.4%-95.0%[23-25,27,31]. In regard to changes in the continence state, Mills[26] reported an improvement in fecal incontinence in all patients during follow-up, including patients with combined ODS and fecal incontinence who reported significant improvement in both complaints.

Anal pressure and sensation assessment of the patients showed variable results. According to Balata *et al*[23], there was a significant increase in the maximum resting pressure (MRP) and maximum squeeze pressure after TPR. In contrast, Ayabaca *et al*[30] reported a non-significant decline in the MRP and maximum squeeze pressure after repair. Two studies reported a significant decrease in the threshold of rectal sensation after TPR[24,27].

Patient satisfaction with the procedure was not commonly assessed in the literature. Balata *et al*[23] documented a significant improvement in the 12-Item POP/Urinary Incontinence Sexual Questionnaire score. Also, they reported a non-significant improvement in sexual satisfaction and a decreased incidence of dyspareunia at 12 mo after repair[23]. Another study[27] reported an improvement in dyspareunia reaching up to 50%, whereas Hirst *et al*[29] reported satisfaction in 78.8% of their patients.

Farid *et al*[27] reported a correlation between the reduction in rectocele size and the improvement in ODS symptoms, in contrast to another study that failed to find significant correlation between the two parameters[31]. Overall, recurrence of rectocele was recorded in 7 (2.3%) patients after TPR, and the rates of recurrence ranged from 6.3%-15.2% across the studies reviewed[23,29]. Complications developed in 43 (14.3%) patients, and the most common complication of TPR was wound infection. Other complications included wound dehiscence, hematoma, and urine retention[23-31].

**Table 1 Results of classical transperineal repair (transperineal repair + levatorplasty ± sphincteroplasty)**

| Ref. | Methodology | *n* | Age | Follow-up | Diagnosis and assessment | Outcome | Complications |
|---|---|---|---|---|---|---|---|
| Balata *et al* [23], 2020 (Egypt) | RCT | 32 (entire cohort *n* = 64) | 45.1 ± 3.5 | 12 mo | Wexner constipation score; Fluoroscopic defecography; ARM; PISQ-12; Satisfaction | Significant improvement (decline) in Wexner score (Pre = 18.3 ± 0.7, PO = 7.2 ± 1.4, *P* < 0.0001)<br>Significant decline in rectocele depth (Pre = 4.6 ± 0.8 cm, PO = 1.4 ± 0.9 cm, *P* < 0.0001)<br>Significant rise of MRP (Pre = 60.7 ± 8.5 mmHg, PO = 67.1 ± 4.2 mmHg, *P* = 0.0003)<br>Significant rise of MSP (Pre = 136.4 ± 3.5 mmHg, PO = 141.2 ± 2.1 mmHg, *P* < 0.0001)<br>Significant improvement (decline) in PISQ-12 score (Pre = 26.4 ± 2.1, PO = 18.2 ± 0.7, *P* < 0.0001)<br>Sexual satisfaction (Pre = 23 patient, PO = 24 patient, *P* = 0.8) | Complications (*n* = 6); Dyspareunia (Pre = 11, PO =13, *P* = 0.8); Recurrence (*n* = 2) |
| Emile *et al* [24], 2020 (Egypt) | Retrospective case series | 46 | 43.2 ± 10.7 | 13.9 mo (12.0-18.0) | Wexner constipation score; Fluoroscopic defecography; ARM | Significant improvement (*n* = 30), no improvement (*n* = 16)<br>Significant improvement (decline) in Wexner score (Pre = 17.8 ± 2.7, PO = 9.2 ± 4.7, *P* < 0.001)<br>Significant decline in rectocele depth (Pre = 4.7 ± 1.2, PO = 2.2 ± 1.4, *P* < 0.001)<br>Significant improvement (decline) in rectal sensation volumes | Wound dehiscence (*n* = 6), hematoma (*n* = 2) |
| Tomita *et al* [25], 2012 (Japan) | Prospective case series | 12 | 63.3 (33.0-82.0) | 24 mo | Symptom assessment; Fluoroscopic defecography | Symptom improvement [excellent (*n* = 6 patient), good (*n* = 4 patient), fair (*n* = 2 patient)]<br>Significant decline in rectocele depth (Pre = 4 ± 0.8 cm, PO = 0.2 ± 0.5 cm, *P* <0.001)<br>Complete resolution of rectocele (*n* = 10 patient) | Wound infection (*n* = 2) |
| Mills[26], 2011 (South Africa) | Retrospective case series | 117 | 24-85 | 6 mo (at least) | Symptom assessment; Trans-labial US; Rectocele wall thickness by Harpenden Skinfold Caliper (*n* = 50 patient); Trans-illumination (*n* = 50 patient) | Negative trans-illumination immediately after repair (*n* = 50 patient)<br>Rectocele wall thickness increased from 2.4 mm to 4.8 mm immediately after repair ( *n* = 50 patient)<br>No PO manifestations of FI (*n* = 109 patient)<br>Patients with combined ODS and FI became normal (*n* = 43 patient) | Wound infection (*n* = 2) |
| Farid *et al*[27], 2010 (Egypt) | RCT | 16 (entire cohort *n* = 47) | 48.4 ± 12.6 | 6 mo | Modified ODS score; Fluoroscopic defecography; ARM | Significant improvement (decline) in modified ODS score (Pre = 17.3 ± 5.1, PO = 3.8 ± 1.7, *P* < 0.0001)<br>Significant reduction in rectocele depth (Pre = 4.2 ± 0.8 | Wound infection (6.4%) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | cm, PO = 0.9 ± 0.7 cm, $P$ < 0.0001)<br><br>Significant improvement in rectal sensation volumes; Non-significant decline of dyspareunia (Pre = 6 patients, PO = 3 patients)<br><br>Complete rectal evacuation ($n$ = 13 patient)<br><br>Significant correlation between rectocele depth and ODS score ($P$ = 0.01) | |
| Puigdollers *et al*[28], 2007 (Spain) | Prospective cohort | 24 (entire cohort $n$ = 35) | 52 (28-79) | 12 mo | Questionnaire based on ROME-II criteria (Y/N) | Significant decline in PO score (Pre = 4.2, PO = 1.9, $P$ < 0.0001)<br><br>Improvement: complete improvement [no symptoms] (42.9%), partial improvement [only one symptom] (5.7%), partial improvement [with ≥ 2 symptom] (31.4%), unchanged (20%)<br><br>Improvement of constipation ( $n$ = 11 patient)<br><br>Results were worse after hysterectomy | Hematoma ($n$ = 2) |
| Hirst *et al*[29], 2005 (United Kingdom) | Retrospective cohort | 33 (entire cohort $n$ = 82) | 51, median (25-83) | NP | Clinical assessment; Satisfaction assessment | Surgery outcome: All patients: Cured ($n$ = 21 patient), initial improvement ($n$ = 5 patient), no improvement ($n$ = 7 patient), further surgery ($n$ = 8 patient)<br><br>Patients with rectocele only ($n$ = 6 patients): Cured ($n$ = 5), initial improvement ($n$ = 1), further surgery ($n$ = 0) Satisfaction: ($n$ = 26) | Complications ($n$ = 0); Recurrence ($n$ = 5) |
| Ayabaca *et al* [30], 2002 (Italy) | Retrospective cohort | 11 (entire cohort $n$ = 60) | 56 (21-70) | 48 mo (9-122) | Symptom assessment; FI score; ARM | ODS symptoms improvement: Improved ($n$ = 8 patient), lost to follow-up ($n$ = 3 patient)<br><br>FI score improved (declined: Pre = 4.9 ± 0.9, PO = 4.2 ± 0.8); Non-significant decline in MRP and MSP in patients with FI<br><br>No improvement of FI ($n$ = 1 patient) | Urine retention (10%), wound dehiscence (6.6%), wound infection ($n$ = 3.3%), other complications (10%); Recurrence: $n$ = 0 |
| Van Laarhoven *et al*[31], 1999 (United Kingdom) | Retrospective cohort | 10 (entire cohort $n$ = 22) | 48 (31-63) | 27 mo, median (5-54) | Symptom assessment; Fluoroscopic defecography; Pudendal nerve motor latency | Ability to evacuate rectum: Improved (72.7%), unchanged (22.7%), deteriorated (4.5%)<br><br>Significant decline in rectocele depth (Pre = 2.9 cm, PO = 1.7 cm, $P$ < 0.01)<br><br>Significant decline in rectocele area (Pre = 7.8 cm, PO = 4.3 cm, $P$ < 0.01)<br><br>No correlation between rectocele reduction and symptoms improvement | Wound infection (9.1%) |

ARM: Anorectal manometry; FI: Fecal incontinence; MRP: Maximum resting pressure; MSP: Maximum squeeze pressure; NP: Not provided; ODS: Obstructed defecation syndrome; PISQ-12: 12-Item Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; PO: Postoperative; Pre: Preoperative; RCT: Randomized controlled trial; ROME-II: 2nd edition of criteria of functional gastrointestinal disorders; US: Ultrasonography.

## *Modifications of the classical transperineal repair*

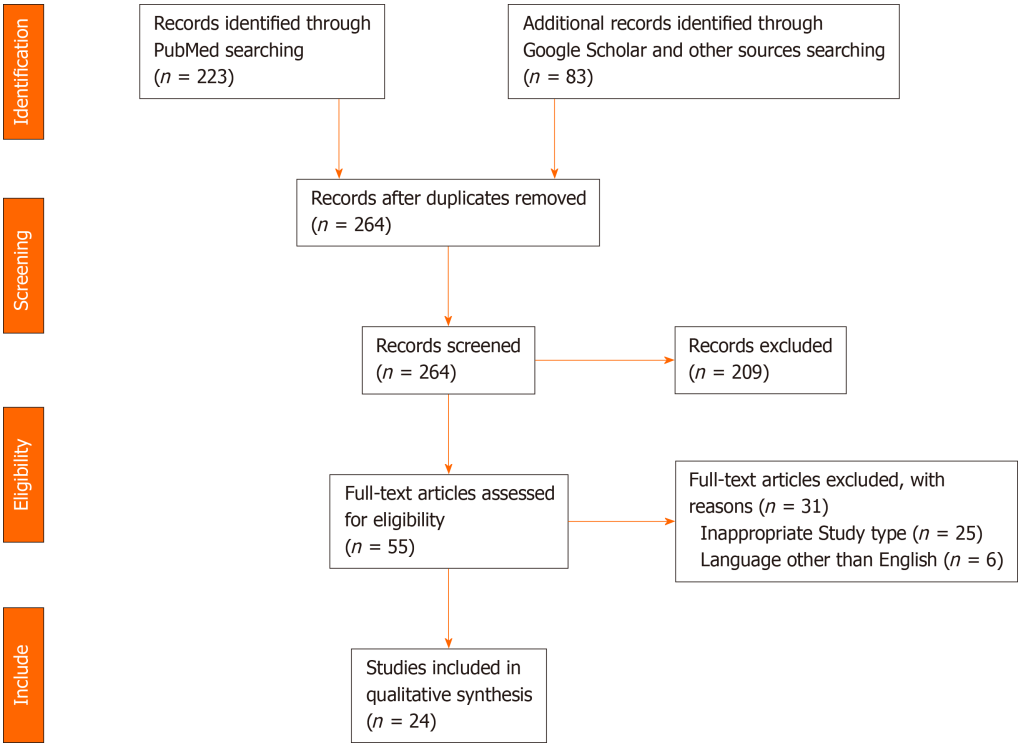


**Figure 1 PRISMA diagram outlining study selection process.**

**Insertion of implant with or without performing the classical repair:** Six studies including 86 patients inserted an implant to reinforce the RVS, with or without performing the classical TPR. The average age of patients ranged from 50.0-58.7 years, and the average follow-up ranged from 9-29 mo (Table 2).

When the classical repair was omitted and an implant only was inserted the median improvement in ODS was 90.9% (range, 70%-100%)[32-35]. A significant drop in ODS score was reported in 30.9%-64.9% of patients[32-34], and significant satisfaction was reported by 83.3% of the patients according to Azanjac and Jorovic[35].

On the other hand, when a synthetic mesh implant was inserted to reinforce the classical transperineal repair, the improvement in ODS ranged from 71.4%-88.9% with a median of 80.1%[29,36]. Watson *et al*[36] reported a reduction in rectocele size and barium entrapment equal to 35.1% and 64.3%, respectively[36], and Hirst *et al*[29] reported complete or partial satisfaction in 85.7% of patients.

Mercer-Jones *et al*[34] compared two types of meshes, polypropylene mesh and composite mesh of polypropylene and polyglycolic acid. The authors reported better outcome with the composite mesh, reaching 100% as compared to 64.3% with polypropylene mesh. New-onset dyspareunia was reported after both techniques[34,36]. Additionally, Watson *et al*[36] reported improvement in dyspareunia in 1 patient and persistence of symptoms in another 2 patients[36].

Overall, only two rectocele recurrences (2.3%) were reported after insertion of mesh implant[29,34]. Twelve (13.9%) patients developed complications. The most common reported complication was wound infection, whereas the most serious complication was mesh erosion, reported in 1.1% of patients[29]. Other complications included wound dehiscence, hematoma, and urine retention[32-36].

**Omission of levatorplasty:** Seven studies including 245 patients performed the classical TPR without performing levatorplasty. The average age of patients ranged from 41.4-52.0 years, and the mean follow-up ranged from 6-54 mo (Table 3).

Omission of levatorplasty only ($n$ = 71): The omission of levatorplasty resulted in postoperative improvement in ODS symptoms in 66.7%-78.2% of patients[27,37,38-40]. The reduction in ODS scores ranged between 32.8% and 53.0%[27,37,40]. A significant reduction in rectocele size was recorded in 45.8%-76.3% of patients[27,37]. Youssef *et al*[40] reported an increase in MRP, in contradiction to another study that reported a decrease in anal pressures[40]. Satisfaction was reported in 70% of patients [40]. Two studies reported an improvement in dyspareunia in 16.7%-35.7% of patients [27,37], whereas another study documented de novo dyspareunia[40]. Two studies reported recurrence rates ranging between 10% and 15%, whereas Sari *et al*[38] did not

**Table 2 Results of modification of classic transperineal repair**

| Ref. | Methodology | Technique | *n* | Age | Follow-up | Diagnosis and Assessment | Outcome | Complications |
|---|---|---|---|---|---|---|---|---|
| Ellis[32], 2010 (United States) | Retrospective cohort | TPI [porcine intestinal submucosal collagen implant (Surgisis®)] ± SP | 32 (entire cohort *n* = 120) | 58.7 ± 8.9 | 12 mo | BBUSQ-22 | Improvement of BBUSQ-22 individual items (total improvement 30.9%): Significant improvement (decline) in 6 items<br><br>Significant deterioration (raise) in pain with bowel movements<br><br>Non-significant changes in 2 items | Urine retention (*n* = 2), Recurrence (*n* = 0) |
| Smart and Mercer-Jones [33], 2007 (United Kingdom) | Prospective case series | TPI [porcine dermal collagen implant (Permacol®)]> Suction drain (last 8 patients) | 10 | 51, median (33-71) | 9 mo, median (5-16) | Watson score | All patients (100%) had improvement in 2 or more symptoms, and 70% in three or more<br><br>Decline of Watson score (Pre = 10.5, PO = 4.5) | Hematoma (*n* = 2) |
| Hirst *et al* [29], 2005 (United Kingdom) | Retrospective cohort | TPR + LP + Implant | 7 (entire cohort *n* = 82) | 51, median (25-83) | NP | Clinical assessment | Surgery outcome: cured (*n* = 5 patient), initial improvement (*n* = 1 patient), no improvement (*n* = 1 patient), further surgery (*n* = 2 patient); Satisfaction: *n* = 6 patient | Mesh erosion (*n* = 1); Recurrence (*n* = 1) |
| Mercer-Jones *et al*[34], 2004 (United Kingdom) | Retrospective case series | TPI ± SPProlene mesh (*n* = 14),Prolene + PGA mesh [Vypro II®] (*n* = 8) | 22 | 53, median (28-66) | 12.5 mo (3.0-47.0) | Watson score | Decline in Watson score (Pre = 11.1, PO = 3.9); Significant ($P < 0.05$) symptomatic improvement (*n* = 20 patient)<br><br>Subjective outcome ($P < 0.05$) in favor of Vypro II® mesh: Moderate to excellent [Prolene (*n* = 9 patient), Vypro II® (*n* = 8 patient)]<br><br>Poor [prolene (*n* = 5 patient), Vypro II® (*n* = 0 patient)] | Wound infection (*n* = 2), wound infection and dehiscence (*n* = 1), dyspareunia (*n* = 1) Recurrence (*n* = 1) |
| Azanjac and Jorovic[35], 1999 (Serbia) | Prospective case series | TPI [prolene mesh (Atrium®)] | 6 | 56 (46-68) | 11 mo (7-18) | Symptom assessment; Satisfaction assessment | Successful rectal evacuation without digitation (*n* = 6 patient); Symptom improvement [markedly (*n* = 2 patient), completely (*n* = 4 patient)]<br><br>Satisfaction [very satisfied (*n* = 5 patient), somewhat (*n* = 1 patient)] | Urine retention (*n* = 1) |
| Watson *et al* [36], 1996 (United Kingdom) | Prospective case series | TPR + LP + Implant [prolene mesh (Marlex®)] | 9 | 50, median (32-61) | 29 mo, median (8-36) | Watson scoreFluoroscopic defecography | Significant decline in PO score (Pre = 11.7, PO = 1.9, $P < 0.05$); No further need for digital evacuation (*n* = 8); Significant decline in rectocele depth (Pre = 3.7, PO = 2.4, $P < 0.05$)<br><br>Significant decline in barium trapping (Pre = 14%, PO = 5%, $P < 0.005$) | Wound infection (*n* = 1); Dyspareunia: Resolved (*n* = 1), abstained (*n* = 2), acquired (*n* = 1) |

BBUSQ-22: 22-Item Birmingham Bowel and Urinary Symptoms Questionnaire; NP: Not provided; PGA: Polyglycolic acid; PO: Postoperative; Pre:

Preoperative; SP: Sphincteroplasty; TPI: Transperineal implant; TPR: Transperineal repair (classic vertical plication); LP: Levatorplasty.

report any recurrence. Complications included wound dehiscence, wound infection, bleeding, and hematomas[27,37,38,40].

Addition of implant ($n$ = 6): Only a small number of patients had a synthetic implant along with omission of levatorplasty. There were not differential results from the entire cohort. The rate of improvement in ODS symptoms after this technique was 78.2%, and the rate of complications was 6.4% with no reported recurrence[38].

Addition of limited internal sphincterotomy (LIS) ($n$ = 30): Only one study[40] combined LIS with transperineal repair in patients with type-I anterior rectocele associated with high resting pressure. This technique resulted in a greater improvement in ODS symptoms in 93.3% of patients as compared to 70.0% when LIS was not performed. Also, the quality-of-life score was better in patients with concomitant LIS than in patients without LIS (12.9 *vs* 11.4, $P$ = 0.02, respectively). Obviously, lower MRP was recorded after LIS as compared to patients without LIS (74.4 mmHg *vs* 87.5 mmHg, $P$ < 0.0001). Complications included fecal incontinence in 2 patients and new-onset dyspareunia in 1 patient. Only 1 patient experienced recurrence of rectocele at 12 mo after TPR combined with LIS.

Horizontal plication ($n$ = 20): Omar *et al*[37] replaced the classical vertical plication of the RVS with craniocaudal or horizontal plication. Although the rate of complete cure of rectocele after horizontal plication was lower than the classical plication (55% *vs* 65%), the postoperative constipation scores were comparable. Horizontal plication managed to confer a more significant reduction in rectocele size, more improvement in dyspareunia, and lower recurrence rate than the classical repair.

Site-specific repair with an implant ($n$ = 118): Replacement of the classical repair with site-specific repair along with the insertion of implants resulted in a greater improvement in ODS symptoms, reaching up to 100%. The improvement in Watson score ranged from 78.8% up to 83.8%. Additionally, three studies[39,41,42] that used site-specific repair reported a significant reduction in rectocele size. Leventoğlu *et al*[42] used POP quantification to assess postoperative anatomic correction. At 6 mo after surgery, 10.8% remained POP quantification stage II, which then increased to 12% at 14 mo. Lisi *et al*[39] reported a non-significant increase in anal pressures. Two studies reported normal sexual functions in sexually active patients[39,41], while another study reported postoperative dyspareunia in 9.6% of patients[42]. Two studies used the 36-Item Short Form Survey to assess the quality of life with non-significant increase in both composites of the tool[39,41]. Leventoğlu *et al*[42] reported that 96.4% of the patients were satisfied and would redo the surgery if the symptoms recurred. Two studies reported recurrence in 16%-20% of patients[39,41]. Complications were delayed wound healing, wound infection, urinary tract infection, and bleeding[39,41,42].

**Omission of RVS plication:** In five studies comprising 189 patients, plication of the RVS was not done, and only levatorplasty or implant insertion was done. The average age of patients ranged from 52.1-59.0 years, and the average follow-up ranged from 14-42 mo (Table 4).

Transperineal levatorplasty ($n$ = 178): This modification resulted in improvement of ODS symptoms in 87.9% to 93.6% of patients[43-45] with lower rates of improvement (72.7%) observed when sphincteroplasty was added to treat coexisting fecal incontinence[44]. Reduction in the rectocele size ranged between 44.1%-50.0%[43,44]. According to two studies, there were non-significant increases in both MRP and maximum squeeze pressure[43,44]. The incidence of continence improvement reached 100% in one study[43]. Satisfaction ranged between 87.5% and 90.0%[43,45], while in patients with baseline fecal incontinence, satisfaction rates were 91% at 12 mo and 54.5% at 36 mo postoperatively[45]. The most serious complication was rectovaginal fistula, and other complications were mostly wound infection[43-45].

Transperineal implant with levatorplasty ($n$ = 11): Only a small number of patients underwent this technique[31,44,46]. Two cohort studies did not report differential results of subgroups[31,44]. Parker and Phillips reported successful rectal evacuation in 75% of patients, and all patients were satisfied with the procedure. No complications were recorded[46].

### *Combined approaches*

Three studies used the transperineal approach as an auxiliary procedure for the main approach. D'Hoore *et al*[47] performed laparoscopic ventral mesh rectopexy combined

**Table 3 Results of modification of classic transperineal repair (with the omission of levatorplasty ± other additions or substitutions)**

| Ref. | Method-ology | Technique (TPR) | *n* | Age | Follow-up | Diagnosis and assessment | Outcome | Complications |
|---|---|---|---|---|---|---|---|---|
| Omar *et al* [37], 2020 (Egypt) | Pilot RCT | Omission of levatorplasty only (*n* = 20) HP instead of classical plication (*n* = 20) | 40 | 44.9 (± 7.7) | 12 mo | Wexner constipation score; Fluoroscopic defecography; ARM | Cure rate: Complete cure: TPR (*n* = 13 patient), HP (*n* = 11 patient)<br><br>Significant improvement TPR (*n* = 6 patient), HP (*n* = 8 patient)<br><br>No improvement TPR (*n* = 1 patient), HP (*n* = 1 patient)<br><br>Comparable significant improvement (decline) in Wexner score in both<br><br>More decline in rectocele depth with HP [TPR = 2.6 ± 0.5 cm, HP = 1.7 ± 0.5 cm, *P* < 0.0001]<br><br>More improvement of dyspareunia with HP [TPR = 9 patient, HP = 2 patient, *P* = 0.03] | TPR [wound dehiscence (*n* = 3), bleeding (*n* = 1), recurrence (*n* = 3)], HP [wound dehiscence (*n* = 1), bleeding (*n* = 1) recurrence (*n* = 1)] |
| Sari *et al* [38], 2019 (Turkey) | Retrospective cohort | Omission of levatorplasty only (*n* = 6)+ Implant [prolene mesh without fixation (*n* = 6)] | 12 (entire cohort *n* = 78) | 52 (31-88) | 54 mo (3-218) | Symptom assessment Fluoroscopic defecography | Patients free of symptoms (78.2%)<br><br>Patients had remaining urinary or defecatory symptoms or PO pain (21.8%) | Wound infection (3.8%), bleeding (2.6%); Recurrence (*n* = 0) |
| Lisi *et al* [39], 2018 (Italy) | Prospective case series | SSR + Implant [porcine dermal collagen implant (Permacol®)] | 25 | 47 (30-62) | 12-24 mo | Watson score; Fluoroscopic defecography; ARMSF-36 | No complaint regarding bowel functions at 2 mo and no sexual problemsSignificant decline in Watson score (Pre = 9.9 ± 2.5, PO = 2.1 ± 0.3, *P* < 0.0001)<br><br>All PO rectocele depths were < 2 cm<br><br>Non-significant rise in MRP and MSP<br><br>Non-significant improvement of both composites of SF-36 | UTI (*n* = 2), delayed wound healing (*n* = 4), Recurrence (*n* = 3) |
| Youssef *et al*[40], 2017 (Egypt) | RCT | Omission of levatorplasty only (*n* = 30)+ LIS (*n* = 30) | 60 | 41.4 (17.0-70.0) | 17.8 mo (6.0-36.0) | Wexner score; Fluoroscopic defecography; ARMPAC-QOL | Complete clinical improvement 70% (TPR) *vs* 93.3% (TPR + LIS)<br><br>More decline in Wexner score with addition of LIS (TPR = 11.1 ± 2.1, TPR + LIS = 8 ± 2, *P* < 0.0001)<br><br>More satisfaction with TPR + LIS<br><br>Score: (TPR = 11.4 ± 2.7, TPR + LIS = 12.9 ± 2.3, *P* = 0.02); *n* of patients: (TPR = 21 patient, TPR + LIS = 28 patient, *P* = 0.04)<br><br>More improvement (decline) in MRP with TPR + LIS (TPR = 87.5 ± 5.1 mmHg, TPR + LIS = 74.4 ± 3.5 mmHg, *P* < 0.0001) | TPR [ecchymosis (*n* = 1), wound dehiscence ( *n* = 2), dyspareunia (*n* = 1), recurrence (*n* = 3)]<br><br>TPR + LIS [wound infection (*n* = 1), wound dehiscence (*n* = 3), FI (*n* = 2), dyspareunia (*n* = 1), recurrence (*n* = 1)] |
| Farid *et al* | RCT | Omission of | 15 | 48.4 ± | 6 mo | Modified ODS | Significant improvement | Wound infection (6.4%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| [27], 2010 (Egypt) | | levatorplasty only | (entire cohort $n$ = 47) | 12.6 | | score; Fluoroscopic defecography; ARM | (decline) in ODS score (Pre = 16.4 ± 6.3, PO = 7.7 ± 2.5, $P$ < 0.001)<br><br>Significant decline in rectocele depth (Pre = 3.8 ± 1 cm, PO = 0.9 ± 0.8 cm, $P$ < 0.001)<br><br>Significant improvement in rectal sensations<br><br>Decline of dyspareunia (Pre = 6 patient, PO = 5 patient)<br><br>Complete rectal evacuation ( $n$ = 10 patient)<br><br>Significant correlation between rectocele depth and ODS score ($P$ = 0.001) | |
| Milito *et al* [41], 2010 (Italy) | Retro-spective case series | SSR + Implant [porcine dermal collagen implant (Permacol®)] | 10 | 47.7 (25.0-70.0) | 2-20 mo | Watson score; Fluoroscopic defecography; ARMSF-36 | Significant decline in Watson score (Pre = 9.6 ± 1.8, PO = 1.6 ± 0.6, $P$ < 0.0001)<br><br>Significant decline in rectocele depth (Pre = 3.8 cm, PO < 2 cm, $P$ < 0.0001) | UTI ($n$ = 1), delayed wound healing ($n$ = 1); Recurrence ($n$ = 2) |
| Leventoğlu *et al*[42], 2007 (Turkey) | Prospective case series | SSR + Implant [PGA mesh (Soft PGA Felt®)] | 83 | 49, median (29-56) | 14 mo, median (6-36) | Watson score; Fluoroscopic defecography ($n$ = 55); POP-Q | Significant improvement of Watson score (Pre = 9.9 ± 1.9, PO = 1.6 ± 0.6, $P$ < 0.0001)<br><br>Subjective cure rate ($n$ = 83 patient); PO rectocele depth < 2cm ($n$ = 21 patient)<br><br>At 6m, anatomical cure ($n$ = 74 patient), POP-Q stage II ( $n$ = 9 patient), at 14 m, POP-Q stage II ($n$ = 10 patient)<br><br>Would redo surgery if symptoms recur ($n$ = 80 patient) | Bleeding ($n$ = 3), wound infection ($n$ = 4), dyspareunia ($n$ = 8); Recurrence (NP) |

ARM: Anorectal manometry; FI: Fecal incontinence; HP: Horizontal plication; LIS: Limited internal sphincterotomy; MRP: Maximum resting pressure; MSP: Maximum squeeze pressure; NP: Not provided; ODS: Obstructed defecation syndrome; PAC-QoL: Patient Assessment of Constipation Quality of Life; PGA: Polyglycolic acid; PO: Postoperative; POP-Q: Pelvic Organ Prolapse Quantification System; Pre: Preoperative; RCT: Randomized controlled trial; TPR: Transperineal repair (classic vertical plication); SF-36: 36-Item Short Form Survey; SSR: Site-specific repair; UTI: Urinary tract infection.

with TPR to facilitate proper mesh placement in large rectoceles[47]. Altomare *et al*[48] adopted the transanal approach and used a circular stapler to repair rectoceles. The combination with transperineal approach helped proper placement of rectal wall into the stapler with sparing of the vaginal wall[48]. Finally, Boccasanta *et al*[44] combined transperineal levatorplasty with different transanal procedures including Block's obliterative suture, Sarles' procedure, and stapled mucosectomy to augment the repairs.

## DISCUSSION

The transperineal repair of rectocele is associated with satisfactory, yet variable, rates of improvement in ODS symptoms with a parallel increase in quality-of-life score. Several modifications of the classical TPR are described. These modifications include omission of levatorplasty, insertion of implants, performing LIS, changing the direction of classical plication, and site-specific repair. The indications for these modifications are not yet fully clear and need further prospective studies to help tailor the technique to rectocele patients.

One of the important modifications of TPR is the insertion of mesh implant to reinforce the repair of the RVS. The insertion of mesh implant along with TPR appeared to reduce the recurrence of rectocele significantly, down to less than 5%,

**Table 4 Results of modification of classic transperineal repair (with the omission of rectovaginal septum plication ± other additions or substitutions)**

| Ref. | Methodology | Technique | *n* | Age | Follow-up | Diagnosis and assessment | Outcome | Complications |
|---|---|---|---|---|---|---|---|---|
| Fischer *et al* [43], 2005 (Germany) | Retrospective cohort | TPLP | 10(entire cohort *n* = 36) | 59 (30-79) | 36 mo (8-110) | Symptom assessment; Fluoroscopic defecography; ARM | Symptom improvement (cured): *n* = 9 patientAll patients (*n* = 7) showed improvement in FI<br><br>3 out of 6 patients showed no rectocele with defecography<br><br>Non-significant rise of both MRP and MSP<br><br>Satisfaction with functional outcomes: *n* = 9 patient | RVF (*n* = 1), wound infection (*n* = 1), dyspareunia (*n* = 1) |
| Boccasanta *et al*[44], 2001 (Italy) | Retrospective cohort | TPLP (addition of prolene mesh in 2 patients) | 126(entire cohort *n* = 317) | 52.4 (28.0-80.0) | 22.8 – 27.5 mo | Symptom assessment; Fluoroscopic defecography; ARM | Outcome (*n* = 110 patient) at 12 m: excellent (*n* = 45 patient), fair (*n* = 58 patient), poor (*n* = 7 patient)<br><br>PO defecography: complete absence (44.1%), residual (55.9%); Non-significant rise of both MRP and MSP | Vaginal stenosis (*n* = 2) |
| Lamah *et al* [45], 2001 (United Kingdom) | Retrospective case series | TPLP ± SP> suction drain | 44 | 57.5 (35.0-82.0) | 42 mo (6-84) | Symptom assessment; Continence assessment; Sexual function assessment; Satisfaction assessment | Symptom assessment: TPLP (*n* = 33 patient): improvement of lump sensation (*n* = 28 patient), improvement of defecation (*n* = 29 patient); TPLP + SP (*n* = 11 patient): improvement of one or both (*n* = 8 patient)<br><br>Continence (*n* = 11 patient): at Pre [continent (*n* = 0), incontinent (*n* = 11)], at 12 mo [continent (*n* = 5), incontinent (*n* = 6)], at 24 mo [continent (*n* = 3), incontinent (*n* = 8)], > 36 mo [continent (*n* = 3), incontinent (*n* = 8)]<br><br>Sexual function: TPLP [Improved (*n* = 8), unchanged (*n* = 9), deteriorated (*n* = 2), declined (*n* = 10)]; TPLP + SP [Improved (*n* = 2), unchanged (*n* = 2), deteriorated (*n* = 0), declined (*n* = 5)]<br><br>Satisfaction (satisfied / total): TPLP [at 2 yr: (*n* = 30/33), at 3.2 yr (*n* = 21/24)]; TPLP + SP [at 2 yr (10/11), at 3.2 yr (6/11)] | Wound infection (*n* = 2), deteriorated FI (*n* = 1), dyspareunia (*n* = 2) |
| Van Laarhoven *et al*[31], 1999 (United Kingdom) | Retrospective cohort | TPI + LP [prolene mesh (Marlex®)] | 5 (entire cohort *n* = 22) | 52.1 (31.0-81.0) | 27 mo, median (5-54) | Symptom assessmentFluoroscopic defecographyPudendal nerve motor latency | Ability to evacuate rectum: improved (72.7%), unchanged (22.7%), deteriorated (4.5%); Significant decline in feeling of incomplete evacuation (Pre = 86.4%, PO = 45.5%, *P* = 0.01); Significant decline in rectocele depth (Pre = 2.9 cm, PO = 1.7 cm, *P* < 0.01); Significant decline in rectocele area (Pre = 7.8 cm, PO = 4.3 cm, *P* < 0.01); No correlation between | Wound infection (9.1%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | rectocele reduction and symptoms improvement | |
| Parker and Phillips [46], 1993 (United Kingdom) | Retrospective case series | TPI + LP [prolene mesh (Marlex®)] | 4 | 42-65 | 14 mo (6-18) | Symptom assessment | Successful rectal evacuation without digitation ($n$ = 3), digitation occasionally ($n$ = 1); Satisfaction ($n$ = 4) | NP |

ARM: Anorectal manometry; FI: Fecal incontinence; LP: Levatorplasty; MRP: Maximum resting pressure; MSP: Maximum squeeze pressure; NP: Not provided; PO: Postoperative; Pre: Preoperative; RVF: Rectovaginal fistula; SP: Sphincteroplasty; TPI: Transperineal implant; TPLP: Transperineal levatorplasty.

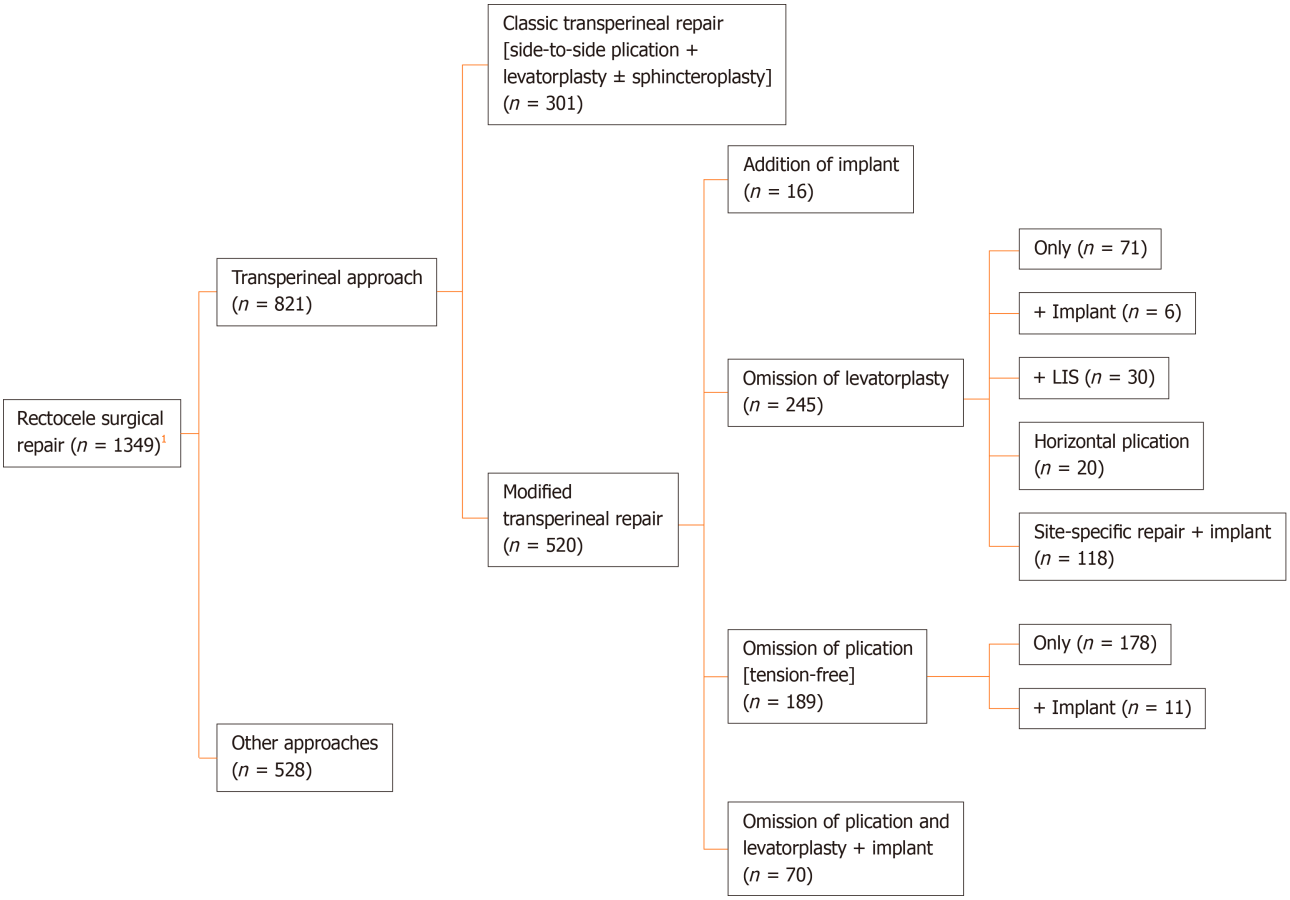


**Figure 2 Diagram illustrating different techniques of transperineal repair assessed in the studies reviewed.** [1]The total number of patients in the whole selected studies; LIS: Limited internal sphincterotomy.

with acceptably low complication rates that mostly comprised of wound infections. Mesh-related complications such as erosion were reported only once after TPR[29]. In contradiction, the Food and Drug Administration has recommended stopping the use of mesh implants to augment transvaginal repair because the agency did not receive sufficient evidence to assure that the potential benefits of mesh implants outweigh their probable risks that include mesh fistulation and erosion[49].

### *Limitations of the review*

The present review has a few limitations that include the small number of studies that assessed the outcome of transperineal repair of rectocele, namely those describing technical modifications. The heterogeneity of data reported in the studies precluded the conduction of a formal meta-analysis of the success and complications of the procedure. Further randomized trials comparing transperineal repair to other repair techniques would add more evidence on the efficacy of this approach.

## CONCLUSION

The transperineal repair of rectocele is associated with satisfactory, yet variable, improvement in ODS symptoms with a parallel increase in quality-of-life score. Several modifications of the classical TPR were described. These modifications include omission of levatorplasty, insertion of implants, performing lateral sphincterotomy, changing the direction of classical plication, and site-specific repair. The indications for these modifications are not yet fully clear and need further prospective studies to help tailor the technique to rectocele patients.

## ARTICLE HIGHLIGHTS

### *Research background*

Rectocele is a common finding in women. However; it may require surgical treatment when associated with symptoms of obstructed defecation. Transperineal repair is one of the common procedures used for rectocele repair with variable outcomes.

### *Research motivation*

The variable outcomes after transperineal repair of rectocele moved us to review the current literature for different technical modifications described to improve the procedure.

### *Research objectives*

To review the technique and outcomes of transperineal repair of rectocele and to investigate the different technical modifications introduced to the original technique of repair.

### *Research methods*

An organized literature search for studies that assessed the outcome of transperineal repair of rectocele was performed. PubMed/Medline and Google Scholar were queried in the period of January 1991 through December 2020.

### *Research results*

Twenty-four studies were included to this review. Nine studies including 301 patients assessed the classical transperineal repair of rectocele. The median rate of postoperative improvement in symptoms was 72.7% (range, 45.8%-83.3%), and reduction in rectocele size ranged from 41.4%-95.0%. Modifications of the classical repair entailed omission of levatorplasty, addition of implant, concomitant lateral internal sphincterotomy, changing the direction of plication of rectovaginal septum, and site-specific repair.

### *Research conclusions*

The transperineal repair of rectocele is associated with satisfactory, yet variable, improvement in obstructed defecation symptoms with parallel increase in quality-of-life score. Several modifications of the classical transperineal repair were described.

### *Research perspectives*

The indications for the technical modifications of transperineal rectocele repair are not yet fully clear and need further prospective studies to help tailor the technique to rectocele patients.

## REFERENCES

1 **Mustain WC**. Functional Disorders: Rectocele. *Clin Colon Rectal Surg* 2017; **30**: 63-75 [PMID: 28144214 DOI: 10.1055/s-0036-1593425]
2 **Dietz HP**. Can the rectovaginal septum be visualized by transvaginal three-dimensional ultrasound? *Ultrasound Obstet Gynecol* 2011; **37**: 348-352 [PMID: 21337655 DOI: 10.1002/uog.8896]
3 **Ladd M**, Tuma F. Rectocele. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2020
4 **Dariane C**, Moszkowicz D, Peschaud F. Concepts of the rectovaginal septum: implications for function and surgery. *Int Urogynecol J* 2016; **27**: 839-848 [PMID: 26690361 DOI:

10.1007/s00192-015-2878-3]
5 **Dietz HP**, Gómez M, Atan IK, Ferreira CSW. Association between vaginal parity and rectocele. *Int Urogynecol J* 2018; **29**: 1479-1483 [PMID: 29464300 DOI: 10.1007/s00192-017-3552-8]
6 **Dietz HP**, Clarke B. Prevalence of rectocele in young nulliparous women. *Aust N Z J Obstet Gynaecol* 2005; **45**: 391-394 [PMID: 16171474 DOI: 10.1111/j.1479-828X.2005.00454.x]
7 **Dietz HP**, Steensma AB. The role of childbirth in the aetiology of rectocele. *BJOG* 2006; **113**: 264-267 [PMID: 16487196 DOI: 10.1111/j.1471-0528.2006.00860.x]
8 **Richardson AC**. The anatomic defects in rectocele and enterocele. *J Pelvic Surg* 1995; **1**: 214-221
9 **Cundiff GW**, Fenner D. Evaluation and treatment of women with rectocele: focus on associated defecatory and sexual dysfunction. *Obstet Gynecol* 2004; **104**: 1403-1421 [PMID: 15572506 DOI: 10.1097/01.AOG.0000147598.50638.15]
10 **Lien KC**, Mooney B, DeLancey JO, Ashton-Miller JA. Levator ani muscle stretch induced by simulated vaginal birth. *Obstet Gynecol* 2004; **103**: 31-40 [PMID: 14704241 DOI: 10.1097/01.AOG.0000109207.22354.65]
11 **Iglesia CB**, Smithling KR. Pelvic Organ Prolapse. *Am Fam Physician* 2017; **96**: 179-185 [PMID: 28762694]
12 **Baden WF**, Walker TA. Genesis of the vaginal profile: a correlated classification of vaginal relaxation. *Clin Obstet Gynecol* 1972; **15**: 1048-1054 [PMID: 4649139 DOI: 10.1097/00003081-197212000-00020]
13 **Persu C**, Chapple CR, Cauni V, Gutue S, Geavlete P. Pelvic Organ Prolapse Quantification System (POP-Q) - a new era in pelvic prolapse staging. *J Med Life* 2011; **4**: 75-81 [PMID: 21505577]
14 **Palmer SL**, Lalwani N, Bahrami S, Scholz F. Dynamic fluoroscopic defecography: updates on rationale, technique, and interpretation from the Society of Abdominal Radiology Pelvic Floor Disease Focus Panel. *Abdom Radiol (NY)* 2021; **46**: 1312-1322 [PMID: 31375862 DOI: 10.1007/s00261-019-02169-y]
15 **Thapar RB**, Patankar RV, Kamat RD, Thapar RR, Chemburkar V. MR defecography for obstructed defecation syndrome. *Indian J Radiol Imaging* 2015; **25**: 25-30 [PMID: 25709162 DOI: 10.4103/0971-3026.150134]
16 **Coura MM**. The Role of Three-Dimensional Endoanal Ultrasound in Preoperative Evaluation of Anorectal Diseases**.** In: Proctological Diseases in Surgical Practice. Cianci P, editor. *Intech Open* 2018 [DOI: 10.5772/intechopen.76620]
17 **Albuquerque A**, Pereira E. Current applications of transperineal ultrasound in gastroenterology. *World J Radiol* 2016; **8**: 370-377 [PMID: 27158423 DOI: 10.4329/wjr.v8.i4.370]
18 **Institute for Quality and Efficiency in Health Care (IQWiG)**. Pelvic organ prolapse: Pelvic floor exercises and vaginal pessaries. [cited 13 July 2021]. In: InformedHealth.org [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525762/
19 **Coolen AWM**, Troost S, Mol BWJ, Roovers JPWR, Bongers MY. Primary treatment of pelvic organ prolapse: pessary use versus prolapse surgery. *Int Urogynecol J* 2018; **29**: 99-107 [PMID: 28600758 DOI: 10.1007/s00192-017-3372-x]
20 **Hall GM**, Shanmugan S, Nobel T, Paspulati R, Delaney CP, Reynolds HL, Stein SL, Champagne BJ. Symptomatic rectocele: what are the indications for repair? *Am J Surg* 2014; **207**: 375-379 [PMID: 24444857 DOI: 10.1016/j.amjsurg.2013.12.002]
21 **Zimmermann EF**, Hayes RS, Daniels IR, Smart NJ, Warwick AM. Transperineal rectocele repair: a systematic review. *ANZ J Surg* 2017; **87**: 773-779 [PMID: 28871666 DOI: 10.1111/ans.14068]
22 **Weledji EP**, Eyongeta DE. How I Do It? Surgical Management of Rectocele: A Transperineal Approach. *J Surg Tech Proced* 2020; **4**: 1035
23 **Balata M**, Elgendy H, Emile SH, Youssef M, Omar W, Khafagy W. Functional Outcome and Sexual-Related Quality of Life After Transperineal Versus Transvaginal Repair of Anterior Rectocele: A Randomized Clinical Trial. *Dis Colon Rectum* 2020; **63**: 527-537 [PMID: 31996580 DOI: 10.1097/DCR.0000000000001595]
24 **Emile SH**, Balata M, Omar W, Khafagy W, Elgendy H. Specific Changes in Manometric Parameters are Associated with Non-improvement in Symptoms after Rectocele Repair. *Int Urogynecol J* 2020; **31**: 2019-2025 [PMID: 32691118 DOI: 10.1007/s00192-020-04444-9]
25 **Tomita R**, Ikeda T, Fujisaki S, Sugito K, Sakurai K, Koshinaga T, Shibata M. Surgical technique for the transperineal approach of anterior levatorplasty and recto-vaginal septum reinforcement in rectocele patients with soiling and postoperative clinical outcomes. *Hepatogastroenterology* 2012; **59**: 1063-1067 [PMID: 22580656 DOI: 10.5754/hge09360]
26 **Mills RP**. Rectocele and anal sphincter defect - surgical anatomy and combined repair. *S Afr J Surg* 2011; **49**: 182-185 [PMID: 22353268]
27 **Farid M**, Madbouly KM, Hussein A, Mahdy T, Moneim HA, Omar W. Randomized controlled trial between perineal and anal repairs of rectocele in obstructed defecation. *World J Surg* 2010; **34**: 822-829 [PMID: 20091310 DOI: 10.1007/s00268-010-0390-y]
28 **Puigdollers A**, Fernández-Fraga X, Azpiroz F. Persistent symptoms of functional outlet obstruction after rectocele repair. *Colorectal Dis* 2007; **9**: 262-265 [PMID: 17298626 DOI: 10.1111/j.1463-1318.2006.01155.x]
29 **Hirst GR**, Hughes RJ, Morgan AR, Carr ND, Patel B, Beynon J. The role of rectocele repair in targeted patients with obstructed defaecation. *Colorectal Dis* 2005; **7**: 159-163 [PMID: 15720355 DOI: 10.1111/j.1463-1318.2004.00768.x]
30 **Ayabaca SM**, Zbar AP, Pescatori M. Anal continence after rectocele repair. *Dis Colon Rectum* 2002;

**45**: 63-69 [PMID: 11786766 DOI: 10.1007/s10350-004-6115-2]
31 **Van Laarhoven CJ**, Kamm MA, Bartram CI, Halligan S, Hawley PR, Phillips RK. Relationship between anatomic and symptomatic long-term results after rectocele repair for impaired defecation. *Dis Colon Rectum* 1999; **42**: 204-210 [PMID: 10211497 DOI: 10.1007/BF02237129]
32 **Ellis CN**. Outcomes after the repair of rectoceles with transperineal insertion of a bioprosthetic graft. *Dis Colon Rectum* 2010; **53**: 213-218 [PMID: 20087097 DOI: 10.1007/DCR.0b013e3181c8e549]
33 **Smart NJ**, Mercer-Jones MA. Functional outcome after transperineal rectocele repair with porcine dermal collagen implant. *Dis Colon Rectum* 2007; **50**: 1422-1427 [PMID: 17429710 DOI: 10.1007/s10350-007-0219-4]
34 **Mercer-Jones MA**, Sprowson A, Varma JS. Outcome after transperineal mesh repair of rectocele: a case series. *Dis Colon Rectum* 2004; **47**: 864-868 [PMID: 15085441 DOI: 10.1007/s10350-004-0526-y]
35 **Azanjac B**, Jorovic M. Transperineal repair of recurrent rectocele using polypropylene mesh. *Tech Coloproctol* 1999; **3**: 39-41 [DOI: 10.1007/s101510050010]
36 **Watson SJ**, Loder PB, Halligan S, Bartram CI, Kamm MA, Phillips RK. Transperineal repair of symptomatic rectocele with Marlex mesh: a clinical, physiological and radiologic assessment of treatment. *J Am Coll Surg* 1996; **183**: 257-261 [PMID: 8784320]
37 **Omar W**, Elfallal AH, Emile SH, Elshobaky A, Fouda E, Fathy M, Youssef M, El-Said M. Horizontal versus vertical plication of the rectovaginal septum in transperineal repair of anterior rectocele: a pilot randomized clinical trial. *Colorectal Dis* 2021; **23**: 923-931 [PMID: 33314521 DOI: 10.1111/codi.15483]
38 **Sari R**, Kus M, Arer I, Yabanoglu H. A Single-center Experience of Clinical Outcomes of Surgical Management for Rectocele Disease. *Turk J Colorectal Dis* 2019; **29**: 183-187 [DOI: 10.4274/tjcd.galenos.2019.2019-4-1]
39 **Lisi G**, Campanelli M, Grande S, Grande M, Mascagni D, Milito G. Transperineal rectocele repair with biomesh: updating of a tertiary refer center prospective study. *Int J Colorectal Dis* 2018; **33**: 1583-1588 [PMID: 29675591 DOI: 10.1007/s00384-018-3054-2]
40 **Youssef M**, Emile SH, Thabet W, Elfeki HA, Magdy A, Omar W, Khafagy W, Farid M. Comparative Study Between Trans-perineal Repair With or Without Limited Internal Sphincterotomy in the Treatment of Type I Anterior Rectocele: a Randomized Controlled Trial. *J Gastrointest Surg* 2017; **21**: 380-388 [PMID: 27778256 DOI: 10.1007/s11605-016-3299-4]
41 **Milito G**, Cadeddu F, Selvaggio I, Grande M, Farinon AM. Transperineal rectocele repair with porcine dermal collagen implant. A two year clinical experience. *Pelviperineology* 2010; **29**: 76-78
42 **Leventoğlu S**, Menteş BB, Akin M, Karen M, Karamercan A, Oğuz M. Transperineal rectocele repair with polyglycolic acid mesh: a case series. *Dis Colon Rectum* 2007; **50**: 2085-2092 [PMID: 18049839 DOI: 10.1007/s10350-007-9067-5]
43 **Fischer F**, Farke S, Schwandner O, Bruch HP, Schiedeck T. [Functional results after transvaginal, transperineal and transrectal correction of a symptomatic rectocele]. *Zentralbl Chir* 2005; **130**: 400-404 [PMID: 16220434 DOI: 10.1055/s-2005-836877]
44 **Boccasanta P**, Venturi M, Calabrò G, Trompetto M, Ganio E, Tessera G, Bottini C, Pulvirenti D'Urso A, Ayabaca S, Pescatori M. Which surgical approach for rectocele? *Tech Coloproctol* 2001; **5**: 149-156 [PMID: 11875682 DOI: 10.1007/s101510100017]
45 **Lamah M**, Ho J, Leicester RJ. Results of anterior levatorplasty for rectocele. *Colorectal Dis* 2001; **3**: 412-416 [PMID: 12790940 DOI: 10.1046/j.1463-1318.2001.00245.x]
46 **Parker MC**, Phillips RK. Repair of rectocoele using Marlex mesh. *Ann R Coll Surg Engl* 1993; **75**: 193-194 [PMID: 8323216]
47 **D'Hoore A**, Vanbeckevoort D, Penninckx F. Clinical, physiological and radiological assessment of rectovaginal septum reinforcement with mesh for complex rectocele. *Br J Surg* 2008; **95**: 1264-1272 [PMID: 18720463 DOI: 10.1002/bjs.6322]
48 **Altomare DF**, Rinaldi M, Veglia A, Petrolino M, De Fazio M, Sallustio P. Combined perineal and endorectal repair of rectocele by circular stapler: a novel surgical technique. *Dis Colon Rectum* 2002; **45**: 1549-1552 [PMID: 12432306 DOI: 10.1007/s10350-004-6465-9]
49 **Food and Drug Administration**. Urogynecologyic surgical mesh implant. July 10, 2019 [cited 13 July 2021]. Available from: https://www.fda.gov/medical-devices/implants-and-prosthetics/urogynecologic-surgical-mesh-implants

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*World J Gastrointest Surg* 2021 September 27; 13(9): 1079-1094

DOI: 10.4240/wjgs.v13.i9.1079

ISSN 1948-9366 (online)

META-ANALYSIS

# Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis

Hao-Han Hai, Phoebe Aw, Thomas Zheng Jie Teng, Vishal G Shelat

**ORCID number:** Hao-Han Hai 0000-0001-6210-5578; Phoebe Aw 0000-0003-1663-3489; Thomas Zheng Jie Teng 0000-0001-7355-9591; Vishal G Shelat 0000-0003-3988-8142.

**Author contributions:** Hai HH and Aw P performed the analysis of the results and writing of the manuscript; Teng TZJ contributed to editing the manuscript and interpreting the results; Shelat VG designed and directed the project; All authors discussed the results and commented on the manuscript.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



**Hao-Han Hai, Phoebe Aw,** NUS Yong Loo Lin School of Medicine, Singapore 119228, Singapore

**Thomas Zheng Jie Teng, Vishal G Shelat,** NTU Lee Kong Chian School of Medicine, Singapore 308232, Singapore

**Vishal G Shelat,** Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433, Singapore

**Corresponding author:** Vishal G Shelat, FRCS (Ed), FEBS, Adjunct Associate Professor, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. vgshelat@gmail.com

## Abstract

### *BACKGROUND*

Hepatic resection (HR) results in an inflammatory response that can be modified by perioperative steroid administration. However, it remains to be determined if this response's attenuation translates to a reduction in complications.

### *AIM*

To evaluate if perioperative administration of steroids reduces complications following HR.

### *METHODS*

A systematic review of randomized controlled trials (RCTs) was conducted on PubMed, Embase, and Cochrane Central Register of Controlled Trials to evaluate the effect of perioperative steroid (compared to placebo or no intervention) use in patients undergoing HR. Clinical outcomes were extracted, and meta-analysis was performed.

### *RESULTS*

8 RCTs including 590 patients were included. Perioperative steroid administration was associated with significant reduction in postoperative complications [odds ratios: 0.58; 95% confidence intervals (CI): 0.35-0.97, $P$ = 0.04]. There was also improvement in biochemical and inflammatory markers, including serum bilirubin on postoperative day 1 [MD: -0.27; 95%CI: (-0.47, -0.06), $P$ = 0.01], C-reactive protein on postoperative day 3 [MD: -4.89; 95%CI: (-5.83, -3.95), $P$ < 0.001], and interleukin-6 on postoperative day 1 [MD: -54.84; 95%CI: (-63.91, -45.76), $P$ < 0.001].

**Manuscript source:** Invited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Singapore

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** January 26, 2021
**Peer-review started:** January 26, 2021
**First decision:** March 29, 2021
**Revised:** April 3, 2021
**Accepted:** June 16, 2021
**Article in press:** June 16, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Aoki T, Bredt LC, Karamarkovic AR
**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Li JH

*CONCLUSION*

Perioperative steroids administration in HR may reduce overall complications, postoperative bilirubin, and inflammation. Further studies are needed to determine the optimal dose and duration and patient selection.

**Key Words:** Steroid; Liver resection; Outcome; Systematic review



**Core Tip:** Hepatic resection results in an inflammatory response that can be modified by perioperative steroid administration. However, it remains to be determined if this response's attenuation translates to a reduction in complications. This systematic review compares eight randomized controlled trials including 590 patients. We found that perioperative steroid administration was associated with a significant reduction in postoperative complications. There was also improvement in biochemical and inflammatory markers.

**Citation:** Hai HH, Aw P, Teng TZJ, Shelat VG. Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis. *World J Gastrointest Surg* 2021; 13(9): 1079-1094
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1079.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1079

## INTRODUCTION

Stress from major surgery results in an inflammatory response secondary to cytokine and free radical release. This inflammatory response is essential for healing and restoring physiologic function; however, it can increase morbidity, mortality and worsen postoperative outcomes if excessive[1]. Modifying the inflammatory response by perioperative steroid administration could improve surgical outcomes. In a rabbit experiment conducted almost five decades ago, Santiago Delpín *et al*[2] demonstrated that preoperative methylprednisolone administration attenuated the inflammatory response secondary to hepatic inflow occlusion[2] and improved survival as compared to postoperative or no steroid administration and concluded that methylprednisolone protects liver during warm ischemia.

With a better understanding of liver anatomy, advances in surgical technology, and improvements in critical care, hepatic resection (HR) is accepted as a gold standard treatment for primary and metastatic liver cancers[3]. HR is major abdominal surgery with the potential for blood loss, tissue hypoperfusion, and acidosis[4]. Further, low central venous pressure anesthesia and hepatic inflow occlusion with resulting ischemia-reperfusion injury aggravate the inflammatory response[5,6]. Perioperative morbidity and mortality following elective HR, though has reduced, further improvements[7] are needed. Besides, inflammatory markers are increasingly shown to predict short-term perioperative and long-term oncologic outcomes following HR [8]. Thus, modulation of inflammatory response to improve surgical outcomes remains an unmet need in hepatic surgery. In a systematic review and meta-analysis on the benefit of preoperative steroid administration in patients undergoing HR, Yang *et al*[9] has shown a reduction in postoperative day 1 bilirubin, postoperative day 1 interleukin-6 (IL-6), and postoperative day 3 C-reactive protein (CRP) levels but no difference in liver failure, bile leak, infectious complications, wound complications and pleural effusion. It is unclear if the advantages of perioperative steroid immunomodulation are nullified by inherent risks associated with steroid therapy itself: Hyperglycemia, predisposition to infection, impairment of wound healing, and reactivation of the hepatitis virus[10]. Thus, it remains to be determined if an inflammatory response's attenuation translates to a reduction in perioperative complications, and more evidence is needed. We report an updated meta-analysis on the benefits of perioperative steroid administration in patients undergoing HR.

## MATERIALS AND METHODS

### Literature search

The search was conducted according to the PRISMA statement[11]. A literature search of published studies on perioperative use of steroids in PubMed, EMBASE, and Cochrane Library databases was independently conducted by two co-authors (Aw P and Hai HH). A combination of subject headings and text words were used as needed to define the use of steroids in liver resection. We employed the terms ("Liver surger*" OR "Liver resection*" OR "Resection of Liver" OR "Resection Liver" OR "HR*" OR Hepatectom* OR "Liver remov*" OR "Liver lobectom*" OR "Hepatic Lobectom*" OR "Lobectomy of Liver" OR "Hemihepatectom*") and ("Steroids" OR "Betamethasone" OR "Dexamethasone" OR "Prednisone" OR "Prednisolone" OR "Fluprednisolone" OR "Methylprednisolone" OR "Fluocortolone" OR "Paramethasone" OR "Cortisone" OR "Cortisol" OR "Hydrocortisone" OR "Fludrocortisone" OR "Hydroxycorticosteroids" OR "Glucocorticoids" OR "Corticosteroids").

### Inclusion criteria and study selection

Only prospective randomized controlled trials (RCTs), either open-label, single or double-blinded, were included in this study. Inclusion criteria were major or minor HR, regardless of pathology. Studies that involved perioperative prophylactic administration of steroids in improving the outcome of HR and which contained a control group (placebo or no intervention) were included. For studies to be included, the outcomes measured should include the following postoperative liver function tests: Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or prothrombin time. When there was a duplication of data, the most recent and comprehensive study was included. Articles not written in English or Mandarin language were excluded. The co-author (Aw P) is a native Mandarin language speaker and translated the Mandarin report into English. We excluded case series and non-human studies. Identified studies were assessed independently by two co-authors (Aw P and Hai HH) for potential inclusion, initially by title and abstract. After the initial screening, the full text was obtained and reviewed in its entirety. Any conflict was resolved by consensus or in consultation with the senior author (Shelat VG). References of included studies were screened to identify for additional study.

### Data extraction and analyses

From each included study, two co-authors (Aw P and Hai HH) independently extracted the following information: Publication details (first author, year of publication), study characteristics (study design, intervention and control group sample, gender, age, type of resection), and study outcomes (postoperative outcomes, morbidity, and mortality). A meta-analysis was performed with data available on postoperative outcomes following perioperative steroids administration using Review Manager Version 5.3 (Cochrane Collaboration). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the Cochrane Mantel Haenszel method test based on the random effects model or dichotomous data, while continuous data were calculated using weighted mean differences and 95%CI. The level of statistical significance was set at $P < 0.05$. To assess heterogeneity between the studies, $I^2$ was calculated to estimate the variability among the included studies. An $I^2$ of > 50% suggested considerable heterogeneity. Studies that presented data in graphical form were omitted as it was not possible to extract the data accurately and attempts to contact the authors of the original studies were unsuccessful. Data excluded are postoperative day 1 (POD1) AST and ALT in the study by Hayashi *et al*[12] and POD1 Bilirubin and ALT from the study by Donadon *et al*[13].

### Outcomes of review

The primary outcomes of interest included the clinical outcomes–postoperative morbidity, length of hospital stay, and mortality. Where possible, data on specific subcategories of complications (hepatobiliary, pulmonary, and infectious complications) were extracted and analyzed. The secondary outcomes of interest included serological outcomes - postoperative liver function parameters (bilirubin, AST, ALT, prothrombin time) and postoperative inflammatory markers (CRP, IL-6).

### Risk of bias and quality assessment

Two co-authors (Aw P and Hai HH) independently assessed and checked the included studies to ensure consistency and check for bias risk. The various risks of bias assessment were done using Review Manager Version 5.3. The biases involving

random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias, were considered. The GRADE approach[14] was used to evaluate the quality of the body of evidence for each outcome measure.

## RESULTS

### Data extraction

A systematic search identified 4684 studies, of which 242 duplicate studies were excluded. Subsequent screening of title and abstract was performed independently by two authors (Aw P and Hai HH), and 61 studies were identified for full-text evaluation. Finally, eight prospective RCTs involving 590 patients were included in this meta-analysis (Table 1 and Table 2). A detailed diagram showing the search process is shown in Figure 1. In total, 296 patients were randomized into the intervention group, consisting of various regimens of perioperative administration of steroids, and 294 patients into the control group (Table 3).

### Use of steroids

The steroids used (Table 3) included methylprednisolone[13,15-20] and hydrocortisone [12], with varying methods of administration. All except one study[12] administered the steroid regime preoperatively, with Hayashi *et al*[12] administering steroids intraoperatively immediately before hepatic-pedicle clamping and subsequent steroid administration on postoperative days 1-3. We elected not to exclude the study by Hayashi *et al*[12] merely due to the difference in choice of steroid as the dose and duration were appropriately modified for equipotency for efficacy.

### Study quality

Heterogeneity of the primary outcomes and secondary outcomes was analyzed. Of note, there was statistically significant heterogeneity in the length of hospital stay ($I^2$ 60%, $P$ = 0.02). Other primary outcomes did not show statistically significant heterogeneity-overall morbidity ($I^2$ = 35%, $P$ = 0.15), hepatobiliary complications ($I^2$ = 0%, $P$ = 0.95), liver dysfunction ($I^2$ = 0%, $P$ = 0.98), bile leakage ($I^2$ = 0%, $P$ = 0.89), pulmonary complications ($I^2$ 40%, $P$ = 0.52), pleural effusion ($I^2$ 3%, $P$ = 0.36), surgical site infection ($I^2$ = 40%, $P$ = 0.21), ascites ($I^2$ = 0%, $P$ = 0.81), and hemorrhage ($I^2$ = 0%, $P$ = 0.99). All of the secondary outcomes showed statistically significant heterogeneity except POD1 IL-6 Levels ($I^2$ 53%, $P$ = 0.08). The heterogeneity for secondary outcomes was as follows: POD1 bilirubin ($I^2$ = 73%, $P$ < 0.001), POD1 AST ($I^2$ = 69%, $P$ = 0.04), POD1 ALT ($I^2$ = 79%, $P$ = 0.003), POD1 prothrombin ($I^2$ = 72%, $P$ = 0.003), and postoperative day 3 (POD3) CRP ($I^2$ = 60%, $P$ = 0.04). Due to the small number of studies, a funnel plot analysis was not conducted. The studies included in this systematic review were assessed with a summary of the Risk of Bias assessment shown in Figure 2. Biases assessed were detailed previously under the "Material and Methods" section.

### Primary outcomes: Postoperative clinical parameters

All 8 studies including a total of 590 patients (296 in the steroids group and 294 in the control group) reported postoperative morbidity. Overall morbidity was lower in the steroid group compared to the control group [OR: 0.58, 95%CI: (0.35, 0.97), $P$ = 0.04] (Figure 3A). Six out of eight studies[12,15-19] including a total of 475 patients (240 in the steroids group and 235 in the control group) reported on hepatobiliary complications, and no statistically significant difference was found between the two groups [OR: 0.65; 95%CI: (0.28, 1.50); $P$ = 0.31] (Figure 3B). 7 out of 8 studies[12,13,15-17,19,20] including a total of 540 patients (271 in the steroid group and 269 in the control group) reported length of hospital stay, and this was not different between the steroid group and the control group [MD: -0.06, 95%CI: (-1.47, 1.35), $P$ = 0.93] (Figure 3C).

Regarding specific hepatobiliary complications, three out of eight studies reported on liver dysfunction or failure[15-17] and five out of eight studies reported on bile leakage[12,16-19]. No statistically significant difference could be found between the two groups in both liver dysfunction or failure [OR: 1.02, 95%CI: (0.20, 5.21), $P$ = 0.98] (Figure 4A) and bile leakage (OR: 0.56, 95%CI: (0.20, 1.52), $P$ = 0.25) (Figure 4B).

Four out of eight studies[12,15,17,20], including a total of 396 patients (198 in the steroids group and 198 in the control group), reported pulmonary complications. For pulmonary complications, no significant difference was detected between the two

**Table 1 Patient profile of included studies (distribution, age, sex, and pathology)**

| Ref. | Number | | Age | | Sex (M/F) | | Pathology | | |
|---|---|---|---|---|---|---|---|---|---|
| | Steroid | Control | Steroid | Control | Steroid | Control | | Steroid | Control |
| Donadon *et al*[13], 2016 | 16 | 16 | 65 (27-80)[1] | 63 (22-77)[1] | 10/6 | 9/7 | Metastasis | 6 | 12 |
| | | | | | | | HCC | 6 | 2 |
| | | | | | | | Cholangiocarcinoma | 4 | 0 |
| | | | | | | | Others | 0 | 2 |
| Hasegawa *et al*[15], 2020 | 50 | 50 | 67 (59-74)[2] | 68 (62–75)[2] | 30/20 | 31/19 | Metastasis | 21 | 14 |
| Hayashi *et al*[12], 2011 | 102 | 98 | 69 (39-81)[1] | 70 (35-82)[1] | - | - | Metastasis | 32 | 23 |
| | | | | | | | HCC | 63 | 66 |
| | | | | | | | Cholangiocarcinoma | 6 | 5 |
| | | | | | | | Others | 1 | 4 |
| Muratore *et al*[20], 2003 | 25 | 28 | 65.4 ± 10.8[3] | 64.1 ± 11.7[3] | 8/17 | 11/17 | - | - | - |
| Pulitanò *et al*[17], 2007 | 37 | 36 | 63 (31-85)[4] | 61.8 (21-78)[4] | 23/14 | 22/14 | Metastasis | 16 | 14 |
| | | | | | | | HCC | 12 | 14 |
| | | | | | | | Cholangiocarcinoma | 5 | 4 |
| | | | | | | | Hemangioendothelioma | 1 | 1 |
| | | | | | | | Benign | 3 | 3 |
| Schmidt *et al*[18], 2007 | 10 | 10 | 575 | 655 | 3/7 | 4/6 | HCC | 2 | 1 |
| | | | | | | | Metastasis | 4 | 4 |
| | | | | | | | Cholangiocarcinoma | 0 | 2 |
| | | | | | | | Benign | 4 | 3 |
| Yamashita *et al*[16], 2001 | 17 | 16 | 60.3 ± 1.8[6] | 56.8 ± 3.9[6] | 4/13 | 11/5 | HCC | 13 | 8 |
| | | | | | | | Metastasis | 0 | 3 |
| | | | | | | | Cholangiocarcinoma | 0 | 1 |
| | | | | | | | Living donor of transplant | 4 | 4 |
| Zi *et al*[19], 2015 | 40 | 39 | 57.55 ± 8.81[3] | 57.51 ± 10.32[3] | 23/17 | 17/22 | Malignant | 31 | 34 |
| | | | | | | | Benign | 9 | 5 |

[1]Median (range).
[2]Median (interquartile range).
[3]mean ± SD.
[4]Mean with range.
[5]Mean.
[6]mean ± SE.
M: Male; F: Female; HCC: Hepatocellular carcinoma.

groups (OR: 0.79, 95%CI: (0.42, 1.47), $P$ = 0.45) (Figure 5A). There was also no significant difference in pleural effusion between the two groups (OR: 0.89, 95%CI: (0.43, 1.88), $P$ = 0.77) (Figure 5B).

Six out of eight studies[12,15-19] including a total of 475 patients (240 in the steroids group and 235 in the control group) reported on postoperative infection rates. There was no statistically significant difference between the two groups (OR: 0.84, 95%CI: (0.39, 1.81), $P$ = 0.66) for infectious complications (Figure 6).

Lastly, five out of eight studies[12,13,15,16,19] including a total of 444 patients (225 in the steroids group and 219 in the control group) reported on postoperative mortality. Mortality was defined as 90-d mortality in Donadon *et al*[13] and Hasegawa *et al*[15]. The remaining three authors did not define mortality. There were no postoperative deaths reported.

**Table 2 Surgical details of included studies (type of resection, duration, blood loss and volume resected)**

| Ref. | Type of resection | | | Duration of operation/min | | Volume of blood loss/mL | | Volume of liver resected/g | |
|---|---|---|---|---|---|---|---|---|---|
| | | Steroid | Control | Steroid | Control | Steroid | Control | Steroid | Control |
| Donadon *et al*[13], 2016 | Minor | 9 | 11 | 383.5 (235-546)[1] | 351 (226-640)[1] | 275 (100-1000)[1] | 200 (0-700)[1] | - | - |
| | Major | 7 | 5 | | | | | | |
| Hasegawa *et al*[15], 2020 | Minor | 40 | 39 | 215 (170-294)[2] | 233 (157-270)[2] | 52 (29-149)[2] | 34 (17-76)[2] | - | - |
| | Major | 10 | 11 | | | | | | |
| Hayashi *et al*[12], 2011 | Hemihepactectomy | 11 | 15 | 330 (165-834)[1] | 316 (136-697)[1] | 324 (5-1577)[1] | 257 (10-1972)[1] | 77 (4-1930)[1] | 75 (6-1300)[1] |
| | Segmentectomy | 59 | 57 | | | | | | |
| | Limited resection | 32 | 26 | | | | | | |
| Muratore *et al*[20], 2003 | Minor | 12 | 13 | - | - | 322.8 ± 261.4[3] | 294.6 ± 271.9[3] | - | - |
| | Major | 13 | 15 | | | | | | |
| Pulitanò *et al*[17], 2007 | Right hepactectomy | 11 | 10 | 440 (220-480)[1] | 408 (240-460)[1] | 662 (300-800)[1] | 621 (350-720)[1] | 40.4 ± 20[3] (%) | 39.5 ± 18[3] (%) |
| | Left hepatectomy | 6 | 8 | | | | | | |
| | Extended right hepatectomy | 5 | 4 | | | | | | |
| | Extended left hepatectomy | 2 | 2 | | | | | | |
| | Bisegmentectomy | 6 | 4 | | | | | | |
| | Segmentectomy | 4 | 5 | | | | | | |
| | Wedge resection | 3 | 3 | | | | | | |
| Schmidt *et al*[18], 2007 | Segment II/III | 4 | 5 | 2224 | 2524 | 3404 | 7804 | - | - |
| | Segment V-VIII | 6 | 5 | | | | | | |
| Yamashita *et al*[16], 2001 | Lobectomy or more | 5 | 6 | 338 ± 21[5] | 352 ± 14[5] | 892 ± 106[5] | 822 ± 55[5] | 239 ± 50[5] | 187 ± 33[5] |
| | Segmentectomy | 2 | 1 | | | | | | |
| | Subsegmentectomy or less | 10 | 9 | | | | | | |
| Zi *et al*[19], 2015 | Major | 22 | 12 | 342.38 ± 129.73[3] | 353.21 ± 168.36[3] | 481.25 ± 415.98[3] | 496.15 ± 391.59[3] | - | - |
| | Minor | 18 | 27 | | | | | | |

[1]Median (range).
[2]Median (interquartile range).
[3]mean ± SD.
[4]Mean.
[5]mean ± SE.

### *Secondary outcomes: Liver function parameters*

Six out of eight studies[12,15,16,18-20] including a total of 485 patients (244 in the steroids group and 241 in the control group) reported bilirubin levels on POD1. We found a statistically significant decrease in POD1 bilirubin levels in the steroid group compared to the control group [MD: -0.27, 95%CI (-0.47, -0.06), $P = 0.01$] (Figure 7A).

Three out of eight studies[15,16,19] including a total of 212 patients (107 in the steroids group and 105 in the control group) reported AST on POD1. For POD1 AST levels, no statistically significant difference was found between the intervention group and control group [MD: 39.22, 95%CI: (-41.19, 119.63), $P = 0.34$] (Figure 7B).

Four out of eight studies[15,16,18,19] including a total of 232 patients (117 in the steroids group and 115 in the control group) reported ALT on POD1. For POD1 ALT levels, no statistically significant difference was found between the intervention group and control group [MD: 46.79, 95%CI: (-45.55, 139.12), $P = 0.32$] (Figure 7C).

**Table 3 Perioperative steroid protocols of included studies**

| Ref. | Study design | Country | Steroid protocol | Control protocol |
|---|---|---|---|---|
| Donadon *et al* [13], 2016 | RCT | Italy | Preoperative bolus infusion (5%) of 500 mg methylprednisolone in 250 mL glucose for 1 h prior to hepatectomy, then continuous infusion for 6 h | 250 mL glucose-5% as bolus and subsequent continuous infusion |
| Hasegawa *et al* [15], 2020 | RCT | Japan | Preoperative, up to 500 mg methylprednisolone in saline solution | Saline only |
| Hayashi *et al* [12], 2011 | RCT | Japan | Intraoperative 500 mg hydrocortisone immediately prior to hepatic-pedicle clamping 300 mg hydrocortisone on POD1 200 mg on POD 2, 100 mg on POD3 | 0 |
| Muratore *et al* [20], 2003 | RCT | Italy | Preoperative (30 min before surgery) 30 mg/kg *per* body weight IV methylprednisolone | 0 |
| Pulitanòet al [17], 2007 | RCT | Italy | Preoperative 500 mg methylprednisolone | 0 |
| Schmidt *et al* [18], 2007 | RCT | Germany | Preoperative (90 min before surgery) 30 mg/kg per body weight IV methylprednisolone | 50 mL IV saline |
| Yamashita *et al* [16], 2001 | RCT | Japan | Preoperative (2 h before surgery) 500 mg IV methylprednisolone | 0 |
| Zi *et al*[19], 2015 | RCT | China | Intraoperative 500 mg methylprednisolone prior to liver resection | Hepatectomy only |

RCT: Randomized controlled trial; IV: Intravenous; POD: Postoperative day.

Six out of eight studies[12,15-18,20] including a total of 449 patients (225 in the steroids group and 224 in the control group) reported data on prothrombin time on POD1. For POD1 prothrombin time, no statistically significant difference was found between perioperative administration of steroids and postoperative prothrombin time [MD: -0.02, 95%CI: (-0.07, 0.03), $P = 0.40$] (Figure 7D).

### *Secondary outcomes: Postoperative inflammatory markers*

Five out of eight studies[12,15,16,18,19] including a total of 432 patients (219 in the steroids group and 213 in the control group) reported CRP levels on POD3. We found a statistically significant decrease in POD3 CRP levels in the steroids group compared to the control group [MD: -4.89, 95%CI: (-5.83, -3.95), $P < 0.001$] (Figure 8A).

Five out of eight studies[12,15,16,18,20] including a total of 239 patients (119 in the steroids group and 120 in the control group) reported POD1 IL-6 levels. We found a statistically significant decrease in the POD1 IL-6 levels between the intervention group and control group [MD: -54.84, 95%CI: (-63.91, -45.76), $P < 0.001$] (Figure 8B).

## DISCUSSION

Steroids were introduced in medicine for almost a century, and their use has evolved with an enhanced understanding of human physiology, pharmacokinetics, and critical care principles. There is substantial evidence for continuing perioperative "stress dose" steroids in patients who are already taking steroids as part of chronic disease management. Recently, the anti-inflammatory and immune-modulating benefits of steroids are exploited to reduce postoperative nausea and vomiting (PONV) and pain. PONV is associated with general anesthesia and implicated in causing aspiration pneumonia, wound complications, psychological distress, and prolonged hospital length of stay; and thus, perioperative steroid use remains attractive to improve clinical outcomes. In a systematic review including 17 clinical trials, Karanicolas *et al* [21] reported that prophylactic dexamethasone decreases the incidence of PONV after laparoscopic cholecystectomy relative to placebo [RR: 0.55, 95%CI: (0.44, 0.67)][21], and the effect was dose-dependent and independent of the use of other anti-emetics. However, there are concerns that the hyperglycemia and immunosuppressive effect of corticosteroids may increase the risk of infectious complications, delay wound healing, and increase hospital length of stay[22].

Further, in patients undergoing HR, coagulation disturbance, and ischemia-reperfusion injury may impact clinical outcomes. The studies reporting perioperative steroid use in patients undergoing HR have shown inconsistent benefits. In a meta-

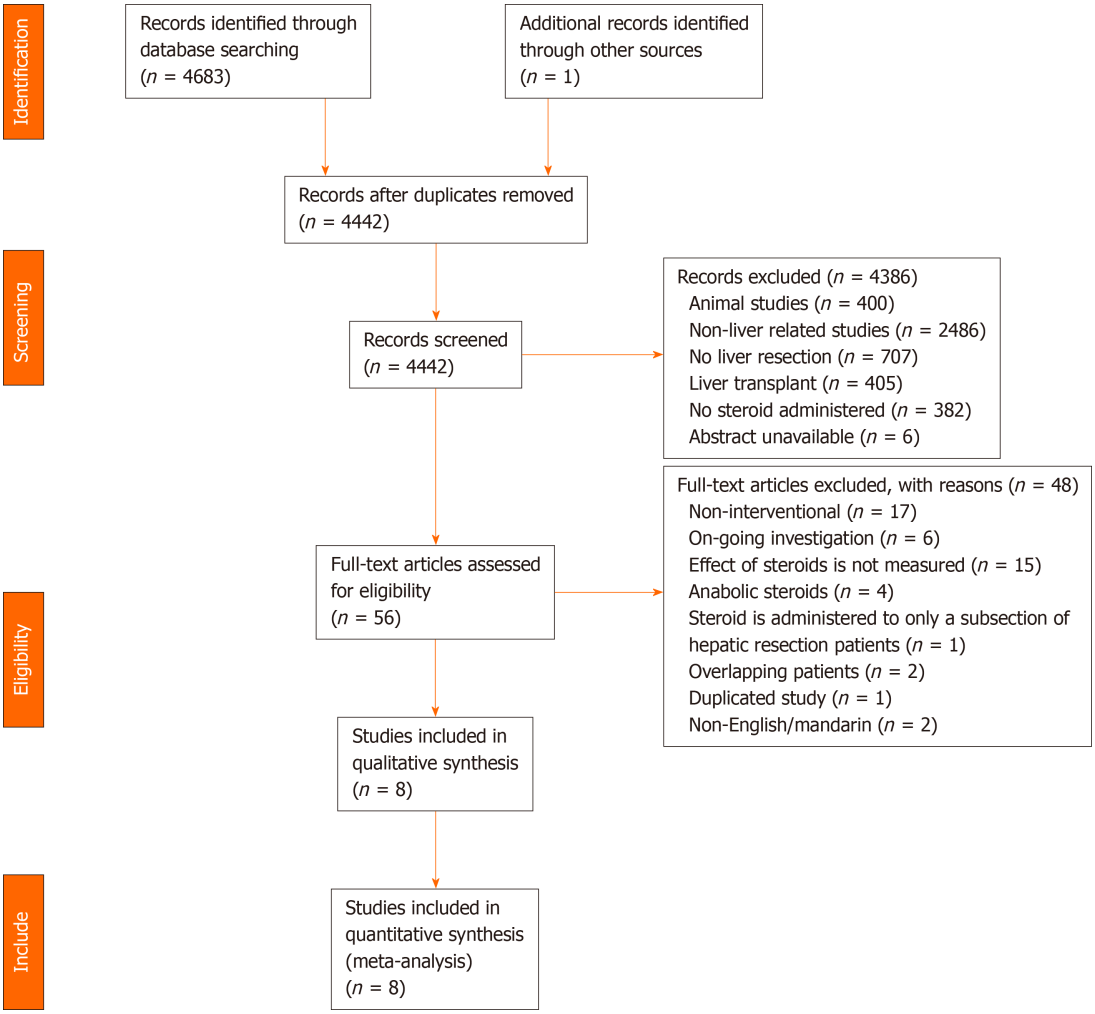


**Figure 1 PRISMA flow diagram of preoperative administration of steroids in liver resection.**

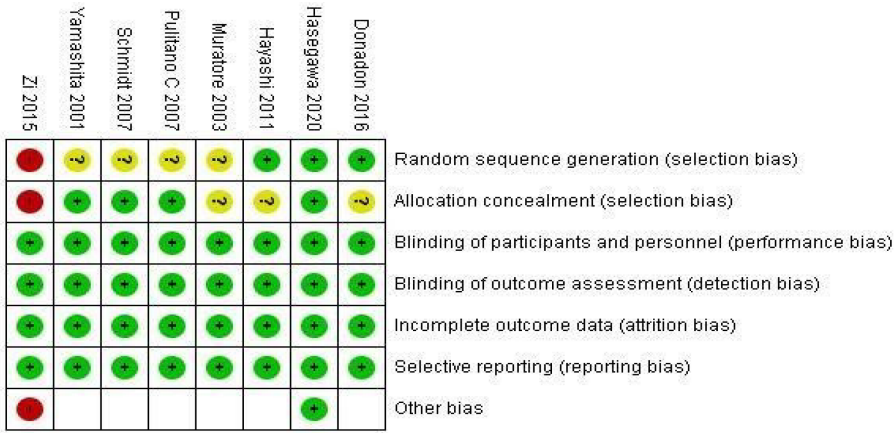


**Figure 2 Risk of bias assessment using Cochrane collaboration's risk of bias tool.**

analysis including six prospective RCTs and 411 patients undergoing HR, Yang *et al*[9] has reported that preoperative administration of steroid promotes the recovery of liver function and inhibits the inflammatory response without increasing postoperative complications[9]. However, there was no benefit in reducing overall morbidity [OR: 0.57, 95%CI: (0.27, 1.17), $P$ = 0.13]. This updated meta-analysis includes 43.6% more patient sample (590 *vs* 411) and shows that perioperative steroid administration reduces overall morbidity. Also, POD1 bilirubin and IL-6 and POD3 CRP levels were lower in patients receiving perioperative steroids. However, perioperative steroid

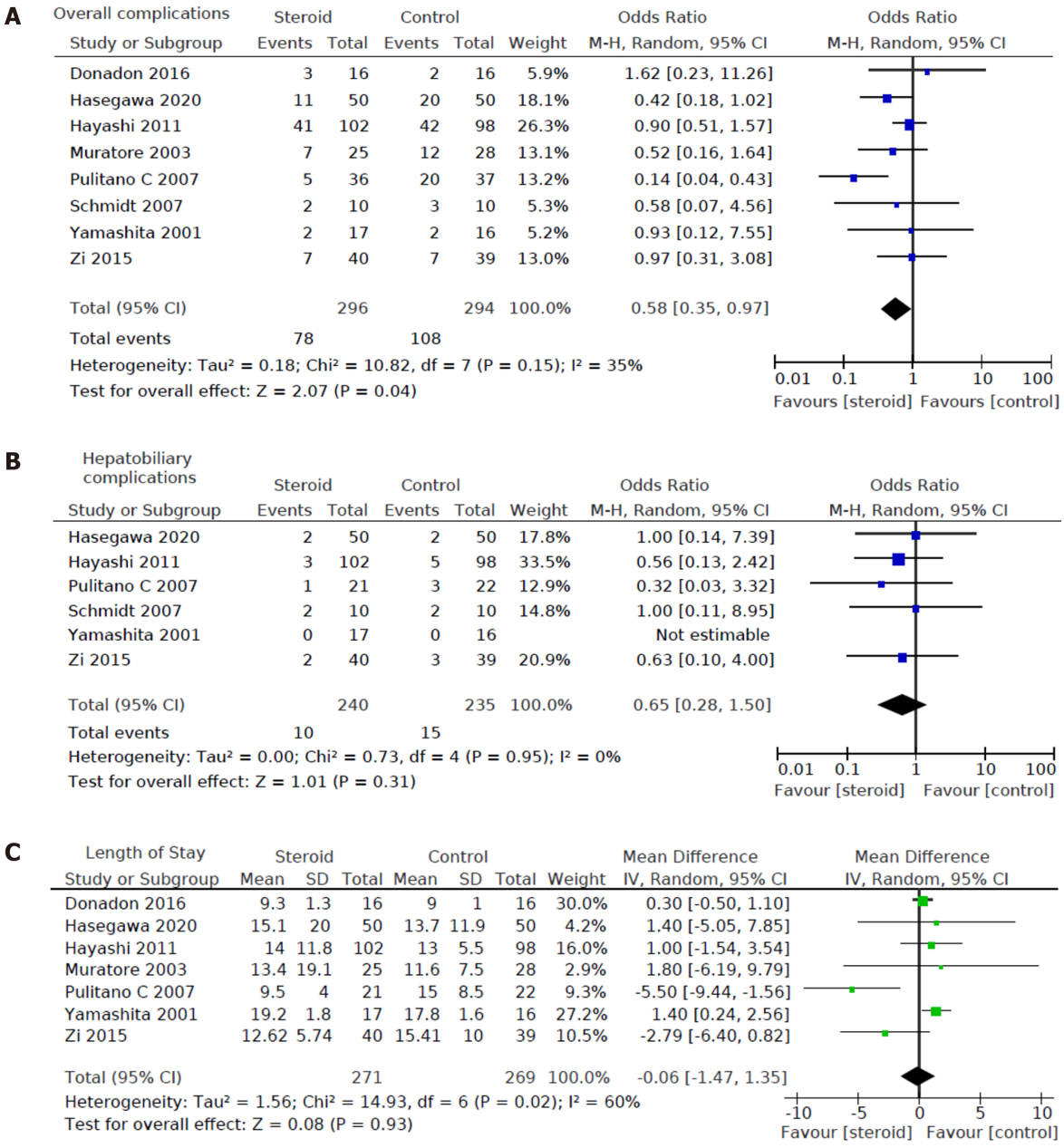


**Figure 3 The pooled results comparing steroids group to the control group.** A: Overall complications; B: Hepatobiliary complications; C: Length of stay, illustrated by forest plots. Random effects model was used. M-H: Mantel-Haenszel; IV: Inverse variance; CI: Confidence interval.

administration did not reduce individual hepatobiliary specific (liver dysfunction and bile leak), pulmonary or infectious complications. The effect of reduction in cumulative overall morbidity could be explained due to small and non-significant reductions in individual organ-specific complications.

Patients undergoing HR are routinely monitored postoperatively with serologic investigations including lactate, blood gas analysis, renal function, liver function, coagulation screen, and full blood count. Elevated serum bilirubin predicts postoperative liver dysfunction and is an important determinant of perioperative outcomes[3,23]. Serum bilirubin is dependent on the prehepatic load of heme, hepatic function, and biliary excretory function. International Study Group of Liver Surgery [24] proposed an elevated international normalized ratio together with hyperbilirubinemia on or after POD5 to predict post-hepatectomy liver failure. Similarly, in a study of 775 patients, Balzan *et al*[25] showed that a prothrombin time less than 50% of normal combined with serum bilirubin > 50 μmol/L on POD5 predicted mortality. Our results show that perioperative steroid administration was associated with lower serum bilirubin at POD1 but did not reduce liver dysfunction incidence, consistent with the previous report by Yang *et al*[9]. This could be due to few possible explanations. The definition of liver dysfunction or failure is heterogeneous in various

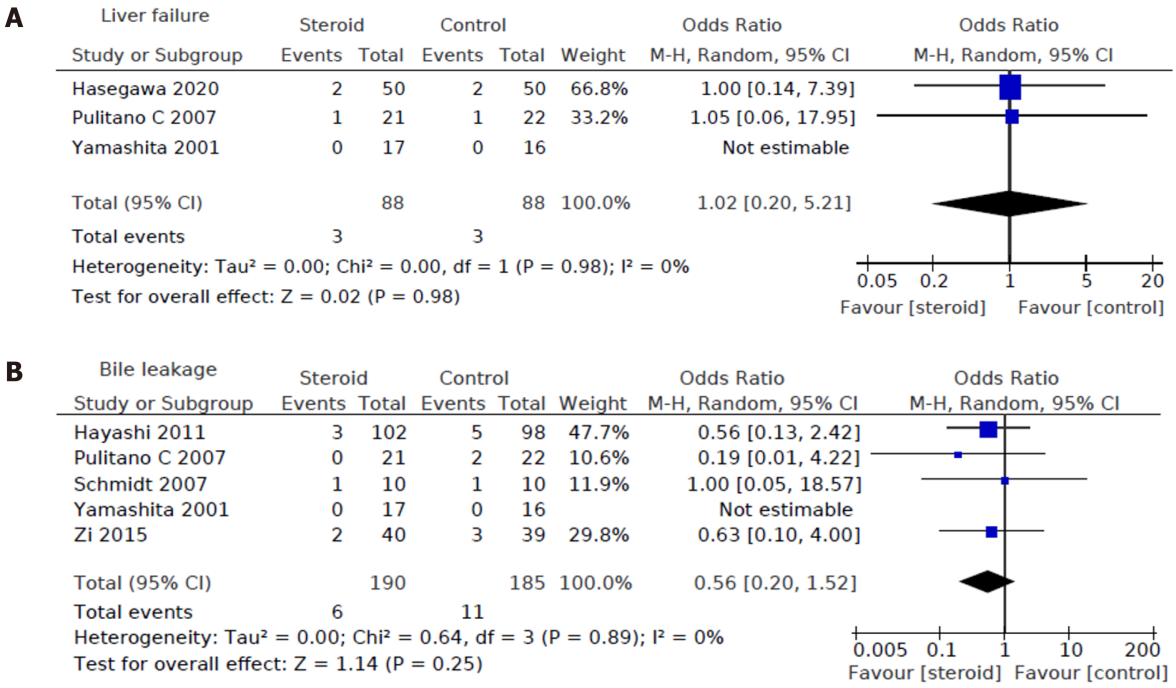


**Figure 4 Pooled results comparing steroids group to the control group.** A: Liver failure; B: Bile leakage, illustrated by forest plots. Random effects model was used. M-H: Mantel-Haenszel; CI: Confidence interval.

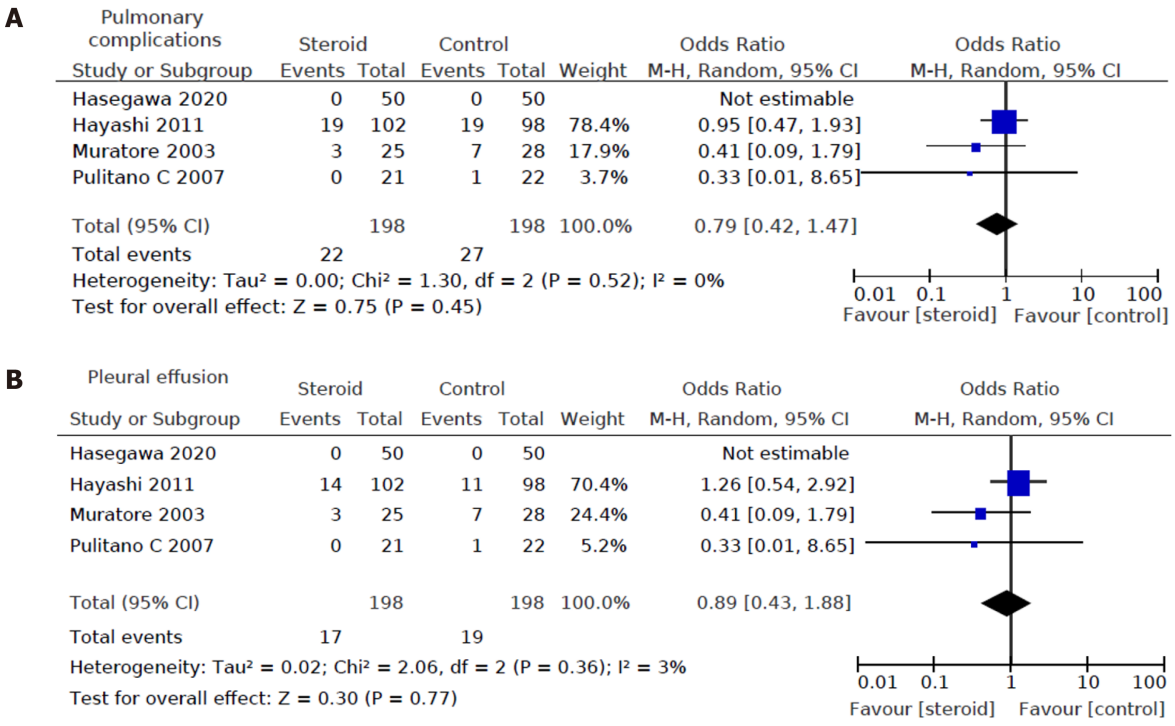


**Figure 5 Pooled results comparing steroids group to the control group.** A: Pulmonary complications; B: Pleural effusion, illustrated by forest plots. Random effects model was used. M-H: Mantel-Haenszel; CI: Confidence interval.

included studies. In addition, POD1 bilirubin is not a reliable predictor of liver dysfunction as liver regeneration occurs over time, and bilirubin trends over the next few days are more critical than POD1 Levels. Lastly, CRP levels that fall too quickly on POD1 are associated with a higher risk of postoperative liver failure[26].

AST/ALT are markers of hepatocellular injury, and their levels tend to peak during the early postoperative period[27]. The levels following HR are influenced by hepatic ischemia and the duration of surgery[28]. Our results show that perioperative steroid modulation does not attenuate AST/ALT elevation, consistent with previous reports

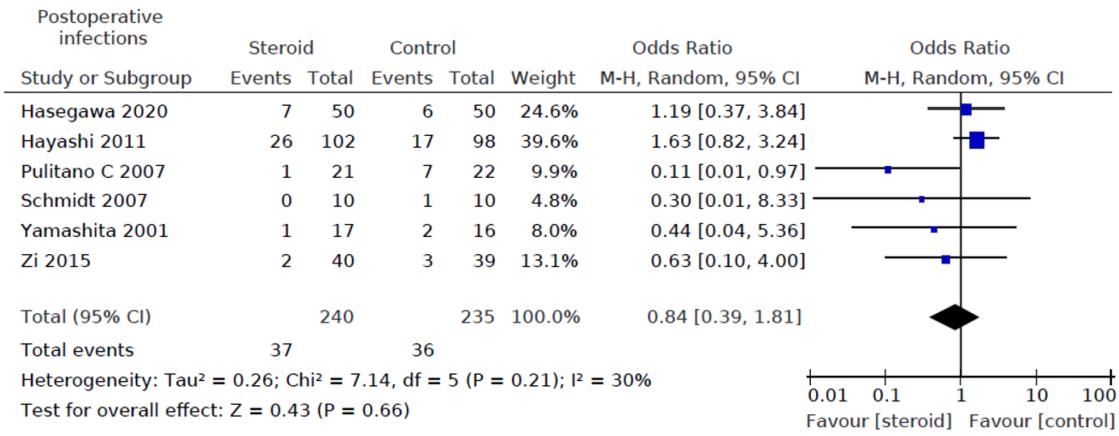


**Figure 6 Pooled results comparing steroids group to the control group.** Postoperative infection rate illustrated by forest plots. The pooled results comparing steroids group to the control group regarding Postoperative infection rate illustrated by forest plots. Random effects model was used. M-H: Mantel-Haenszel; CI: Confidence interval.

[9,20]. In a prospective RCT including 53 patients undergoing HR, Muratore *et al*[20] reported that preoperative administration of methylprednisolone (30 mg/kg 30 min before HR) reduced serum IL-6 levels in all patients. However, the effect on AST/ALT was mostly observed in patients with chronic liver disease[20]. Heterogeneity in patient demography and clinic profile, duration of surgery, blood loss, and anesthetic care may mask the effect of steroids on AST/ALT. Asians have a higher body fat percentage than Caucasians of similar body mass indices[29], which may lead to higher AST and ALT levels.

Inflammatory biomarkers are simple, cheap, readily available, and are increasingly reported to predict short-term perioperative and long-term oncologic outcomes in patients undergoing HR[8]. IL-6 is an acute phase cytokine transiently released in response to tissue injury and infections. Elevated IL-6 is associated with postoperative morbidity[5,17]. Previous studies have linked postoperative cytokines with a higher risk of complications in patients undergoing lung and abdominal surgery, there being a direct relationship between lower cytokine levels and reduced postoperative complications[1]. IL-6 levels also aid risk stratification of postoperative complications [6].

Interestingly, our study revealed a reduction in overall morbidity but not hepato-biliary complications after steroids. This is consistent with previous reports of thoracic and abdominal surgeries. In the context of HR, Hoffmann *et al*[5] showed that IL-6 has a pivotal role in postoperative hepatic regeneration, and patients with a deficient IL-6 response have impaired liver regeneration. Thus, the attenuation of IL-6 response by perioperative steroid administration could negatively influence hepatic regeneration and paradoxically increase liver dysfunction. This needs to be further investigated.

CRP is an acute-phase protein synthesized by the liver, and it depends on IL-6 regulation[30]. CRP upregulates pro- and anti-inflammatory cytokines, enhances phagocytosis, and increases the expression of endothelial adhesion molecules. CRP has a utility to monitor and predict postoperative complications and perioperative sepsis. De Jong *et al*[31] compared perioperative changes in CRP in 24 patients undergoing HR with nine patients undergoing laparotomy only due to unresectable tumors. They observed that CRP response was more significant in the laparotomy group than the HR group, and CRP response returned to normal by POD4[31]. Our study found that the use of steroids lowers the POD1 CRP levels. Thus, the CRP response's blunting could negate the beneficial effects of steroid administration, especially in patients with HR. It is possible that the effect may be different in minor resections with adequate future liver remnant and major resections with diminished capacity of the liver functional reserve, and further studies are warranted. POD1 CRP has a high negative predictive value for postoperative morbidity, which is consistent with our study[32].

Overall, we found that the perioperative administration of steroids did not increase the incidence of ascites, pleural effusion, and hepatobiliary complications following HR. Similarly, the length of hospital stay was also not altered by the administration of steroids. This is akin to the conclusions drawn by Yang *et al*[9] and Richardson *et al* [33]. However, our analysis showed that the use of steroids did not increase the risk of infectious complications. This is corroborated by the conclusion drawn from a meta-analysis, including 379 patients by Li *et al*[34]. There are currently trials being

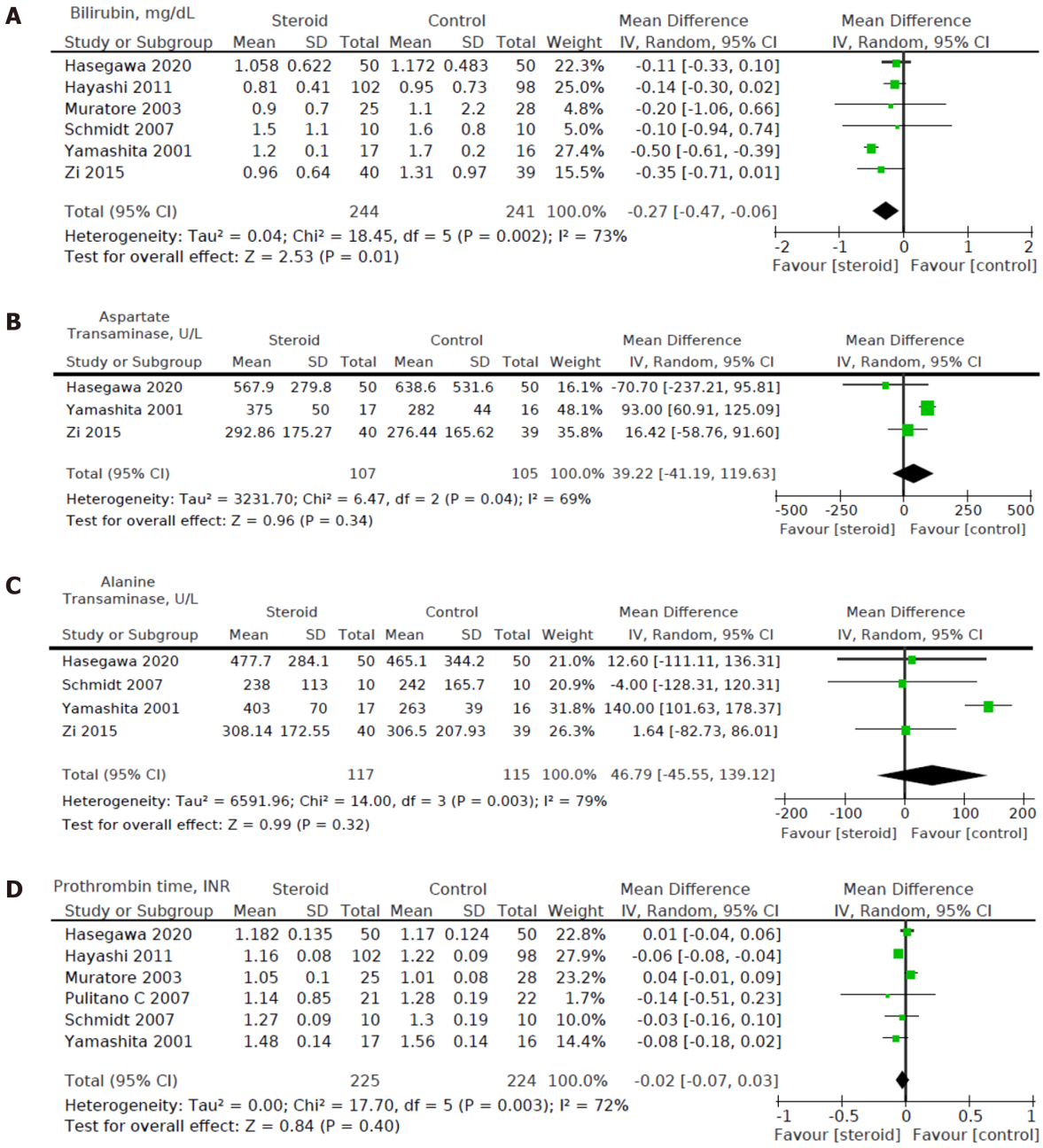


**Figure 7 Pooled results comparing steroids group to the control group.** A: Postoperative day 1 bilirubin level, mg/dL; B: Postoperative day 1 aspartate transaminase level, U/L; C: Postoperative day 1 alanine transaminase level, U/L; D: Postoperative day 1 prothrombin time, international normalized ratio, illustrated by forest plots. Random effects model was used. IV: Inverse variance; CI: Confidence interval.

conducted to precisely evaluate the effect of high dose corticosteroids on postoperative complications[35]. The results of these trials can influence future surgical practice. Rapid increases in postoperative pro-inflammatory cytokines are associated with increased risk of postoperative complications and poorer prognosis; however, postoperative cytokines profile is diverse and nuanced[36]. Increased values of some cytokines such as IL-6 and tumor necrosis factor-α improve hepatic regeneration[37], while decreased CRP levels could either mean liver dysfunction due to reduced hepatic production or association with reduced overall postoperative morbidity. Also, laparoscopic surgery is known to reduce the inflammatory response, and the impact of perioperative steroids could be diverse in patients with open *vs* laparoscopic liver resection. Hasegawa *et al*[15] showed that corticosteroids help to suppress inflammation following laparoscopic liver resection[15].

Further studies need to be done to elucidate the relationship between the different corticosteroid therapies and the degree of effect on different inflammatory cytokines, which might impact open or laparoscopic HR outcomes. This is especially so as the studies included have different steroid administration methods, using steroids of

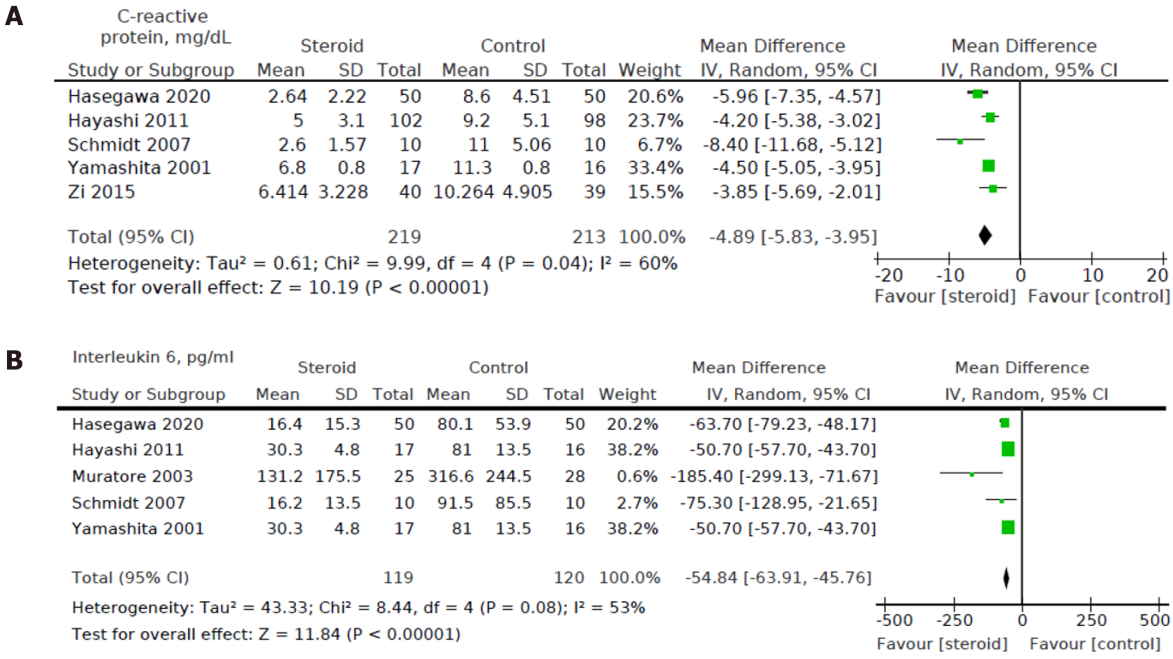


**Figure 8 Pooled results comparing steroids group to the control group.** A: Postoperative day 3 C-reactive protein, mg/dL; B: Postoperative day 1 interleukin 6 levels, pg/mL illustrated by forest plots. Random effects model was used. IV: Inverse variance; CI: Confidence interval.

different potency and dosage. While no significant difference in postoperative complications is noted between laparoscopic and open HR in general, perioperative steroids could impact the incidence of complications[38]. Zi *et al*[19] illustrate different specific instances in which perioperative steroids would be useful in HR, such as when enteral feeding is required. Early enteral feeding is shown to reduce inflammation and overall morbidity following HR[39].

## CONCLUSION

Our meta-analysis has inherent strengths and limitations. The inclusion of two additional studies[15,19] with an increase in 43.6% of sample size enhanced our updated meta-analysis's statistical power. We only included prospective RCTs in our meta-analysis to reduce heterogeneity and increase the reliability and validity of results. Since the studies publishing statistically significant results are more likely to be published in English[40], the exclusion of non-English articles may affect the conclusions' reliability as population factors could be a compounding factor, an issue we have attempted to overcome in our study. However, due to various steroid regimes and different authors reporting different primary and secondary outcomes, we still found significant heterogeneity in many reported variables. The International Study Group on Liver Surgery needs to make recommendations to standardize the perioperative use of steroids in patients undergoing HR liver resection as type, dose, and time of administration of perioperative steroids could impact clinical outcomes. We omitted the data points for variables presented in graphical form as we were unable to contact the authors of the original studies to extract raw data, which could introduce bias. Lastly, there was also a lack of long-term follow-up data, and thus, the impact on survival outcomes is not established. This meta-analysis also reveals the limitations of RCTs. RCTs are traditionally considered higher in the hierarchy of medical scientific evidence. Only one study reported morbidity outcomes using an established classification system, thus limiting the clinical utility of morbidity data[13]. As evidenced in our meta-analysis, all the included RCTs did not report single mortality in patients undergoing HR, where in clinical practice, this is unlikely. RCTs are conducted in a controlled environment with strict inclusion-exclusion criteria with close monitoring and oversight by the study team, and results of RCTs are not generalizable in routine clinical practice, and this needs to be considered by all clinicians who read our results. Lastly, this study also highlights the fact that despite 90 d mortality outcomes are considered as essential key performance indicators for HR, even RCTs continued to be conducted without reporting this essential metric. In conclusion, perioperative steroid

administration reduces overall morbidity in patients undergoing HR.

## ARTICLE HIGHLIGHTS

### *Research background*

Hepatic resection (HR) results in an inflammatory response that can be modified by perioperative steroid administration. However, it remains to be determined if this response's attenuation translates to a reduction in complications.

### *Research motivation*

Stress from major surgery results in an inflammatory response secondary to cytokine and free radical release. This inflammatory response is essential for healing and restoration of physiologic function; however, it can increase morbidity, mortality, and worsen postoperative outcomes if excessive. Modifying the inflammatory response by perioperative steroid administration could improve surgical outcomes. Besides, inflammatory markers are increasingly shown to predict short-term perioperative and long-term oncologic outcomes following HR. Thus, modulation of inflammatory response to improve surgical outcomes remains an unmet need in hepatic surgery.

### *Research objectives*

To evaluate if perioperative administration of steroids reduces complications following HR.

### *Research methods*

A systematic review of randomized controlled trials (RCTs) was conducted on PubMed, Embase, and Cochrane Central Register of Controlled Trials to evaluate the effect of perioperative steroid (compared to placebo or no intervention) use in patients undergoing HR. Clinical outcomes were extracted, and meta-analysis was performed.

### *Research results*

Eight RCTs including 590 patients were included. Perioperative steroid administration was associated with significant reduction in postoperative complications [odds ratios: 0.58; 95% confidence intervals (CI): (0.35, 0.97), $P = 0.04$]. There was also improvement in biochemical and inflammatory markers, including serum bilirubin on postoperative day 1 [MD: -0.27; 95%CI: (-0.47, -0.06), $P = 0.01$], C-reactive protein on postoperative day 3 [MD: -4.89; 95%CI: (-5.83, -3.95), $P < 0.001$], and IL-6 on postoperative day 1 [MD: -54.84; 95%CI: (-63.91, -45.76), $P < 0.001$].

### *Research conclusions*

Perioperative steroids administration in HR may reduce overall complications, postoperative bilirubin, and inflammation. Further studies are needed to determine the optimal dose and duration, and patient selection.

### *Research perspectives*

The International Study Group on Liver Surgery needs to make recommendations to standardize the perioperative use of steroids in patients undergoing HR liver resection as type, dose, and time of administration of perioperative steroids could impact clinical outcomes. Lastly, there was also a lack of long-term follow-up data, and thus, the impact on survival outcomes is not established.

## REFERENCES


1 **Baigrie RJ**, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; **79**: 757-760 [PMID: 1393463 DOI: 10.1002/bjs.1800790813]

2 **Santiago Delpín EA**, Figueroa I, López R, Vázquez J. Protective effect of steroids on liver ischemia. *Am Surg* 1975; **41**: 683-685 [PMID: 1181954]

3 **Madhavan S**, Shelat VG, Soong SL, Woon WWL, Huey T, Chan YH, Junnarkar SP. Predicting morbidity of liver resection. *Langenbecks Arch Surg* 2018; **403**: 359-369 [PMID: 29417211 DOI: 10.1007/s00423-018-1656-3]

4 **Jerin A**, Pozar-Lukanovic N, Sojar V, Stanisavljevic D, Paver-Erzen V, Osredkar J. Balance of pro- and anti-inflammatory cytokines in liver surgery. *Clin Chem Lab Med* 2003; **41**: 899-903 [PMID:

12940515 DOI: 10.1515/CCLM.2003.136]
5 **Hoffmann K**, Nagel AJ, Tanabe K, Fuchs J, Dehlke K, Ghamarnejad O, Lemekhova A, Mehrabi A. Markers of liver regeneration-the role of growth factors and cytokines: a systematic review. *BMC Surg* 2020; **20**: 31 [PMID: 32050952 DOI: 10.1186/s12893-019-0664-8]
6 **Rettig TC**, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EM, Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. *Ann Surg* 2016; **263**: 1207-1212 [PMID: 26135695 DOI: 10.1097/SLA.0000000000001342]
7 **Chan KS**, Chia CLK, Ng FKL, Seow WHJ, Leong DY, Shelat VG. Impaired Handgrip Strength Does Not Predict Postoperative Morbidity in Major Hepatobiliary Surgery. *J Surg Res* 2020; **256**: 549-556 [PMID: 32799004 DOI: 10.1016/j.jss.2020.07.012]
8 **Shelat VG**. Role of inflammatory indices in management of hepatocellular carcinoma-neutrophil to lymphocyte ratio. *Ann Transl Med* 2020; **8**: 912 [PMID: 32953712 DOI: 10.21037/atm-2020-90]
9 **Yang L**, Zhang Z, Kong J, Wang W. Systematic Review and Meta-Analysis of the Benefit and Safety of Preoperative Administration of Steroid in Patients Undergoing Liver Resection. *Front Pharmacol* 2019; **10**: 1442 [PMID: 31849683 DOI: 10.3389/fphar.2019.01442]
10 **Polderman JAW**, Farhang-Razi V, van Dieren S, Kranke P, DeVries JH, Hollmann MW, Preckel B, Hermanides J. Adverse side-effects of dexamethasone in surgical patients - an abridged Cochrane systematic review. *Anaesthesia* 2019; **74**: 929-939 [PMID: 30821852 DOI: 10.1111/anae.14610]
11 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**: 1006-1012 [PMID: 19631508 DOI: 10.1016/j.jclinepi.2009.06.005]
12 **Hayashi Y**, Takayama T, Yamazaki S, Moriguchi M, Ohkubo T, Nakayama H, Higaki T. Validation of perioperative steroids administration in liver resection: a randomized controlled trial. *Ann Surg* 2011; **253**: 50-55 [PMID: 21233606 DOI: 10.1097/SLA.0b013e318204b6bb]
13 **Donadon M**, Molinari AF, Corazzi F, Rocchi L, Zito P, Cimino M, Costa G, Raimondi F, Torzilli G. Pharmacological Modulation of Ischemic-Reperfusion Injury during Pringle Maneuver in Hepatic Surgery. A Prospective Randomized Pilot Study. *World J Surg* 2016; **40**: 2202-2212 [PMID: 27094558 DOI: 10.1007/s00268-016-3506-1]
14 **Schünemann HJ**, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW Jr, Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008; **336**: 1106-1110 [PMID: 18483053 DOI: 10.1136/bmj.39500.677199.AE]
15 **Hasegawa Y**, Nitta H, Takahara T, Katagiri H, Kanno S, Umemura A, Akiyama Y, Iwaya T, Otsuka K, Sasaki A. Glucocorticoid use and ischemia-reperfusion injury in laparoscopic liver resection: Randomized controlled trial. *Ann Gastroenterol Surg* 2020; **4**: 76-83 [PMID: 32021961 DOI: 10.1002/ags3.12298]
16 **Yamashita Y**, Shimada M, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Sugimachi K. Effects of preoperative steroid administration on surgical stress in hepatic resection: prospective randomized trial. *Arch Surg* 2001; **136**: 328-333 [PMID: 11231856 DOI: 10.1001/archsurg.136.3.328]
17 **Pulitanò C**, Aldrighetti L, Arru M, Finazzi R, Catena M, Guzzetti E, Soldini L, Comotti L, Ferla G. Preoperative methylprednisolone administration maintains coagulation homeostasis in patients undergoing liver resection: importance of inflammatory cytokine modulation. *Shock* 2007; **28**: 401-405 [PMID: 17577134 DOI: 10.1097/shk.0b013e318063ed11]
18 **Schmidt SC**, Hamann S, Langrehr JM, Höflich C, Mittler J, Jacob D, Neuhaus P. Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. *J Hepatobiliary Pancreat Surg* 2007; **14**: 484-492 [PMID: 17909718 DOI: 10.1007/s00534-006-1200-7]
19 **Zi X**, Yao H, Qiu Y, Fu X, Mao L, Zhou T, Chen C. Effect of intraoperative methylprednisolone in combination with perioperative enteral nutrition support on recovery after hepatectomy. *Zhonghua Linchuang Yingyang Zazhi* 2015; **23**: 89-94 [DOI: 10.3760/cma.j.issn.1674-635X.2015.02.005]
20 **Muratore A**, Ribero D, Ferrero A, Bergero R, Capussotti L. Prospective randomized study of steroids in the prevention of ischaemic injury during hepatic resection with pedicle clamping. *Br J Surg* 2003; **90**: 17-22 [PMID: 12520569 DOI: 10.1002/bjs.4055]
21 **Karanicolas PJ**, Smith SE, Kanbur B, Davies E, Guyatt GH. The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. *Ann Surg* 2008; **248**: 751-762 [PMID: 18948802 DOI: 10.1097/SLA.0b013e3181856024]
22 **Coutinho AE**, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol* 2011; **335**: 2-13 [PMID: 20398732 DOI: 10.1016/j.mce.2010.04.005]
23 **Helling TS**. Liver failure following partial hepatectomy. *HPB (Oxford)* 2006; **8**: 165-174 [PMID: 18333270 DOI: 10.1080/13651820510035712]
24 **Rahbari NN**, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**: 713-724 [PMID: 21236455 DOI: 10.1016/j.surg.2010.10.001]
25 **Balzan S**, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg*

2005; **242**: 824-828, discussion 828 [PMID: 16327492 DOI: 10.1097/01.sla.0000189131.90876.9e]
26 **Rahman SH**, Evans J, Toogood GJ, Lodge PA, Prasad KR. Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. *Arch Surg* 2008; **143**: 247-53; discussion 253 [PMID: 18347271 DOI: 10.1001/archsurg.2007.75]
27 **Olthof PB**, Huiskens J, Schulte NR, Wicherts DA, Besselink MG, Busch OR, Heger M, van Gulik TM. Postoperative peak transaminases correlate with morbidity and mortality after liver resection. *HPB (Oxford)* 2016; **18**: 915-921 [PMID: 27600437 DOI: 10.1016/j.hpb.2016.07.016]
28 **Giovannini I**, Chiarla C, Giuliante F, Vellone M, Ardito F, Sarno G, Nuzzo G. Analysis of the components of hypertransaminasemia after liver resection. *Clin Chem Lab Med* 2007; **45**: 357-360 [PMID: 17378732 DOI: 10.1515/CCLM.2007.078]
29 **Szanto KB**, Li J, Cordero P, Oben JA. Ethnic differences and heterogeneity in genetic and metabolic makeup contributing to nonalcoholic fatty liver disease. *Diabetes Metab Syndr Obes* 2019; **12**: 357-367 [PMID: 30936733 DOI: 10.2147/DMSO.S182331]
30 **Hurlimann J**, Thorbecke GJ, Hochwald GM. The liver as the site of C-reactive protein formation. *J Exp Med* 1966; **123**: 365-378 [PMID: 4379352 DOI: 10.1084/jem.123.2.365]
31 **de Jong KP**, Hoedemakers RM, Fidler V, Bijzet J, Limburg PC, Peeters PM, de Vries EG, Slooff MJ. Portal and systemic serum growth factor and acute-phase response after laparotomy or partial hepatectomy in patients with colorectal liver metastases: a prognostic role for C-reactive protein and hepatocyte growth factor. *Scand J Gastroenterol* 2004; **39**: 1141-1148 [PMID: 15545174 DOI: 10.1080/00365520410009609]
32 **Späth C**, Srinivasa S, Walsh M, Singh P, Rodgers M, Koea J. Role of post-operative serum C-reactive protein levels as a predictor of complications in upper gastrointestinal surgery. *ANZ J Surg* 2019; **89**: 74-78 [PMID: 30207031 DOI: 10.1111/ans.14789]
33 **Richardson AJ**, Laurence JM, Lam VW. Use of pre-operative steroids in liver resection: a systematic review and meta-analysis. *HPB (Oxford)* 2014; **16**: 12-19 [PMID: 23461716 DOI: 10.1111/hpb.12066]
34 **Li N**, Gu WL, Weng JF, Lin F, Zhu GH, Lu MQ, Cao J. Short-term administration of steroids does not affect postoperative complications following liver resection: Evidence from a meta-analysis of randomized controlled trials. *Hepatol Res* 2015; **45**: 201-209 [PMID: 24655315 DOI: 10.1111/hepr.12332]
35 **Steinthorsdottir KJ**. Preoperative high dose steroids for liver resection: Effect on complications in the immediate postoperative period (STEREO). 2020. [cited 27 January 2021]. Available from: https://www.wuxuwang.com/cpsus/3a5298aa-a186-11ea-82b4-00163e0eafb3
36 **Kimura F**, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Nozawa S, Furukawa K, Mitsuhashi N, Sawada S, Takeuchi D, Ambiru S, Miyazaki M. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. *J Surg Res* 2006; **133**: 102-112 [PMID: 16386757 DOI: 10.1016/j.jss.2005.10.025]
37 **Taub R**. Liver regeneration: from myth to mechanism. *Nat Rev Mol Cell Biol* 2004; **5**: 836-847 [PMID: 15459664 DOI: 10.1038/nrm1489]
38 **Chen J**, Li H, Liu F, Li B, Wei Y. Surgical outcomes of laparoscopic *vs* open liver resection for hepatocellular carcinoma for various resection extent. *Medicine (Baltimore)* 2017; **96**: e6460 [PMID: 28328863 DOI: 10.1097/MD.0000000000006460]
39 **Warner SG**, Jutric Z, Nisimova L, Fong Y. Early recovery pathway for hepatectomy: data-driven liver resection care and recovery. *Hepatobiliary Surg Nutr* 2017; **6**: 297-311 [PMID: 29152476 DOI: 10.21037/hbsn.2017.01.18]
40 **Nunan D**, Heneghan C, Spencer EA. Catalogue of bias: allocation bias. *BMJ Evid Based Med* 2018; **23**: 20-21 [PMID: 29367320 DOI: 10.1136/ebmed-2017-110882]

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*World J Gastrointest Surg* 2021 September 27; 13(9): 1095-1101

DOI: 10.4240/wjgs.v13.i9.1095

ISSN 1948-9366 (online)

CASE REPORT

# Three colonic cancers, two sites of complete occlusion, one patient: A case report

Eric Bergeron, Thibaut Maniere, Xuan Vien Do, Michael Bensoussan, Eric De Broux

**ORCID number:** Eric Bergeron 0000-0002-7482-5801; Thibaut Maniere 0000-0002-8229-8888; Xuan Vien Do 0000-0002-8480-5185; Michael Bensoussan 0000-0002-2165-6282; Eric De Broux 0000-0002-7056-0500.

**Author contributions:** Bergeron E and De Broux E reviewed the record; Bergeron E, De Broux E, Maniere T, Bensoussan M analyzed and interpreted the data; Do XV was involved in the provision of study material and reviewed CT imaging; and all authors critically reviewed and approved the final version of the article.

**Informed consent statement:** Patient's consent is joined.

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**CARE Checklist (2016) statement:** The manuscript was revised according to the Care checklist.



**Eric Bergeron,** Department of General Surgery, Charles-LeMoyne Hospital, Greenfield Park J4V2H1, Quebec, Canada

**Thibaut Maniere, Michael Bensoussan,** Department of Gastroenterology, Charles-LeMoyne Hospital, Greenfield Park J4V2H1, Quebec, Canada

**Xuan Vien Do,** Department of Medical Imaging, Charles-LeMoyne Hospital, Greenfield Park J4V2H1, Quebec, Canada

**Eric De Broux,** Department of Digestive Surgery, Centre Hospitalier Universitaire de Montréal, Montreal H2X3E4, Quebec, Canada

**Corresponding author:** Eric Bergeron, MD, MSc, Surgeon, Department of General Surgery, Charles-LeMoyne Hospital, 3120 Taschereau, Greenfield Park J4V2H1, Quebec, Canada. erb_taz2001@yahoo.com

## Abstract

*BACKGROUND*

Synchronous colonic cancer incidence is uncommon, and awareness about this rare condition is improved recently. However, in the presence of acute colonic obstruction, investigation and management of synchronous colonic cancer can be difficult and challenging.

*CASE SUMMARY*

A patient presented with acute colonic obstruction with impending rupture and complete examination of this patient revealed the presence of three colonic cancers, of which two were completely occluding.

*CONCLUSION*

The presence of multiple colonic cancers must be ruled out in order to plan the best management. We present the case with a review of literature and discuss the management of the case.

**Key Words:** Colon cancer; Synchronous cancers; Colonoscopy; Obstructive cancer; Colostomy; Case report

**Manuscript source:** Unsolicited manuscript

**Specialty type:** Surgery

**Country/Territory of origin:** Canada

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 17, 2021
**Peer-review started:** March 17, 2021
**First decision:** May 4, 2021
**Revised:** May 15, 2021
**Accepted:** August 20, 2021
**Article in press:** August 20, 2021
**Published online:** September 27, 2021

**P-Reviewer:** De Nardi P, Kim CW
**S-Editor:** Wang JL
**L-Editor:** A
**P-Editor:** Wu RR

**Core Tip:** Synchronous colorectal cancer is not unusual. More than two colon cancers may be encountered occasionally. Consequently, the colon has to be fully evaluated before definitive surgery. However, in emergency situations such as obstructive cancer, investigation and management may become very challenging. We present and discuss about a case with three colon cancers at the same time, of which two were completely occlusive, rendering the management even more difficult.

**Citation:** Bergeron E, Maniere T, Do XV, Bensoussan M, De Broux E. Three colonic cancers, two sites of complete occlusion, one patient: A case report. *World J Gastrointest Surg* 2021; 13(9): 1095-1101
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1095.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1095

## INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death in the world[1]. The frequency of synchronous CRC (sCRC) may reach 20% in patients with familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, chronic ulcerative colitis[2] and serrated polyposis syndrome[3]. In patients without these risk factors, prevalence of sCRC is estimated to be 3.5%[4], while the current improved awareness increased these estimates from 5% up to 8.4%[5-7].

Reports on the occurrence of triple or more sCRC range from 0.1% to 0.7%[8-13], and up to 1.6% in a recent review[7]. This review described a series of 1005 patients, of whom seven patients (0.7%) had four CRC and one patient (0.1%) had 5 CRC[7]. In another case, up to seven CRC in the same patient have been reported[14]. The importance of preoperative endoscopic examination of the entire colon to rule out polyps or secondary cancers is well established. However, in emergency situations such as obstruction, perforation or ischemic disease, management may become particularly challenging[1,15,16].

We report a patient who presented with acute and severe obstruction of the sigmoid colon due to a cancer, which was managed initially with a loop colostomy. The patient was subsequently discovered to have two more cancers on the right side, one of which was also completely occluding the caecum. The case and its management are discussed.

## CASE PRESENTATION

### *Chief complaints*

A 77-year-old patient presented at the emergency room on February 13th, 2019, with an overly distended abdomen.

### *History of present illness*

The patient was vomiting fecaloid material for the last 24 h. He passed no stools or gas in the last three days.

### *History of past illness*

The patient reported rectal bleeding for almost one year. He never had colonoscopy.

### *Personal and family history*

The patient is a diabetic male with obesity (Body mass index = 35). There is no personal or familial history of polyposis or inflammatory bowel disease. There was no colonic cancer in the family of the patient.

### *Physical examination*

Upon arrival, vital signs were within the normal limits. The patient was afebrile. The abdomen was very tense but without signs of peritonitis. There was no mass on rectal

exam.

### *Laboratory examinations*

Hemoglobin, white cell count, liver and renal function tests were within normal limits. Carcinoembryonic antigen (CEA) was 2.3 μg/L; (Normal: 0-4.9 μg/L). Colonoscopy was well tolerated. An obstructive cancer of the proximal sigmoid colon was confirmed. Two other cancers were found on the right side: one at the caecum and another one at the mid part of the ascending colon. No polyposis was found.

### *Imaging examinations*

Computed tomography (CT)-scan showed significant dilatation of the small bowel loops and colon, secondary to a neoplastic sigmoid lesion (Figure 1). Some free fluid was also seen. There was no evidence of metastatic disease. Retrospectively, caecal (Figure 2A) and middle right colonic tumors (Figure 2B) could be identified on CT-scan but were difficult to diagnose prospectively in an emergency setting without associated acute bowel caliber change.

## FINAL DIAGNOSIS

Three colonic cancers. Occlusive cancers at the ileocaecal valve and at sigmoid colon. Final pathology report identified three adenocarcinomas. The sigmoid cancer was a pT4 adenocarcinoma, invading the surrounding tissues. Incidentally, there was a concealed perforated diverticulitis. The cancer of the caecum was a pT3 obstructing adenocarcinoma at the ileocaecal valve. The lesion of the ascending colon was a circumferential pT3 adenocarcinoma. It was situated 10 cm distally from the cancer of the caecum. Seven nodes were positive for the presence of metastasis. There was no polyp and no evidence of inflammatory bowel disease. TNM classification was T4N2M0.

## TREATMENT

The patient was initially hydrated. A nasogastric tube was installed, which evacuated brownish material. The patient was brought to the operating room during the evening and a left-sided loop colostomy was carried out. The colostomy was fashioned through a small left paramedian incision directly over the junction of the descending and sigmoid colon.

During the postoperative period, the colostomy was functional and allowed the stools to evacuate. The size of the abdomen significantly reduced. This window permitted the evaluation and stabilization of the medical condition of the patient. A colonoscopy was done through the rectum and to the proximal colon *via* the colostomy.

The patient was planned for a total colectomy with ileorectal anastomosis, nine days after the first intervention. Meanwhile, there was recurrence of abdominal distension and the discharge from colostomy had become minimal. The intervention was done through a midline incision. It was technically difficult owing to the distended small bowel, secondary to an evident occlusion from the tumor of the caecum. The intestinal wall was diffusely thickened demonstrating a process originating for many weeks. There was no evidence of peritoneal metastases. A subtotal colectomy was carried out keeping as much distal sigmoid as possible to allow a side-to-side ileosigmoid anastomosis and alleviate potential postoperative diarrheas.

One week later, postoperative course became complicated with an anastomotic leak that was treated with reoperation, drainage and proximal ileostomy. The patient had a further complicated course with abdominal abscesses, pneumonia, and enterocutaneous fistula originating from small bowel proximal to the ileostomy. This latter was treated with bowel rest and parenteral nutrition.

## OUTCOME AND FOLLOW-UP

Hospital stay was for almost six months. Before discharge, the patient was reoperated after ensuring that the ileocolonic anastomosis was free of leakage and permeable. A short resection of the small bowel was done at the site of fistula and the ileostomy was

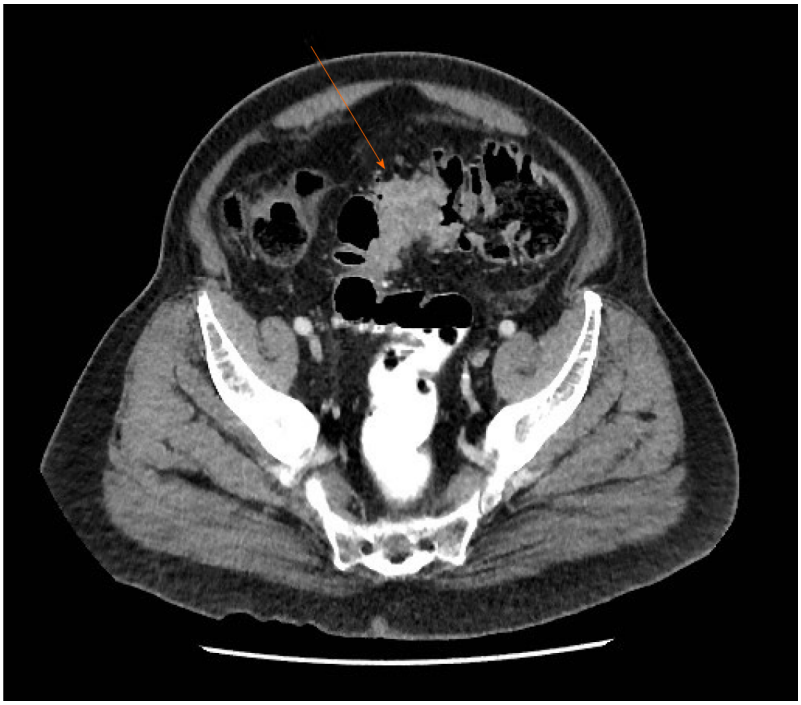

**Figure 1 Axial contrast-enhanced computed tomography image.** A short segment circumferential soft tissue mass within the sigmoid colon and luminal narrowing (arrow) consistent with a tumor. There is a small lymph node adjacent to the lesion.

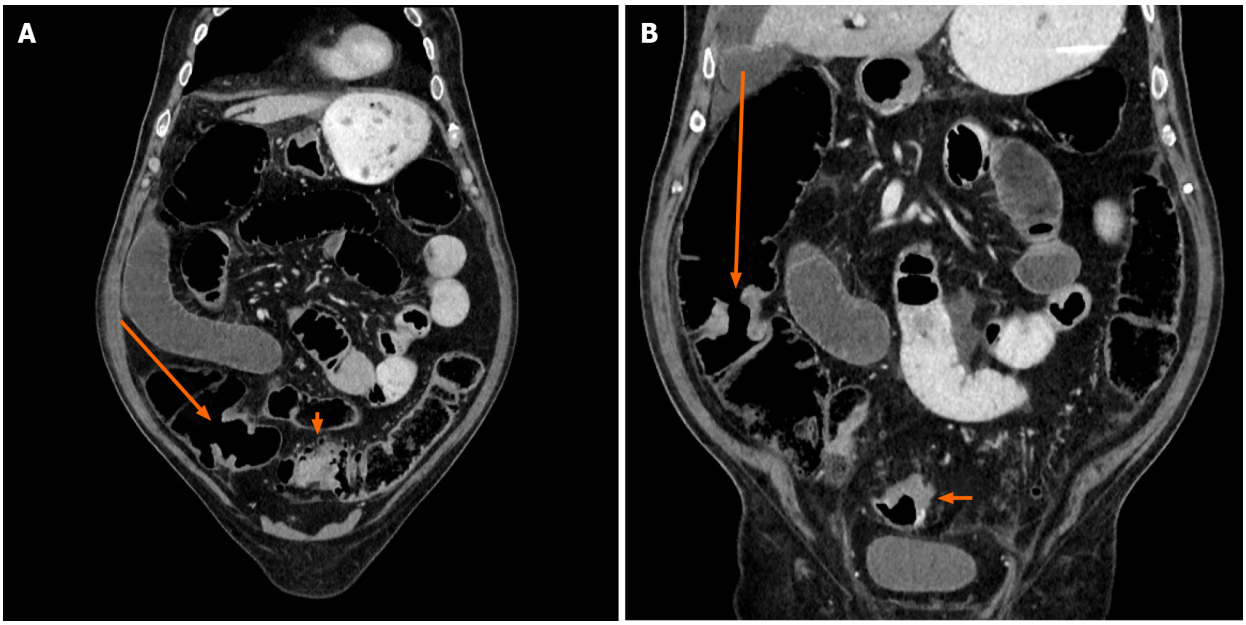


**Figure 2 Coronal contrast-enhanced computed tomography image.** A: The proximal right colonic tumor (long arrow) at the level of the ileocecal valve, evidenced by a focal mild circumferential wall thickening. Sigmoid cancer is partially seen (short arrow); B: The middle right colonic tumor (long arrow), evidenced by a focal circumferential wall thickening without obstruction. Sigmoid cancer is partially seen (short arrow).

closed. Postoperative period was uneventful. Because of the complicated postoperative course and the delay at discharge from the surgery, adjuvant chemotherapy was not planned.

One year later, there was no clinical or radiologic evidence of recurrent or metastatic disease. CEA was 5.8 μg/L (Normal: 0-4.9 μg/L). Endoscopic examination of the remaining 30 cm of the rectum and colon showed no lesion. An incisional hernia was repaired. Two years later, the patient is still functioning well and in good condition. However, CEA was found to be increased to 17.1 μg/L (Normal: 0-4.9 μg/L) subsequently, but no recurrent disease could be demonstrated with thoracoabdominal CT scan and positron emission tomography-CT. However, favourable clinical

evolution notwithstanding, locoregional recurrence remains of concern.

## DISCUSSION

CRC is the second and third most common malignancy in males and females, respectively[1,3,7]. Synchronous CRC is reported between 3% and 8% in recent reports on large groups of patients[5,6,11,12,17]. Incidence of sCRC reaches 20% in patients with risk factors[2,3]. Mean prevalence of sCRC is estimated at 3.5%[4].

Occurrence of three or more colon cancers at the same time in an individual is an unusual situation[7-13,15,18,19] but such incidence has been reported to be up to 1.6% [7]. Reports of the occurrence of two or more sCRC up to 12%[20] emphasize the mandatory investigation of the entire colon to rule out synchronous tumors and plan proper management[21].

The more challenging cases occur in patients presenting with a surgical emergency. Fifteen to 30% of sCRC cases present as an emergency occlusive situation[1,22,23]. The sigmoid colon is the most common location of CRC obstruction; 75% of the tumours are located distal to the splenic flexure[21].

In the present case, initial management was dictated by the overly distended abdomen in the patient in bad condition. Facing an occlusive sigmoid cancer while unaware of the concurrent occlusive caecal cancer, the possible management options at this time were proximal colostomy, Hartmann's procedure or total colectomy[1]. However, the last two options take longer time and may be technically challenging, because of intestinal distension as well as potentially threatening procedures for the patient[1].

The colostomy allowed the patient to be stabilized and medically evaluated for subsequent procedure. Impending rupture of the colon and presence of stools contra-indicated colonoscopy right after creating the colostomy. The colostomy should have allowed the obstruction to resolve but in this particular case, the occlusion of the ileocaecal valve, imperceptible at the time of initial intervention, eventually failed to achieve this goal. On the other hand, the necessity to investigate the entire colon and rectum was realized. Moreover, the obstruction at ileocecal valve was not complete initially since the oral preparation for the colonoscopy was effective.

It is important to completely visualize the proximal colon through the colostomy, as well as the distal part of the large bowel through the rectum. Colonic stenting as a bridge to definitive surgery[24-26] was not considered in this situation due to potential impending rupture and immediate unavailability of this modality. Moreover, stent of an obstructing cancer is yet to be recommended as a standard treatment, and colonoscopy may be dangerous through a colonic stent even though feasible[26]. The colon may also be satisfactorily evaluated with imaging modalities (virtual coloscopy, CT-colonography, magnetic resonance colonography, intra-operative or post-operative coloscopy)[1,15,20,27]. Thus, every reasonable effort should be made to evaluate the entire colon before planning definitive intervention[26].

If the obstructing lesion of the caecum had been identified initially, a total colectomy with or without ileostomy could have been carried out. However, due to the bad condition of the patient, such a procedure would have been technically difficult and potentially risky. A simple ileostomy would have left in place a close loop obstruction of the colon with a remaining risk of rupture. The proper management would have probably been damage control procedure with laparotomy, loop colostomy and ileostomy, leaving an open abdomen, stabilizing the medical condition, allowing the intestine to decompress, and proceeding with total or subtotal colectomy and ileocolonic anastomosis. Whatever the contemplated intervention, either of the options was associated with major concerns.

The complicated and prolonged postoperative course is unfortunate and beyond the scope of discussion. Consequently, the patient could not receive adjuvant chemotherapy. In spite of the complicated issues, primary ileocolonic anastomosis remained, in our opinion, the proper choice either at the first procedure or subsequently[1]. The presence of two completely obstructing lesions at two different sites is very unique but complicated the management of the patient and surely contributed to the outcome.

This case emphasizes the importance to keep in mind, the possibility of additional colonic cancers that could be difficult to identify particularly in emergency and complicated situations. Reasonable efforts must be made to evaluate the entire colon in order to plan definitive management. A temporary colostomy in severe colonic obstruction allows the obstruction to resolve, the colon to be entirely evaluated, and the patient to be stabilized for definitive management. A total colectomy cannot be

recommended straightaway[1] since a frequency of 3.5% for synchronous cancers[4] does not justify such an extensive procedure. Similarly, if a Hartmann's procedure is done, investigation of the colon is mandatory before reoperation.

## CONCLUSION

Considering this case and the review of literature, we can draw the following conclusions and recommendations: (1) Colon cancer has a high incidence, with a rate of sCRC between 3% and 12%, and thus represents a not so rare condition; (2) Obstructing colonic cancer is frequent at initial presentation and carries the same prevalence of sCRC; (3) A colostomy allows relieving obstruction of the colon and stabilization of a patient and gives access to the entire colon for investigation; (4) Every effort should be made to evaluate the entire colon and rectum before definitive treatment; and (5) The presence of two obstructing cancer at the same time remains a unique situation and management can be difficult.

## REFERENCES


1 **Pisano M**, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, Agresta F, Allievi N, Bellanova G, Coccolini F, Coy C, Fugazzola P, Martinez CA, Montori G, Paolillo C, Penachim TJ, Pereira B, Reis T, Restivo A, Rezende-Neto J, Sartelli M, Valentino M, Abu-Zidan FM, Ashkenazi I, Bala M, Chiara O, De' Angelis N, Deidda S, De Simone B, Di Saverio S, Finotti E, Kenji I, Moore E, Wexner S, Biffl W, Coimbra R, Guttadauro A, Leppäniemi A, Maier R, Magnone S, Mefire AC, Peitzmann A, Sakakushev B, Sugrue M, Viale P, Weber D, Kashuk J, Fraga GP, Kluger I, Catena F, Ansaloni L. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg* 2018; **13**: 36 [PMID: 30123315 DOI: 10.1186/s13017-018-0192-3]

2 Gastrointestinal: synchronous and metachronous colorectal cancers. *J Gastroenterol Hepatol* 2003; **18**: 457 [PMID: 12653896 DOI: 10.1046/j.1440-1746.2003.03031.x]

3 **Pyleris E**, Koutsounas IS, Karantanos P. Three Colon Adenocarcinomas Arising in a Patient with Serrated Polyposis Syndrome: Case Report and Review of the Literature. *Viszeralmedizin* 2014; **30**: 136-139 [PMID: 26286237 DOI: 10.1159/000360386]

4 **Lam AK**, Chan SS, Leung M. Synchronous colorectal cancer: clinical, pathological and molecular implications. *World J Gastroenterol* 2014; **20**: 6815-6820 [PMID: 24944471 DOI: 10.3748/wjg.v20.i22.6815]

5 **Bos ACRK**, Matthijsen RA, van Erning FN, van Oijen MGH, Rutten HJT, Lemmens VEPP. Treatment and Outcome of Synchronous Colorectal Carcinomas: A Nationwide Study. *Ann Surg Oncol* 2018; **25**: 414-421 [PMID: 29159744 DOI: 10.1245/s10434-017-6255-y]

6 **Chin CC**, Kuo YH, Chiang JM. Synchronous colorectal carcinoma: predisposing factors and characteristics. *Colorectal Dis* 2019; **21**: 432-440 [PMID: 30578740 DOI: 10.1111/codi.14539]

7 **Kato T**, Alonso S, Muto Y, Noda H, Miyakura Y, Suzuki K, Tsujinaka S, Saito M, Perucho M, Rikiyama T. Clinical characteristics of synchronous colorectal cancers in Japan. *World J Surg Oncol* 2016; **14**: 272 [PMID: 27776528 DOI: 10.1186/s12957-016-1027-x]

8 **Chen HS**, Sheen-Chen SM. Synchronous and "early" metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Dis Colon Rectum* 2000; **43**: 1093-1099 [PMID: 10950007 DOI: 10.1007/BF02236556]

9 **Oya M**, Takahashi S, Okuyama T, Yamaguchi M, Ueda Y. Synchronous colorectal carcinoma: clinico-pathological features and prognosis. *Jpn J Clin Oncol* 2003; **33**: 38-43 [PMID: 12604723 DOI: 10.1093/jjco/hyg010]

10 **Papadopoulos V**, Michalopoulos A, Basdanis G, Papapolychroniadis K, Paramythiotis D, Fotiadis P, Berovalis P, Harlaftis N. Synchronous and metachronous colorectal carcinoma. *Tech Coloproctol* 2004; **8** Suppl 1: s97-s100 [PMID: 15655657 DOI: 10.1007/s10151-004-0124-y]

11 **Fukatsu H**, Kato J, Nasu JI, Kawamoto H, Okada H, Yamamoto H, Sakaguchi K, Shiratori Y. Clinical characteristics of synchronous colorectal cancer are different according to tumour location. *Dig Liver Dis* 2007; **39**: 40-46 [PMID: 16996329 DOI: 10.1016/j.dld.2006.07.015]

12 **Latournerie M**, Jooste V, Cottet V, Lepage C, Faivre J, Bouvier AM. Epidemiology and prognosis of synchronous colorectal cancers. *Br J Surg* 2008; **95**: 1528-1533 [PMID: 18991301 DOI: 10.1002/bjs.6382]

13 **Bae JM**, Cho NY, Kim TY, Kang GH. Clinicopathologic and molecular characteristics of synchronous colorectal cancers: heterogeneity of clinical outcome depending on microsatellite instability status of individual tumors. *Dis Colon Rectum* 2012; **55**: 181-190 [PMID: 22228162 DOI: 10.1097/DCR.0b013e31823c46ce]

14 **Kaibara N**, Koga S, Jinnai D. Synchronous and metachronous malignancies of the colon and rectum in Japan with special reference to a coexisting early cancer. *Cancer* 1984; **54**: 1870-1874 [PMID: 6478423 DOI: 10.1002/1097-0142(19841101)54:9<1870::aid-cncr2820540917>3.0.co;2-5]

15 **Yeh CC**, Hsi SC, Chuu CP, Kao YH. Synchronous triple carcinoma of the colon and rectum. *World J*

*Surg Oncol* 2013; **11**: 66 [PMID: 23497155 DOI: 10.1186/1477-7819-11-66]

16 **Park BS**, Cho SH, Kim SJ, Kim TU, Kim DI, Son GM, Kim HS. Synchronous Quadruple Colon Cancer With Two Lesions Previously Obscured by Ischemic Colitis, Plus Bladder Cancer and Thymoma: A Case Report. *Ann Coloproctol* 2021; **37**: S44-S47 [PMID: 32972096 DOI: 10.3393/ac.2020.06.18]

17 **Mulder SA**, Kranse R, Damhuis RA, de Wilt JH, Ouwendijk RJ, Kuipers EJ, van Leerdam ME. Prevalence and prognosis of synchronous colorectal cancer: a Dutch population-based study. *Cancer Epidemiol* 2011; **35**: 442-447 [PMID: 21470938 DOI: 10.1016/j.canep.2010.12.007]

18 **Jiang X**, Xu C, Tang D, Wang D. Laparoscopic subtotal colectomy for synchronous triple colorectal cancer: A case report. *Oncol Lett* 2016; **12**: 1525-1528 [PMID: 27446464 DOI: 10.3892/ol.2016.4803]

19 **Bádon ES**, Mokánszki A, Mónus A, András C, Damjanovich L, Méhes G. Quadruplicate Synchronous Adenocarcinoma of the Colon with Distant Metastases-Long-Term Molecular Follow-Up by KRAS and TP53 Mutational Profiling. *Diagnostics (Basel)* 2020; **10** [PMID: 32560038 DOI: 10.3390/diagnostics10060407]

20 **Yang J**, Peng JY, Chen W. Synchronous colorectal cancers: a review of clinical features, diagnosis, treatment, and prognosis. *Dig Surg* 2011; **28**: 379-385 [PMID: 22156665 DOI: 10.1159/000334073]

21 **Frago R**, Ramirez E, Millan M, Kreisler E, del Valle E, Biondo S. Current management of acute malignant large bowel obstruction: a systematic review. *Am J Surg* 2014; **207**: 127-138 [PMID: 24124659 DOI: 10.1016/j.amjsurg.2013.07.027]

22 **Barnett A**, Cedar A, Siddiqui F, Herzig D, Fowlkes E, Thomas CR Jr. Colorectal cancer emergencies. *J Gastrointest Cancer* 2013; **44**: 132-142 [PMID: 23371864 DOI: 10.1007/s12029-012-9468-0]

23 **Ansaloni L**, Andersson RE, Bazzoli F, Catena F, Cennamo V, Di Saverio S, Fuccio L, Jeekel H, Leppäniemi A, Moore E, Pinna AD, Pisano M, Repici A, Sugarbaker PH, Tuech JJ. Guidelenines in the management of obstructing cancer of the left colon: consensus conference of the world society of emergency surgery (WSES) and peritoneum and surgery (PnS) society. *World J Emerg Surg* 2010; **5**: 29 [PMID: 21189148 DOI: 10.1186/1749-7922-5-29]

24 **Trompetas V**. Emergency management of malignant acute left-sided colonic obstruction. *Ann R Coll Surg Engl* 2008; **90**: 181-186 [PMID: 18430330 DOI: 10.1308/003588408X285757]

25 **Costas-Chavarri A**, Nandakumar G, Temin S, Lopes G, Cervantes A, Cruz Correa M, Engineer R, Hamashima C, Ho GF, Huitzil FD, Malekzadeh Moghani M, Sharara AI, Stern MC, Teh C, Vázquez Manjarrez SE, Verjee A, Yantiss R, Shah MA. Treatment of Patients With Early-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. *J Glob Oncol* 2019; **5**: 1-19 [PMID: 30802158 DOI: 10.1200/JGO.18.00214]

26 **van Hooft JE**, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, Dumonceau JM, Glynne-Jones RG, Hassan C, Jiménez-Perez J, Meisner S, Muthusamy VR, Parker MC, Regimbeau JM, Sabbagh C, Sagar J, Tanis PJ, Vandervoort J, Webster GJ, Manes G, Barthet MA, Repici A; European Society of Gastrointestinal Endoscopy. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2014; **46**: 990-1053 [PMID: 25325682 DOI: 10.1055/s-0034-1390700]

27 **Flor N**, Zanchetta E, Di Leo G, Mezzanzanica M, Greco M, Carrafiello G, Sardanelli F. Synchronous colorectal cancer using CT colonography vs. other means: a systematic review and meta-analysis. *Abdom Radiol (NY)* 2018; **43**: 3241-3249 [PMID: 29948053 DOI: 10.1007/s00261-018-1658-1]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2021 September 27; 13(9): 1102-1109

DOI: 10.4240/wjgs.v13.i9.1102

ISSN 1948-9366 (online)

CASE REPORT

# Fluorescence *in situ* hybridization-based confirmation of acute graft-*vs*-host disease diagnosis following liver transplantation: A case report

Jing-Jing Xiao, Jin-Yu Ma, Jun Liao, Di Wu, Chao Lv, Hai-Yang Li, Shi Zuo, Hai-Tao Zhu, Hua-Jian Gu

**ORCID number:** Jing-Jing Xiao 0000-0002-5651-5711; Jin-Yu Ma 0000-0002-5115-8399; Jun Liao 0000-0003-0883-6956; Di Wu 0000-0002-7929-0084; Chao Lv 0000-0001-9789-7608; Hai-Yang Li 0000-0002-5679-0056; Shi Zuo 0000-0002-5624-2343; Hai-Tao Zhu 0000-0002-9889-7625; Hua-Jian Gu 0000-0002-9670-7320.

**Author contributions:** Xiao JJ and Ma JY were the patients' surgeons and designed the research; Liao J, Wu D, and Lv C reviewed the literature and contributed to the drafting of the manuscript; Li HY and Zhu HT collected the surgical data and recordings; Zuo S processed the operation screenshots; Gu HJ was responsible for language editing and revision of the manuscript and supervised the revision of the manuscript; All authors took part in the final approval for the version to be submitted.

**Informed consent statement:** Informed written consent was obtained from the patients for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:**

**Jing-Jing Xiao, Jin-Yu Ma, Jun Liao, Di Wu, Chao Lv,** School of Clinical Medicine, Guizhou Medical University, Guiyang 550004, Guizhou Province, China

**Hai-Yang Li, Shi Zuo, Hai-Tao Zhu,** Department of Hepatobiliary Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou Province, China

**Hua-Jian Gu,** Department of Pediatric Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang 550004, Guizhou Province, China

**Corresponding author:** Hua-Jian Gu, MD, Chief Physician, Department of Pediatric Surgery, The Affiliated Hospital of Guizhou Medical University, No. 16 Beijing Road, Guiyang 550004, Guizhou Province, China. zhaoyaree@sina.com

## Abstract

***BACKGROUND***

Although acute graft-*vs*-host disease (aGvHD) is a rare complication of liver transplantation, it is poorly understood and has an extremely high mortality rate. No standardized diagnostic criteria or treatment regimens currently exist.

***CASE SUMMARY***

The present study investigated the etiology, diagnosis, and treatment of aGvHD following liver transplantation. Presentation, diagnosis, disease course, histology, and treatment of an aGvHD case are reported, and associated literature is reviewed. A 64-year-old female required LTx due to primary biliary cirrhosis. The donor was a 12-year-old male. Three weeks following liver transplantation, the recipient developed pyrexia, diarrhea, rashes, and antibiotic-unresponsive pancytopenia. Clinical symptoms together with laboratory investigations suggested a diagnosis of aGvHD, which was confirmed *via* peripheral blood fluorescent *in situ* hybridization. Donor XY chromosome fluorescent *in situ* hybridization indicating early chimerism achieved 93% sensitivity in the detection of GvHD. Existing immunosuppressants were discontinued, and high-dose intravenous methylprednisolone was initiated along with antibiotics. While diarrhea resolved, the patient's general condition continued to deteriorate until demise due to multi-system organ failure at 37 d post-liver transplantation. This case illustrates the life-threatening nature of aGvHD.

***CONCLUSION***

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Manuscript source:** Unsolicited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** March 20, 2021
**Peer-review started:** March 20, 2021
**First decision:** June 5, 2021
**Revised:** June 5, 2021
**Accepted:** July 20, 2021
**Article in press:** July 20, 2021
**Published online:** September 27, 2021

**P-Reviewer:** Ferreira GSA
**S-Editor:** Wu YXJ
**L-Editor:** Filipodia
**P-Editor:** Wu RR

Herein, we have summarized a post-LTx aGvHD case and reviewed associated literature in order to increase awareness and provide potentially risk-mitigating recommendations.

**Key Words:** Liver transplantation; Graft-*vs*-host disease; Fluorescence *in situ* hybridization cytogenetics; Chimerism; Diagnosis; Case report



**Core Tip:** At present, the risk factors, pathogenesis, optimal treatment, and prognosis associated with acute graft-*vs*-host disease following liver transplantation are unclear. Currently, the most reliable diagnostic method is specific immunostaining for donor-specific antigens. If the donor is male and the recipient is female, fluorescent *in situ* hybridization-based detection of the Y chromosome is a diagnostic option. In the present case, acute graft-*vs*-host disease was confirmed *via* fluorescent *in situ* hybridization, demonstrating the presence of male donor DNA.

**Citation:** Xiao JJ, Ma JY, Liao J, Wu D, Lv C, Li HY, Zuo S, Zhu HT, Gu HJ. Fluorescence *in situ* hybridization-based confirmation of acute graft-*vs*-host disease diagnosis following liver transplantation: A case report. *World J Gastrointest Surg* 2021; 13(9): 1102-1109
**URL:** https://www.wjgnet.com/1948-9366/full/v13/i9/1102.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v13.i9.1102

## INTRODUCTION

Acute graft-*vs*-host disease (aGvHD) is one of the most dangerous complications following liver transplantation (LTx)[1]. It involves overactivation of donor helper T lymphocytes by recipient antigen-presenting cells, leading to a local inflammatory reaction against recipient tissue. Although the rate of aGvHD incidence after LTx is low (1%-2%), the mortality rate is extremely high (85%-90%)[2]. Skin rash and pyrexia are the most frequently noted early signs, followed by leukopenia. Although aGvHD was first proposed as a clinical entity in 1988, its mechanisms and optimal treatment strategies remain controversial[3]. Modification of the post-transplant treatment plan, including incorporation of more effective immunosuppressants, has a limited effect on the course of aGvHD[4,5]. In most cases, death results from overwhelming sepsis or gastrointestinal hemorrhage as a consequence of bone marrow involvement[6]. Due to the low incidence (but high mortality) of aGvHD following LTx, analysis of the present case with respect to existing literature is worthwhile in order to raise awareness regarding the condition, which may assist in the early diagnosis of suspected cases. It will also help improve diagnostic criteria and establish standardized evidence-based treatment regimens. Moreover, we wish to draw attention to the diagnostic utility of sex chromosome fluorescent *in situ* hybridization (FISH) when the donor and recipient are of different chromosomal sexes.

## CASE PRESENTATION

### *Chief complaints*

The patient was a 64-year-old female with primary biliary cirrhosis, esophageal-fundal variceal hemo-rrhages, and decompensated hepatocirrhosis in September 2017.

### *History of present illness*

A 64-year-old female received a liver from an ABO-matched (A-positive) 12-year-old male cadaveric donor. The donor and recipient details are shown in Table 1. The donor was a 12-year-old male. Three weeks following liver transplantation, the recipient developed pyrexia, diarrhea, rashes, and antibiotic-unresponsive pancytopenia.

**Table 1 Recipient and donor demographic, clinical, and typing data**

| Recipient | Donor | |
|---|---|---|
| Age | 64 | 12 |
| Sex | Female | Male |
| Primary complaint | PBC | Hypoxic-ischemic encephalopathy |
| Special history | Low-dose glucocorticoids | NA |
| Blood group | A | A |
| HLA | NA | NA |

PBC: Primary biliary cirrhosis; HLA: Human leukocyte antigen; NA: Not applicable.

### *History of past illness*

A 64-year-old female with primary biliary cirrhosis, esophageal-fundal variceal hemorrhages, and decompensated hepatocirrhosis.

### *Personal and family history*

The patient grew up in her locality, denies any contact with contaminated water or radiation exposure, and denies smoking and alcohol consumption.

### *Physical examination*

On physical examination, we found her poor nutritional status, the abdomen was moderately distended with mild tenderness, and there was moderately yellow staining of the skin and mucous membranes. The rest of the physical examination revealed no abnormal findings.

### *Laboratory examinations*

The following timeline of events refers to post-operative days. On day 22, the patient developed pyrexia of unknown origin, fluctuating between 38.2 °C and 39.3 °C. On day 26, sex chromosome FISH was performed on peripheral venous blood samples. No gastrointestinal tract lesions were apparent, and no evidence of aGvHD was noted on gastrointestinal endoscopic biopsy (histologically normal esophagus, stomach, and ileum). On day 31, the presumptive diagnosis of GvHD was made based on the following clinical ground observations: Generalized maculopapular eruption (largely involving the back, neck, and face), pyrexia, pancytopenia, low blood pressure, and watery diarrhea (Figure 1 and Table 2). FISH revealed chimerism (presence of the fluorescently stained donor XY chromosome) consistent with aGvHD (Figure 2).

Two days following the development of thrombocytopenia, a bone marrow biopsy revealed marked hypocellularity. No skin rash was yet apparent. The findings of detai -led post-operative laboratory investigation are summarized in Table 3. Because no sample of indwelling peripheral blood from the donor prior to LTx was available, donor lymphocytes could not be identified in recipient peripheral blood using short tandem repeat sequencing or human leukocyte antigen (HLA) typing.

### *Imaging examinations*

Abdominal computed tomography and color ultrasound findings suggested laminar portal vein, inferior vena cava, hepatic artery, and hepatic venous flow (Figure 3).

## FINAL DIAGNOSIS

aGvHD, primary biliary cirrhosis, esophageal-fundal variceal hemorrhages, and decom-pensated hepatocirrhosis.

## TREATMENT

Initial treatment involved tapering the dosage of immunosuppressants to allow the recipient immune system to reject donor lymphocytes. Due to the inefficacy of this

**Table 2 Clinical manifestation and treatment timeline**

| | Manifestations | | | | Drugs | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PO day | Temperature (°C) | Skin rash | Diarrhea | Myelosuppression | Tacrolimus (mg/d) | MMF (g/d) | MP | IgG (g/d) | Antibiotics |
| 22 | 38.3 | Palm | 2 | NA | 3 | 0.25 | 500 | 10 | Yes |
| 24 | 38.6 | Neck | 3 | NA | 2 | 0 | 500 | 10 | Yes |
| 26 | 38.5 | Face | 6 | Yes | 2 | 0 | 120 | NA | Yes |
| 28 | 38.2 | Trunk | 7 | Yes | 2 | 0 | 40 | NA | Yes |
| 30 | 39 | > 35% | 6 | Yes | 2 | 0 | 20 | NA | Yes |
| 32 | 38.6 | > 50% | 5 | Yes | 1.5 | 0 | 20 | 10 | Yes |
| 34 | 38.7 | > 55% | 4 | Yes | 1.5 | 0 | 20 | 10 | NA |
| 36 | Demise | | | | | | | | |

PO: Post-operative; NA: Not applicable; MMF: Two oral formulations of mycophenolate mofetil; MP: Methylprednisolone; IgG: Immunoglobulin G. Antibiotics: Melophenan (1 g every 8 h) + carpophennet (50 mg per day) + vancomycin (0.5 g every 6 h).

**Table 3 Post-operative laboratory investigation timeline**

| Post-operative laboratory investigation timeline | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Value/PO day | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 26 | 30 | 34 | 36 |
| AST (U/L) | 643 | 47.6 | 56 | 48 | 64 | 75 | 63 | 56 | 44 | 52 | 74 |
| ALT (U/L) | 772 | 88.1 | 96 | 86 | 107.3 | 62 | 59 | 64 | 66 | 71 | 83 |
| Total bilirubin (mg/dL) | 231.4 | 123.5 | 119.5 | 76.9 | 65.5 | 23.7 | 25.8 | 24.2 | 35.1 | 45.6 | 48.7 |
| Direct bilirubin (mg/dL) | 146.1 | 63.2 | 59.3 | 43.2 | 38.1 | 13.3 | 15.6 | 16.5 | 24.7 | 28.5 | 31.2 |
| Leukocyte count × $10^9$/L | 17.5 | 8.7 | 12.4 | 17.3 | 7.2 | 6.7 | 1.3 | 0.39 | 0.24 | 0.12 | 0.08 |
| Neutrophil % | 93 | 79 | 86 | 92 | 81 | 80 | 63 | 17.9 | 0 | 0 | 0 |
| Hemoglobin (g/L) | 89 | 92 | 176 | 113 | 92 | 85 | 75 | 63 | 58 | 53 | 47 |
| Hematocrit % | 42 | 46 | 50 | 32 | 26.5 | 23.3 | 22 | 17.6 | 16.5 | 15.6 | 14.8 |
| Platelets × $10^9$/L | 21 | 26 | 44 | 58 | 77 | 73 | 71 | 56 | 47 | 46 | 41 |
| Prothrombin time (s) | 17.9 | 19.9 | 16.5 | 22.4 | 13.5 | 13.1 | 12.7 | 13.1 | 12.8 | 13.2 | 13.6 |
| INR | 1.82 | 1.7 | 1.34 | 1.98 | 1.05 | 1.01 | 0.97 | 0.99 | 0.98 | 1.02 | 1.07 |
| Sodium (mmol/L) | 147 | 145 | 142 | 139 | 136 | 134 | 143 | 141 | 138 | 139 | 143 |
| Potassium (mmol/L) | 3.8 | 4.5 | 3.1 | 3.4 | 3.6 | 3.8 | 3.9 | 4.2 | 4.1 | 3.9 | 3.7 |
| Urea (mmol/L) | 32.52 | 29.8 | 16.42 | 4.55 | 4.77 | 4.46 | 4.13 | 3.8 | 4.17 | 3.74 | 4.02 |
| Creatinine (μmol/L) | 89.73 | 85.64 | 64.59 | 43.78 | 58.44 | 53.76 | 49.19 | 46.52 | 27.26 | 24.54 | 30.45 |
| PCT (ng/mL) | 5.73 | 3.86 | 11.5 | 5.1 | 1.86 | 2.65 | 2.58 | 2.45 | 2.18 | 3.65 | 4.53 |

PO: Post-operative; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio; PCT: Procalcitonin.

approach, the following treatment was administered subsequently: High-dose (500 mg/d) intravenous methylprednisolone, antibiotics, and immunoglobulin G (Table 2).

## OUTCOME AND FOLLOW-UP

Severe inflammation induced multi-system organ failure, which led to the patient's demise on post-operative day 37.

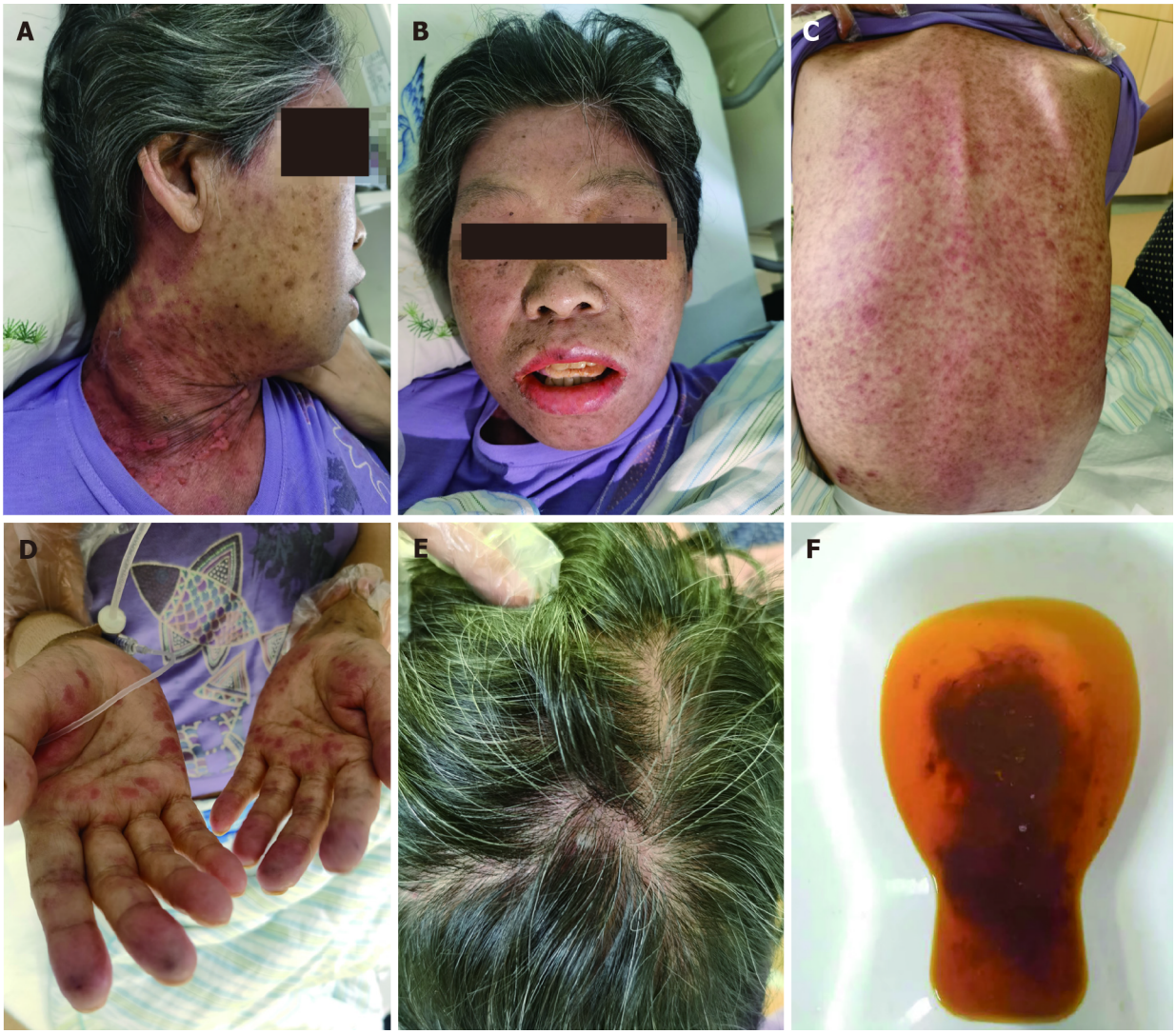


**Figure 1 Clinical ground observations of graft-*vs*-host disease.** A: Anterior cervical rash on post-operative day 24; B: Oral ulcers on post-operative day 25; C: Dorsal rash on post-operative day 25; D and E: Palmar rash on post-operative day 22; F: Scalp rash on post-operative day 27; G: Passage of three or more loose or liquid stools per day.

## DISCUSSION

At present, the risk factors, pathogenesis, optimal treatment, and prognosis associated with aGvHD following LTx are unclear. Current (incomplete) understanding of aGvHD pathogenesis may be summarized as follows. The conditioning regimen induces initial recipient tissue damage, followed by auto- and alloantigen denudation in the recipient concomitant with antigen-presenting cell activation and massive inflammatory cytokine release (a "cytokine storm"). If a sufficient number of donor lymphocytes, especially T lymphocytes, of the correct specificity are present, direct recognition of and activation by antigen-presenting cell (either locally or within secondary lymphoid tissues) results in T lymphocyte interleukin (IL)-2 and IL-2R expression. Activated T-cells then stimulate donor monocytes to produce significant levels of myeloid cytokines (*e.g.*, IL-1 and tumor necrosis factor) and also trigger a cascade of cytotoxic signal transduction pathways, such as the perforin/granzyme B or Fas/FasL pathways (although direct cytokine-mediated injury is also possible). Finally, inflammatory infiltration in the digestive tract, skin, and bone marrow leads to severe clinical presentations[7]. In the present case, abnormally high numbers of CD8+ T lymphocytes were present during the acute phase of GvHD, while the CD4+ T lymphocyte:CD8+ T lymphocyte ratio was less than 0.1. This indicates that perhaps cytotoxic T lymphocytes (with a minor contribution by helper T lymphocytes) are the cells primarily involved in GvHD pathogenesis. In summary, the necessary conditions for the occurrence of aGvHD[8-10] include the presence of donor immunoreactive cells within graft tissue, presence of recipient tissue antigens not present in donor organ

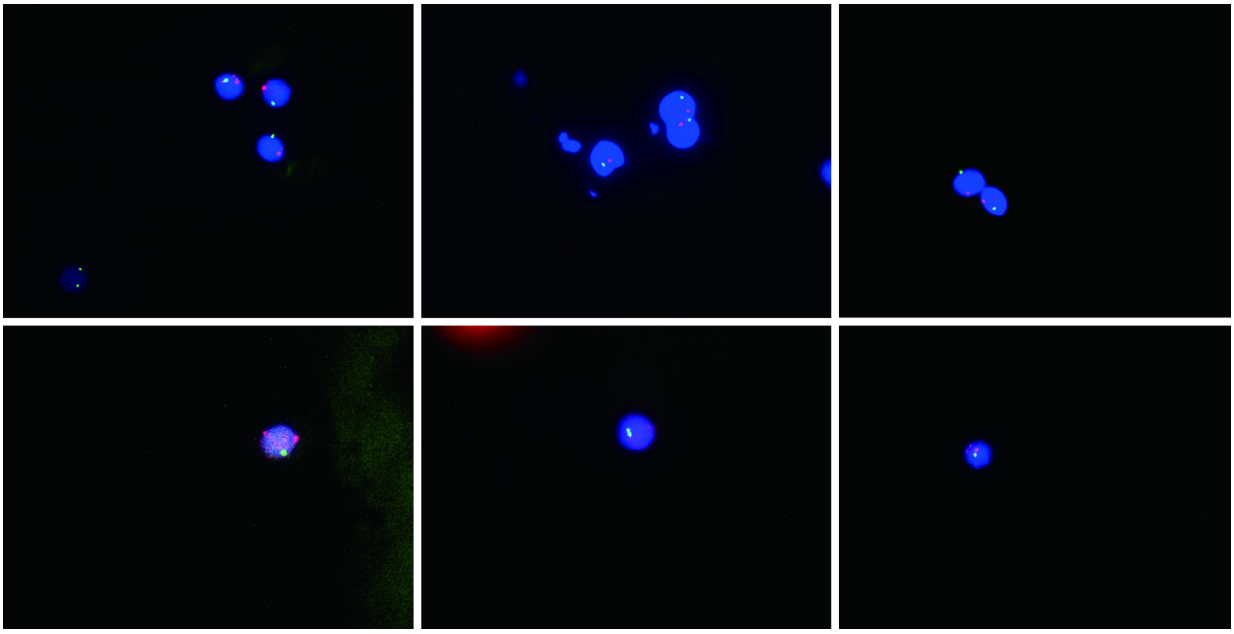

**Figure 2 Twelve erythrocytes analyzed, 11 showed an XY signal pattern, while one showed an XX signal pattern (91.7% showed one X and one Y signal, and 8.3% showed two X signals).** Y is the red fluorescent signal; X is the green fluorescent signal.

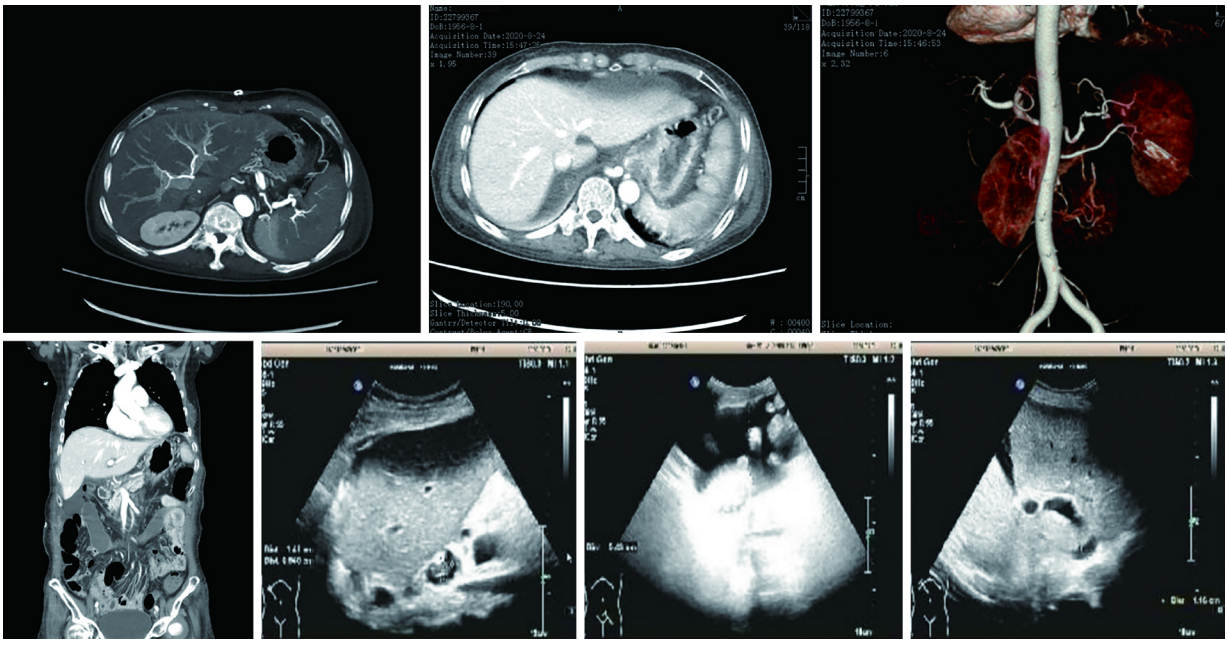

**Figure 3 The portal vein, inferior vena cava, hepatic artery, and hepatic venous blood flow were smooth.**

tissue, and inability of the recipient immune system to eliminate effectively donor leukocytes.

Triulzi *et al*[9] have described the diagnostic criteria for aGvHD following LTx in the following three requirements: (1) Characteristic clinical symptoms affecting related organ systems (*e.g.*, skin, gastrointestinal tract, and bone marrow), including rash, diarrhea, and pancytopenia, among others; (2) Abnormal skin or digestive tract histology; and (3) HLA or DNA evidence of donor immunoreactive lymphocytes in involved organs or peripheral blood of the recipient. In addition to the above criteria, T lymphocyte counts and cytokine quantitation provide clear diagnostic support. Currently, the most reliable diagnostic method is specific immunostaining for donor-specific antigens. If the donor is male and the recipient is female, FISH-based detection of the Y chromosome is a diagnostic option[9,11,12]. At present, no false negatives have been reported for this method. In the present case, aGvHD was confirmed *via*

FISH, demonstrating the presence of male donor DNA.

Due to inter-individual differences in post-operative GvHD pathogenesis and presentation, no unified treatment plan exists. Each hospital follows a unique treatment plan associated with unique advantages and disadvantages. A commonality across most centers is reduction of the tacrolimus dose, cessation of anti-metabolic immunosuppressants, decreasing the steroid dose, and administering antilymphocyte globulin[13-15]. Successful treatment *via* increasing immunosuppressant dosages has also been reported, with recommendations for cessation of all immunosuppressants in favor of isolated anti-human thymocyte globulin treatment[16]. Certain patients also exhibit drug resistance or even resistance to the effects of some hormones[17]. Treatment with anti-tumor necrosis factor-α or anti-IL-2 receptor monoclonal antibodies may prove beneficial[18,19]. Currently, corticosteroids are the best-recognized first-line treatment agents for GvHD. Glucocorticoids exert efficient anti-inflammatory effects and can induce donor lymphocyte apoptosis. High-dose corticosteroid pulse therapy is administered during the acute phase of GvHD. It can inhibit inflammatory cell activation, thereby blocking the inflammatory cytokine cascade to improve systemic signs and symptoms. In cases of observation of GvHD symptoms (gastrointestinal disturbance, immunodeficiency despite overzealous inflammation, and deficient coagulation), hydration, electrolyte and acid-base rebalancing, nutritional support, restoration of gastrointestinal mucosal integrity, correction of microfloral imbalance, and transfusion of plasma and platelets can help mitigate poor outcomes, including severe infection[13,20].

In order to lessen mortality resulting from aGvHD, early detection and optimal standardized treatment are paramount. Additionally, an improved understanding of pathogenesis may assist in the prevention and treatment of this disorder. Based on our experience and the literature review, we make the following recommendations: Baseline (presurgical) donor and recipient blood samples should be obtained and cryopreserved. High-risk patients should routinely undergo HLA typing as a preliminary risk evaluation step. Ideally, the age difference between matched donors and recipients should not exceed 20 years. Pre-existing use of oral immunosuppressants should be minimized or discontinued prior to transplantation wherever possible. During perfusion of the donor abdominal aorta and portal vein, the effluent should run clear and the liver texture should soften. Finally, minimizing blood product infusion may lessen the rate of complications[15].

## CONCLUSION

In the present case, aGvHD was confirmed *via* FISH, demonstrating the presence of male donor DNA. If the donor is male and the recipient is female, FISH-based detection of the Y chromosome is a diagnostic option.

## REFERENCES


1 **Perri R**, Assi M, Talwalkar J, Heimbach J, Hogan W, Moore SB, Rosen CB. Graft vs. host disease after liver transplantation: a new approach is needed. *Liver Transpl* 2007; **13**: 1092-1099 [PMID: 17663410 DOI: 10.1002/Lt.21203]

2 **Taylor AL**, Gibbs P, Bradley JA. Acute graft *vs* host disease following liver transplantation: the enemy within. *Am J Transplant* 2004; **4**: 466-474 [PMID: 15023138 DOI: 10.1111/j.1600-6143.2004.00406.x]

3 **Burdick JF**, Vogelsang GB, Smith WJ, Farmer ER, Bias WB, Kaufmann SH, Horn J, Colombani PM, Pitt HA, Perler BA. Severe graft-versus-host disease in a liver-transplant recipient. *N Engl J Med* 1988; **318**: 689-691 [PMID: 3278235 DOI: 10.1056/NEJM198803173181107]

4 **Lee SJ**, Onstad L, Chow EJ, Shaw BE, Jim HSL, Syrjala KL, Baker KS, Buckley S, Flowers ME. Patient-reported outcomes and health status associated with chronic graft-*versus*-host disease. *Haematologica* 2018; **103**: 1535-1541 [PMID: 29858386 DOI: 10.3324/haematol.2018.192930]

5 **Qian L**, Dima D, Berce C, Liu Y, Rus I, Raduly LZ, Petrushev B, Berindan-Neagoe I, Irimie A, Tanase A, Jurj A, Shen J, Tomuleasa C. Protein dysregulation in graft *vs* host disease. *Oncotarget* 2018; **9**: 1483-1491 [PMID: 29416707 DOI: 10.18632/oncotarget.23276]

6 **Taylor AL**, Gibbs P, Sudhindran S, Key T, Goodman RS, Morgan CH, Watson CJ, Delriviere L, Alexander GJ, Jamieson NV, Bradley JA, Taylor CJ. Monitoring systemic donor lymphocyte macrochimerism to aid the diagnosis of graft-versus-host disease after liver transplantation. *Transplantation* 2004; **77**: 441-446 [PMID: 14966423 DOI: 10.1097/01.TP.0000103721.29729.FE]

7 **Schrager JJ**, Vnencak-Jones CL, Graber SE, Neff AT, Chari RS, Wright KJ Jr, Pinson CW, Stewart JH, Gorden DL. Use of short tandem repeats for DNA fingerprinting to rapidly diagnose graft-versus-

host disease in solid organ transplant patients. *Transplantation* 2006; **81**: 21-25 [PMID: 16421472 DOI: 10.1097/01.tp.0000190431.94252.3f]

8 **Jacobs MT**, Olson M, Ferreira BP, Jin R, Hachem R, Byers D, Witt C, Ghobadi A, DiPersio JF, Pusic I. The use of ruxolitinib for acute graft-versus-host disease developing after solid organ transplantation. *Am J Transplant* 2020; **20**: 589-592 [PMID: 31446673 DOI: 10.1111/ajt.15579]

9 **Triulzi D**, Duquesnoy R, Nichols L, Clark K, Jukic D, Zeevi A, Meisner D. Fatal transfusion-associated graft-versus-host disease in an immunocompetent recipient of a volunteer unit of red cells. *Transfusion* 2006; **46**: 885-888 [PMID: 16734803 DOI: 10.1111/j.1537-2995.2006.00819.x]

10 **Kanehira K**, Riegert-Johnson DL, Chen D, Gibson LE, Grinnell SD, Velgaleti GV. FISH diagnosis of acute graft-versus-host disease following living-related liver transplant. *J Mol Diagn* 2009; **11**: 355-358 [PMID: 19460938 DOI: 10.2353/jmoldx.2009.080172]

11 **Gonultas F**, Akbulut S, Barut B, Kutluturk K, Yilmaz S. Graft-versus-host disease after living donor liver transplantation: an unpredictable troublesome complication for liver transplant centers. *Eur J Gastroenterol Hepatol* 2020; **32**: 95-100 [PMID: 31524772 DOI: 10.1097/MEG.0000000000001530]

12 **Di Ianni M**, Del Papa B, Baldoni S, Di Tommaso A, Fabi B, Rosati E, Natale A, Santarone S, Olioso P, Papalinetti G, Giancola R, Accorsi P, Di Bartolomeo P, Sportoletti P, Falzetti F. NOTCH and Graft-Versus-Host Disease. *Front Immunol* 2018; **9**: 1825 [PMID: 30147692 DOI: 10.3389/fimmu.2018.01825]

13 **Triulzi DJ**, Nalesnik MA. Microchimerism, GVHD, and tolerance in solid organ transplantation. *Transfusion* 2001; **41**: 419-426 [PMID: 11274601 DOI: 10.1046/j.1537-2995.2001.41030419.x]

14 **Perkins JL**, Neglia JP, Ramsay NK, Davies SM. Successful bone marrow transplantation for severe aplastic anemia following orthotopic liver transplantation: long-term follow-up and outcome. *Bone Marrow Transplant* 2001; **28**: 523-526 [PMID: 11593328 DOI: 10.1038/sj.bmt.1703177]

15 **Ramachandran V**, Kolli SS, Strowd LC. Review of Graft-Versus-Host Disease. *Dermatol Clin* 2019; **37**: 569-582 [PMID: 31466596 DOI: 10.1016/j.det.2019.05.014]

16 **Hill L**, Alousi A, Kebriaei P, Mehta R, Rezvani K, Shpall E. New and emerging therapies for acute and chronic graft *versus* host disease. *Ther Adv Hematol* 2018; **9**: 21-46 [PMID: 29317998 DOI: 10.1177/2040620717741860]

17 **Schroeder T**, Haas R, Kobbe G. Treatment of graft-versus-host disease with monoclonal antibodies and related fusion proteins. *Expert Rev Hematol* 2010; **3**: 633-651 [PMID: 21083479 DOI: 10.1586/ehm.10.46]

18 **Aladağ E**, Kelkitli E, Göker H. Acute Graft-Versus-Host Disease: A Brief Review Turk J Haematol 2020; 37: 1-4 [PMID: 31475512 DOI: 10.4274/tjh.galenos.2019.2019.0157]

19 **Murray J**, Stringer J, Hutt D. Graft-Versus-Host Disease (GvHD). 2017 Nov 22. In: Kenyon M, Babic A, editors. The European Blood and Marrow Transplantation Textbook for Nurses: Under the Auspices of EBMT [Internet]. Cham (CH): Springer; 2018. Chapter 11 [PMID: 31314308 DOI: 10.1007/978-3-319-50026-3_11]

20 **Whalen JG**, Jukic DM, English JC 3rd. Rash and pancytopenia as initial manifestations of acute graft-versus-host disease after liver transplantation. *J Am Acad Dermatol* 2005; **52**: 908-912 [PMID: 15858489 DOI: 10.1016/j.jaad.2005.01.126]

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