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REVIEW

# Operable gastro-oesophageal junctional adenocarcinoma: Where to next?

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## Abstract

Oesophageal junctional adenocarcinoma is a challenging and increasingly common disease. Optimisation of pre-operative staging and consolidation of surgery in large volume centres have improved outcomes, however the preferred adjunctive treatment approach remains a matter of debate. This review examines the benefits of neoadjuvant, peri-operative, and post-operative chemotherapy and chemoradiotherapy in this setting in an attempt to reach an evidence based conclusion. Recent findings relating to the molecular characterisation of oesophagogastric cancer and their impact on therapeutics are explored, in addition to the potential benefits of fluoro-deoxyglucose positron emission tomography (FDG-PET) directed therapy. Finally, efforts to decrease the incidence of junctional adenocarcinoma using early intervention in Barrett's oesophagus are discussed, including the roles of screening, endoscopic mucosal resection, ablative therapies and chemoprevention.



**Key words:** Oesophageal adenocarcinoma; Junctional adenocarcinoma; Gastric adenocarcinoma; Peri-operative chemotherapy; Pre-operative chemoradiotherapy; Molecular profiling; Fluoro-deoxyglucose-positron emission tomography; Barrett's oesophagus; Chemoprevention

**Core tip:** Cancer of the gastro-oesophageal junction is an increasingly common phenomenon. For patients with operable junctional cancer, the only curative treatment option is surgery, however the optimal peri-operative treatment is controversial. We review the evidence supporting the use of chemotherapy and chemoradiotherapy in the pre- and postoperative settings for these patients, and go on to highlight how current research into the molecular mechanisms underpinning gastro-oesophageal cancer may lead to future effective treatment options.

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## INTRODUCTION

Adenocarcinoma of the oesophagogastric junction presents an increasingly common dilemma in many affluent countries, and the optimal treatment approach for patients with resectable disease is a matter of some controversy[1]. In addition to surgery for their cancer, and depending on geographical location and physician preference patients may undergo neoadjuvant, peri-operative, or post-operative chemotherapy, or pre- or post-operative chemoradiotherapy[2-4]. Unfortunately, despite improvements in staging and patient selection, long term survival following resection remains relatively poor and further refinement of treatment paradigms and novel therapeutic interventions are required. This aim of this review is to assess the current status of our knowledge on tumours of the gastroesophageal junction with respect to tumour

**Table 1 Selected trials of peri-operative therapy for junctional oesophageal adenocarcinoma**

| Trial | Year | % Junctional adenocarcinoma or lower oesophageal tumours | *n* | Treatment | Survival (%) |
|---|---|---|---|---|---|
| Peri-operative chemotherapy | | | | | |
| MAGIC[5] | 2006 | Adenocarcinoma 100% | 503 | Surgery | 23.00 |
| | | Lower oesophageal/GEJ 26% | | Peri-operative chemotherapy | 36.30 (5-year-OS) |
| FNCLCC-FFCD[6] | 2011 | Adenocarcinoma 100% | 224 | Surgery | 24 |
| | | Lower oesophagus 11%, GEJ 64% | | Peri-operative chemotherapy | 38 (5-year-OS) |
| OEO2[7,8] | 2009 | Adenocarcinoma 66.5% | 802 | Surgery | 17.10 |
| | | Lower 1/3 and cardia 75% | | Neoadjuvant chemotherapy | 23.00 (5-year-OS) |
| Pre-operative chemoradiotherapy | | | | | |
| Stahl[13] | 2009 | Adenocarcinoma 100% | 126 | Neoadjuvant chemotherapy | 27.70 |
| | | GEJ 100% | | Neoadjuvant chemoradiotherapy | 47.40 (3-year-OS) |
| Tepper[14] | 2009 | Adenocarcinoma 75% | 56 | Surgery | 1.79y |
| | | Distal oesophagus/GEJ 100% | | Neoadjuvant chemoradiotherapy | 4.48y (median OS) |
| CROSS[15] | 2012 | Adenocarcinoma 74% | 366 | Surgery | 44 |
| | | Distal 1/3 oesophagus 57, GEJ 24% | | Neoadjuvant chemoradiotherapy | 58 (3-year-OS) |
| Post-operative chemoradiotherapy | | | | | |
| INT-0116[16] | 2001 | Adenocarcinoma 100% | 556 | Surgery | 41 |
| | | Cardia 20% | | Adjuvant chemoradiotherapy | 50 (3-year-OS) |

DFS: Disease free survival; GEJ: Gastroesophageal junction; OS: Overall survival; SCC: Squamous cell carcinoma.

biology and therapy and to examine how developments in targeted therapy, radiotherapy, screening, and chemoprevention may improve outcomes for patients with this disease.

## PERI-OPERATIVE CHEMOTHERAPY

In Western populations, many patients presenting with junctional adenocarcinoma have relatively locally advanced disease at presentation, and whilst there may be debate regarding the optimal treatment approach, there is agreement that something more than surgery is required to increase survival (Table 1). In Europe and selected United States academic centres, peri-operative chemotherapy is the treatment of choice for these patients. This choice is based on the United Kingdom MRC MAGIC trial, which treated over 500 patients with stomach, junctional or oesophageal tumours to either surgery alone or surgery plus peri-operative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (5-FU)[5]. Peri-operative chemotherapy led to a 37% reduction in the risk of progression following surgical resection and improved 5 year survival from 23% in the surgery alone arm to 36% in those treated with chemotherapy (HR = 0.75, 95%CI: 0.60-0.93; $P = 0.009$). In MAGIC one quarter of patients had tumours of the gastroesophageal junction (GEJ) or lower oesophagus and subgroup analysis demonstrates that the greatest benefit was seen in patients with junctional tumours. These results are supported by the results of the randomised phase Ⅲ FNCLCC/FFCD French study in which 224 patients were randomised to surgery alone or peri-operative cisplatin and 5-fluorouracil chemotherapy[6]. The results from this study (in which 75% of patients had junctional tumours) are remarkably similar to those seen in MAGIC, with an improvement in 5 year overall survival from 24% to 38% (HR = 0.69, $P = 0.02$) for the interventional arm.

The aim of peri-operative chemotherapy is two-fold; firstly to downstage the primary tumour with a view to obtaining an R0 resection, and secondly to treat occult micro-metastatic disease. The neoadjuvant component of both MAGIC and the French study improved curative resection rates for patients in both these trials, in MAGIC 79.3% of chemotherapy patients were curatively resected compared to 70.3% in the surgery alone arm ($P = 0.03$), these figures are 84% and 73% respectively for the FFCD trial ($P = 0.04$). That subclinical micrometastases are eliminated is demonstrated by the almost uniform 35%-37% reduction in disease recurrence which seen across the two studies.

## NEO-ADJUVANT CHEMOTHERAPY ALONE: IS IT ENOUGH?

Interestingly, a neo-adjuvant chemotherapy alone approach (with no post-operative component) does not appear to provide the same benefit to patients with oesophagogastric cancer. In the MRC OE02 study 802 patients with primarily oesophageal cancer (two thirds adenocarcinoma) were randomised to surgery alone or 2 cycles of cisplatin and 5-FU prior to surgery[7,8]. Although this study did demonstrate a survival benefit for patients treated with chemotherapy regardless of histology (5 year survival 23% *vs* 17%, $P = 0.03$), these results are not consistent with the results of the RTOG 8911 trial ($n = 467$) in which no difference was seen in the survival outcomes for a similar group patients treated with pre-operative chemotherapy[9]. Consistent with the negative results of the RTOG 8911 study are those of the smaller EORTC 40954 trial ($n = 144$, of whom half were junctional tumours). This study demonstrated an increase in the R0 resection rate following pre-operative cisplatin and 5-FU chemotherapy, but no improvement in overall survival[10]. These somewhat heterogeneous results have been combined in a meta-analysis which did demonstrate an improvement in survival for the neoadjuvant chemotherapy approach (HR = 0.90 for neoadjuvant chemotherapy, 95%CI: 0.81-1.00, $P = 0.05$)[11]. The benefit seen

appears to be due to the adenocarcinoma population (HR = 0.78, $P$ = 0.014) as no significant difference was seen in the squamous cell carcinoma analysis. Therefore, although neoadjuvant chemotherapy alone for junctional tumours is not as clearly advantageous as treatment given both pre- and post-operatively, it is a reasonable choice if patients cannot tolerate post-operative chemotherapy.

## NEOADJUVANT CHEMORADIOTHERAPY: DOES MAXIMISING LOCAL CONTROL LEAD TO IMPROVED SURVIVAL?

Response rates to radiotherapy are high, and if tumour downstaging in order to improve operative outcomes is the aim of therapy then radiotherapy has clearly defined benefits. However, if long term survival is the goal of treatment, many studies in junctional adenocarcinoma provide conflicting results. Analysis of the results of these studies must be careful, with consideration given to the external validity or generalizability of the data presented. Many trials present results based on both squamous cell carcinoma and adenocarcinoma patients between whom there are clear biological differences. Squamous cell carcinoma is exquisitely radiosensitive and may not require surgical resection if a pathological complete response is obtained following chemoradiotherapy. Adenocarcinoma is less likely to demonstrate such a response and will always require surgery in order to maximise the chance of long term survival. As such, caution must be used when extrapolating results from clinical trials as whole to biologically distinct patient groups.

Older studies of chemoradiotherapy for junctional cancers demonstrate mixed results. One of the first trials of neo-adjuvant cisplatin/5-FU based chemoradiotherapy for junctional type adenocarcinoma demonstrated a significant increase in survival for patients treated with combined modality therapy compared to those treated with surgery alone (16 m *vs* 11 m, $P$ = 0.01)[12]. However, interpretation of these results should be made with care as this trial was small ($n$ = 58), patients underwent limited staging by current standards (CXR and abdominal ultrasound only), and survival was poor in the control arm of the study. Following this two other small studies also demonstrated a benefit to this combined modality approach; the POET study randomised 126 patients with junctional adenocarcinoma to pre-operative chemotherapy and surgery or to induction chemotherapy followed by chemoradiotherapy and then surgery[13]. Survival was numerically improved by the addition of chemoradiotherapy (3 year survival 47% *vs* 28%, $P$ = 0.07), but the study was underpowered due to low accrual and this did not reach statistical significance. CALGB 9781 (75% adenocarcinoma) also utilized a tri-modality approach in its experimental arm and demonstrated statistically superior survival for chemoradiotherapy when compared to surgery alone [Overall survival (OS) 4.5 years *vs* 1.8 years, $P$ = 0.002], however the small number of patients in this trial ($n$ = 56) and the lack of histological subgroup analysis limit interpretation of these interesting results[14].

The publication of the phase Ⅲ randomised CROSS trial which compared chemoradiotherapy (weekly carboplatin and paclitaxel with 41.4 Gy radiotherapy in 23 fractions over 5 wk) to surgery alone have lead to a paradigm shift in the treatment of junctional cancers in many institutions[15]. Three hundred and sixty six patients with oesophageal cancer (75% adenocarcinoma, 23% squamous cell carcinoma, 2% undifferentiated) were randomised, of whom the majority had tumours of the distal oesophagus (58%) or gastroesophageal junction (24%). Overall survival results for chemoradiotherapy in CROSS are compelling; survival was 24 mo for surgery alone compared to 49 mo for chemoradiotherapy (HR = 0.67, $P$ = 0.003). However, several caveats apply. Firstly, the control arm in CROSS was surgery alone and the benefits of chemoradiotherapy compared to a contemporary control such as neoadjuvant chemotherapy are unknown. Secondly, in the adjusted survival analysis, the benefit of combination therapy is not significant for adenocarcinoma patients ($P$ = 0.07), providing evidence that the overall results for the study were driven by the radiosensitivity of the squamous cell carcinoma patient population.

Chemoradiotherapy provides a clear advantage over chemotherapy alone in terms of pathological complete response and local recurrence. In CROSS 29% of patients overall demonstrated a complete response, however this was much more common in squamous cell cancers (49%) than in adenocarcinoma (23%). It is worth noting however, that although pathological complete response is an attractive endpoint, it is not necessary in order to achieve either tumour downstaging or an R0 resection, and that peri-operative chemotherapy alone can help to achieve both these endpoints as demonstrated in FNCLCC/FFCD and MAGIC[5,6]. Patients with junctional adenocarcinoma are also much more likely to harbour systemic micro-metastatic disease, and there is some concern that the systemic chemotherapy dose in CROSS is insufficient to eliminate these. This concern is highlighted by the fact that patients in CROSS with N1 or greater staging at presentation did not appear to benefit from chemoradiotherapy in the adjusted survival analysis ($P$ = 0.21), implying that those at high risk of systemic relapse require a higher dose of systemic therapy in addition to an effective local treatment. Ultimately, there is no doubt that chemoradiotherapy is an excellent and frequently curative treatment for squamous cell carcinoma, and perhaps for very early node negative adenocarcinoma, but for patients with more locally advanced disease (who comprise the majority of patients seen), the evidence is less robust. A clinical trial comparing pre-operative chemoradiotherapy to peri-operative chemotherapy is underway (NCT01726452) and may in time give clarification to this important issue.

## POST-OPERATIVE ADJUVANT CHEMORADIOTHERAPY

Post-operative adjuvant chemoradiotherapy is a strategy

more often adopted for resected gastric cancers in the United States[16]. In the landmark INT0116 study 556 patients were randomised to no treatment following surgery or to chemoradiotherapy consisting of 45 Gy with fluorouracil and leucovorin on a Mayo-type regimen schedule. A recently published 10 year follow up of this study demonstrated a long term survival benefit -50% of patients treated with chemoradiotherapy survived for five years, compared to 41% who received no further treatment with a 51% reduction in the risk of recurrence and a 32% reduction in the risk of death attributable to the interventional arm[17]. Although the majority (80%) of patients in the Intergroup study had true stomach cancers, approximately 20% had junctional adenocarcinoma, and for patients who have not undergone pre-operative treatment, this remains an evidence based treatment option. Of significant concern is the fact that most patients in this study did not have an adequate surgical resection (although this is more significant for gastric patients as opposed to oesophageal), and therefore radiotherapy in the post operative setting may merely compensate for insufficient surgery. A second problem with adjuvant chemoradiotherapy relates to tolerability; post-operative morbidity associated with gastrectomy is significant, and preoperative therapy tends to be much more tolerable to patients than post-operative. For example, in MAGIC and the FNCLCC/FFCD trials of peri-operative chemotherapy more than 85% of patients completed the neoadjuvant component of therapy, compared to less than 50% who complete the post-operative treatment[5,6]. Furthermore, as many patients with junctional adenocarcinoma have relatively bulky tumours which benefit from downstaging withholding therapy until the post-operative period may disadvantage the patient if attempting to achieve a curative R0 resection. Finally, although adjuvant chemotherapy alone as used in the ACTS-GC and CLASSIC studies provides a well defined survival benefit, these trials were almost completely composed of patients with resected gastric cancer, not junctional cancers, and also conducted in Asian populations with distinct surgical patterns and pharmacogenomic profiles[4,18]. For these reason, we prefer a pre-operative treatment approach for most patients with junctional adenocarcinoma if this is possible.

## STRATEGIES TO IMPROVE OUTCOMES: NOVEL TARGETS, IMAGING AND EARLY INTERVENTION

### *Understanding disease biology leads to new targets for drug development*

Despite the fact that oesophagogastric cancer is most prevalent in the affluent West and frequently in patients of higher socioeconomic status, survival remains mediocre. Although neoadjuvant or peri-operative therapy improves survival by over one third, relapse is common[5,6,15]. Interval improvement in outcomes have been due to stage migration which occurs as a result of improved staging, routine use of pre-operative positron emission tomography-computed tomography (PET-CT) and laparoscopy (in particular for patients with type Ⅲ tumours) may prevent futile surgery in up to one fifth of patients[19]. In order to build on these gains, it will be necessary to exploit the biology of the disease with changes in treatment approach to targeted drugs and/or immunotherapies, strategies which have yielded immense returns in other malignancies such as melanoma[20-22]. Although gastroesophageal cancer is currently treated as a single disease entity, this designation is based on anatomy, not biology and in future treatment paradigms may differ according to the underlying dysregulated molecular characteristics rather than the spatial location. From an epidemiological perspective, lower oesophageal and junctional cancers have a distinct set of risk factors, quite separate from distal gastric cancer. Whereas antral cancers are endemic in high risk areas, strongly correlated with *Helicobacter pylori* (*H. pylori*) infection, associated with poor diet and high salt intake, proximal cancers do not appear to be related to *H. pylori*, but are associated with obesity and chronic reflux oesophagitis[23-26]. Despite these differences, junctional and distal tumours both progress through a predictable path of histological changes en route to a Lauren's intestinal cancer phenotype and display similar biological behaviours. Ultimately junctional and distal cancers are more similar in nature to each other than to diffuse gastric cancer, a disease which when non-hereditary has no known epidemiological risk factors or precursor lesions, and which has a characteristic pattern of infiltrative peritoneal spread[27,28].

Molecular characterisation of gastric cancer has moved forward in recent years, with several groups attempting to define molecular signatures which may correlate with Lauren's pathological classification, provide information on prognosis or predict response to chemotherapy[29,30]. To date these approaches remain exploratory and require further validation in larger patient cohorts. Genome wide sequencing approaches have failed to identify many any significant driver mutations in oesophagogastric cancer; mutation rates in most well known oncogenes such as *BRAF*, *KRAS* and *PIK3CA* are relatively low and therefore it is difficult to determine whether they are associated with prognosis or response to chemotherapy[31,32]. Interestingly, in one study specifically exploring the genomic landscape of junctional adenocarcinoma almost half (49%) of recurrently mutated genes were unique to this tumour subsite when compared to previously reported mutations in gastric cancer[33]. Mutations are more frequent in key tumour suppressor genes such as *p53* and *ARID1A*, but unfortunately these are currently more difficult to exploit therapeutically, although potentially actionable activating mutations have also been documented in genes such as *FGFR4* and *HGF*[32,33]. Outside the spectrum of activating driver mutations, a significant proportion of gastroesophageal cancers demonstrate predominantly mutually exclusive amplification of receptor tyrosine kinases which may be targeted successfully with novel agents[34]. Over one third of cancers demonstrate amplification of one of *ERBB2*, *MET*, *FGFR*, *KRAS* or *EGFR*, and while it

appears that these cancers may be more clinically aggressive, they may also potentially benefit from treatment with novel targeted drugs[34-36].

Trastuzumab, the monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER-2) receptor tyrosine kinase, was the first targeted therapy do demonstrate efficacy in oesophagogastric cancer, with an improvement in median overall survival to an unprecedented 16 mo for patients with advanced HER2 immunohistochemistry (IHC)3+ or IHC2+ fluorescence *in situ* hybridisation (FISH) positive tumours treated with chemotherapy plus trastuzumab[37]. This compares very favourably to median survival for similar patients treated with standard chemotherapy regimens which is generally less than one year[38,39]. In breast cancer, trastuzumab is associated with increased response rates and improved surgical outcomes when administered neoadjuvantly, and is curative in the adjuvant setting[40,41]. It is therefore a matter of regret that no registration study for trastuzumab was performed in conjunction with peri-operative chemotherapy for resectable gastroesophageal cancer, where up to 25% of patients with junctional cancers (who overexpress HER-2) could benefit[42]. However, for those who prefer a trimodality approach, a United States study will assess the benefits of the addition of trastuzumab to a CROSS like regimen of chemoradiotherapy for patients with resectable HER-2 positive oesophageal cancer (NCT01196390). The addition of pertuzumab (the monoclonal antibody inhibitor of HER-2 dimerization) to trastuzumab therapy has led to significant gains in overall survival for patients with metastatic breast cancer, as has the anti-HER2 antibody drug conjugate TDM1, and both pertuzumab (NCT01774786) and TDM1 (NCT01641939) are currently being evaluated in large, international randomised trials in HER2 positive gastric cancer in the first and second line setting respectively[43]. Therefore in future it is hoped it that these may play a role in the peri-operative setting.

Other potential pathways of interest for patients with gastroesophageal cancer include targeting angiogenesis, MET and fibroblast growth factor receptor (FGFR). Therapies targeting MET and FGFR, although promising from a preclinical perspective, have limited clinical evidence for efficacy at this stage beyond anecdotal reports from early phase clinical trials. However, there is substantial evidence to support an anti-angiogenic approach in operable gastroesophageal cancer. In a placebo controlled phase Ⅲ randomised trial the anti-VEGFR2 antibody ramicurumab led to a significant improvement in survival compared to best supportive care in previously treated advanced gastric cancer (OS 5.2 m *vs* 3.8 m HR = 0.78, $P = 0.047$)[44]. Interestingly, the benefit seen in terms of overall survival was comparable to that demonstrated in randomised studies of cytotoxic therapies in the same setting[45]. Ramicurumab has also improved survival when added to paclitaxel in the second line setting resulting in a median overall survival of an unprecedented 9.63 m for previously treated patients (HR = 0.807, 95%CI: 0.678-0.962; $P = 0.0169$)[46]. Furthermore, although in the phase Ⅲ randomised AVAGAST study for patients with advanced gastric cancer the addition of bevacizumab to cisplatin-fluoropyrimidine chemotherapy did not lead to a benefit in terms of overall survival, significant improvements in response rate and progression free survival were seen in the experimental arm[47]. As the goal of therapy in the peri-operative setting is to maximise response rate in order to achieve an R0 resection, then the addition of bevacizumab to peri-operative chemotherapy would appear to be a rational choice. This approach has been adopted in the large United Kingdom MRC ST03 trial, which will evaluate the addition of bevacizumab to peri-operative epirubicin, cisplatin and capecitabine chemotherapy (NCT00450203). This study completed recruitment of over one thousand patients in late 2013 and preliminary results are expected within the next two years.

## IMAGE DIRECTED THERAPY: LARGER PATIENT COHORTS ARE NEEDED TO VALIDATE THIS PROMISING BIOMARKER

The routine use of PET-CT is helpful in staging patients with potentially operable junctional adenocarcinoma and may decrease the rate of futile surgery by identifying patients with CT-occult metastatic disease[19]. PET-CT has the potential to become a useful tool in assessing early response to treatment in oesophagogastric cancer, however studies evaluating this as a predictor of response have been small and lack validation. In the MUNICON I study of 54 patients with oesophageal cancer who failed to demonstrate a metabolic response following one cycle neoadjuvant chemotherapy (defined as ⩽ 35% decrease in SUV) no patient had a histological response and median survival for these patients was significantly worse than those who had a metabolic response (HR = 2.18, 95%CI: 1.32-3.62, $P = 0.002$)[48]. In the follow up MUNICON Ⅱ study patients who failed to demonstrate a metabolic (PET) response to a single cycle of pre-operative chemotherapy were treated with salvage chemoradiotherapy[49]. Although this did increase the pathological response rate compared to chemotherapy alone in the previous study it did not improve the R0 resection rate, and PET-non responders had almost half the rate of 2 year progression free survival of metabolic responders (64% for PET responders and 33% for PET non-responders (HR = 2.22, $P = 0.035$), highlighting the aggressive disease biology of non-responding patients. Unfortunately despite these intriguing findings the small number of patients in the MUNICON studies preclude these changing clinical practice and larger clinical trials will be required in order to do this; the CALGB group have initiated a study in which over two hundred patients with junctional adenocarcinoma are randomised induction chemotherapy with either FOLFOX (oxaliplatin plus fluorouracil) or carboplatin and paclitaxel with interval PET being performed following three cycles of treatment (NCT01333033). Patients who fail to respond on PET (⩽ 35% reduction in SUV) will cross over to the alternate treatment arm

of the study for concurrent chemoradiotherapy. The primary endpoint of this study is to increase the rate of pathological complete response in the initial PET non-responders to 20%, with progression free and overall survival being secondary endpoints. The UK MRC ST03 study (NCT00450203) which is evaluating the addition of bevacizumab to peri-operative chemotherapy is also performing a PET substudy which may provide further important information on this topic.

## DECREASING CANCER RELATED MORTALITY WITH EARLY INTERVENTION

By the time symptoms such as dysphagia become apparent for patients with junctional adenocarcinoma the disease is often well established and frequently not amenable to surgery. Additionally, for those who are suitable for an operative approach the morbidity associated with such invasive surgery and peri-operative therapy is such that many patients may be excluded from curative treatment due to co-morbidity or performance status. However, for the small number of patients who are diagnosed with early stage cancers endoscopic resection may provide comparable results to surgical resection with less morbidity[50,51]. For patients with intramucosal carcinoma or high grade dysplasia with visible lesions endoscopic resection in a high volume centre is recommended with subsequent management dictated by the depth of tumour invasion on pathology[52]. Radiofrequency ablation is recommended for patients with early cancer or high grade dysplasia with no visible lesions/flat lining and for complete eradication of residual visible Barrett's oesophagus following endoscopic mucosal resection[51-55]. Based on randomised trial data, endoscopic resection of the entire Barrett's mucosa does not appear to provide any increased benefit over endoscopic resection of only visible lesions and radiofrequency ablation of the remainder of visible areas of Barrett's[56]. The case for endoscopic intervention is less clear for patients with low grade dysplasia, although there is clear evidence that ablative therapies can eradicate low grade dysplasia, given the low incidence of progression of such lesions to overt malignancy the benefit of this approach to patients is not definitively proved[52,57-60]. A randomised trial (SUrveillance *vs* RadioFrequency ablation - SURF) is currently addressing this issue[61].

Based on the non-operative interventions which are successful in treating Barrett's oesophagus it has been suggested that population screening for this condition could decrease oesophageal cancer related mortality. Although previously the rate of conversion was frequently estimated at approximately 0.5% annually the true rate is likely to be less than this[62,63]. Two recently published large population based studies containing almost twenty thousand patients between them estimate the risk to be between 0.12%-0.38% per annum[64,65]. If rates of conversion of Barrett's oesophagus to oesophageal adenocarcinoma are indeed this low, stratification of patients into high and low risk patient groups for screening will be necessary in order to maximise benefits to screened patients while optimising resource utilization. American Gastroenterological Association Guidelines suggest screening for Barrett's neoplasia only in persons with multiple risk factors such as chronic reflux, hiatus hernia, age $\geqslant$ 50, male sex, white race, elevated body mass index, and intra-abdominal body fat distribution, and British Society of Gastroenterology guidelines broadly concur with these, recommending surveillance in persons with at least of the above three risk factors, and also in those with a first degree relative with Barrett's oesophagus or oesophageal adenocarcinoma[52,66]. The recommendation to screen first degree relatives is based on research demonstrating that familial clustering of Barrett's oesophagus is not uncommon, with up to 28% first degree relatives of patients with oesophageal junctional adenocarcinoma or Barrett's with high grade dysplasia also demonstrating a Barrett's mucosa[67,68]. Recent gene wide association studies have confirmed this genetic propensity with Barrett's associated loci demonstrated in the MHC and on Ch16q24[69]. With respect to risk stratification of patients for consideration of endoscopy, there is some evidence that the frequency of symptoms of gastroesophageal reflux influences the risk of oesophageal adenocarcinoma ($\geqslant$ once per week symptoms odds ratio 4.9 $\geqslant$ daily symptoms odds ratio 7.4), however, as up to 40% of patients with oesophageal cancer have no history of reflux, focusing solely on symptomatic patients will have limited benefits with respect to mortality[70,71]. As the potential morbidity of endoscopic surveillance not insignificant, novel non-invasive techniques for screening for Barrett's have been developed. These include a capsule sponge (Cytosponge) where the patients ingests a gelatin capsule containing a mesh which is attached to a string, which is then withdrawn through the oesophagus collecting cells which are identified as Barrett's using an immunohistochemical marker[72]. In a prospective cohort study of 504 patients who had undergone 3 mo or more acid suppression therapy in the previous five years compared to the gold standard of endoscopic surveillance, the sensitivity and sensitivity of the Cytosponge were 73% and 94% for 1 cm or more circumferential length Barrett's and 90% and 94% for clinically relevant segments of 2 cm or more. However, given the low incidence of Barrett's in the population studied (3%), clearly improved patient selection for screening is required.

## CHEMOPREVENTION

The effects of aspirin therapy on the risk of cancer occurrence have been demonstrated in the multiple observational studies; use of aspirin is associated with a significantly decreased risk of cancer death in patients both with and without pre-existing malignancies[73,74]. The prostaglandin pathway is dysregulated in the development of oesophageal cancer, as increased expression of cyclooxygenase 2 (COX-2) has been demonstrated in Barrett's oesophagus and inhibition of COX-2 activity leads

to growth inhibition of oesophageal cancer cell lines *in vitro*[75,76]. Inhibition of COX-1 (and modification of COX-2 activity) using high dose (≥ 325 mg/d) aspirin appears to decrease the risk of developing Barrett's oesophagus in a case control study (OR = 0.36; $P = 0.001$), and a meta-analysis of multiple cohort studies confirms that aspirin (OR = 0.64, 95%CI: 0.52-0.79) or other NSAID (HR = 0.65, 95%CI: 0.50-0.85) use is associated with a lower risk of oesophageal adenocarcinoma[77,78]. The large UK ASPECT trial (NCT00357682) has recruited over 2500 patients with Barrett's oesophagus and randomised these to aspirin plus acid suppression therapy *vs* acid suppression therapy alone; the results of this study are eagerly awaited. A further large randomised worldwide study (Add-Aspirin) will begin recruitment in 2014 to assess whether aspirin given following surgical resection of oesophageal cancer will decrease the risk of recurrent disease. Although the epidemiological evidence for risk reduction due to aspirin is compelling, due to the lack of randomised data available, the potential toxicity associated with aspirin use, and potential biases of the current data, neither the American Gastroenterological Association nor the British Society of Gastroenterology recommend routine use of aspirin as a chemopreventative measure for decreasing the risk of Barrett's or oesophageal adenocarcinoma, although screening patients for cardiovascular risk factors for which aspirin therapy may be indicated is warranted[52,67].

## CONCLUSION

Junctional adenocarcinoma is a challenging disease. The rate of its rapid increase in prevalence does not appear to have peaked, and if levels of obesity also continue to escalate worldwide it is likely to become a significant global health issue. Although precursor lesions exist which are amenable to curative therapy, identification of at risk patients who would benefit from screening is currently difficult. Once an invasive cancer is established it is clear that for most patients further therapy in addition to surgery will help improve survival. Whether this is peri-operative chemotherapy or neoadjuvant chemoradiotherapy is a matter of contention. This question has been difficult to answer in a straightforward manner due to the design of previous clinical trials, where patients with junctional adenocarcinoma have been treated alongside patients with squamous cell carcinoma of the proximal oesophagus or distal gastric cancers. For the purpose of clarity we believe that any future trials should not include squamous cell cancers, which have an entirely different disease biology, and if including distal gastric cancers are powered for a relevant subset analysis. Exploitation of the underlying molecular aberrations seen in oesophagogastric cancer, in particular amplification of receptor tyrosine kinases may lead to significant improvements in survival - however use of these agents is at this time predominantly limited to the metastatic setting. Increased uptake of PET directed therapy may allow superior selection of patients for intensified pre-operative regimens or immediate resection in the absence of response and this widely available biomarker is currently underutilised. Finally, it is hoped developments in the field of chemoprevention using the widely available and inexpensive medications such as aspirin may decrease the risk of progression of Barrett's oesophagus to overt malignancy at low cost and toxicity.

## REFERENCES


1 **Wu H**, Rusiecki JA, Zhu K, Potter J, Devesa SS. Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 1945-1952 [PMID: 19531677 DOI: 10.1158/1055-9965.epi-09-0250]

2 **Stahl M**, Mariette C, Haustermans K, Cervantes A, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi51-vi56 [PMID: 24078662 DOI: 10.1093/annonc/mdt342]

3 **Waddell T**, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi57-vi63 [PMID: 24078663 DOI: 10.1093/annonc/mdt344]

4 **Bang YJ**, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Kim YH, Ji J, Yeh TS, Button P, Sirzén F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012; **379**: 315-321 [PMID: 22226517 DOI: 10.1016/s0140-6736(11)61873-4]

5 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

6 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/jco.2010.33.0597]

7 **Allum WH**, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062-5067 [PMID: 19770374 DOI: 10.1200/jco.2009.22.2083]

8 **Medical Research Council Oesophageal Cancer Working Group.** Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**: 1727-1733 [PMID: 12049861 DOI: 10.1016/s0140-6736(02)08651-8]

9 **Kelsen DP**, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, Ajani JA, Kocha W, Minsky BD, Roth JA, Willett CG. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol* 2007; **25**: 3719-3725 [PMID: 17704421 DOI: 10.1200/jco.2006.10.4760]

10 **Schuhmacher C**, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach

and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010; **28**: 5210-5218 [PMID: 21060024 DOI: 10.1200/jco.2009.26.6114]
11 **Gebski V**, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8**: 226-234 [PMID: 17329193 DOI: 10.1016/s1470-2045(07)70039-6]
12 **Walsh TN**, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335**: 462-467 [PMID: 8672151 DOI: 10.1056/NEJM199608153350702]
13 **Stahl M**, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851-856 [PMID: 19139439 DOI: 10.1200/jco.2008.17.0506]
14 **Tepper J**, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; **26**: 1086-1092 [PMID: 18309943 DOI: 10.1200/jco.2007.12.9593]
15 **van Hagen P**, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]
16 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741 DOI: 10.1056/NEJMoa010187]
17 **Smalley SR**, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012; **30**: 2327-2333 [PMID: 22585691 DOI: 10.1200/jco.2011.36.7136]
18 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]
19 **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]
20 **Chapman PB**, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; **364**: 2507-2516 [PMID: 21639808 DOI: 10.1056/NEJMoa1103782]
21 **Bauer L**, Langer R, Becker K, Hapfelmeier A, Ott K, Novotny A, Höfler H, Keller G. Expression profiling of stem cell-related genes in neoadjuvant-treated gastric cancer: a NOTCH2, GSK3B and β-catenin gene signature predicts survival. *PLoS One* 2012; **7**: e44566 [PMID: 22970250 DOI: 10.1371/journal.pone.0044566]
22 **Choi SC**, Yun KJ, Kim TH, Kim HJ, Park SG, Oh GJ, Chae SC, Oh GJ, Nah YH, Kim JJ, Chung HT. Prognostic potential of glutathione S-transferase M1 and T1 null genotypes for gastric cancer progression. *Cancer Lett* 2003; **195**: 169-175 [PMID: 12767525 DOI: 10.1016/s0304-3835(03)00158-7]
23 **Polk DB**, Peek RM. Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer* 2010; **10**: 403-414 [PMID: 20495574 DOI: 10.1038/nrc2857]
24 **Wang XQ**, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol* 2009; **15**: 2204-2213 [PMID: 19437559 DOI: 10.3748/wjg.15.2204]
25 **Deenen MJ**, Cats A, Beijnen JH, Schellens JH. Part 4: pharmacogenetic variability in anticancer pharmacodynamic drug effects. *Oncologist* 2011; **16**: 1006-1020 [PMID: 21659612 DOI: 10.1634/theoncologist.2010-0261]
26 **Tahara T**, Shibata T, Nakamura M, Yamashita H, Yoshioka D, Okubo M, Yonemura J, Ishizuka T, Maruyama N, Kamano T, Kamiya Y, Fujita H, Nakagawa Y, Nagasaka M, Iwata M, Yamada H, Hirata I, Arisawa T. Effect of genetic polymorphisms related to DNA repair and the xenobiotic pathway on the prognosis and survival of gastric cancer patients. *Anticancer Res* 2011; **31**: 705-710 [PMID: 21378360]
27 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]
28 **Shah MA**, Kelsen DP. Gastric cancer: a primer on the epidemiology and biology of the disease and an overview of the medical management of advanced disease. *J Natl Compr Canc Netw* 2010; **8**: 437-447 [PMID: 20410336]
29 **Tan IB**, Ivanova T, Lim KH, Ong CW, Deng N, Lee J, Tan SH, Wu J, Lee MH, Ooi CH, Rha SY, Wong WK, Boussioutas A, Yeoh KG, So J, Yong WP, Tsuburaya A, Grabsch H, Toh HC, Rozen S, Cheong JH, Noh SH, Wan WK, Ajani JA, Lee JS, Tellez MS, Tan P. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology* 2011; **141**: 476-485, 485.e1-e11 [PMID: 21684283 DOI: 10.1053/j.gastro.2011.04.042]
30 **Shah MA**, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H, Kelsen DP. Molecular classification of gastric cancer: a new paradigm. *Clin Cancer Res* 2011; **17**: 2693-2701 [PMID: 21430069 DOI: 10.1158/1078-0432.ccr-10-2203]
31 **Nock NL**, Bock C, Neslund-Dudas C, Beebe-Dimmer J, Rundle A, Tang D, Jankowski M, Rybicki BA. Polymorphisms in glutathione S-transferase genes increase risk of prostate cancer biochemical recurrence differentially by ethnicity and disease severity. *Cancer Causes Control* 2009; **20**: 1915-1926 [PMID: 19568698 DOI: 10.1007/s10552-009-9385-0]
32 **Zang ZJ**, Cutcutache I, Poon SL, Zhang SL, McPherson JR, Tao J, Rajasegaran V, Heng HL, Deng N, Gan A, Lim KH, Ong CK, Huang D, Chin SY, Tan IB, Ng CC, Yu W, Wu Y, Lee M, Wu J, Poh D, Wan WK, Rha SY, So J, Salto-Tellez M, Yeoh KG, Wong WK, Zhu YJ, Futreal PA, Pang B, Ruan Y, Hillmer AM, Bertrand D, Nagarajan N, Rozen S, Teh BT, Tan P. Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. *Nat Genet* 2012; **44**: 570-574 [PMID: 22484628 DOI: 10.1038/ng.2246]
33 **Chong IY**, Cunningham D, Barber LJ, Campbell J, Chen L, Kozarewa I, Fenwick K, Assiotis I, Guettler S, Garcia-Murillas I, Awan S, Lambros M, Starling N, Wotherspoon A, Stamp G, Gonzalez-de-Castro D, Benson M, Chau I, Hulkki S, Nohadani M, Eltahir Z, Lemnrau A, Orr N, Rao S, Lord CJ,

Ashworth A. The genomic landscape of oesophagogastric junctional adenocarcinoma. *J Pathol* 2013; **231**: 301-310 [PMID: 24308032]

34 **Deng N**, Goh LK, Wang H, Das K, Tao J, Tan IB, Zhang S, Lee M, Wu J, Lim KH, Lei Z, Goh G, Lim QY, Tan AL, Sin Poh DY, Riahi S, Bell S, Shi MM, Linnartz R, Zhu F, Yeoh KG, Toh HC, Yong WP, Cheong HC, Rha SY, Boussioutas A, Grabsch H, Rozen S, Tan P. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut* 2012; **61**: 673-684 [PMID: 22315472 DOI: 10.1136/gutjnl-2011-301839]

35 **Lennerz JK**, Kwak EL, Ackerman A, Michael M, Fox SB, Bergethon K, Lauwers GY, Christensen JG, Wilner KD, Haber DA, Salgia R, Bang YJ, Clark JW, Solomon BJ, Iafrate AJ. MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. *J Clin Oncol* 2011; **29**: 4803-4810 [PMID: 22042947 DOI: 10.1200/jco.2011.35.4928]

36 **Graziano F**, Galluccio N, Lorenzini P, Ruzzo A, Canestrari E, D'Emidio S, Catalano V, Sisti V, Ligorio C, Andreoni F, Rulli E, Di Oto E, Fiorentini G, Zingaretti C, De Nictolis M, Cappuzzo F, Magnani M. Genetic activation of the MET pathway and prognosis of patients with high-risk, radically resected gastric cancer. *J Clin Oncol* 2011; **29**: 4789-4795 [PMID: 22042954 DOI: 10.1200/jco.2011.36.7706]

37 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210]

38 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173]

39 **Ajani JA**, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Marabotti C, Van Cutsem E. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastro-esophageal cancer adenocarcinoma: the V-325 Study Group. *J Clin Oncol* 2007; **25**: 3205-3209 [PMID: 17664467 DOI: 10.1200/jco.2006.10.4968]

40 **Grau JJ**, Caballero M, Monzó M, Muñoz-García C, Domingo-Domenech J, Navarro A, Conill C, Campayo M, Bombí JA. Dihydropyrimidine dehydrogenases and cytidine-deaminase gene polymorphisms as outcome predictors in resected gastric cancer patients treated with fluoropyrimidine adjuvant chemotherapy. *J Surg Oncol* 2008; **98**: 130-134 [PMID: 18537153 DOI: 10.1002/jso.21096]

41 **Scartozzi M**, Maccaroni E, Giampieri R, Pistelli M, Bittoni A, Del Prete M, Berardi R, Cascinu S. 5-Fluorouracil pharmacogenomics: still rocking after all these years? *Pharmacogenomics* 2011; **12**: 251-265 [PMID: 21332317 DOI: 10.2217/pgs.10.167]

42 **Sobrero A**. TAS-102 in refractory colorectal cancer: caution is needed. *Lancet Oncol* 2012; **13**: 959-961 [PMID: 22951286 DOI: 10.1016/s1470-2045(12)70376-5]

43 **Yoshino T**, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2012; **13**: 993-1001 [PMID: 22951287 DOI: 10.1016/s1470-2045(12)70345-5]

44 **Ito H**, Inoue H, Sando N, Kimura S, Gohda K, Sato J, Murakami K, Ito S, Odaka N, Satodate H, Kudo SE. Prognostic impact of detecting viable circulating tumour cells in gastric cancer patients using a telomerase-specific viral agent: a prospective study. *BMC Cancer* 2012; **12**: 346 [PMID: 22873704 DOI: 10.1186/1471-2407-12-346]

45 **Kang JH**, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, Hwang IG, Lee SC, Nam E, Shin DB, Lee J, Park JO, Park YS, Lim HY, Kang WK, Park SH. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**: 1513-1518 [PMID: 22412140 DOI: 10.1200/jco.2011.39.4585]

46 **Wilke H**, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov ON, Kim T-Y, Cunningham D, Ohtsu A, Rougier P, Emig M, Carlesi R, Chandrawansa K, Muro K. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE). *ASCO Meeting Abstracts* 2014; **32** (3_suppl): LBA7

47 **Kang Y**, Ohtsu A, Van Cutsem E, Rha SY, Sawaki A, Park S, Lim H, Wu J, Langer B, Shah MA. AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). *J Clin Oncol* (Meeting Abstracts) 2010; **28** (18_suppl): LBA4007-62

48 **Lordick F**, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol* 2007; **8**: 797-805 [PMID: 17693134 DOI: 10.1016/S1470-2045(07)70244-9]

49 **zum Büschenfelde CM**, Herrmann K, Schuster T, Geinitz H, Langer R, Becker K, Ott K, Ebert M, Zimmermann F, Friess H, Schwaiger M, Peschel C, Lordick F, Krause BJ. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med* 2011; **52**: 1189-1196 [PMID: 21764790 DOI: 10.2967/jnumed.110.085803]

50 **Pech O**, May A, Manner H, Behrens A, Pohl J, Weferling M, Hartmann U, Manner N, Huijsmans J, Gossner L, Rabenstein T, Vieth M, Stolte M, Ell C. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 2014; **146**: 652-660. e1 [PMID: 24269290 DOI: 10.1053/j.gastro.2013.11.006]

51 **Prasad GA**, Wu TT, Wigle DA, Buttar NS, Wongkeesong LM, Dunagan KT, Lutzke LS, Borkenhagen LS, Wang KK. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. *Gastroenterology* 2009; **137**: 815-823 [PMID: 19524578 DOI: 10.1053/j.gastro.2009.05.059]

52 **Fitzgerald RC**, di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, O'Donovan M, Bird-Lieberman E, Bhandari P, Jankowski JA, Attwood S, Parsons SL, Loft D, Lagergren J, Moayyedi P, Lyratzopoulos G, de Caestecker J. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014; **63**: 7-42 [PMID: 24165758 DOI: 10.1136/gutjnl-2013-305372]

53 **Ell C**, May A, Pech O, Gossner L, Guenter E, Behrens A, Nachbar L, Huijsmans J, Vieth M, Stolte M. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007; **65**: 3-10 [PMID: 17185072 DOI: 10.1016/j.gie.2006.04.033]

54 **Pech O**, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, Manner H, Guenter E, Huijsmans J, Vieth M, Stolte M, Ell C. Long-term results and risk factor analysis for recur-

rence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 2008; **57**: 1200-1206 [PMID: 18460553 DOI: 10.1136/gut.2007.142539]

55 **Shaheen NJ**, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; **360**: 2277-2288 [PMID: 19474425 DOI: 10.1056/NEJMoa0808145]

56 **van Vilsteren FG**, Pouw RE, Seewald S, Alvarez Herrero L, Sondermeijer CM, Visser M, Ten Kate FJ, Yu Kim Teng KC, Soehendra N, Rösch T, Weusten BL, Bergman JJ. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. *Gut* 2011; **60**: 765-773 [PMID: 21209124 DOI: 10.1136/gut.2010.229310]

57 **Spechler SJ**. Barrett's Esophagus without dysplasia: wait or ablate? *Dig Dis Sci* 2011; **56**: 1926-1928 [PMID: 21509560 DOI: 10.1007/s10620-011-1706-y]

58 **Ragunath K**, Krasner N, Raman VS, Haqqani MT, Cheung WY. A randomized, prospective cross-over trial comparing methylene blue-directed biopsy and conventional random biopsy for detecting intestinal metaplasia and dysplasia in Barrett's esophagus. *Endoscopy* 2003; **35**: 998-1003 [PMID: 14648410 DOI: 10.1055/s-2003-44599]

59 **Ackroyd R**, Kelty CJ, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Eradication of dysplastic Barrett's oesophagus using photodynamic therapy: long-term follow-up. *Endoscopy* 2003; **35**: 496-501 [PMID: 12783347 DOI: 10.1055/s-2003-39676]

60 **Sharma RA**, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, Bower G, Shannon JA, Gibbs P, Steward WP. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007; **25**: 1099-1106 [PMID: 17369573 DOI: 10.1200/jco.2006.08.7916]

61 Available from: URL: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1198

62 **Parrilla P**, Martínez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J, Canteras M. Long-term results of a randomized prospective study comparing medical and surgical treatment of Barrett's esophagus. *Ann Surg* 2003; **237**: 291-298 [PMID: 12616111 DOI: 10.1097/01.sla.0000055269.77838.8e]

63 **Gatenby PA**, Ramus JR, Caygill CP, Charlett A, Winslet MC, Watson A. Treatment modality and risk of development of dysplasia and adenocarcinoma in columnar-lined esophagus. *Dis Esophagus* 2009; **22**: 133-142 [PMID: 19018855 DOI: 10.1111/j.1442-2050.2008.00886.x]

64 **Bhat S**, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 2011; **103**: 1049-1057 [PMID: 21680910 DOI: 10.1093/jnci/djr203]

65 **Hvid-Jensen F**, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011; **365**: 1375-1383 [PMID: 21995385 DOI: 10.1056/NEJMoa1103042]

66 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]

67 **Juhasz A**, Mittal SK, Lee TH, Deng C, Chak A, Lynch HT. Prevalence of Barrett esophagus in first-degree relatives of patients with esophageal adenocarcinoma. *J Clin Gastroenterol* 2011; **45**: 867-871 [PMID: 21617543 DOI: 10.1097/MCG.0b013e31821f44a8]

68 **Chak A**, Lee T, Kinnard MF, Brock W, Faulx A, Willis J, Cooper GS, Sivak MV, Goddard KA. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. *Gut* 2002; **51**: 323-328 [PMID: 12171951]

69 **Su Z**, Gay LJ, Strange A, Palles C, Band G, Whiteman DC, Lescai F, Langford C, Nanji M, Edkins S, van der Winkel A, Levine D, Sasieni P, Bellenguez C, Howarth K, Freeman C, Trudgill N, Tucker AT, Pirinen M, Peppelenbosch MP, van der Laan LJ, Kuipers EJ, Drenth JP, Peters WH, Reynolds JV, Kelleher DP, McManus R, Grabsch H, Prenen H, Bisschops R, Krishnadath K, Siersema PD, van Baal JW, Middleton M, Petty R, Gillies R, Burch N, Bhandari P, Paterson S, Edwards C, Penman I, Vaidya K, Ang Y, Murray I, Patel P, Ye W, Mullins P, Wu AH, Bird NC, Dallal H, Shaheen NJ, Murray LJ, Koss K, Bernstein L, Romero Y, Hardie LJ, Zhang R, Winter H, Corley DA, Panter S, Risch HA, Reid BJ, Sargeant I, Gammon MD, Smart H, Dhar A, McMurtry H, Ali H, Liu G, Casson AG, Chow WH, Rutter M, Tawil A, Morris D, Nwokolo C, Isaacs P, Rodgers C, Ragunath K, MacDonald C, Haigh C, Monk D, Davies G, Wajed S, Johnston D, Gibbons M, Cullen S, Church N, Langley R, Griffin M, Alderson D, Deloukas P, Hunt SE, Gray E, Dronov S, Potter SC, Tashakkori-Ghanbaria A, Anderson M, Brooks C, Blackwell JM, Bramon E, Brown MA, Casas JP, Corvin A, Duncanson A, Markus HS, Mathew CG, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Trembath RC, Viswanathan AC, Wood N, Trynka G, Wijmenga C, Cazier JB, Atherfold P, Nicholson AM, Gellatly NL, Glancy D, Cooper SC, Cunningham D, Lind T, Hapeshi J, Ferry D, Rathbone B, Brown J, Love S, Attwood S, MacGregor S, Watson P, Sanders S, Ek W, Harrison RF, Moayyedi P, de Caestecker J, Barr H, Stupka E, Vaughan TL, Peltonen L, Spencer CC, Tomlinson I, Donnelly P, Jankowski JA. Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus. *Nat Genet* 2012; **44**: 1131-1136 [PMID: 22961001 DOI: 10.1038/ng.2408]

70 **Rubenstein JH**, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2010; **32**: 1222-1227 [PMID: 20955441 DOI: 10.1111/j.1365-2036.2010.04471.x]

71 **Lagergren J**, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340**: 825-831 [PMID: 10080844 DOI: 10.1056/nejm199903183401101]

72 **Kadri SR**, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, Blazeby JM, Emery J, Boussioutas A, Morris H, Walter FM, Pharoah P, Hardwick RH, Fitzgerald RC. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. *BMJ* 2010; **341**: c4372 [PMID: 20833740]

73 **Rothwell PM**, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, Belch JF, Wilson M, Mehta Z, Meade TW. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012; **379**: 1602-1612 [PMID: 22440946 DOI: 10.1016/s0140-6736(11)61720-0]

74 **Rothwell PM**, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012; **379**: 1591-1601 [PMID: 22440947 DOI: 10.1016/s0140-6736(12)60209-8]

75 **Wilson KT**, Fu S, Ramanujam KS, Meltzer SJ. Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas. *Cancer Res* 1998; **58**: 2929-2934 [PMID: 9679948]

76 **Souza RF**, Shewmake K, Beer DG, Cryer B, Spechler SJ.

Selective inhibition of cyclooxygenase-2 suppresses growth and induces apoptosis in human esophageal adenocarcinoma cells. *Cancer Res* 2000; **60**: 5767-5772 [PMID: 11059772]

77 **Abnet CC**, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer* 2009; **100**: 551-557 [PMID: 19156150 DOI: 10.1038/sj.bjc.6604880]

78 **Omer ZB**, Ananthakrishnan AN, Nattinger KJ, Cole EB, Lin JJ, Kong CY, Hur C. Aspirin protects against Barrett's esophagus in a multivariate logistic regression analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 722-727 [PMID: 22426086 DOI: 10.1016/j.cgh.2012.02.031]

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REVIEW

# Primary tumor resection in colorectal cancer with unresectable synchronous metastases: A review

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## Abstract

At the time of diagnosis, 25% of patients with colorectal cancer (CRC) present with synchronous metastases, which are unresectable in the majority of patients. Whether primary tumor resection (PTR) followed by chemotherapy or immediate chemotherapy without PTR is the best therapeutic option in patients with asymptomatic CRC and unresectable metastases is a major issue, although unanswered to date. The aim of this study was to review all published data on whether PTR should be performed in patients with CRC and unresectable synchronous metastases. All aspects of the management of CRC were taken into account, especially prognostic factors in patients with CRC and unresectable metastases. The impact of PTR on survival and quality of life were reviewed, in addition to the characteristics of patients that could benefit from PTR and the possible underlying mechanisms. The risks of both approaches are reported. As no randomized study has been performed to date, we finally discussed how a therapeutic strategy's trial should be designed to provide answer to this issue.



**Key words:** Colorectal cancer; Colorectal surgery; Chemotherapy; Colorectal primary tumor; Survival; Liver metastases

**Core tip:** The present review aimed to analyze all published data on whether primary tumor resection should be performed before chemotherapy administration in patients with colorectal cancer and unresectable synchronous metastases.

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## INTRODUCTION

With nearly 150000 new cases in the United States annually (about 1 million in developed countries) and 55000 annual deaths (about 500000 in developed countries), colorectal cancer (CRC) stands as the second leading cause of cancer death in Western countries and a significant public health issue[1]. In approximately 20% of patients, distant metastases are already present at the time of diagnosis[2]. The liver is the most common metastatic site. Surgery plays an important role in the treatment of patients with limited metastatic disease with 20%-50% rates of cure and long-term survival after complete R0 resection[3]. However, for the majority (75%-90%) of these CRC patients with synchronous liver metastases (SLM), there are no curative options, but a significant benefit in median overall survival (OS) and quality of life can be achieved with palliative systemic treatment, namely effective chemotherapy regimens and targeted biotherapies[4,5].

Patients with CRC and unresectable SLM may present with a variable degree of symptoms of their primary tumor. The indication of palliative primary tumor resection (PTR) prior to the initiation of systemic treatment is obvious in patients with primary tumor-related symptoms or complications (obstruction, bleeding, or perforation). However, in asymptomatic CRC patients with unresectable SLM, the indication of PTR as initial management remains questionable and its effect on survival and quality of life is uncertain. No randomized trial has answered to these questions to date[6-13].

Historically, many surgeons have advocated PTR, mainly to avoid potential related complications such as bleeding, perforation or obstruction and because it allows precise tumor staging[14,15]. However, during the past decade, several highly active systemic agents have become available for the treatment of metastatic CRC patients. These agents have increased the median survival duration from 9 to 12 mo with 5-fluorouracil alone, to 24 mo with the addition of modern cytotoxic and targeted agents[16-20]. Owing to the increased efficacy of chemotherapy on metastatic CRC as well as on primary tumor[21], complications from unresected primary tumor have become relatively infrequent. Therefore, there is a tendency among surgeons not to perform PTR in case of unresectable metastases. The possible influence of PTR on survival of patients with CRC and unresectable SLM has never been assessed properly. It has been suggested that PTR, in the setting of unresectable metastatic disease, was related to prolonged survival on multivariate analysis in the majority of these series[6-10,12,13,22]. Nevertheless, most studies reporting an association between PTR and prolonged survival have been limited by numerous selection biases. In addition, whether these two strategies impact patient's quality of life has never been evaluated. Finally, the relative low post-operative morbidity rates reported after laparoscopic resection in stage Ⅳ CRC[23-25] and the progress in perioperative management of these patients, have reinforced the debate between the two strategies (PTR *vs* no PTR). While waiting for a randomized study, the objective of the present work was to review the state of the art on the management of CRC patients with unresectable synchronous metastases, with particular focus on PTR.

## TREATMENT OF METASTATIC COLORECTAL CANCER

When metastases of CRC patients are restricted to the liver, possible curative treatment can be obtained by surgical resection of the metastases. Patients with oligometastases restricted to the lungs may also be candidates for surgical resection. Complete surgical resection of metastatic lesions substantially improves overall survival rates to around 35%-60% in selected patients[3]. Even extra-hepatic disease is no longer a contraindication for surgery in selected patients[26]. Hyperthermic intraperitoneal chemotherapy is a promising treatment in selected patients with limited peritoneal carcinomatosis and long term survival can be achieved[27]. In all other cases, CRC patients with unresectable metastases are treated with systemic combination chemotherapy regimens. Most common combinations are oxaliplatin or irinotecan in addition to a fluoropyrimidine (capecitabine or 5-fluorouracil). Since the last decade, targeted biotherapies have been possibly administered in addition, such as antiangiogenic therapy (*i.e.*, bevacizumab) and anti-epidermal growth factor receptor antibodies *(i.e.*, panitumumab and cetuximab) in the setting of *KRAS* wild-type tumors. These systemic chemotherapeutic combinations have raised response rates to 40%-75% resulting in a median overall survival rate of approximately 24 mo[5,19,28,29]. With current chemotherapy regimens, around 20% of the tumors initially judged unresectable have been converted to resectable, leading to secondary curative surgery and similar prognosis than in patients who underwent surgery for initially resectable liver metastases[3,30].

## IMPACT OF PRIMARY TUMOR RESECTION ON THE SURVIVAL OF PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES

In patients with asymptomatic primary tumor and unresectable SLM, PTR prior to the initiation of systemic treatment is questioned. Its effects on survival and quality of life are uncertain[6-18,31,32]. No randomized control trial has been conducted to date.

Several studies have been performed to analyze the survival in patients with unresectable stage Ⅳ CRC un-

**Table 1 Median survival (mo) in patients with unresectable metastatic colorectal cancer, according to whether primary tumor resection was performed or not**

| Ref. | Study period | Resection/ No resection | No.of patients | OS (mo) | *P* value |
|---|---|---|---|---|---|
| Scoggins *et al*[82] | 1985-1997 | Resection | 66 | 14.5 | 0.59 |
| | | No resection | 23 | 16.6 | |
| Tebbutt *et al*[34] | 1990-1999 | Resection | 280 | 14 | 0.08 |
| | | No resection | 82 | 8.2 | |
| Ruo *et al*[44] | 1996-1999 | Resection | 127 | 16 | < 0.001 |
| | | No resection | 103 | 9 | |
| Michel *et al*[90] | 1996-1999 | Resection | 31 | 21 | 0.718 |
| | | No resection | 23 | 14 | |
| Law *et al*[35] | 1996-1999 | Resection | 150 | 7 | < 0.001 |
| | | No resection | 30 | 3 | |
| Benoist *et al*[79] | 1997-2002 | Resection | 32 | 23 | NS |
| | | No resection | 27 | 22 | |
| Stelzner *et al*[45] | 1995-2001 | Resection | 128 | 11.4 | < 0.0001 |
| | | No resection | 58 | 4.6 | |
| Konyalian *et al*[36] | 1991-2002 | Resection | 62 | 13 | < 0.0001 |
| | | No resection | 47 | 5 | |
| Costi *et al*[91] | 1994-2003 | Resection | 83 | 9 | < 0.001 |
| | | No resection | 47 | 4 | |
| Yun *et al*[37] | 1994-2004 | Resection | 283 | 15.3 | < 0.001 |
| | | No resection | 93 | 5.3 | |
| Kaufman *et al*[92] | 1998-2003 | Resection | 115 | 22 | < 0.0001 |
| | | No resection | 69 | 3 | |
| Galizia *et al*[38] | 1995-2005 | Resection | 42 | 15.2 | 0.03 |
| | | No resection | 23 | 12.3 | |
| Evans *et al*[70] | 1999-2006 | Resection | 45 | 11 | < 0.0001 |
| | | No resection | 57 | 2 | |
| Bajwa *et al*[39] | 1999-2005 | Resection | 32 | 14 | 0.005 |
| | | No resection | 35 | 6 | |
| Mik *et al*[40] | 1996-2000 | Resection | 52 | 21 | NS |
| | | No resection | 82 | 14 | |
| Frago *et al*[93] | 2004-2008 | Resection | 12 | 23.7 | 0.008 |
| | | No resection | 43 | 4.4 | |
| Aslam *et al*[41] | 1998-2007 | Resection | 366 | 14.5 | < 0.005 |
| | | No resection | 281 | 5.83 | |
| Chan *et al*[11] | 2000-2002 | Resection | 286 | 14 | < 0.001 |
| | | No resection | 125 | 6 | |
| Seo *et al*[94] | 2001-2008 | Resection | 114 | 22 | 0.076 |
| | | No resection | 83 | 14 | |
| Karoui *et al*[33] | 1998-2007 | Resection | 128 | 30.7 | 0.031 |
| | | No resection | 85 | 21.9 | |
| Ferrand *et al*[22] | 1997-2001 | Resection | 156 | 16.3 | < 0.0001 |
| | | No resection | 60 | 9.5 | |

OS: Overall survival.

dergoing PTR, in comparison with those who did not (Table 1). All were non-randomized and most were single-center and retrospective. In addition, the major drawback of these studies is that patients with a better World Health Organization performance status (WHO-PS) and better prognosis at baseline (less metastatic sites involved) were more likely to undergo surgery. Conversely, patients with extensive disease were more likely to be offered chemotherapy rather than surgery thus standing as a major selection bias. Similarly, only patients with good WHO-PS were able to tolerate a complete course of potentially toxic chemotherapeutic agents such as irinotecan and oxaliplatin. Another limitation is that reported data on the use of systemic therapy are scarce, which hardens the assessment of the influence of PTR on outcome. Despite these limitations, the median OS was improved in resected patients in the vast majority of studies.

Our group recently reported a 10-year retrospective experience of the management of metastatic colonic cancer in chemotherapy-eligible patients, managed in 6 Parisian university hospitals[33]. The primary aim of this study was to compare outcomes, including survival, in 208 patients with unresectable distant metastases undergoing either PTR ($n$ = 85) or systemic chemotherapy ($n$ = 123) as their initial treatment. Most patients had not received targeted therapy as first-line treatment. Median OS was nearly 9 mo longer after PTR than after initial systemic chemotherapy (30.7 mo *vs* 21.9 mo, adjusted HR= 0.56; $P$ = 0.031). In this series, the 2 groups were different with respect to baseline carcinoembryonic antigen (CEA) level, which was lower in the colectomy group ($P$ = 0.008), suggesting a lower disease burden[33]. Despite similar rates of chemotherapy administration, the secondary curative resection rate was higher in the PTR group than in patients treated with initial chemotherapy (32.9% *vs* 20.3%; $P$ = 0.04), suggesting a lower metastatic burden and other potential unmeasured differences contributing to a greater response to chemotherapy. In an effort to take into account these differences, a propensity score was performed and used for adjustment. On multivariate analysis, first-intent PTR, secondary curative resection, well-differentiated primary tumor, liver-only metastases and addition of targeted therapy were independently associated with survival. After adjusting on the propensity score quartiles, as well as for the quantitative value of this score, these five factors were still independently associated with survival[33].

A recent meta-analysis of 8 retrospective comparative studies including 1062 patients has reported an improvement in the survival of those with palliative PTR, with an estimated median gain of 6 mo (standardized HR = 0.55; 95%CI: 0.29-0.82; $P$ < 0.001)[8]. The initial heterogeneity between the studies was amended after excluding one study[34], in which survival was not the primary endpoint. The authors also reported that PTR was not associated with increased secondary resectability of metastases following chemotherapy, in comparison with patients treated with chemotherapy alone (HR = 0.85; 95%CI: 0.4-1.8, $P$ = 0.66)[8].

Venderbosch *et al*[12] performed a retrospective analysis of two phase Ⅲ studies (CAIRO and CAIRO2), investigating the prognostic and predictive value of PTR in patients with synchronous stage Ⅳ CRC treated with systemic therapy. In the CAIRO study, 258 patients underwent PTR (*vs* 141 who did not) and showed increased median OS (16.7 mo *vs* 11.4 mo, respectively; HR = 0.61; $P$ < 0.0001) and progression-free survival (PFS) (6.7 mo *vs* 5.9 mo, respectively; HR = 0.74; $P$ = 0.004). Similarly, in the CAIRO2 study, 289 patients underwent PTR (*vs* 159 who did not) and showed increased median OS (20.7 *vs* 13.4 mo; HR = 0.65; $P$ < 0.0001) and PFS (10.5 mo *vs* 7.8 mo; HR = 0.78; $P$ = 0.014)[12]. A major limitation of these results consisted in the fact that the decision of PTR was made prior to study inclusion. Besides, no information about the reasons for non-resection were provided, such as absence of symptoms, unresectability of the primary

**Table 2 Prognostic factors associated with overall survival in patients with unresectable metastatic colorectal cancer, according to whether primary tumor resection was performed or not**

| Ref. | Resection/No resection | No. of patients | OS (mo) | *P* value | PTR on multivariate analysis [95%CI] | Other independent prognostic factors |
|---|---|---|---|---|---|---|
| Tebbutt *et al*[34] | Resection | 280 | 14 | 0.08 | No | WHO-PS < 2, no peritoneal dissemination, low phosphatase alkaline and serum albumin levels |
| | No resection | 82 | 8.2 | | | |
| Law *et al*[35] | Resection | 150 | 7 | < 0.001 | OR = 0.42 (0.27–0.66)[1] | Unilobar LM involvement, no ascites, no chemotherapy |
| | No resection | 30 | 3 | | *P* < 0.001 | |
| Stelzner *et al*[45] | Resection | 128 | 11.4 | < 0.0001 | HR = 0.50 (0.27–0.90) | No chemotherapy, ASA score < 3, WHO-PS < 2, CEA level, age < 75 yr, extent of metastases, extent of primary tumor |
| | No resection | 58 | 4.6 | | *P* = 0.021[2] | |
| Konyalian *et al*[36] | Resection | 62 | 13 | < 0.0001 | HR = 0.3 (0.2–0.6) | Liver involvement < 50% |
| | No resection | 47 | 5 | | *P* < 0.0001[3] | |
| Yun *et al*[37] | Resection | 283 | 15.3 | < 0.001 | HR = 0.53 (0.38–0.73) | Metastatic site ⩽ 1, high CEA level, chemotherapy, well-differentiated primary tumor |
| | No resection | 93 | 5.3 | | *P* < 0.001 | |
| Galizia *et al*[38] | Resection | 42 | 15.2 | 0.03 | OR = 3.91 (2.83-4.99) | WHO-PS < 2, liver involvement < 50% |
| | No resection | 23 | 12.3 | | 0.26 (0.20-0.35)[1] *P* = 0.001 | |
| Bajwa *et al*[39] | Resection | 32 | 14 | 0.005 | OR = 0.26 (0.13-0.52) | Left sided primary tumor, unique primary tumor |
| | No resection | 35 | 6 | | *P* = 0.0001 | |
| Mik *et al*[40] | Resection | 52 | 21 | NS | HR = 0.58 (0.36–0.82)[1] | Unilobar LM involvement |
| | No resection | 82 | 14 | | *P* = 0.004 | |
| Aslam *et al*[41] | Resection | 366 | 14.5 | < 0.005 | *P* < 0.001 | Age < 80 yr, non-locally advanced primary tumor, N + stage |
| | No resection | 281 | 5.83 | | | |
| Karoui *et al*[33] | Resection | 128 | 30.7 | 0.031 | HR = 0.56 (0.38–0.83)[1] | Secondary curative resection, well-differentiated primary tumor, anti-VEGF treatment, no extra-hepatic metastases |
| | No resection | 85 | 21.9 | - | *P* = 0.004 | |
| Platell *et al*[83] | Resection | 243 | - | | HR = 0.51 (0.37–0.69) | Chemotherapy, radiotherapy, ASA score < 3 |
| | No resection | 70 | - | | *P* = 0.0001 | |
| Venderbosch *et al*[12] | Resection | 286 | 14 | < 0.001 | HR = 0.73 (0.58-0.93) | - |
| | No resection | 125 | 6 | | *P* = 0.01 | |
| Ferrand *et al*[22] | Resection | 156 | 16.3 | < 0.0001 | HR = 0.42 (0.30-0.60) | WHO-PS < 2, distal colon or rectal primary tumor, one metastatic site and alkaline phosphatase ⩽ 300 UI/L |
| | | | | | *P* < 0.0001 | |
| | No resection | 60 | 9.5 | | | |

[1]For readability of the Table, some ORs and HRs have been recalculated with " No resection" as reference for the multivariate analysis of survival; [2]excluding postoperative mortality and complicated primary tumor; [3]PTR was independently associated with increased survival probability, while adjusting on patient's age, sex and degree of hepatic tumor involvement. OS: Overall survival; PTR: Primary tumor resection; OR: Odds ratio; HR: Hazard ratio; LM: Liver metastases; ASA: American society of anesthesiology; CEA: Carcinoembryonic antigen; VEGF: Vascular-endothelial growth factor; WHO-PS: World health organization performance status; NS: Not significant.

tumor, poor patient condition and/or symptomatic metastases requiring rapid initiation of systemic treatment. Obviously, many differences were likely to stand between patients undergoing PTR or not. However, on multivariate analysis, PTR remained a significant prognostic factor in the CAIRO2 study and in the subgroup of patients with one metastatic site in the CAIRO study[12].

Finaly, Ferrand *et al*[22] recently performed an analysis of 260 patients included in the Fédération Francophone de Cancérologie Digestive 9601 phase Ⅲ trial, which compared different first-line single-agent chemotherapy regimens in patients with stage Ⅳ CRC. Two-year OS and 6-mo PFS were significantly better in the resection group than in the non-resection group (24% *vs* 10%; *P* < 0.0001 and 38% *vs* 22%; *P* = 0.001, respectively). The gain of OS was 6.8 mo. These results remained significant even after exclusion of the 49 patients with rectal cancer. In multivariate analysis, PTR was the most significant prognostic factor (HR = 0.42; 95%CI: 0.30-0.60, *P* < 0.0001). In this study, 4 factors were associated with a decreased survival: poor WHO-PS, multiple metastatic sites, proximal colonic primary tumor and high baseline alkaline phosphatase level.

## WHICH PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES ARE LIKELY TO BENEFIT FROM PRIMARY TUMOR RESECTION?

Some comparative studies conducted multivariate analysis to determine which clinical, tumor and therapy variables were associated with survival between patients managed by primary surgery or immediate chemotherapy[10] (Table 2). In addition to PTR, several factors were found to have independent prognostic influence: age, American society of anesthesiology (ASA) score, WHO-PS, preoperative CEA levels, primary tumor location, size and differentiation, extent of metastatic liver spread, peritoneal dissemination and extra-hepatic metastases. Other independent factors have been less frequently reported, such as serum albumin, alkaline phosphatase levels, lymph node involvement, ascites, number of metastatic sites and the administration of targeted therapy. Some works also emphasized that tumor burden (primary tumor and/or metastatic

**Table 3 Prognostic factors after primary tumor resection on multivariate analyzes**

| Ref. | Metastatic spread | No. of patients | Prognostic factors or predictive factors of postoperative morbimortality |
|---|---|---|---|
| Rosen *et al*[43] | Liver, Peritoneum | 125 | Age < 65 yr, limited LM, no peritoneal carcinomatosis |
| Ruo *et al*[44] | Liver, peritoneum, retroperitoneal lymph nodes, lung, bone, brain | 123 | Liver involvement < 25% |
| Stelzner *et al*[45] | Mainly liver | 186 | WHO-PS, ASA grade, low CEA level, metastatic load, chemotherapy |
| Vibert *et al*[47] | Liver | 80 | Serum AST level < 50 IU/l, age < 75 yr |
| Yun *et al*[37] | Liver, peritoneum, lung | 503 | CEA level, well-differentiated primary tumor, chemotherapy |
| Kleespies *et al*[46] | Mainly liver, lung, peritoneum | 233 | Liver involvement < 50%, chemotherapy, pT4 and/or N+ stage |
| Costi *et al*[48] | Mainly liver, peritoneum | 71 | Age < 80 yr, nodal stage |
| Stillwell *et al*[31] | Liver and extra-hepatic | 379 | Nodal stage < N2, well-differentiated primary tumor, no postoperative complications, no apical lymph-node |

LM: Liver metastases; ASA: American society of anesthesiology; CEA: Carcinoembryonic antigen; WHO-PS: World health organization performance status.

disease) was significantly related to survival[22,33-42]. Bilobar liver metastases were associated with decreased survival compared to unilobar location, the risk of cancer-related death being five-fold increase in case of > 50% liver involvement[35,36,38,40]. Similarly, peritoneal and omental metastases are significantly related to poorer survival[34].

Furthermore, several studies reported multivariate analysis of predictive factors affecting outcome after PTR in patients with CRC and unresectable SLM. The main factors influencing outcome were the extent of liver disease[42-46], age[43,47,48] and tumor differentiation[31,37] (Table 3).

The results of the study by Vibert *et al*[47] suggested that patients older than 70 years with elevated aspartate aminotransferase enzymes may not benefit from palliative PTR and could be offered chemotherapy if suitable. A retrospective review of 503 palliative PTR found that predictors of survival included serum CEA level, degree of differentiation of the tumor, successful PTR and the use of chemotherapy[37]. In another study, age > 65, the presence of carcinomatosis and extensive bilobar liver involvement were not only associated with decreased survival after PTR, but with increased morbidity and mortality as well[43]. Kuo *et al*[49] suggested that patients older than 65 with multiple-site metastases, intestinal obstruction, preoperative CEA levels > 500 ng/mL, lactate dehydrogenase > 350 units/L, hemoglobin < 10 g/dL, or liver tumor burden > 25% exhibited worse survival following surgery than those without.

To summarize, most of studies suggested that liver burden > 50% and extra-hepatic metastatic disease (peritoneal carcinomatosis, lung metastases) were poor prognostic factors in patients with CRC and unresectable SLM, as well as advanced age and poor WHO-PS. Interestingly, this appears to have remained unchanged with time despite the advances in the surgery and systemic therapy. Thus, patient selection is a critical issue, and the decision for PTR should take into account these prognostic factors.

## UNDERLYING HYPOTHESES FOR INCREASED SURVIVAL IN PATIENTS UNDERGOING PTR

Reasons why PTR is associated with better outcomes in patients with CRC and unresectable metastases are still unclear. The improvement in survival following PTR may be attributed to a better response to chemotherapy after reduction of tumor burden. This has been demonstrated by the proven benefit of resecting primary renal and ovarian tumors in the presence of metastatic disease[50,51]. Survival of resected patients might also be improved because they are less likely to develop obstruction and perforation, complications known to carry heavy operative mortality and morbidity[8]. Besides, surgical removal of primary tumor may restore immunocompetence, even at a metastatic stage, as shown in a murine model xenografted with 4T1 mammary carcinoma[52].

It has been suggested that the interaction between primary tumor and target organs of metastasis dictates the progression from micro- to macrometastases[53]. Indeed, the primary tumor may induce, in these distant organs, a prosperous environment to enhance the growth of metastatic deposit (seed and soil theory). Vascular endothelial growth factor receptor 2 (VEGFR-2) expressing circulating tumor cells settle in the pre-metastatic niches, previously colonized by hematopoietic cells expressing VEGFR-1[54]. The recent study by van der Wal *et al*[55] suggested that PTR could prevent the liver parenchyma from soiling from micrometastases. Indeed, the authors demonstrated that the expression levels of angiogenetic markers (CD31, VEGF-A, VEGFR-1, VEGFR-2, Placental Growth Factor, Hypoxia-induced Factor 1 alpha, Angiopoietin-2 and its receptor Tie-2, all assessed using reverse transcription-polymerase chain reaction) were higher in the liver parenchyma adjacent to metastases, both in patients with simultaneous resection of both their primary tumor and liver metastases, and in those who underwent metastases removal several months after PTR. Moreover, the simultaneous resection group showed the highest Ang-2/Ang-1 (proangiogenic) ratio both in the metastases and the adjacent liver. These results suggested that in the presence of the primary tumor, the liver parenchyma adjacent to metastases provided an angiogenic prosperous soil for metastatic tumor growth and may explain the association of PTR with improved survival[55]. These results are also in concordance with the prognostic role of anti-VEGF based treatment we found on multivariate analysis in our series[33].

In contrast, several studies based on PET-scan and histology showed an increased growth of liver metastases following PTR, as determined by an increased vascular density, proliferation rate, and metabolic growth rate[56-59]. These data suggest that the outgrowth of metastatic disease may, at least partly, be downregulated by the primary tumor, notably by inhibiting metastatic angiogenesis. In mouse models, pulmonary metastases showed rapid progression after PTR, which was considered to be the result of depletion of the antiangiogenic compound angiostatin produced by the primary tumor[53,56,60]. After PTR, antiangiogenic effects disappear, and metastases undergo an "angiogenic switch", leading to angiogenesis and enhanced tumor growth[60]. In addition, major surgery induces a transient immunodepression which may promote tumor growth[61,62]. Romano *et al*[63] reported that 29% of CRC patients had lymphocytopenia at baseline. In comparison, 14 d after surgery, values below normal range for total lymphocyte count and helper T-cells were found in 44% and 53% of cases, respectively. Recovery of postoperative surgery-related lymphocytopenia occurred late only in patients with normal count at baseline. In a rat model, perioperative restoration of lymphocyte proliferation levels either by levamisole or maleic anhydride-divinyl ether-2 resulted in fewer hepatic metastases, suggesting the critical role of immunomodulation in the development of metastases[64,65]. Notably, perioperative blood transfusions have been shown to exert an immunosuppressive effect on patients with CRC and are independently associated with a poor prognosis[66,67].

However, these pro-tumoral effects seem to be counterbalanced by previously described anti-tumoral effects of PTR, as most studies have reported an association between PTR an improved outcome. Overall, it seems ethically relevant to perform a clinical trial comparing PTR to conservative strategy, as data remains controversial regarding PTR consequences on tumor evolution. Indeed, influence of primary tumor on angiogenesis of metastases are based on experimental studies, which does not necessarily translate clinically into a modification of patient survival. Studies that showed an advantage of PTR had such selection bias that interpretation of their findings are difficult, even with the use of multivariate analyzes or propensity scores. Definitive response regarding the interest of PTR in stage Ⅳ CRC patients could only be obtained with a randomized trial with selective inclusion criteria and comparable arms.

## IMPACT OF PRIMARY TUMOR RESECTION ON QUALITY OF LIFE OF PATIENTS WITH COLORECTAL CANCER AND UNRESECTABLE SYNCHRONOUS LIVER METASTASES

The effect of PTR and chemotherapy on quality of life has never been specifically evaluated. In the palliative care setting, determining the effect of PTR on quality of life would help clinicians and patients deciding the most adapted primary strategy. Primary-related symptoms or complications, postoperative morbidity following PTR (either electively or for complications), total length of hospital stay and tolerability of chemotherapy (according to the presence or absence of the primary tumor) may all contribute to impact quality of life. They should thus stand as secondary endpoints in a future prospective randomized study evaluating the impact of PTR in CRC patients with unresectable synchronous metastases. Quality of life could be assessed in both arms with the use of validated questionnaires such as the european organization for research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) and EORTC-CR29, at baseline and after initiation of treatment (surgery or chemotherapy) with longitudinal follow-up.

## WHAT ARE THE RISKS OF UNRESECTED PRIMARY TUMOR-RELATED COMPLICATIONS UNDER CHEMOTHERAPY?

PTR has been traditionally advocated in the setting of metastatic CRC, to prevent symptoms and complications linked to primary tumor, such as obstruction, perforation or bleeding. Emergency surgery is associated with high morbidity and even mortality[45,68-70]. The risk of local complications related to tumor left in situ, during initial chemotherapy, varied from 8.5% to 30% and was dominated by the risk of obstruction (6%-29%) (Table 4). These results require cautious interpretation, as they came from old retrospective series that involved few patients supported for long periods with heterogeneous chemotherapy regimens. In addition, many of these series have included patients with primary tumor-related symptoms or complications at initial presentation[33,44,71].

With recent advances in systemic chemotherapy, the risks and benefits of immediate or deferred surgical strategy have changed. In contrast to the response rates of approximately 15% to 5-fluorouracil, combinations with modern chemotherapy regimens, such as infusional 5-fluorouracil/leucovorin with oxaliplatin or irinotecan, have yielded response rates of 50% and disease control rates of 85% in prospective clinical trials[72,73]. Furthermore, the addition of the targeted agents bevacizumab or cetuximab to the above combinations has provided clinically significant improvement in response rates[5,28,29,74]. In the setting of these effective chemotherapy regimens, the risk of primary tumor-related complications and the need of subsequent urgent intervention are low, less than 15% in most series (Table 4).

In series in which patients were mainly treated with effective chemotherapy (oxaliplatin, irinotecan, targeted agents) and had asymptomatic or uncomplicated primary tumor at presentation, the risk of complications was inferior to 10%, which can be explained by the significant tumor response to chemotherapy[21,75,76]. In addition, the risk of emergency colectomy for complications varies from 2% to 29%, with a rate of less than 7% in the two

**Table 4 Complications related to in situ tumor in patients with unresectable stage IV colorectal cancer treated with chemotherapy as initial management *n* (%)**

| Ref. | No. of patients | Primary tumor-related complications (%) | Type of complication during chemotherapy | | | Surgery required for complication (%) |
|---|---|---|---|---|---|---|
| | | | Obstruction | Bleeding | Perforation | |
| Scoggins *et al*[82] | 23 | 9 | 2 (9) | 0 | 0 | 9 |
| Sarela *et al*[71] | 24 | 29 | 4 (17) | 0 | 0 | 21 |
| Ruo *et al*[44] | 103 | 29 | 30 (29) | 0 | 0 | 29 |
| Tebbut *et al*[34] | 82 | 23 | 11 (13) | 3 (4%) | 5 (6) | 10 |
| Michel *et al*[90] | 23 | 22 | 5 (22) | 0 | 0 | 22 |
| Benoist *et al*[79] | 27 | 15 | 4 (15) | 0 | 0 | 15 |
| Muratore *et al*[75] | 35 | 8.5 | 2 (6) | 1 (3%) | 0 | 3 |
| Galizia *et al*[38] | 23 | 30 | 4 (17) | 1 (4%) | 2 (9) | 17 |
| Evans *et al*[70] | 52 | 23 | 3 (6) | 9 (17%) | 0 | 2 |
| Poultsides *et al*[76] | 233 | 11 | 18 (8) | 0 | 5 (2) | 7 |
| Karoui *et al*[33] | 123 | 19 | 21 (17) | 0 | 2 (2) | 12 |
| McCahill *et al*[77] | 86 | 16 | 10 (12) | 0 | 1 (1) | 12 |

most recent series. In a series reporting 233 consecutive patients treated with primary chemotherapy, 26 (11%) patients developed a complication related to the primary tumor: colonic obstruction in 18 cases (9 effectively treated with a colonic stent), perforation in 5 cases, and pelvic pain in 3 patients with rectal cancer[76]. Among the 26 patients with a complication, only 16 (7%) required an intervention. In this series, no factor was correlated with the risk of primary tumor-related complication requiring an intervention under chemotherapy.

Lastly, in a phase Ⅱ trial, McCahill *et al*[77] recently reported a major morbidity rate of 16.3% (14 patients) in 86 patients with an intact primary tumor, receiving a chemotherapy by FOLFOX and bevacizumab. Primary tumor-related complications occurred in the first 12 mo following inclusion in 83.3% of cases. It consisted in 10 surgical interventions for primary tumor-related symptoms and two deaths attributed to complications of the intact primary. Among these 10 surgeries, indications were colonic obstruction in eight, perforation in one and abdominal pain in one. Six interventions were performed in emergency, three implicated performing definitive stoma and one postoperative death occurred. Four more patients had primary-related-complications, including two cases of bowel obstruction, which were managed without surgery, accounting for minor morbidity. In balance, 27 (31.4%) patients suffered from chemotherapy-related events and eight patients underwent a surgical resection with curative intent[77].

Although the expected risk is low, primary tumor-related complications may require urgent colonic stenting, or surgery with stoma creation, and may delay or even preclude chemotherapy administration. These risks should be clearly explained to patients before choosing between first-intention PTR or chemotherapy; and close follow-up performed to minimize their eventual proper consequences.

## IS CHEMOTHERAPY-RELATED TOXICITY INCREASED IN THE PRESENCE OF THE PRIMARY TUMOR?

No specific studies have explored whether the presence or absence of the primary tumor could influence chemotherapy tolerance and safety. In the EORTC phase Ⅲ study[78], comparing perioperative FOLFOX chemotherapy with surgery alone, in patients with initially resectable liver metastases (≤ 4 metastases), no increased toxicity was reported in patients (34%) who had the primary tumor in place at the time of randomization. In several retrospective studies, no difference in chemotherapy-related toxicity was reported, regardless of whether the PT was in place or not[6,39,79].

Bevacizumab has been associated with a 1%-2% gastrointestinal perforation in prospective clinical trials[17,80]. Most bevacizumab-related perforations were observed in the first 3 mo of treatment, especially within the first month. It may occur throughout the entire gastrointestinal tract, including the site of the primary tumor. In the study reported by Poultsides *et al*[76] 48% of the patients received bevacizumab. Only two of the five perforations observed (all at the site of the primary tumor) occurred during bevacizumab therapy and one patient experienced perforation 6 mo after the last administration of bevacizumab, whereas two had never received it. Although the small number of patients who developed this complication may have precluded definitive conclusions, bevacizumab have not appeared to significantly increase the rate of perforation. Our group has reported similar results in a retrospective multicentric study[33]. In a recent study, among 86 patients receiving FOLFOX + bevacizumab without PTR, 23 (27%) had serious adverse events, including 4 (5%) chemotherapy-related deaths and 6 life-threatening toxicities[77]. Although not reported as serious adverse events but as primary tumor-related major morbidities, two patients had a bowel perforation, which was likely to be facilitated by bevacizumab.

For patients with *KRAS* wild-type tumor, anti-EGFR antibodies are also a possibility, although no study has yet examined the effect of these antibodies in metastatic CRC patients with the primary tumor in place[5]. Accordingly, in the particular case of colon cancer with unresectable SLM and a primary tumor in place, the literature does not currently justify a strategy different from that for CRC in general[81].

**Table 5 Postoperative outcome after primary tumor resection in patients with unresectable stage IV colorectal cancer**

| Ref. | Study period | No. of patients | Mortality (%) | Morbidity (%) |
|---|---|---|---|---|
| Scoggins *et al*[82] | 1985-1997 | 66 | 5 | 30 |
| Rosen *et al*[43] | 1984-1998 | 120 | 6 | 22.5 |
| Tebbutt *et al*[34] | 1990-1999 | 280 | NM | 13 |
| Ruo *et al*[44] | 1996-1999 | 127 | 2 | 21 |
| Michel *et al*[90] | 1996-1999 | 31 | 0 | NM |
| Benoist *et al*[79] | 1997-2002 | 32 | 0 | 19 |
| Stelzner *et al*[45] | 1995-2001 | 128 | 11.7 | - |
| Galizia *et al*[38] | 1995-2005 | 42 | 0 | 21 |
| Evans *et al*[70] | 1999-2006 | 45 | 16 | NM |
| Bajwa *et al*[39] | 1999-2005 | 32 | 3 | 22 |
| Kleespies *et al*[46] | 1996-2002 | 233 | 4.7 | 46 |
| Mik *et al*[40] | 1996-2000 | 52 | 7.7 | 40 |
| Costi *et al*[48] | 1994-2003 | 71 | 8.5 | 24 |
| Stillwell *et al*[31] | 1984-2004 | 379 | 9.2 | 48.3 |

NM: Not mentioned.

Overall, no data suggest that the presence of the primary tumor increases the toxicity of chemotherapy. Chemotherapy modalities, combined or not with targeted agents, should be the same as in the metachronous setting.

## WHAT IS THE RISK OF COMPLICATIONS AFTER PALLIATIVE PRIMARY TUMOR RESECTION IN THE METASTATIC SETTING?

Several studies suggested that PTR was associated with high postoperative morbidity and mortality rates in the presence of metastases[12,45,82] (Table 5). One study reported that 15 of 128 patients (11.7%) patients died within 30 d postoperatively[45]. However, in this study many patients were symptomatic and underwent emergency surgery. The same series found a 27.8% mortality rate in patients who had emergency surgery *vs* only 7.3% mortality rate with elective procedure ($P = 0.002$)[45]. The high postoperative mortality rate of 5% reported by Scoggins *et al*[82] included patients who were symptomatic at the time of resection and the patient who died after surgery were noted to have severe carcinomatosis.

These mortality rates were higher that noted in the recently published meta-analysis where collectively, perioperative mortality was 1.7% (95%CI: 0.7-3.9)[8]. This lower mortality rate can be accounted for the preeminent number of patients that were asymptomatic and managed electively. In this meta-analysis, postoperative morbidity occurred in 23% (95%CI: 18.5-21.8) of patients. The most frequent complication was wound infection and could be mostly managed conservatively; however, in some instances, major complication arose whereby patients required additional surgery as management. Anastomotic leakage, occurring in 1.7% of patients, is more commonly a significant complication of rectal cancer resection. It often leads to sepsis, significantly prolongs hospital stay and delay or even precludes chemotherapy administration[8].

In a recent large monocentric series, this same group analyzed the postoperative outcomes in 379 CRC patients with unresectable synchronous metastases undergoing PTR[31]. In the postoperative period, mortality and morbidity rates were 9.2% and 48.3%, respectively. Postoperative surgical and medical complication rates were 35.6% and 25.3%, respectively. Among these patients, 33 required one or more reinterventions in the same admission to manage these complications. The most common surgical complications included wound infections and the most common medical complications comprised respiratory events followed by cardiac events. However, 45% of patients were aged of more than 70 years in this series, 60% had a locally advanced primary tumor and nearly 30% had rectal cancer[31].

These results need to be interpreted with caution as these studies suffered from several limitations. Firstly, morbidity rates were not always separated between minor and severe complications. Secondly, inclusion periods were very long and progresses in surgery and postoperative care have not been taken into account. In a recent series of 313 patients treated for unresectable synchronous stage IV CRC over different time periods, Platell *et al*[83] reported that the 30-d postoperative mortality (12.6% *vs* 2.7%, $P = 0.036$) and the duration of hospital stay (13 d *vs* 9 d, $P = 0.026$) have decreased significantly from 1996-2002 to 2003-2009 periods, despite increased numbers (28% *vs* 46.4%, $P = 0.001$) of patients with severe comorbidity (*i.e.*, ASA score 3 or 4). Another limitation resides in the heterogeneity of populations, as studied patients included those with symptomatic or locally advanced primary tumor, patients with rectal primary, patients with advanced age and severe comorbities, those with extensive and extra-hepatic metastatic spread or patients with poor general condition[8,31]. Fourthly, in all but two studies[31,46], there was no mention of the use of laparoscopy in patients electively undergoing PTR, which has been convinced to decrease postoperative morbidity compared to laparotomy. Indeed, in several phase Ⅲ trials, overall surgical morbidity following elective colectomy for cancer was 0.7%-3% and 20%-28%, in patients operated with laparoscopy and laparotomy, respectively[84]. Finally, one should note that in all series reporting the postoperative outcome after PTR in stage Ⅳ CRC patients, there was no mention of the use of perioperative immunonutrition which has also been demonstrated to improve postoperative outcomes in patients operated for various types of digestive cancers[85].

Few studies have performed a multivariate logistic regression analysis to determine independent factors associated with postoperative mortality and morbidity in patients with stage IV CRC. In the series reported by Stelzner *et al*[45] postoperative mortality (11.7%) was not associated with PTR but was significantly related to ASA score IV (ASA score III, 7% *vs* ASA score IV, 26.4%, $P = 0.002$), higher age (≤ 75 years, 7.6% *vs* > 75 years, 20%, $P = 0.015$) and emergency operations (27.8%, *vs* elec-

tive, 7.3%, $P = 0.002$). In the largest series of 379 resected patients with an unresectable stage Ⅳ CRC, Stillwell *et al*[31] found that at multivariate analysis, 30-d postoperative mortality was independently associated with medical complications ($P < 0.001$), emergency interventions ($P = 0.001$) and age (≥ 70 years, $P = 0.007$). Conversely, patients with liver-only metastases were less likely to die in the postoperative period than those with advanced local disease and/or extra-hepatic disease ($P = 0.004$). In this large series, emergency interventions were also linked to morbidity, a fact that is well established in literature[45,68-70]. In another series, independent determinants of an increased postoperative morbidity (total rate of 46%) were primary rectal cancer, hepatic tumor involvement > 50%, and comorbidity > 1 organ[46].

To summarize, after palliative PTR in metastatic patients, most studies suggested that baseline characteristics (age, WHO-PS, comorbidity, ASA score), advanced local and metastatic disease and rectal primary tumor to be related to postoperative morbidity and mortality. Taken together, these findings suggest that one issue for a phase Ⅲ study would be to assume that the acceptable risks of postoperative mortality and severe morbidity rates would be less than 10% and 30%, respectively. These rates could be even lower with the use of laparoscopic approach, which is known to improve short-term outcomes, including postoperative morbidity, compared to open surgery[23-25,86]. Besides, perioperative nutrition should be systematically recommended. Finally, these anticipated morbidity and mortality rates are those expected in a population of selected patients, constituted after the exclusion of patients which would not be likely to benefit from PTR (patients in poor general condition, with severe comorbidities, rectal cancer, extra-hepatic metastatic disease, complicated primary tumor).

## SPECIFIC ISSUES OF RECTAL CANCER

By its particular location in the pelvis, rectal cancer differs from colon cancer on several points: first, unresected rectal tumors can lead to disabling symptoms (pelvic pain, rectal syndrome) and local related complications such as urinary obstruction, perforation with pelvic abscess or recto vaginal fistula that can be disastrous and difficult to manage; secondly, for locally advanced mid and/or low rectal tumors (*i.e.*, staged cT3, T4 and/or cN-positive disease) neoadjuvant treatment (short-course radiotherapy (RT) or long-course chemoradiotherapy) has been demonstrated to decrease the risk of local recurrence with no effect on survival; finally rectal resection with total mesorectal excision is a demanding surgery with high postoperative complications rates (which may delay or even preclude chemotherapy administration), risk of long-term functional disorders (digestive, sexual, urinary) that can negatively impact on quality of life and lead to permanent stoma in up to 20% of operated patients[87].

In patients with rectal cancer and synchronous unresectable metastases, up-front chemotherapy administration before considering the need to resect the primary tumor may represent an attractive therapeutic option for the following reasons: surgery (with or without neoadjuvant treatment) is avoided in patients with rapidly progressive metastatic disease which should be regarded as a biological marker for poor prognosis and an indication for administering second-line treatment. In a retrospective study of 22 patients with rectal cancer and unresectable synchronous metastases, Stelzner *et al*[88] reported that, in patients without progression under first-line chemotherapy, median OS was significantly increased in patients who underwent PTR compared to those with the primary tumor left in place (27.2 mo *vs* 12.4 mo, $P = 0.017$). In addition, systemic chemotherapy has also an effect on primary tumor in rectal carcinoma. In a phase 2 trial evaluating neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in 105 patients with locally advanced rectal cancer, Chua *et al*[89] emphasized that morphological reevaluation after neoadjuvant chemotherapy showed an objective response in 78 patients (74%). Based on these results, patients could receive short-course RT or even no RT at all before rectal surgery in case of partial or complete radiological response after neoadjuvant chemotherapy. In conclusion, for patients with rectal cancer and unresectable SLM, it seems relevant that chemotherapy should be the first treatment and surgery should only be proposed when there is no progression during preoperative chemotherapy. Patients with a poor prognosis due to progressive metastatic disease are thereby spared the risks of major rectal surgery with a long hospital stay and unnecessary surgical complications.

## DISCUSSION: WHAT DESIGN FOR A STUDY ATTEMPTING TO ANSWER THIS ISSUE?

Whether PTR should be performed prior chemotherapy administration in unresectable stage Ⅳ CRC patients remains unknown. When the primary tumor is not resected and uncomplicated (asymptomatic) and the patient has started with palliative chemotherapy, the rate of unplanned or emergency surgery is relatively low and therefore does not warrant surgery of the primary in future patients. This relative low rate of primary tumor-related complications under chemotherapy may be partly explained by the effectiveness of chemotherapy regimens and targeted agents. With regard to survival, most retrospective studies favor PTR, but results are likely to be influenced by selection biases. These studies suggested that liver burden > 50%-75%, extra-hepatic metastatic disease (peritoneal carcinomatosis, lung metastases), advanced age and poor WHO-PS were poor prognostic factors in CRC patients with unresectable SLM even for those who undergo PTR. These factors, in addition to rectal primary location, have also been reported to be associated with high postoperative mortality and morbidity following PTR. In summary, data from the literature highlight that patient selection taking into account all the above men-

tioned factors is a critical issue for a future randomized trial aiming to determine whether OS is improved by PTR in patients with CRC and unresectable liver metastastic.

Definition of metastases unresectability is also a critical issue. Among patients with CRC liver metastases, no consensual precise definition of resectability or unresectability has been reached to date[3]. The resectability of liver metastases may differ from one hospital to another, depending on the available equipment and the level of surgical expertise. The definition also depends, understandably, on patient-specific data, such as general health, comorbidities, nutritional status, and more specifically, the presence of a possible underlying liver disease. For these reasons and to provide a rigorous framework, a relevant definition of liver metastases unresectability would be the inability to achieve a macroscopically complete resection (with clear margins) of all metastases, in one- or two-stage, without compromising postoperative liver function because of the insufficiency of either the remaining liver volume or biliary and venous vascularization and drainage. Unresectability of liver metastases would have to be assessed on a helical or multi-slice abdominal CT-scan with contrast enhancement, or liver MRI if CT is impossible (kidney failure, allergy to iodine) or insufficient to characterize lesions[81]. Radiological criteria for liver metastases unresectability would gather involvement of all hepatic veins, or both portal branches, or one portal branch and the controlateral hepatic vein(s), and a predictable post-hepatectomy liver volume < 25%-30%.

Then, all eligible patients would be randomized to undergo either PTR followed by chemotherapy ± targeted agent or chemotherapy ± targeted agent without PTR. Randomization would be stratified according to the study center and the metastatic liver involvement (≤ 50% *vs* > 50%) as determined by the pretreatment CT-scan or liver MRI staging.

The primary endpoint would be the difference in OS between the two treatment arms. Secondary endpoints would be quality of life, rate of primary tumor-related complications in the arm with chemotherapy alone and postoperative morbidity in the PTR arm. Besides, the tolerability of chemotherapy, objective tumor response, PFS, time to metastatic progression and the rate of secondary curative resection (R0) of both the primary and metastases should be assessed in both treatment arms.

No randomized study has been performed yet. The entire international community wishes to answer this question. One should emphasized that since 2010 until today, 14 papers on the present subject have been published including 9 individual series, 5 reviews or meta-analyses, 1 editorial and 1 guidelines from the French authorities. In all these publications, the need to perform a randomized trial evaluating the impact of PTR on survival in patients with CRC and unresectable metastases is underlined.

## CONCLUSION

The present review assessed whether OS and quality of life are improved in patients with asymptomatic unresectable metastatic CRC treated with surgery followed by chemotherapy *vs* chemotherapy alone with the primary in place. Reported data from the literature support the view that PTR should be discussed and validated by a phase III trial in selected patients: asymptomatic primary tumor, age ≤ 70 years, WHO-PS < 2, no extra-hepatic metastatic disease, liver burden of less than 50%. In these patients, PTR, when performed laparoscopically and after preoperative immuno-nutrition, may lead to an increased OS. In all other cases, reported postoperative mortality and morbidity rates related to PTR are high and up-front chemotherapy with the primary tumor left in place may represent the more reasonable option.

## REFERENCES


1 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187.e1-e3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]

2 **van der Pool AE**, Damhuis RA, Ijzermans JN, de Wilt JH, Eggermont AM, Kranse R, Verhoef C. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Colorectal Dis* 2012; **14**: 56-61 [PMID: 21176063 DOI: 10.1111/j.1463-1318.2010.02539.x]

3 **Nordlinger B**, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P, Sobrero A, Ychou M. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann Oncol* 2009; **20**: 985-992 [PMID: 19153115 DOI: 10.1093/annonc/mdn735]

4 **Golfinopoulos V**, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007; **8**: 898-911 [PMID: 17888735 DOI: 10.1016/S1470-2045(07)70281-4]

5 **Tol J**, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA, Richel DJ, Voest EE, Dijkstra JR, Vink-Börger ME, Antonini NF, Mol L, van Krieken JH, Dalesio O, Punt CJ. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 563-572 [PMID: 19196673 DOI: 10.1056/NEJMoa0808268]

6 **Eisenberger A**, Whelan RL, Neugut AI. Survival and symptomatic benefit from palliative primary tumor resection in patients with metastatic colorectal cancer: a review. *Int J Colorectal Dis* 2008; **23**: 559-568 [PMID: 18330581 DOI: 10.1007/s00384-008-0456-6]

7 **Scheer MG**, Sloots CE, van der Wilt GJ, Ruers TJ. Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases. *Ann Oncol* 2008; **19**: 1829-1835 [PMID: 18662955 DOI: 10.1093/annonc/mdn398]

8 **Stillwell AP**, Buettner PG, Ho YH. Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. *World J Surg* 2010; **34**: 797-807 [PMID: 20054541 DOI: 10.1007/s00268-009-0366-y]

9 **Anwar S**, Peter MB, Dent J, Scott NA. Palliative excisional surgery for primary colorectal cancer in patients with incurable metastatic disease. Is there a survival benefit? A systematic review. *Colorectal Dis* 2012; **14**: 920-930 [PMID: 21899714 DOI: 10.1111/j.1463-1318.2011.02817.x]

10 **Stillwell AP**, Ho YH, Veitch C. Systematic review of prog-

nostic factors related to overall survival in patients with stage IV colorectal cancer and unresectable metastases. *World J Surg* 2011; **35**: 684-692 [PMID: 21181473 DOI: 10.1007/s00268-010-0891-8]

11 **Chan TW**, Brown C, Ho CC, Gill S. Primary tumor resection in patients presenting with metastatic colorectal cancer: analysis of a provincial population-based cohort. *Am J Clin Oncol* 2010; **33**: 52-55 [PMID: 19704367 DOI: 10.1097/COC.0b013e31819e902d]

12 **Venderbosch S**, de Wilt JH, Teerenstra S, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Mol L, Punt CJ, Koopman M. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann Surg Oncol* 2011; **18**: 3252-3260 [PMID: 21822557 DOI: 10.1245/s10434-011-1951-5]

13 **Verhoef C**, de Wilt JH, Burger JW, Verheul HM, Koopman M. Surgery of the primary in stage IV colorectal cancer with unresectable metastases. *Eur J Cancer* 2011; **47** Suppl 3: S61-S66 [PMID: 21944031 DOI: 10.1016/S0959-8049(11)70148-4]

14 **Temple LK**, Hsieh L, Wong WD, Saltz L, Schrag D. Use of surgery among elderly patients with stage IV colorectal cancer. *J Clin Oncol* 2004; **22**: 3475-3484 [PMID: 15337795 DOI: 10.1200/JCO.2004.10.218]

15 **Cook AD**, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Ann Surg Oncol* 2005; **12**: 637-645 [PMID: 15965730 DOI: 10.1245/ASO.2005.06.012]

16 **Hochster HS**, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, Wong L, Fehrenbacher L, Abubakr Y, Saif MW, Schwartzberg L, Hedrick E. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008; **26**: 3523-3529 [PMID: 18640933 DOI: 10.1200/JCO.2007.15.4138]

17 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]

18 **Van Cutsem E**, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, Mazier MA, Canon JL, Georgoulias V, Peeters M, Bridgewater J, Cunningham D. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009; **20**: 1842-1847 [PMID: 19406901 DOI: 10.1093/annonc/mdp233]

19 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]

20 **Bokemeyer C**, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 663-671 [PMID: 19114683 DOI: 10.1200/JCO.2008.20.8397]

21 **Karoui M**, Koubaa W, Delbaldo C, Charachon A, Laurent A, Piedbois P, Cherqui D, Tran Van Nhieu J. Chemotherapy has also an effect on primary tumor in colon carcinoma. *Ann Surg Oncol* 2008; **15**: 3440-3446 [PMID: 18850249 DOI: 10.1245/s10434-008-0167-9]

22 **Ferrand F**, Malka D, Bourredjem A, Allonier C, Bouché O, Louafi S, Boige V, Mousseau M, Raoul JL, Bedenne L, Leduc B, Deguiral P, Faron M, Pignon JP, Ducreux M. Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: results from the multicenter, randomised trial Fédération Francophone de Cancérologie Digestive 9601. *Eur J Cancer* 2013; **49**: 90-97 [PMID: 22926014 DOI: 10.1016/j.ejca.2012.07.006]

23 **Hida K**, Hasegawa S, Kinjo Y, Yoshimura K, Inomata M, Ito M, Fukunaga Y, Kanazawa A, Idani H, Sakai Y, Watanabe M. Open versus laparoscopic resection of primary tumor for incurable stage IV colorectal cancer: a large multicenter consecutive patients cohort study. *Ann Surg* 2012; **255**: 929-934 [DOI: 10.1097/SLA.0b013e31824a99e4]

24 **Akagi T**, Inomata M, Kitano S, Hida K, Sakai Y, Hasegawa S, Kinjo Y, Yoshimura K, Ito M, Fukunaga Y, Kanazawa A, Idani H, Watanabe M. Multicenter study of short- and long-term outcomes of laparoscopic palliative resection for incurable, symptomatic stage IV colorectal cancer in Japan. *J Gastrointest Surg* 2013; **17**: 776-783 [PMID: 23435696 DOI: 10.1007/s11605-013-2173-x]

25 **Yang TX**, Billah B, Morris DL, Chua TC. Palliative resection of the primary tumour in patients with Stage IV colorectal cancer: systematic review and meta-analysis of the early outcome after laparoscopic and open colectomy. *Colorectal Dis* 2013; **15**: e407-e419 [PMID: 23895669 DOI: 10.1111/codi.12256]

26 **Adam R**, de Haas RJ, Wicherts DA, Vibert E, Salloum C, Azoulay D, Castaing D. Concomitant extrahepatic disease in patients with colorectal liver metastases: when is there a place for surgery? *Ann Surg* 2011; **253**: 349-359 [PMID: 21178761 DOI: 10.1097/SLA.0b013e318207bf2c]

27 **Maggiori L**, Elias D. Curative treatment of colorectal peritoneal carcinomatosis: current status and future trends. *Eur J Surg Oncol* 2010; **36**: 599-603 [PMID: 20605396 DOI: 10.1016/j.ejso.2010.05.007]

28 **Emmanouilides C**, Sfakiotaki G, Androulakis N, Kalbakis K, Christophylakis C, Kalykaki A, Vamvakas L, Kotsakis A, Agelaki S, Diamandidou E, Touroutoglou N, Chatzidakis A, Georgoulias V, Mavroudis D, Souglakos J. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer* 2007; **7**: 91 [PMID: 17537235 DOI: 10.1186/1471-2407-7-91]

29 **Ychou M**, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, Delpero JR, Rivoire M, Quénet F, Portier G, Nordlinger B. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. *Cancer Chemother Pharmacol* 2008; **62**: 195-201 [PMID: 17901955 DOI: 10.1007/s00280-007-0588-3]

30 **Adam R**, Lucidi V, Bismuth H. Hepatic colorectal metastases: methods of improving resectability. *Surg Clin North Am* 2004; **84**: 659-671 [PMID: 15062667 DOI: 10.1016/j.suc.2003.12.005]

31 **Stillwell AP**, Buettner PG, Siu SK, Stitz RW, Stevenson AR, Ho YH. Predictors of postoperative mortality, morbidity, and long-term survival after palliative resection in patients with colorectal cancer. *Dis Colon Rectum* 2011; **54**: 535-544 [PMID: 21471753 DOI: 10.1007/DCR.0b013e3182083d9d]

32 **Chang GJ**. Primary tumor resection in stage IV colorectal cancer: the debate continues. *Dis Colon Rectum* 2011; **54**: 919-920 [PMID: 21730777 DOI: 10.1097/DCR.0b013e31821ccf05]

33 **Karoui M**, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, Louvet C, Landi B, Tiret E, Sobhani I. Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study. *Dis Colon Rectum* 2011; **54**: 930-938 [PMID: 21730780 DOI: 10.1097/DCR.0b013e31821cced0]

34 **Tebbutt NC**, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, Livingston S, Andreyev J. Intestinal complications after chemotherapy for patients with unresected primary

colorectal cancer and synchronous metastases. *Gut* 2003; **52**: 568-573 [PMID: 12631671]
35 **Law WL**, Chan WF, Lee YM, Chu KW. Non-curative surgery for colorectal cancer: critical appraisal of outcomes. *Int J Colorectal Dis* 2004; **19**: 197-202 [PMID: 14618348 DOI: 10.1007/s00384-003-0551-7]
36 **Konyalian VR**, Rosing DK, Haukoos JS, Dixon MR, Sinow R, Bhaheetharan S, Stamos MJ, Kumar RR. The role of primary tumour resection in patients with stage IV colorectal cancer. *Colorectal Dis* 2007; **9**: 430-437 [PMID: 17504340 DOI: 10.1111/j.1463-1318.2007.01161.x]
37 **Yun HR**, Lee WY, Lee WS, Cho YB, Yun SH, Chun HK. The prognostic factors of stage IV colorectal cancer and assessment of proper treatment according to the patient's status. *Int J Colorectal Dis* 2007; **22**: 1301-1310 [PMID: 17486358 DOI: 10.1007/s00384-007-0315-x]
38 **Galizia G**, Lieto E, Orditura M, Castellano P, Imperatore V, Pinto M, Zamboli A. First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. *Arch Surg* 2008; **143**: 352-358; discussion 358 [PMID: 18427022 DOI: 10.1001/archsurg.143.4.352]
39 **Bajwa A**, Blunt N, Vyas S, Suliman I, Bridgewater J, Hochhauser D, Ledermann JA, O'Bichere A. Primary tumour resection and survival in the palliative management of metastatic colorectal cancer. *Eur J Surg Oncol* 2009; **35**: 164-167 [PMID: 18644695 DOI: 10.1016/j.ejso.2008.06.005]
40 **Mik M**, Dziki L, Galbfach P, Trzcinski R, Sygut A, Dziki A. Resection of the primary tumour or other palliative procedures in incurable stage IV colorectal cancer patients? *Colorectal Dis* 2010; **12**: e61-e67 [PMID: 19486103 DOI: 10.1111/j.1463-1318.2009.01860.x]
41 **Aslam MI**, Kelkar A, Sharpe D, Jameson JS. Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers. *Int J Surg* 2010; **8**: 305-313 [PMID: 20380899 DOI: 10.1016/j.ijsu.2010.03.005]
42 **Yamamura T**, Tsukikawa S, Akaishi O, Tanaka K, Matsuoka H, Hanai A, Oikawa H, Ozasa T, Kikuchi K, Matsuzaki H, Yamaguchi S. Multivariate analysis of the prognostic factors of patients with unresectable synchronous liver metastases from colorectal cancer. *Dis Colon Rectum* 1997; **40**: 1425-1429 [PMID: 9407979]
43 **Rosen SA**, Buell JF, Yoshida A, Kazsuba S, Hurst R, Michelassi F, Millis JM, Posner MC. Initial presentation with stage IV colorectal cancer: how aggressive should we be? *Arch Surg* 2000; **135**: 530-534; discussion 534-535 [PMID: 10807276]
44 **Ruo L**, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. *J Am Coll Surg* 2003; **196**: 722-728 [PMID: 12742204 DOI: 10.1016/S1072-7515(03)00136-4]
45 **Stelzner S**, Hellmich G, Koch R, Ludwig K. Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. *J Surg Oncol* 2005; **89**: 211-217 [PMID: 15726622 DOI: 10.1002/jso.20196]
46 **Kleespies A**, Füessl KE, Seeliger H, Eichhorn ME, Müller MH, Rentsch M, Thasler WE, Angele MK, Kreis ME, Jauch KW. Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. *Int J Colorectal Dis* 2009; **24**: 1097-1109 [PMID: 19495779 DOI: 10.1007/s00384-009-0734-y]
47 **Vibert E**, Bretagnol F, Alves A, Pocard M, Valleur P, Panis Y. Multivariate analysis of predictive factors for early postoperative death after colorectal surgery in patients with colorectal cancer and synchronous unresectable liver metastases. *Dis Colon Rectum* 2007; **50**: 1776-1782 [PMID: 17710496 DOI: 10.1007/s10350-007-9025-2]
48 **Costi R**, Di Mauro D, Veronesi L, Ardizzoni A, Salcuni P, Roncoroni L, Sarli L, Violi V. Elective palliative resection of incurable stage IV colorectal cancer: who really benefits from it? *Surg Today* 2011; **41**: 222-229 [PMID: 21264758 DOI: 10.1007/s00595-009-4253-9]
49 **Kuo LJ**, Leu SY, Liu MC, Jian JJ, Hongiun Cheng S, Chen CM. How aggressive should we be in patients with stage IV colorectal cancer? *Dis Colon Rectum* 2003; **46**: 1646-1652 [PMID: 14668590 DOI: 10.1097/01.DCR.0000093624.29029.3A]
50 **Flanigan RC**, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR, Munshi N, Crawford ED. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001; **345**: 1655-1659 [PMID: 11759643 DOI: 10.1056/NEJMoa003013]
51 **van der Burg ME**, Vergote I. The role of interval debulking surgery in ovarian cancer. *Curr Oncol Rep* 2003; **5**: 473-481 [PMID: 14521806]
52 **Danna EA**, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. *Cancer Res* 2004; **64**: 2205-2211 [PMID: 15026364]
53 **Holmgren L**, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat Med* 1995; **1**: 149-153 [PMID: 7585012]
54 **Kaplan RN**, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald DD, Jin DK, Shido K, Kerns SA, Zhu Z, Hicklin D, Wu Y, Port JL, Altorki N, Port ER, Ruggero D, Shmelkov SV, Jensen KK, Rafii S, Lyden D. VEGFR1-positive haematopoietic bone marrow progenitors initiate the premetastatic niche. *Nature* 2005; **438**: 820-827 [PMID: 16341007 DOI: 10.1038/nature04186]
55 **van der Wal GE**, Gouw AS, Kamps JA, Moorlag HE, Bulthuis ML, Molema G, de Jong KP. Angiogenesis in synchronous and metachronous colorectal liver metastases: the liver as a permissive soil. *Ann Surg* 2012; **255**: 86-94 [PMID: 22156924 DOI: 10.1097/SLA.0b013e318238346a]
56 **Peeters CF**, de Waal RM, Wobbes T, Ruers TJ. Metastatic dormancy imposed by the primary tumor: does it exist in humans? *Ann Surg Oncol* 2008; **15**: 3308-3315 [PMID: 18685897 DOI: 10.1245/s10434-008-0029-5]
57 **Peeters CF**, de Waal RM, Wobbes T, Westphal JR, Ruers TJ. Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. *Int J Cancer* 2006; **119**: 1249-1253 [PMID: 16642475 DOI: 10.1002/ijc.21928]
58 **Peeters CF**, Westphal JR, de Waal RM, Ruiter DJ, Wobbes T, Ruers TJ. Vascular density in colorectal liver metastases increases after removal of the primary tumor in human cancer patients. *Int J Cancer* 2004; **112**: 554-559 [PMID: 15382035]
59 **Scheer MG**, Stollman TH, Vogel WV, Boerman OC, Oyen WJ, Ruers TJ. Increased metabolic activity of indolent liver metastases after resection of a primary colorectal tumor. *J Nucl Med* 2008; **49**: 887-891 [PMID: 18483084 DOI: 10.2967/jnumed.107.048371]
60 **Naumov GN**, Folkman J, Straume O, Akslen LA. Tumor-vascular interactions and tumor dormancy. *APMIS* 2008; **116**: 569-585 [PMID: 18834403 DOI: 10.1111/j.1600-0463.2008.01213.x]
61 **Elias D**. Impact of tumor doubling time on the therapeutic strategy: application to so-called synchronous metastases of colorectal cancers. *Ann Chir* 1998; **52**: 413-420 [PMID: 9752479]
62 **Elias D**, Farace F, Triebel F, Hattchouel JM, Pignon JP, Lecesne A, Rougier P, Lasser P, Duvillard P, Escudier B. Phase I-II randomized study on prehepatectomy recombinant interleukin-2 immunotherapy in patients with metastatic carcinoma of the colon and rectum. *J Am Coll Surg* 1995; **181**: 303-310 [PMID: 7551323]
63 **Romano F**, Uggeri F, Crippa S, Di Stefano G, Scotti M, Scaini A, Caprotti R, Uggeri F. Immunodeficiency in different his-

totypes of radically operable gastrointestinal cancers. *J Exp Clin Cancer Res* 2004; **23**: 195-200 [PMID: 15354402]
64 **Weese JL**, Gilbertson EM, Syrjala SE, Starling JR. Prevention of rat colon cancer metastases by perioperative immunostimulation. *Surgery* 1984; **96**: 420-426 [PMID: 6463870]
65 **Weese JL**, Gilbertson EM, Syrjala SE, Whitney PD, Starling JR. Reduced incidence of rat colon cancer metastases by perioperative immunostimulation with maleic anhydride-divinyl ether-2 (MVE-2). *Dis Colon Rectum* 1985; **28**: 217-221 [PMID: 3979221]
66 **Corman J**, Arnoux R, Péloquin A, St-Louis G, Smeesters C, Giroux L. Blood transfusions and survival after colectomy for colorectal cancer. *Can J Surg* 1986; **29**: 325-329 [PMID: 3756652]
67 **Arnoux R**, Corman J, Péloquin A, Smeesters C, St-Louis G. Adverse effect of blood transfusions on patient survival after resection of rectal cancer. *Can J Surg* 1988; **31**: 121-126 [PMID: 3349375]
68 **Longo WE**, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, Phelan MA, Henderson WG, Daley J, Khuri SF. Risk factors for morbidity and mortality after colectomy for colon cancer. *Dis Colon Rectum* 2000; **43**: 83-91 [PMID: 10813129]
69 **Legendre H**, Vanhuyse F, Caroli-Bosc FX, Pector JC. Survival and quality of life after palliative surgery for neoplastic gastrointestinal obstruction. *Eur J Surg Oncol* 2001; **27**: 364-367 [PMID: 11417981 DOI: 10.1053/ejso.2001.1120]
70 **Evans MD**, Escofet X, Karandikar SS, Stamatakis JD. Outcomes of resection and non-resection strategies in management of patients with advanced colorectal cancer. *World J Surg Oncol* 2009; **7**: 28 [PMID: 19284542 DOI: 10.1186/1477-7819-7-28]
71 **Sarela AI**, Guthrie JA, Seymour MT, Ride E, Guillou PJ, O' Riordain DS. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br J Surg* 2001; **88**: 1352-1356 [PMID: 11578291 DOI: 10.1046/j.0007-1323.2001.01915.x]
72 **Tournigand C**, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**: 229-237 [PMID: 14657227 DOI: 10.1200/JCO.2004.05.113]
73 **Goldberg RM**, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**: 23-30 [PMID: 14665611 DOI: 10.1200/JCO.2004.09.046]
74 **Van Cutsem E**, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P, Ciardiello F. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; **29**: 2011-2019 [PMID: 21502544 DOI: 10.1200/JCO.2010.33.5091]
75 **Muratore A**, Zorzi D, Bouzari H, Amisano M, Massucco P, Sperti E, Capussotti L. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol* 2007; **14**: 766-770 [PMID: 17103261 DOI: 10.1245/s10434-006-9146-1]
76 **Poultsides GA**, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009; **27**: 3379-3384 [PMID: 19487380 DOI: 10.1200/JCO.2008.20.9817]
77 **McCahill LE**, Yothers G, Sharif S, Petrelli NJ, Lai LL, Bechar N, Giguere JK, Dakhil SR, Fehrenbacher L, Lopa SH, Wagman LD, O'Connell MJ, Wolmark N. Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. *J Clin Oncol* 2012; **30**: 3223-3228 [PMID: 22869888 DOI: 10.1200/JCO.2012.42.4044]
78 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016 [PMID: 18358928 DOI: 10.1016/S0140-6736(08)60455-9]
79 **Benoist S**, Pautrat K, Mitry E, Rougier P, Penna C, Nordlinger B. Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. *Br J Surg* 2005; **92**: 1155-1160 [PMID: 16035135 DOI: 10.1002/bjs.5060]
80 **Giantonio BJ**, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; **25**: 1539-1544 [PMID: 17442997 DOI: 10.1200/JCO.2006.09.6305]
81 **Zalinski S**, Mariette C, Farges O. Management of patients with synchronous liver metastases of colorectal cancer. Clinical practice guidelines. Guidelines of the French society of gastrointestinal surgery (SFCD) and of the association of hepatobiliary surgery and liver transplantation (ACHBT). Short version. *J Visc Surg* 2011; **148**: e171-e182 [PMID: 21703959 DOI: 10.1016/j.jviscsurg.2011.05.015]
82 **Scoggins CR**, Meszoely IM, Blanke CD, Beauchamp RD, Leach SD. Nonoperative management of primary colorectal cancer in patients with stage IV disease. *Ann Surg Oncol* 1999; **6**: 651-657 [PMID: 10560850]
83 **Platell C**, Ng S, O'bichere A, Tebbutt N. Changing management and survival in patients with stage IV colorectal cancer. *Dis Colon Rectum* 2011; **54**: 214-219 [PMID: 21228671 DOI: 10.1007/DCR.0b013e3182023bb0]
84 **Kuhry E**, Schwenk W, Gaupset R, Romild U, Bonjer J. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. *Cancer Treat Rev* 2008; **34**: 498-504 [PMID: 18468803 DOI: 10.1016/j.ctrv.2008.03.011]
85 **Chambrier C**, Sztark F, the working group of the Société Francophone de Nutrition Clinique et Métabolisme (SFNEP) and the Société Française d'Anesthésie et Réanimation (SFAR). French clinical guidelines on perioperative nutrition. Update of the 1994 consensus conference on perioperative artificial nutrition after elective surgery in adults. Available from: URL: http://www.sfar.org/_docs/articles/ RecommandationsNutritionPeriop090111SFAR.pdf
86 **Ohtani H**, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. *J Cancer* 2012; **3**: 49-57 [PMID: 22315650 DOI: 10.7150/jca.3621]
87 **den Dulk M**, Smit M, Peeters KC, Kranenbarg EM, Rutten HJ, Wiggers T, Putter H, van de Velde CJ. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol* 2007; **8**: 297-303 [PMID: 17395102 DOI: 10.1016/S1470-2045(07)70047-5]
88 **Stelzner S**, Hellmich G, Jackisch T, Ludwig K, Witzigmann H. Selective surgical treatment of patients with rectal carci-

noma and unresectable synchronous metastases based on response to preoperative chemotherapy. *J Gastrointest Surg* 2008; **12**: 1246-1250 [PMID: 18340498 DOI: 10.1007/s11605-008-0506-y]

89 **Chua YJ**, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, Tait D, Massey A, Tebbutt NC, Chau I. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. *Lancet Oncol* 2010; **11**: 241-248 [PMID: 20106720 DOI: 10.1016/S1470-2045(09)70381-X]

90 **Michel P**, Roque I, Di Fiore F, Langlois S, Scotte M, Tenière P, Paillot B. Colorectal cancer with non-resectable synchronous metastases: should the primary tumor be resected? *Gastroenterol Clin Biol* 2004; **28**: 434-437 [PMID: 15243315]

91 **Costi R**, Mazzeo A, Di Mauro D, Veronesi L, Sansebastiano G, Violi V, Roncoroni L, Sarli L. Palliative resection of colorectal cancer: does it prolong survival? *Ann Surg Oncol* 2007; **14**: 2567-2576 [PMID: 17541693 DOI: 10.1245/s10434-007-9444-2]

92 **Kaufman MS**, Radhakrishnan N, Roy R, Gecelter G, Tsang J, Thomas A, Nissel-Horowitz S, Mehrotra B. Influence of palliative surgical resection on overall survival in patients with advanced colorectal cancer: a retrospective single institutional study. *Colorectal Dis* 2008; **10**: 498-502 [PMID: 17949445 DOI: 10.1111/j.1463-1318.2007.01384.x]

93 **Frago R**, Kreisler E, Biondo S, Salazar R, Dominguez J, Escalante E. Outcomes in the management of obstructive unresectable stage IV colorectal cancer. *Eur J Surg Oncol* 2010; **36**: 1187-1194 [PMID: 20864304 DOI: 10.1016/j.ejso.2010.09.005]

94 **Seo GJ**, Park JW, Yoo SB, Kim SY, Choi HS, Chang HJ, Shin A, Jeong SY, Kim DY, Oh JH. Intestinal complications after palliative treatment for asymptomatic patients with unresectable stage IV colorectal cancer. *J Surg Oncol* 2010; **102**: 94-99 [PMID: 20578086 DOI: 10.1002/jso.21577]

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MINIREVIEWS

# Monoclonal antibodies that target the immunogenic proteins expressed in colorectal cancer

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## Abstract

In an attempt to improve upon the end results obtained in treating colorectal cancer it was apparent that the earlier the diagnosis that could be obtained, the better the chance for obtaining desired results. In the case of more advanced tumors typified by later stage colorectal cancer, surgical debulking is an important part of the treatment strategy. Here the use of additional therapeutic modalities including chemotherapy and present day immunotherapy has failed to accomplish the desired improvements that have been sought after. Adjuvant therapy, has offered little to the overall survival. The concept of early detection is now recognized as the initial step in reaching proper end results and can readily be demonstrated from colorectal cancer studies. Here survival has been found to be a reflection of the stage at which the tumor is first identified and treated. When specific monoclonals targeting colorectal cancer are employed diagnostically, we have been able to demonstrate detection of colorectal cancer at its inception as a premalignant lesion, such that genotypic features can be identified before the phenotypic appearance of cancer can be noted.



**Key words:** Colorectal cancer; Monoclonal antibodies; Immunohistochemistry; Antibody dependent cell cytotoxicity; Tumor associated antigens

**Core tip:** The ideal monoclonal antibody to be employed in cancer management is one targeting an immunogenic protein expressed in a specific cancer system. Those presently employed in cancer management, target a growth factor or carbohydrate antigen seen in both cancer and normal tissue. Their value as such is limited. The monoclonals described herein are directed against colon cancer tumor associated antigen and have value in both diagnostic and therapeutic uses for controlling this disease.

Arlen M, Arlen P, Coppa G, Crawford J, Wang X, Saric O, Dubeykovskiy A, Molmenti E. Monoclonal antibodies that target the immunogenic proteins expressed in colorectal cancer. *World J Gastrointest Oncol* 2014; 6(6): 170-176 Available from: URL: http://www.wjgnet.com/1948-5204/full/v6/i6/170.htm DOI: http://dx.doi.org/10.4251/wjgo.v6.i6.170

## INTRODUCTION

For most malignancies such as colorectal cancer, the earlier the diagnosis the better the chance for offering the patient the opportunity to be cured[1-5]. The addition of additional methods to help improve survival, especially in the post operative period, have offered little to achieve a better response[6-9]. In order to define methods for earlier intervention, we began to look at behavioral patterns seen in various stages of colorectal cancer, attempting to define those patterns related to tumor antigen expression. We were able as such, to identify and characterize a unique group of immunogenic proteins that appeared

to be expressed in all colorectal carcinomas that were examined. These tumor (associated) antigens were found to be present in all stages of colorectal tumor development, from inception to metastasis. Following the separation of these proteins from pooled tumor cell membranes, monoclonal antibodies targeting these proteins were developed. Hybridomas were produced by injection of BALBc mice with the antigens/proteins so obtained.

By employing those monoclonal antibodies derived against the tumor proteins, it appeared that the antigen, noted to be expressed in the earliest stages of tumor development, continued to be present throughout later stages of progression of tumor growth. As a result, we were able to define the appearance of genetic alterations occurring in normal appearing cells that first characterized the transformation process. This initial pattern of cellular transformation was typified by the expression of immunogenic tumor proteins in the earliest stages of genotypic transformation when phenotypic features still appeared normal by standard HE. As with the invasive cell which sheds its antigen into the serum, the premalignant cell similarly sheds antigen into the stool which can easily be identified by a stool enzyme-linked immunosorbent assay (ELISA). Tissue biopsies studied by immunohistochemistry to define cells expressing tumor antigen and examination of stool for the presence of tumor antigen can now offer the asymptomatic patient the opportunity for proper screening. As a result one can now offer a practical process for early detection of a developing malignancy when optimum results can almost always be anticipated.

We now believe that it is possible to define the presence or absence of colon cancer during the screening process of the asymptomatic patient. If validated by our studies, the need to employ colonoscopy would be markedly reduced and relegated to those patients where there is a high likely hood for defining an early malignancy or when biopsy is required for confirmation of as well as staging of the disease process.

As noted above, the early premalignant cells undergoing transformation, as well as polypoid tumors and larger malignancies do shed tumor antigen into the stool where they can be detected by stool ELISA using our colon tumor monoclonals. This procedure can be used as a confirmatory measure to determine whether colonoscopy is or is not indicated as a follow up in post op patients in order to detect early developing lesions as well as possible anastomotic recurrences.

These same antibodies, used for detecting colon specific tumor associated antigens, also have therapeutic efficacy. Should the clinical work up of a malignant lesion demonstrate spread of tumor, the monoclonals that were employed for diagnosis of the tumor marker, can now be delivered intravenously to target those cells producing tumor antigen and destroy them through the process of antibody dependent cell cytotoxicity (ADCC).

## DISCUSSION

At the present time, most of the tumor markers employed commercially for tumor detection and diagnosis are non specific. Those clinically available, best serve to monitor the response to the therapy being employed rather than to detect and diagnose the presence of a lesion. Those markers that appear in the serum are mostly derived from carbohydrate antigens that are shed into the serum. They are not only expressed by the tumor, but also by adjacent normal tissue that may have been effected by an ongoing inflammatory process[10-12].

In order to detect the presence of colon tumors at the ideal time, it is important to be able to define a specific marker or family of markers on the tumor when clinical symptoms were minimal if not totally absent. Such markers have been shown to best be represented by one or several immunogenic proteins or glycoproteins expressed on the cell surface membrane and found to shed into the serum as well as surrounding tissue. Those immunogenic proteins that characterize colon cancer have been isolated and characterized by our group at Precision Biologics. Pooled allogeneic specimens of colon cancer were used to retrieve tumor membrane proteins, separate them by molecular weight and then skin test the patient to define that specific group of proteins producing delayed cutaneous sensitivity. Further separation by isoelectrophoresis yielded three distinct glycoproteins that proved to represent oncofetal proteins first expressed in the fetus and later in a mutated form, representing specific colon cancer proteins that help induce a mild immune response. The failure to achieve a full immune response proved to be due to minimal expression of antigen in the tumor that was necessary to induce a proper immune response.

Using monoclonal antibodies developed against these immunogens, a serum ELISA was also developed that is capable of identifying shed markers with a high degree of sensitivity and specificity[13]. The monoclonal antibodies that specifically target these tumor proteins, have demonstrated that these proteins serve both as diagnostic markers and a therapeutic targets[14].

It is well known that of the many methods being developed to control the more aggressive colon lesions, not only does one rely on newer chemotherapeutic agents, but additionally through enhancement of the immune system. This can be accomplished by combining chemotherapy with a monoclonal antibody such as the one directed against the epidermal growth factor 1[15]. The process of adding an immunotherapeutic agent to standard chemotherapeutic drugs does rely on the nature of the antigen expressed by the tumor. This of course can be accomplished by immunohistochemical analysis of the tumor. The same effective monoclonal antibody that detected the presence of the tumor antigen/marker in the biopsy specimen can then be used intravenously along with chemotherapy, to attack the marker as a therapeutic target. In such combinations, the chemotherapeutic agent may serve to minimize the presence of any shed blocking material from the tumor to secondarily enhancing the immune response. Such enhancement in immune reactivity frequently helps the host defense mechanisms to control

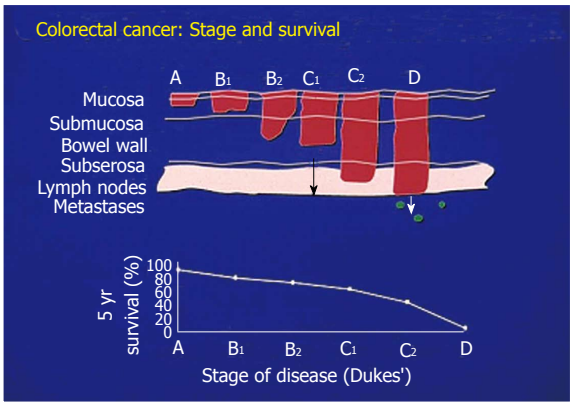


**Figure 1 Correlating the extent of local tumor progression with survival in colorectal cancer.**

disease progression[16-19].

When a primary colon tumor is confined to the mucosa of the bowel, cure is just about guaranteed by surgical removal. However, when the tumor is found to penetrate into the muscular layers of the bowel, or invades the serosal surface with regional nodes possibly being involved, the opportunity for cure diminishes (Figure 1). Here additional modalities of therapy are essential if improvement in survival is to be accomplished.

The size of a tumor mass becomes part of the overall picture of how the lesion is viewed regarding its management. A greater host immune response is required in the more advanced cases as typified by bulky disease. This almost always necessitates surgical debulking to eliminate the larger number of tumor cells that are required to be brought under control. The presence of bulky tumor is in addition, frequently associated with a source of inhibitory surface molecules. When shed from the tumor cell membrane into the serum, these molecules function to inhibit those immunosurveillance mechanisms needed for helping to eliminate existing tumor cells that may have remained in the region of surgical resection or among those cells having entered the circulation[20]. As a consequence, a greater host immune response is required in the more advanced cases which is usually typified by bulky disease. There is little disagreement as such, that the ability to achieve an improved cure rate depends on early diagnosis and when possible, complete removal of the existing tumor.

The concept for achieving the early diagnosis of a malignant lesion was espoused by Lee Hartwell of the Fred Hutchinson Cancer Center, who evaluated procedures for achieving such early diagnosis as the more effective way of curing cancer. He looked at later stages of disease in solid tumor malignancies, where chemotherapy was employed to help improve survival. In such situations he found that this approach rarely resulted in cure, especially when the primary lesion had undergone the process of metastasis[21].

Hartwell stressed the need for finding a tumor protein expressed early in the onset of disease, functioning in a manner that the Pap smear had accomplished for cervix cancer. When such a tumor protein, functioning as a marker, could be detected by a monoclonal antibody, the clinical course of the disease would be altered in favor of an almost guaranteed cure. Larry Norton of the Sloan Kettering Cancer Center emphasized that if the tumor markers that Hartwell was hoping to find were immunogenic, then the monoclonal antibody that could determine the presence of the malignant lesion would be the same monoclonal that when delivered intravenously, would hunt, seek and destroy any cell in the metastatic setting that presented with such a marker. Essentially the presence of immunogenic tumor associated antigens (TAA's) on the cell surface membrane serve to illustrate the tumor in the form of a coin displaying two sides. On the reverse side of the coin, the proper monoclonal can detect the tumor antigen as a diagnostic marker. The antigen on the opposite (head) side of the coin would now act as a therapeutic target for tumor destruction by utilizing the same monoclonal antibody delivered intravenously (Figure 2).

Such tumor immunogenic proteins (TAA's) were isolated from a number of different malignancies including colon cancer and later characterized at Precision Biologics. The monoclonals that were derived from colon cancer antigen and later used to immunize BALBc mice for hybridoma production, are presently being tested clinically for both diagnostic and therapeutic efficacy. They have been found to be capable of detecting the earliest lesion in a manner illustrated by Figure 2. These colon tumor specific monoclonals are capable of functioning to diagnose the presence of the colon malignancy by both immuno-histochemistry of the resected specimen as well as serum ELISA. Should the tumor have invaded the blood stream, the metastatic lesions resulting from such invasion can now be effectively targeted. Extrapolating from animal studies with colon cancer transplants, metastatic foci from of these tumors can now be approached thru intravenous infusion of the monoclonal antibody with doses of the IgG1 delivered Ⅳ at 4-5 mg/kg. Phase Ⅱ B studies are now in progress with these antibodies.

When Ariel Hollinshead (1985)[22] employed pooled allogeneic tumor membrane antigen for treating a variety of malignant lesions, it became apparent that when the antigen was delivered at threshold levels and specifically for the malignancy expressing suboptimal levels of innate antigen, that the immune system could be shifted from one of performing immune-surveillance to that of providing a therapeutic mechanism for attacking and destroying the tumor, resulting in improvement in survival[23,24].

Clinical studies employing pooled allogeneic tumor antigen in the form of a vaccine, defined by its ability to turn on both cell and humoral immunity, resulted in improved survival over those where patients underwent surgery alone. In order to achieve an optimum response, the antigen had to be delivered at doses of between 750 and 1000 μg in 3 divided doses, given along with an oil based adjuvant. This allowed the now homogenized antigen to remain at the site of delivery for an extended period of

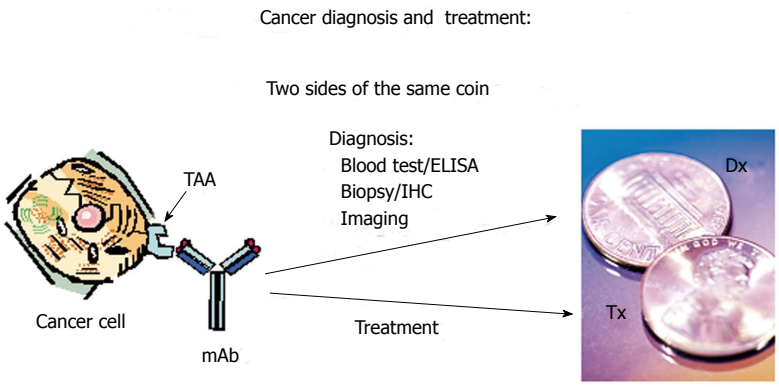


**Figure 2 Depicts the ideal monoclonal antibody that can define the presence of a tumor associated antigen for diagnosis by Immunohistochemistry and then when delivered Ⅳ, can hunt and destroy the tumor which contains the diagnostic marker.** IHC: Immunohistochemistry; TAA: Tumor associated antigen; ELISA: Enzyme-linked immunosorbent assay.

time.

To define the nature of the tumor protein or proteins capable of inducing enhancement in tumor recognition, monoclonals were developed in BALBc mice. Three of the antibodies obtained from the fusion and subsequent hybridoma development showed specificity for colon cancer. There was minimal if any evidence of cross reactivity of these antibodies to the surrounding normal colonic tissue. When employed for therapy, first chimeric and then the humanized or human version of the antibodies were produced.

In reviewing the nature of the clinical response obtained following the initial trials employing pooled colon cancer antigen, all patients immunized had a strong delayed cutaneous hypersensitivity response as previously noted. This was response was associated with enhancement in cellular immunity as well a strong humoral response in most patients, with resulting high serum titers of an IgG1 targeting the antigen expressed on the tumor cells[25]. Those among the 10%-20% of patients showing signs of recurrent disease after immunization, were found to be unable to mount the needed humoral response needed to control the tumor. The cell lmediated immunity almost appeared to function in a bystander manner. The monoclonals described above that were developed from the original Hollinshead tumor antigen were then specifically produced GMP for initiation of food and drug administration (FDA) clinical trails. The IgG1 format developed for the trials was found to function in the same manner as those antibodies found in the host circulation in response to administration of the tumor vaccine.

A detailed analysis of the monoclonals so produced against the colon antigen revealed each to be capable of inducing a strong ADCC response. Similarly, these mAbs showed effectiveness in a serum ELISA with a high degree of sensitivity and specificity. Using Immunohistochemistry (IHC) to define expression of antigen in the tissue under examination, cells that have undergone the initial genotypic changes can now be clearly defined even though the phenotypic features of cancer are not yet available for recognition by the pathologist. Studies to date have suggested that the colonocytes adjacent to a malignant lesion, have for the most part undergone genotypic transformation (Figure 3). It appears that this process of malignant transformation occurs several months before phenotypic features of cancer can be detected[26]. Obviously during resection of a primary colon lesion by colectomy, it is essential for the pathologist to guarantee that transformed colonocytes not be left behind in the margins of resection that are to be re-anastomosed. This appears to be best achieved by employing IHC with the monoclonal antibodies targeting colon tumor antigen. Along with the standard HE protocol. We plan to have antibody kits available in the OR so that frozen sections taken from margins of bowel following colectomy can be obtained for IHC.

Tumor antigen structure was analyzed, defined and characterized following immunoprecipitation of the pooled allogeneic colon cancer membrane material that had been used as a vaccine. Mass spectroscopy indicated that there were three separate antigens, seen alone and in combination in various colon cancers, each representing an oncofetal protein needed in the development of the human GI tract. These proteins were usually turned off as the fetus matured by re: methylation of the gene. In the adult, the onset of malignant transformation of the cell occurs *via* an oncogenic mutation. This appears to result in a modification of the protein structure through a mutation in the synthetic pathway or possibly thru a post translational modification of the oncofetal protein. The resulting tumor protein was found then to be immunogenic and serves to characterize the tumor system in which it is expressed. The immunogenic proteins that we identified were shown to be related to MUC5ac, A33, and CEAcam 5,6. While our monoclonals clearly define these proteins on Immunohistochemistry, commercial monoclonals used to define the known non modified antigens (oncofetal proteins) failed to recognize expression of the modified antigen in the malignant system.

All of the monoclonals that we have developed fit into a unique class of IgG's that are both diagnostic as well as therapeutic in solid tumor malignancies. Mutated MUC5c antigen is defined by monoclonal Neo-101 and its newer version Neo 102, CEAcam5,6 by monoclonal 16C3/Neo 201 and altered A33 by monoclonal 31.1. To date no other anti-tumor IgG monoclonals have been found capable of performing in a similar fashion. The epidermal antibodies targeting epidermal growth factor I and II all have corresponding targets in normal tissue.

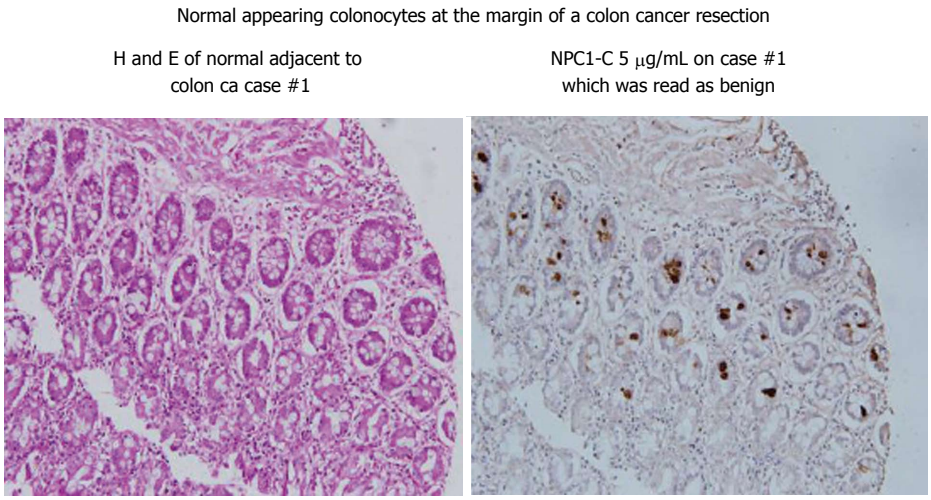


**Figure 3 Reveals expression of tumor antigen in those colonocytes adjacent to the malignant lesion where the colonocytes appear normal by H and E.**

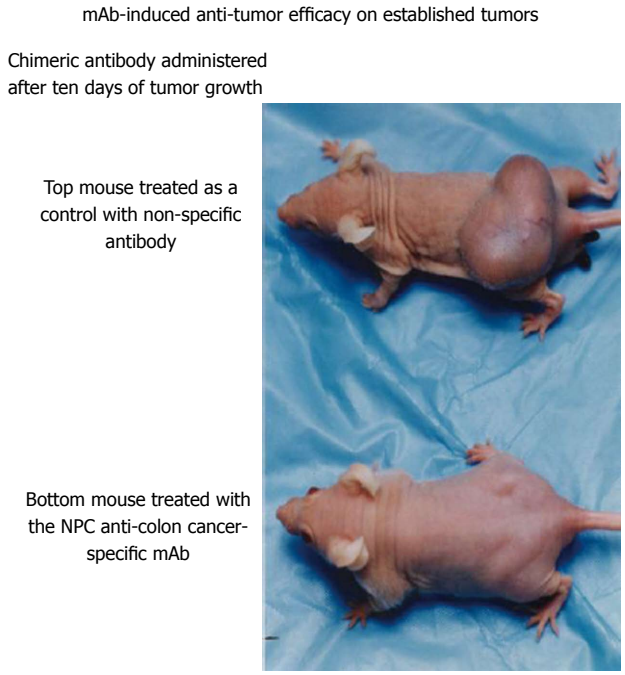


**Figure 4 Animal models (nude mice) growing human malignancy to compare untreated and treated animals.** The upper model received a control mAb while the lower animal model having had a much smaller tumor mass at 10 d received mAb NPC-1.

Knowing that the targeted antigen in colorectal cancer can result in tumor destruction, animal studies prior to initiation of clinical trials using therapeutic monoclonals, were devised to demonstrate *in vivo* tumor destruction Figure 4.

The ADCC response for most of the Precision monoclonals, range from 50%-70% tumor destruction in a 6-8 h. period of time, at an effector to tumor (E:T) ratio of 80-100:1 to over 90% with monoclonal 31.1. When these antibodies are delivered intraperitoneally in the animal model following establishment of tumor growth 10 d after subcutaneous administration of 10-20 million tumor cells in the thigh of nude mice, more than 50% of the animals were found to have a marked reduction in size the tumor mass. This can be seen at 10-15 d after immunization. The dosage of intraperitoneal IgG delivered along with human effector cells to assure an optimum ADCC response, was found to require approximately 400 μg in the animal model or an equivalent of approximately 400 mg in a 70 kg patient, this represents about 4-5 mg/kg of monoclonal antibody delivered at about 1 mg/min.

Considering the lack of toxicity following Ⅳ administration of our monoclonals in phase Ⅰ FDA therapeutic trial, we began phase Ⅱ studies. One of the problems encountered in the original GMP antibody preparation for FDA was that NEO-101 mAb was expressed at low levels and therefore not suitable for commercial production. Using a newer expression system, we are now able to produce the new monoclonal at a significantly higher level. Of interest was that while the sequence of the newly produced antibody, NEO-102 was virtually unchanged, we did see an approximate a definite improvement in ADCC as well as improvement in the quality of staining where background staining was virtually eliminated. This new version of the mAb, NEO-102 is being utilized in phase Ⅱ and is being tested in escalating doses. Phase Ⅱb has been designed to test the optimum dose of NEO-102 in combination with chemotherapy[27].

As mentioned above, the antibodies developed at Precision Biologics have their clinical efficacy in their capability of defining the tumor marker expressed in the tumor cell as a target for tumor detection as well as destruction. In tracing the pattern of expression of these markers, it became readily apparent that they were expressed not only in the later stages of tumor development where they could serve as an ideal therapeutic target, but at a time when genotypic changes were taking place in the normal but transforming cell, as noted above, and where the features of malignancy could not be readily recognized by the pathologist. We are now looking at the issue of Field Effect with regard to the genetic alterations occurring at the time of tumor induction. As such we are attempting to define the extent of premalignant

alterations surrounding the primary lesion[28].

In terms of colon cancer, the mechanism for tumor induction whether by virus or carcinogen, probably effects an area in the bowel resulting in a pattern of genotypically altered colonocytes expressing tumor antigen, the so called Field Effect as noted above. Within this Field, further mutations lead to the eventual appearance of the early polypoid changes that may suppress the genotypically altered surrounding colonocytes. This polypoid lesion then continues with further mutational changes leading to the eventual appearance of an infiltrating colonocytic lesion. Resection of the polypoid lesion, leaving the altered colonocytic field intact, could then result in further progression of cellular changes in the premalignant cells. Such a concept, if proven correct as per an ongoing study at North Shore University Hospital and Precision Biologics will assist the pathologist, at the time of bowel resection, to define the extent of the Field Effect by immuno histochemistry.

In our ongoing therapeutic trials, phase Ⅱb is in the process of initiation with the addition of chemotherapy to the therapeutic monoclonals being employed. It is generally agreed upon that Immunochemotherapy can be more effective than either chemotherapy or immunotherapy when employed alone. In general chemotherapy can diminish the immune inhibitory effect derived from the tumor and enhances the overall therapeutic response[29,30]. Finally we have prepared an alpha particle labeled NEO-102 monoclonal antibody to be introduced at a later date as part of the overall therapeutic approach to tumor control.

The availability of monoclonals targeting an immunogenic protein expressed in all phases of colon cancer development should be useful for both diagnosis and therapy and should have a major impact on how colon cancer is treated and the outcome that can be expected.

## REFERENCES


1 **Winawer SJ**, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977-1981 [PMID: 8247072 DOI: 10.1056/NEJM199312303292701]

2 **Martínez ME**, Baron JA, Lieberman DA, Schatzkin A, Lanza E, Winawer SJ, Zauber AG, Jiang R, Ahnen DJ, Bond JH, Church TR, Robertson DJ, Smith-Warner SA, Jacobs ET, Alberts DS, Greenberg ER. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* 2009; **136**: 832-841 [PMID: 19171141 DOI: 10.1053/j.gastro.2008.12.007]

3 **Brenner H**, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007; **56**: 1585-1589 [PMID: 17591622 DOI: 10.1136/gut.2007.122739]

4 **Lieberman DA**, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ, Schnell TG, Chejfec G, Campbell DR, Kidao J, Bond JH, Nelson DB, Triadafilopoulos G, Ramirez FC, Collins JF, Johnston TK, McQuaid KR, Garewal H, Sampliner RE, Esquivel R, Robertson D. Five-year colon surveillance after screening colonoscopy. *Gastroenterology* 2007; **133**: 1077-1085 [PMID: 17698067 DOI: 10.1053/j.gastro.2007.07.006]

5 **Higaki S**, Hashimoto S, Harada K, Nohara H, Saito Y, Gondo T, Okita K. Long-term follow-up of large flat colorectal tumors resected endoscopically. *Endoscopy* 2003; **35**: 845-849 [PMID: 14551863 DOI: 10.1055/s-2003-42622]

6 **André T**, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009; **27**: 3109-3116 [PMID: 19451431 DOI: 10.1200/JCO.2008.20.6771]

7 **Quasar Collaborative Group**, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007; **370**: 2020 [DOI: 10.1016/S0140-6736(07)61866-2]

8 **Sauer R**, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**: 1731-1740 [PMID: 15496622 DOI: 10.1056/NEJMoa040694]

9 **Mitry E**, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, Nitti D, Torri V, Elias D, O'Callaghan C, Langer B, Martignoni G, Bouché O, Lazorthes F, Van Cutsem E, Bedenne L, Moore MJ, Rougier P. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; **26**: 4906-4911 [PMID: 18794541 DOI: 10.1200/JCO.2008.17.3781]

10 **Bigbee W**, Herberman RB. Tumor markers and immunodiagnosis. In: Bast RC Jr., Kufe DW, Pollock RE, et al., editors. Cancer Medicine. 6th ed. Hamilton, Ontario, Canada: BC Decker Inc., 2003

11 **Walsh JM**, Terdiman JP. Colorectal cancer screening: scientific review. *JAMA* 2003; **289**: 1288–1296 [DOI: 10.1001/jama.289.10.1288]

12 **Carpelan-Holmström M**, Louhimo J, Stenman UH, Alfthan H, Järvinen H, Haglund C. Estimating the probability of cancer with several tumor markers in patients with colorectal disease. *Oncology* 2004; **66**: 296-302 [PMID: 15218297 DOI: 10.1159/000078330]

13 **Arlen M**, Arlen P, Wang X, Saric O, Martin DA, Deutsch G, Sathyanaryyana SA. The clinical detection of Pancreatic Carcinoma: A comparison of the Standard Biomarkers to that of a Newer Class of Biomarkers used for both diagnosis and Therapy. *Pancreatic Disorders and Therapy* 2013; **10**: 4172-4178

14 **Arlen M**, Tsang KY, Bartal A, Wolf J, Saric O. Monoclonal Antibodies to Immunoreactive Tumor Associated Antigen (TAA) from Human Colon Cancer. *Antibody Immunoconjugates and Radiopharmaceuticals* 1991; **4**: 2

15 **Patel SP**, Bristol A, Saric O, Wang XP, Dubeykovskiy A, Arlen PM, Morse MA. Anti-tumor activity of a novel monoclonal antibody, NPC-1C, optimized for recognition of tumor antigen MUC5AC variant in preclinical models. *Cancer Immunol Immunother* 2013; **62**: 1011-1019 [PMID: 23591984 DOI: 10.1007/s00262-013-1420-z]

16 **Nimmerjahn F**, Ravetch JV. Translating basic mechanisms of IgG effector activity into next generation cancer therapies. *Cancer Immun* 2012; **12**: 13 [PMID: 22896758]

17 **Lim SH**, Beers SA, French RR, Johnson PW, Glennie MJ, Cragg MS. Anti-CD20 monoclonal antibodies: historical and future perspectives. *Haematologica* 2010; **95**: 135-143 [PMID: 19773256 DOI: 10.3324/haematol.2008.001628]

18 **Nimmerjahn F**, Ravetch JV. Antibodies, Fc receptors and cancer. *Curr Opin Immunol* 2007; **19**: 239-245 [PMID: 17291742 DOI: 10.1016/j.coi.2007.01.005]

19 **Desjarlais JR**, Lazar GA. Modulation of antibody effector function. *Exp Cell Res* 2011; **317**: 1278-1285 [PMID: 21459085 DOI: 10.1016/j.yexcr.2011.03.018]

20 **Arlen M**. Escape Mechanisms employed by tumor cells to allow for Growth, Invasion and Metastasis In Chemoimmunosensitization of Resistant Tumor Cells to Cell Death by Apoptosis. *Bonavida* 2006; 243-261

21 Hartwell NCI Cancer bulletin February 3, 2004; 1: 5. Available from: URL: http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2004/020304/page6

22 **Hollinshead A**, Elias EG, Arlen M, Buda B, Mosley M, Scherrer J. Specific active immunotherapy in patients with adenocarcinoma of the colon utilizing tumor-associated antigens (TAA). A phase I clinical trial. *Cancer* 1985; **56**: 480-489 [PMID: 4005810 DOI: 10.1002/1097-0142(19850801)56]

23 **Arlen M**, Arlen P, Tsang A, Wang XP. The Therapeutic Value of Monoclonal Antibodies Directed Against Immunogenie Tumor Glycoproteins J. *Cancer* 2010; 1: 209-222 [DOI: 10.7150/jca.1.209]

24 **Bartal A**, Tsang KY, Saric O, Wooding M. Monoclonal Antibody defining an Antigen present within a purified Tumor Membrane Vaccine. Proc. Am. Assoc. *Cancer Res* 1990; 1539

25 **Arlen M**, Tsang KY. Monoclonal antibodies and their role in modulation of the immune response. *J Surg Oncol* 1993; **54**: 103-108 [PMID: 8412155 DOI: 10.1002/jso.2930540210]

26 **Arlen M**, Saric O, Wang X, Dubeykovskiy A, Arlen P. Nanocytology vs. Immunohistochemistry of Intestinal Colonocytes to Assess the Risk of Colon Cancer based on Field Cancerization - A Preliminary Report. *J Cancer* 2013; **4**: 165-169 [PMID: 23412851 DOI: 10.7150/jca.5468]

27 **Arlen M**, Wang X, Luka J, Gupta R, Saric O, Arlen PM. The use of specific monoclonal antibodies to target immunogenic tumor membrane proteins in patients with recurrent pancreatic and colon cancer. *Curr Drug Deliv* 2012; **9**: 52-56 [PMID: 22283657 DOI: 10.2174/156720112798376087]

28 **Arlen M**, Arlen P. Optimizing the immune system to achieve control of the metastatic malignant lesion. *J Cancer* 2013; **4**: 427-432 [PMID: 23833687 DOI: 10.7150/jca.6572]

29 **Liu WM**, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. *Br J Cancer* 2010; **102**: 115-123 [PMID: 19997099 DOI: 10.1038/sj.bjc.6605465]

30 **Ramakrishnan R**, Assudani D, Nagaraj S, Hunter T, Cho HI, Antonia S, Altiok S, Celis E, Gabrilovich DI. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. *J Clin Invest* 2010; **120**: 1111-1124 [PMID: 20234093 DOI: 10.1172/JCI40269]


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SYSTEMATIC REVIEW

# Current status of pharmacological treatment of colorectal cancer

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## Abstract

**AIM:** To review the clinical trials for the development in drugs for chemotherapeutic treatment of colorectal cancer (CRC).

**METHODS:** A systematic review identified randomized controlled trials (RCTs) assessing drugs for the treatment of CRC or adenomatous polyps from www.clinicaltrials.gov. Various online medical databases were searched for relevant publications.

**RESULTS:** Combination treatment regimens of standard drugs with newer agents have been shown to improve overall survival, disease-free survival, time to progression and quality of life compared to that with standard drugs alone in patients with advanced colorectal cancer. The FOLFOXIRI regimen has been associated with a significantly higher response rate, progression-free survival and overall survival compared to the FOLFIRI regimen.

**CONCLUSION:** Oxaliplatin plus intravenous bolus fluorouracil and leucovorin has been shown to be superior for disease-free survival when compared to intravenous bolus fluorouracil and leucovorin. In addition, oxaliplatin regimens were more likely to result in successful surgical resections. First line treatment with cetuximab plus fluorouracil, leucovorin and irinotecan has been found to reduce the risk of metastatic progression in patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases. The addition of bevacizumab has been shown to significantly increase overall and progression-free survival when given in combination with standard therapy.



**Key words:** Colorectal cancer; Metastasis; Chemotherapy; 5-fluorouracil; Leucovorin; Epidermal growth factor receptor inhibitor

**Core tip:** A systematic review was undertaken to identify randomized controlled trials (RCTs) assessing synthetic drugs for the treatment of colorectal cancer and/or adenomatous polyps from various medical databases, including clinicaltrials.gov, and a total of around 2300 RCTs were screened. After reviewing data from RCTs of synthetic drugs, alone or in combination with biological agents, for the treatment of colorectal cancer, it was concluded that combination regimens of standard chemotherapeutic drugs with new cytotoxic and targeted agents have led to an increase in overall and progression-free survival and have also contributed to increased rates of resectability and improved health-related quality of life in patients.

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## INTRODUCTION

Colorectal cancer (CRC) is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). It is the third most common cancer in males and the second in females. Countries such as Australia, New Zealand, Canada, the United States and parts of Europe have the highest incidence rates, whereas China, India, parts of Africa and South America have the lowest risk of colorectal cancer in the world[1]. This geographical variation in incidence across the world can be attributed to differences in the consumption of red and processed meat, fiber and alcohol as well as body weight and physical activity[2-7]. However, the incidence of colorectal cancer is increasing in Japan and other Asian countries as there has been a shift towards westernized diets and lifestyles[2]. The survival rate for colorectal cancer varies with stage of disease at diagnosis and typically varies from 90% for cancers detected at the localized stage to 10% for distant metastatic cancer. The incidence of colorectal cancer has been known to increase with age. The likelihood of colorectal cancer diagnosis increases progressively from a younger age (< 40 years) and rises sharply after the age of 50 years[8,9]. Several factors such as poor quality diets[10], lack of physical activity, obesity[11], cigarette smoking[12] and heavy alcohol consumption[13] are associated with an increased risk of colorectal cancer. An individual with a history of adenomatous polyps or inflammatory bowel disease has an increased risk of developing colorectal cancer compared to an individual with no history of either[12,14].

Colorectal cancer includes malignant growths from the mucosa of the colon and rectum. Cancer cells may eventually spread to nearby lymph nodes and subsequently to more remote lymph nodes and other organs in the body like the liver and lungs, among others. The treatment, prognosis and survival rate largely depends on the stage of disease at diagnosis. Screening for colorectal cancer is particularly effective. Screening can prevent cancer from occurring as it can detect adenomatous polyps that can be successfully removed[15]. Treatment for colorectal cancer varies by tumor location and stage at diagnosis. Surgical removal of tumor and nearby lymph nodes is the most common treatment for early stage (stage I or Ⅱ) colorectal cancer. For patients with late-stage disease, chemotherapy alone or in combination with radiation therapy is often given before or after surgery.

## MATERIALS AND METHODS

A systematic review was undertaken to identify randomized controlled trials (RCTs) assessing drugs for the treatment of colorectal cancer and/or adenomatous polyps from www.clinicaltrials.gov. Trials with unknown status were excluded. The following electronic databases were searched for RCTs of clinical effectiveness: MEDLINE, Medline In-Process and EMBASE. A separate literature search was undertaken to identify relevant articles from various online databases such as PubMed. The search was conducted using the following key words and phrases: colon cancer, colorectal cancer, clinical trials and drugs in colon/colorectal cancer.

## RESULTS

The search identified 1663 RCTs of synthetic drugs, alone and/or in combination with biological agents, including on-going, completed and suspended/withdrawn/terminated studies in colorectal cancer.

### *Fluoropyrimidines*

Fluoropyrimidines are anti-metabolite agents widely used in the treatment of various cancers. The principal mechanism of action of fluoropyrimidines has been considered to be the inhibition of thymidylate synthase. The response to 5-fluorouracil (5-FU) as a first line monotherapy is low, so it is given in combination with other cytotoxic agents, like oxaliplatin and irinotecan. 5-FU is commonly given either as a bolus injection with leucovorin (folinic acid) or a continuous infusion. While 5-FU bolus treatment favors RNA damage, continuous treatment with 5-FU favors DNA damage[16]. 5FU when given orally is associated with unpredictable levels in the plasma with extensive interpatient and intrapatient variability[17]. The primary cause of variability in plasma levels is the extensive first pass metabolism of the drug in the gut wall and liver. It was also thought to result from its erratic intestinal absorption due to a difference in concentration of dihydropyrimidine dehydrogenase or DPD (rate-limiting enzyme involved in 5-FU metabolism) in the mucosa. This problem can be overcome by administration of a fluorouracil that is not catabolized by DPD[18] and the coadministration of oral fluorouracil with an inhibitor of DPD[19]. Prodrugs of 5-FU are absorbed intact through the gastrointestinal mucosa and undergo enzymatic activation by one or more enzyme systems to release 5-FU intracellularly.

### *Multi-drug chemotherapy*

The Gruppo Oncologico Nord Ovest (GONO) conducted a phase Ⅲ study involving 244 patients with previously untreated metastatic CRC, comparing fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI). The results of the study demonstrated that the FOLFOXIRI regimen was associated with a significantly higher response rate, progression-free survival and overall survival compared to the FOLFIRI regimen[20]. In a phase Ⅱ study of 44 patients with unresectable metastatic colorectal cancer, neoadjuvant chemotherapy with fluorouracil, leucovorin and oxaliplatin (FOLFOX4) was associated with a high response rate, thus allowing for successful resection of disease in a portion of patients[21].

Oxaliplatin is a diaminocyclohexane platinum compound that acts by impairing DNA replication and induces cellular apoptosis[22,23]. In the National Surgical Adjuvant Breast and Bowel Project C-07 trial involving 2409 patients, oxaliplatin plus intravenous bolus fluo-

rouracil and leucovorin was superior for disease-free survival (HR = 0.82; 95%CI: 0.72-0.93; $P$ = 0.002) when compared to intravenous bolus fluorouracil and leucovorin. Treatment with oxaliplatin significantly improved overall survival in patients younger than 70 (HR = 0.80; 95%CI: 0.68-0.95; $P$ = 0.013), while no positive effect was evident in older patients. In this study, treatment with oxaliplatin in patients > 60 years and females was associated with increased incidence of bowel wall injury[24]. In another trial involving 2246 patients who had undergone curative resection for stage Ⅱ or Ⅲ colon cancer, the rate of disease-free survival at three years was 78.2% (95%CI: 75.6-80.7) in the group given fluorouracil and leucovorin (FL) plus oxaliplatin and 72.9% (95%CI: 70.2-75.7) in the FL group[25]. In the National Cancer Institute-sponsored trial N9741 involving 1508 patients with locally advanced or metastatic colorectal cancer, oxaliplatin plus fluorouracil and leucovorin (FOLFOX4) was found to be more likely to produce a complete response than treatment with irinotecan plus fluorouracil and leucovorin (IFL) or irinotecan plus oxaliplatin (IROX). In addition, oxaliplatin regimens were more likely to result in successful surgical resections[26]. However, severe gastrointestinal toxicity and high mortality rates were observed with combination regimens containing daily bolus 5-FU/LV and oxaliplatin or irinotecan[27].

Irinotecan, a semisynthetic derivative of the natural alkaloid camptothecin, acts by inhibiting the action of topoisomerase I. Although in a previous study combination treatment with irinotecan plus weekly bolus IFL had proven superior to fluorouracil and leucovorin in patients with metastatic CRC[28], it did not result in a statistically significant improvement in either disease-free or overall survival in patients with stage Ⅲ colon cancer[29]. In a phase Ⅰ/Ⅱ study involving 23 patients with metastatic colorectal cancer, treatment with capecitabine plus oxaliplatin and irinotecan was well tolerated and the recommended daily dose of capecitabine was 1400 mg/m$^2$[30].

### Capecitabine

Capecitabine, an oral prodrug of doxifluridine (prodrug of 5-FU), is absorbed through the gastrointestinal mucosa[18]. Oral capecitabine in combination with intravenous irinotecan was an active regimen in a phase Ⅱ study involving 65 patients with previously untreated metastatic colorectal cancer[31]. A Dutch Colorectal Cancer Group (DCCG) phase Ⅲ trial involving 820 patients with advanced colorectal cancer evaluated sequential versus combination chemotherapy with a fluoropyrimidine, irinotecan and oxaliplatin. In the DCCG trial, capecitabine plus irinotecan appeared to be a feasible first-line treatment; however, combination treatment did not significantly improve overall survival compared to the sequential use of cytotoxic drugs in advanced CRC[32,33]. In a Roswell Park Cancer Institute phase Ⅰ/Ⅱ study involving 25 patients with stage Ⅱ or Ⅲ rectal cancer, weekly intravenous oxaliplatin with daily oral capecitabine and radiotherapy was associated with a greater rate of pathological responses and demonstrated to be an effective neoadjuvant combination[34]. Capecitabine when administered in combination with perifosine showed promising clinical activity compared with single agent chemotherapy in a phase Ⅱ RCT involving 381 patients with previously untreated metastatic CRC[35]. Results of a phase Ⅱ study involving 146 patients with Stage T3 or T4 rectal cancer who received preoperative chemoradiotherapy with capecitabine plus oxaliplatin demonstrated significant clinical activity and acceptable toxicity[36]. This regimen is currently being evaluated in a phase Ⅲ randomized trial.

Ftorafur (tegafur) is a prodrug which is coadministered with an inhibitor of DPD (uracil). Coadministration allows for better bioavailability and uniform absorption[37]. In a RCT of 1608 patients, uracil/ftorafur (UFT) was associated with a higher convenience of care; thus, patients perceived adjuvant treatment with UFT plus leucovorin as more convenient than standard Ⅳ treatment with fluorouracil and leucovorin[38]. However, both therapies achieved similar disease-free and overall survival[39]. In the adjuvant treatment of 610 patients with stage Ⅲ colon or rectal cancer, postoperative treatment with UFT was successfully tolerated and improved relapse-free and overall survival in patients with rectal cancer; however, the expected benefits were not observed in colon cancer (HR = 0.89)[40]. In a phase Ⅱ RCT involving 58 elderly patients (range, 75 to 90 years) (range, 75 to 90 years) with measurable disease and no prior chemotherapy for metastatic disease, the UFT plus leucovorin regimen was moderately well tolerated and its activity was comparable to intravenous fluorouracil plus leucovorin, although there was increased GI toxicity in most patients[41,42].

### Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR), a 170 kD transmembrane glycoprotein, is a member of the tyrosine kinase receptor family, ErbB. It is known to be overexpressed in malignancies of multiple tissues, including those of the colon, breast, lung and head and neck[43]. EGFR acts by affecting cell proliferation and survival and therefore has been known to contribute to metastatic progression[44]. Anti-EGFR therapies include monoclonal antibodies to EGFR and tyrosine kinase inhibitors.

In a multicenter phase Ⅱ trial of 74 patients with metastatic colorectal cancer, cetuximab seemed to positively interact with oxaliplatin and capecitabine[45]; however, its correct use in first-line treatment needs to be assessed in phase Ⅲ trials. In another phase Ⅱ study of 344 patients with metastatic colorectal cancer, cetuximab in combination with fluorouracil, leucovorin and oxaliplatin (FOLFOX4) demonstrated a higher overall response rate (46% *vs* 36%)[46] and significantly improved progression-free survival (HR = 0.567, $P$ = 0.0064) compared to FOLFOX4 alone[47]. First line treatment with cetuximab plus fluorouracil, leucovorin and irinotecan was found to reduce the risk of metastatic progression in a Phase Ⅲ study of 1198 patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases[48]. A significant increase in resectability was demonstrated by cetuximab in a phase Ⅱ study of

patients with non-resectable colorectal liver metastases when given in combination with FOLFOX6 or FOLFIRI as neoadjuvant chemotherapy[49]. Moreover, biweekly cetuximab plus irinotecan as second-line treatment has shown significant anti-tumor activity in patients with irinotecan-refractory metastatic CRC[50]. Panitumumab, a humanized monoclonal antibody to EGFR, when given in combination with fluorouracil, leucovorin and irinotecan as first-line treatment, has been well tolerated and showed promising activity in patients with metastatic colorectal cancer[51]. In another phase Ⅱ study, panitumumab monotherapy was found to be active in Japanese patients with chemotherapy-refractory metastatic CRC[52]. Immunogenicity of panitumumab when given in combination with oxaliplatin or irinotecan-based chemotherapy was found to be similar to the immunogenicity observed in the monotherapy setting in a phase Ⅲ study of patients with metastatic CRC[53].

Although the mechanism of action and safety profile of tyrosine kinase inhibitors such as gefitinib, sunitinib and erlotinib warrant further study in combination with standard regimens, early phase Ⅰ/Ⅱ studies showed promising activity and results suggest that they can be safely combined with standard regimens as first-line treatment[54-57].

### *Angiogenesis inhibitors*

Another strategy to control cell proliferation in malignant tissues is the inhibition of new blood vessel formation. As of now, the main focus has been on inhibiting the protein that stimulates blood vessel proliferation, *i.e.*, the vascular endothelial growth factor (VEGF). The role of bevacizumab, a humanized monoclonal antibody against VEGF, is currently being studied in several randomized trials in the United States and Europe. Bevacizumab, when given in combination with oxaliplatin-based adjuvant therapy, did not prolong disease-free survival and demonstrated a detrimental effect in a phase Ⅲ study on patients with resected stage Ⅲ colon cancer[58]. Although an uncommon occurrence, use of bevacizumab in colorectal cancer has been shown to be associated with an increased risk of bowel perforation and fistula formation that occurs in a small proportion of CRC patients[59]; however, high dose bevacizumab when administered with IFL was well tolerated and regarded as a highly active regimen in patients with previously untreated CRC[60]. In a phase Ⅱ study in patients with previously untreated metastatic CRC, bevacizumab in combination with dose-reduced capecitabine and irinotecan was well tolerated and resulted in favorable outcomes[61]. In another randomized phase Ⅱ study of patients with previously untreated metastatic CRC receiving a fluorouracil-based chemotherapy regimen, addition of bevacizumab significantly increased overall and progression-free survival[62,63].

## DISCUSSION

Although during the last decade substantial progress has been made in the diagnosis and successful treatment of colorectal cancer, clinicians and researchers still face challenges in the detection and management of the disease. Further clarification of the pathology of colorectal cancer at the molecular level may improve treatment options. The ultimate goal of scientists and clinicians in the field of cancer research is aimed not only at long-term survival of patients with this condition but also improvement of health-related quality of life. Pharmacological treatment of colorectal cancer has increased the rate of survival. While incorporation of new cytotoxic drugs and targeted agents has widened the treatment options for patients with metastatic colorectal cancer, combination regimens of standard chemotherapeutic drugs with newer agents have led to an increase in overall as well as progression-free survival. These newer combination regimens have contributed to increased rates of resectability in patients with potentially resectable tumors as well as improved health-related quality of life. Technology has improved the precision of radiation delivery to deep seated tumors. In order to gain the most benefit from these newer chemotherapeutic regimens and technologies, it is imperative to incorporate well-designed, multicenter studies with internationally standardized detection protocols in clinical trials with close collaboration between researchers and clinicians to cope with the vast quantity of data generated.

## COMMENTS

### *Background*

This review aims to explore the status of drug regimens, including synthetic drugs alone or in combination with biological agents, available for the treatment of colorectal cancer.

### *Research frontiers*

Several new agents, both synthetic and biological, are currently being studied in clinical trials for their potential as part of the regular drug regimens for treatment of colorectal cancer.

### *Innovations and breakthroughs*

After screening around 2300 randomized controlled trials, the authors found that the newer agents are well-tolerated and their addition to the standard chemotherapeutic drug regimens have led to an improvement in overall as well as progression-free survival in patients with metastatic colorectal cancer.

### *Applications*

This review provides an update on the status of the synthetic drugs and treatment regimens available for the treatment of colorectal cancer.

### *Terminology*

Fluoropyrimidines: Fluoropyrimidines are anti-metabolite agents widely used in the treatment of various cancers that act by inhibiting the enzyme thymidylate synthase. Angiogenesis: Angiogenesis is a physiological process of formation of new blood vessels from pre-existing vessels. EGFR: Epidermal growth factor receptor, a transmembrane glycoprotein, is a member of the tyrosine kinase receptor family, ErbB.

### *Peer review*

This manuscript is a meta-analysis of current pharmacological treatments for colorectal cancer. The data presented are generally good and may be interesting for clinicians involved in this field.

## REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **International Agency for Research on Cancer**. World Cancer Report 2008. Boyle P, LevinI B, editor. Available from:

URL: http: //www.iarc.fr/en/publications/pdfs-online/wcr/2008/index.php
3 **Larsson SC**, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 2006; **119**: 2657-2664 [PMID: 16991129]
4 **Moskal A**, Norat T, Ferrari P, Riboli E. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. *Int J Cancer* 2007; **120**: 664-671 [PMID: 17096321]
5 **Moghaddam AA**, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 2533-2547 [PMID: 18086756]
6 **Wolin KY**, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer* 2009; **100**: 611-616 [PMID: 19209175 DOI: 10.1038/sj.bjc.6604917]
7 **Ferrari P**, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, Tjønneland A, Overvad K, Jensen MK, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Rohrmann S, Linseisen J, Boeing H, Bergmann M, Kontopoulou D, Trichopoulou A, Kassapa C, Masala G, Krogh V, Vineis P, Panico S, Tumino R, van Gils CH, Peeters P, Bueno-de-Mesquita HB, Ocké MC, Skeie G, Lund E, Agudo A, Ardanaz E, López DC, Sanchez MJ, Quirós JR, Amiano P, Berglund G, Manjer J, Palmqvist R, Van Guelpen B, Allen N, Key T, Bingham S, Mazuir M, Boffetta P, Kaaks R, Riboli E. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 2007; **121**: 2065-2072 [PMID: 17640039]
8 **Jemal A**, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, Wingo PA, Howe HL, Anderson RN, Edwards BK. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. *Cancer* 2004; **101**: 3-27 [PMID: 15221985]
9 **Steele SR**, Park GE, Johnson EK, Martin MJ, Stojadinovic A, Maykel JA, Causey MW. The impact of age on colorectal cancer incidence, treatment, and outcomes in an equal-access health care system. *Dis Colon Rectum* 2014; **57**: 303-310 [PMID: 24509451 DOI: 10.1097/DCR.0b013e3182a586e7]
10 **Birt DF**, Phillips GJ. Diet, genes, and microbes: complexities of colon cancer prevention. *Toxicol Pathol* 2014; **42**: 182-188 [PMID: 24129759 DOI: 10.1177/0192623313506791]
11 **Boyle P**, Langman JS. ABC of colorectal cancer: Epidemiology. *BMJ* 2000; **321**: 805-808 [PMID: 11009523]
12 **El Fakir S**, Abda N, Najdi A, Bendahou K, Obtel M, Berraho M, Nejjari C. Cancer screening practices of general practitioners working in the Fez Prefecture health center. *Sante Publique* 2013; **25**: 685-691 [PMID: 24418432]
13 **Tsong WH**, Koh WP, Yuan JM, Wang R, Sun CL, Yu MC. Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer* 2007; **96**: 821-827 [PMID: 17311023]
14 **de Jong AE**, Morreau H, Nagengast FM, Mathus-Vliegen EM, Kleibeuker JH, Griffioen G, Cats A, Vasen HF. Prevalence of adenomas among young individuals at average risk for colorectal cancer. *Am J Gastroenterol* 2005; **100**: 139-143 [PMID: 15654793]
15 **Winawer SJ**, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977-1981 [PMID: 8247072]
16 **Humeniuk R**, Menon LG, Mishra PJ, Gorlick R, Sowers R, Rode W, Pizzorno G, Cheng YC, Kemeny N, Bertino JR, Banerjee D. Decreased levels of UMP kinase as a mechanism of fluoropyrimidine resistance. *Mol Cancer Ther* 2009; **8**: 1037-1044 [PMID: 19383847 DOI: 10.1158/1535-7163.MCT-08-0716]
17 **Fraile RJ**, Baker LH, Buroker TR, Horwitz J, Vaitkevicius VK. Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. *Cancer Res* 1980; **40**: 2223-2228 [PMID: 7388790]
18 **Pentheroudakis G**, Twelves C. The rational development of capecitabine from the laboratory to the clinic. *Anticancer Res* 2002; **22**: 3589-3596 [PMID: 12552961]
19 **Meropol NJ**. Oral fluoropyrimidines in the treatment of colorectal cancer. *Eur J Cancer* 1998; **34**: 1509-1513 [PMID: 9893621]
20 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860]
21 **Alberts SR**, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, Levitt R, Rowland K, Nair S, Sargent DJ, Donohue JH. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005; **23**: 9243-9249 [PMID: 16230673]
22 **Raymond E**, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**: 1053-1071 [PMID: 9834817]
23 **Raymond E**, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998; **25**: 4-12 [PMID: 9609103]
24 **Yothers G**, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, Wolmark N. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011; **29**: 3768-3774 [PMID: 21859995 DOI: 10.1200/JCO.2011.36.4539]
25 **André T**, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**: 2343-2351 [PMID: 15175436]
26 **Dy GK**, Krook JE, Green EM, Sargent DJ, Delaunoit T, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pockaj BA, Sticca RP, Alberts SR, Pitot HC, Goldberg RM. Impact of complete response to chemotherapy on overall survival in advanced colorectal cancer: results from Intergroup N9741. *J Clin Oncol* 2007; **25**: 3469-3474 [PMID: 17687151]
27 **Delaunoit T**, Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Findlay BP, Thomas SP, Salim M, Schaefer PL, Stella PJ, Green E, Mailliard JA. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. *Cancer* 2004; **101**: 2170-2176 [PMID: 15470715]
28 **Saltz LB**, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; **343**: 905-914 [PMID: 11006366]
29 **Van Cutsem E**, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, Topham C, Tabernero J, André T, Sobrero AF, Mini E, Greil R, Di Costanzo F, Collette L, Cisar L, Zhang X, Khayat D, Bokemeyer C, Roth AD, Cunningham D. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009; **27**: 3117-3125 [PMID: 19451425]
30 **von Moos R**, Roth A, Ruhstaller T, Widmer L, Uhlmann C, Cathomas R, Köberle D, Simcock M, Lanz D, Popescu R. Oxaliplatin, irinotecan and capecitabine (OCX) for first-line treatment of advanced/metastatic colorectal cancer: a phase

I trial (SAKK 41/03). *Onkologie* 2010; **33**: 295-299 [PMID: 20523092 DOI: 10.1159/000313598]
31 **Meropol NJ**, Gold PJ, Diasio RB, Andria M, Dhami M, Godfrey T, Kovatich AJ, Lund KA, Mitchell E, Schwarting R. Thymidine phosphorylase expression is associated with response to capecitabine plus irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24**: 4069-4077 [PMID: 16943524]
32 **Koopman M**, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Akkermans-Vogelaar JM, Punt CJ. Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) phase III study. *Ann Oncol* 2006; **17**: 1523-1528 [PMID: 16873425]
33 **Koopman M**, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; **370**: 135-142 [PMID: 17630036]
34 **Fakih MG**, Bullarddunn K, Yang GY, Pendyala L, Toth K, Andrews C, Rustum YM, Ross ME, Levea C, Puthillath A, Park YM, Rajput A. Phase II study of weekly intravenous oxaliplatin combined with oral daily capecitabine and radiotherapy with biologic correlates in neoadjuvant treatment of rectal adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2008; **72**: 650-657 [PMID: 18565686 DOI: 10.1016/j.ijrobp.2008.01.020]
35 **Bendell JC**, Nemunaitis J, Vukelja SJ, Hagenstad C, Campos LT, Hermann RC, Sportelli P, Gardner L, Richards DA. Randomized placebo-controlled phase II trial of perifosine plus capecitabine as second- or third-line therapy in patients with metastatic colorectal cancer. *J Clin Oncol* 2011; **29**: 4394-4400 [PMID: 21969495 DOI: 10.1200/JCO.2011.36.1980]
36 **Wong SJ**, Winter K, Meropol NJ, Anne PR, Kachnic L, Rashid A, Watson JC, Mitchell E, Pollock J, Lee RJ, Haddock M, Erickson BA, Willett CG. Radiation Therapy Oncology Group 0247: a randomized Phase II study of neoadjuvant capecitabine and irinotecan or capecitabine and oxaliplatin with concurrent radiotherapy for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1367-1375 [PMID: 21775070 DOI: 10.1016/j.ijrobp.2011.05.027]
37 **Sulkes A**, Benner SE, Canetta RM. Uracil-ftorafur: an oral fluoropyrimidine active in colorectal cancer. *J Clin Oncol* 1998; **16**: 3461-3475 [PMID: 9779725]
38 **Kopec JA**, Yothers G, Ganz PA, Land SR, Cecchini RS, Wieand HS, Lembersky BC, Wolmark N. Quality of life in operable colon cancer patients receiving oral compared with intravenous chemotherapy: results from National Surgical Adjuvant Breast and Bowel Project Trial C-06. *J Clin Oncol* 2007; **25**: 424-430 [PMID: 17264338]
39 **Lembersky BC**, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol* 2006; **24**: 2059-2064 [PMID: 16648506]
40 **Hamaguchi T**, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y. Final results of randomized trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). *Cancer Chemother Pharmacol* 2011; **67**: 587-596 [PMID: 20490797 DOI: 10.1007/s00280-010-1358-1]
41 **Hochster HS**, Luo W, Popa EC, Lyman BT, Mulcahy M, Beatty PA, Benson AB. Phase II study of uracil-tegafur with leucovorin in elderly (& gt; or = 75 years old) patients with colorectal cancer: ECOG 1299. *J Clin Oncol* 2007; **25**: 5397-5402 [PMID: 18048821]
42 Popa EC, Luo W, Hochster H. A phase II study of orzel (UFT leucovorin) in elderly (=75 years old) patients with colorectal cancer: Results of ECOG 1299. 2005 ASCO Meeting Proceedings. *J Clin Oncol* 2005; **23**: abstr 3608
43 **Spaulding DC**, Spaulding BO. Epidermal growth factor receptor expression and measurement in solid tumors. *Semin Oncol* 2002; **29**: 45-54 [PMID: 12422313]
44 **Baselga J**. Why the epidermal growth factor receptor? The rationale for cancer therapy. *Oncologist* 2002; **7** Suppl 4: 2-8 [PMID: 12202782]
45 **Borner M**, Koeberle D, Von Moos R, Saletti P, Rauch D, Hess V, Trojan A, Helbling D, Pestalozzi B, Caspar C, Ruhstaller T, Roth A, Kappeler A, Dietrich D, Lanz D, Mingrone W. Adding cetuximab to capecitabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the Swiss Group for Clinical Cancer Research SAKK. *Ann Oncol* 2008; **19**: 1288-1292 [PMID: 18349029 DOI: 10.1093/annonc/mdn058]
46 **Bokemeyer C**, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 663-671 [PMID: 19114683 DOI: 10.1200/JCO.2008.20.8397]
47 **Bokemeyer C**, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M, Koralewski P. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011; **22**: 1535-1546 [PMID: 21228335 DOI: 10.1093/annonc/mdq632]
48 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]
49 **Folprecht G**, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczynski C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F, Köhne CH. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; **11**: 38-47 [PMID: 19942479 DOI: 10.1016/S1470-2045(09)70330-4]
50 **Kang MJ**, Hong YS, Kim KP, Kim SY, Baek JY, Ryu MH, Lee JL, Chang HM, Kim MJ, Chang HJ, Kang YK, Kim TW. Biweekly cetuximab plus irinotecan as second-line chemotherapy for patients with irinotecan-refractory and KRAS wild-type metastatic colorectal cancer according to epidermal growth factor receptor expression status. *Invest New Drugs* 2012; **30**: 1607-1613 [PMID: 21706149 DOI: 10.1007/s10637-011-9703-8]
51 **Berlin J**, Posey J, Tchekmedyian S, Hu E, Chan D, Malik I, Yang L, Amado RG, Hecht JR. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. *Clin Colorectal Cancer* 2007; **6**: 427-432 [PMID: 17531105]
52 **Muro K**, Yoshino T, Doi T, Shirao K, Takiuchi H, Hamamoto Y, Watanabe H, Yang BB, Asahi D. A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. *Jpn J Clin Oncol* 2009; **39**: 321-326 [PMID: 19287023 DOI: 10.1093/jjco/hyp016]
53 **Weeraratne D**, Chen A, Pennucci JJ, Wu CY, Zhang K, Wright J, Pérez-Ruixo JJ, Yang BB, Kaliyaperumal A, Gupta S, Swanson SJ, Chirmule N, Starcevic M. Immunogenicity

of panitumumab in combination chemotherapy clinical trials. *BMC Clin Pharmacol* 2011; **11**: 17 [PMID: 22070868 DOI: 10.1186/1472-6904-11-17]

54 **Meyerhardt JA**, Zhu AX, Enzinger PC, Ryan DP, Clark JW, Kulke MH, Earle CC, Vincitore M, Michelini A, Sheehan S, Fuchs CS. Phase II study of capecitabine, oxaliplatin, and erlotinib in previously treated patients with metastastic colorectal cancer. *J Clin Oncol* 2006; **24**: 1892-1897 [PMID: 16622264]

55 **Meyerhardt JA**, Clark JW, Supko JG, Eder JP, Ogino S, Stewart CF, D'Amato F, Dancey J, Enzinger PC, Zhu AX, Ryan DP, Earle CC, Mayer RJ, Michelini A, Kinsella K, Fuchs CS. Phase I study of gefitinib, irinotecan, 5-fluorouracil and leucovorin in patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2007; **60**: 661-670 [PMID: 17216531]

56 **Wolpin BM**, Clark JW, Meyerhardt JA, Earle CC, Ryan DP, Enzinger PC, Zhu AX, Blaszkowsky L, Battu S, Fuchs CS. Phase I study of gefitinib plus FOLFIRI in previously untreated patients with metastatic colorectal cancer. *Clin Colorectal Cancer* 2006; **6**: 208-213 [PMID: 17026790]

57 **Saltz LB**, Rosen LS, Marshall JL, Belt RJ, Hurwitz HI, Eckhardt SG, Bergsland EK, Haller DG, Lockhart AC, Rocha Lima CM, Huang X, DePrimo SE, Chow-Maneval E, Chao RC, Lenz HJ. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol* 2007; **25**: 4793-4799 [PMID: 17947727]

58 **de Gramont A**, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, Cunningham D, Cartwright TH, Hecht JR, Rivera F, Im SA, Bodoky G, Salazar R, Maindrault-Goebel F, Shacham-Shmueli E, Bajetta E, Makrutzki M, Shang A, André T, Hoff PM. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 2012; **13**: 1225-1233 [PMID: 23168362 DOI: 10.1016/S1470-2045(12)70509-0]

59 **Ganapathi AM**, Westmoreland T, Tyler D, Mantyh CR. Bevacizumab-associated fistula formation in postoperative colorectal cancer patients. *J Am Coll Surg* 2012; **214**: 582-588; discussion 588-590 [PMID: 22321523 DOI: 10.1016/j.jamcollsurg.2011.12.030]

60 **Giantonio BJ**, Levy DE, O'dwyer PJ, Meropol NJ, Catalano PJ, Benson AB. A phase II study of high-dose bevacizumab in combination with irinotecan, 5-fluorouracil, leucovorin, as initial therapy for advanced colorectal cancer: results from the Eastern Cooperative Oncology Group study E2200. *Ann Oncol* 2006; **17**: 1399-1403 [PMID: 16873427]

61 **Renouf DJ**, Welch S, Moore MJ, Krzyzanowska MK, Knox J, Feld R, Liu G, MacKay H, Petronis J, Wang L, Chen E. A phase II study of capecitabine, irinotecan, and bevacizumab in patients with previously untreated metastatic colorectal cancer. *Cancer Chemother Pharmacol* 2012; **69**: 1339-1344 [PMID: 22349811 DOI: 10.1007/s00280-012-1843-9]

62 **Kabbinavar FF**, Wallace JF, Holmgren E, Yi J, Cella D, Yost KJ, Hurwitz HI. Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and leucovorin or 5-fluorouracil and leucovorin for metastatic colorectal cancer. *Oncologist* 2008; **13**: 1021-1029 [PMID: 18776057 DOI: 10.1634/theoncologist.2008-0003]

63 **Kabbinavar FF**, Hurwitz HI, Yi J, Sarkar S, Rosen O. Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. *J Clin Oncol* 2009; **27**: 199-205 [PMID: 19064978 DOI: 10.1200/JCO.2008.17.7931]

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SYSTEMATIC REVIEW

# Robotic surgery for rectal cancer: A systematic review of current practice

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## Abstract

**AIM:** To give a comprehensive review of current literature on robotic rectal cancer surgery.

**METHODS:** A systematic review of current literature *via* PubMed and Embase search engines was performed to identify relevant articles from january 2007 to november 2013. The keywords used were: "robotic surgery", "surgical robotics", "laparoscopic computer-assisted surgery", "colectomy" and "rectal resection".

**RESULTS:** After the initial screen of 380 articles, 20 papers were selected for review. A total of 1062 patients (male 64.0%) with a mean age of 61.1 years and body mass index of 24.9 kg/m$^2$ were included in the review. Out of 1062 robotic-assisted operations, 831 (78.2%) anterior and low anterior resections, 132 (12.4%) intersphincteric resection with coloanal anastomosis, 98 (9.3%) abdominoperineal resections and 1 (0.1%) Hartmann's operation were included in the review. Robotic rectal surgery was associated with longer operative time but with comparable oncological results and anastomotic leak rate when compared with laparoscopic rectal surgery.

**CONCLUSION:** Robotic colorectal surgery has continued to evolve to its current state with promising results; feasible surgical option with low conversion rate and comparable short-term oncological results. The challenges faced with robotic surgery are for more high quality studies to justify its cost.



**Key words:** Rectal cancer; Robotics; Minimal invasive surgery; Systematic review; Rectal surgery

**Core tip:** This systematic review summarizes current evidence on the role of robotic surgery for the treatment of rectal cancer. It is a timely article as minimal invasive surgery has proven to benefit patients with colonic cancers but conventional laparoscopic surgery for the treatment for rectal cancer remains controversial due to its steep learning curve. Robotic-assisted surgery has technological advances, which may have the potential to overcome some of the limitations of conventional laparoscopic surgery.

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## INTRODUCTION

Minimally invasive surgery over the past two decades has revolutionised surgical management of colorectal cancers. Despite its initial scepticism, various randomised controlled trials have now demonstrated its short-term and long-term benefits over conventional open surgery in the treatment of colonic cancer such as faster recovery, decreased morbidity and reduced hospital length of stay with comparable oncological result and survival outcome[1-4]. However, laparoscopic colorectal surgery has limitations. These concerns were high-lighted not only by the high conversion rate but also the initially high proportion of circumferential resection margin (CRM) positive rates in the medical research council colorectal cancer (MRC-CLASICC) trial for laparoscopic rectal surgery[5]. The ability to perform total mesorectal excision (TME) laparoscopically requires intensive training. Limitations of conventional laparoscopic surgery include: 2-dimension view, unstable assistant controlled camera, poor ergonomics, straight tip instruments, fulcrum effect and enhanced tremor effect.

Various attempts have been made to seek alternative techniques to overcome some of these limitations. For example, single incision laparoscopic surgery has reduced the number of incisions and ports required for minimal invasive colonic surgery producing a better cosmetic result and reduction in wound pain[6]. Natural orifice translumenal endoscopic surgery (NOTES) aims to eliminate external incision by gaining access using the transvaginal, transgastric, transvesical and transrectal approach, which has been shown to be feasible on animal models[7-9]. However, there are still many hurdles in NOTES (*e.g.*, determining a safe access into the peritoneal cavity, developing a reliable method on the closure of viscotomy, minimising the infection and tumour seedling risk, developing a stable and versatile platform for suturing, managing complications from NOTES and training issues), which need to be addressed before its routine application on Human subjects.

The da Vinci® robot is the first robotic surgical system approved by the United States Food and Drug Administration in 2000. It has evolved from its first generation robot in 1999, the da Vinci standard®, to the current third generation da Vinci-Si HD®, which was launched in 2009. The da Vinci Si-HD® has features such as: (1) dual operating console capability for combined operating and training; (2) enhanced operator-controlled 3D high-definition vision; (3) endowrist™ technology allowing 7 degrees of freedom intra-abdominally; and (4) tremor elimination with improved dexterity. Weber *et al*[10] and Hashizume *et al*[11] first performed colorectal robotics surgery in 2002[10,11]. Prior to this, robotic surgery was already successfully performed on cardiothoracic, urological and general surgical[12-14] patients.

Robotic rectal surgery has potential advantages over conventional laparoscopic rectal surgery: Surgeon motion filter for tremor-free surgery, high definition three-dimensional images, surgeon control camera on a stable platform and increased degree of freedom of the operating instruments. The master and slave system allows improved ergonomics for the surgeon. As the surgical field mainly confines to the pelvic cavity, it allows a stable platform for precision surgery to be performed in a confined space. For the above reasons, robotic technology may be more suitable and may translate more benefits when used for rectal cancers than colonic cancers.

Several review articles have attempted to summarize up-to-date practice and results of robotic colorectal surgery. However some studies included data from both robotic colonic and rectal resections, which may not give a focused overview of the benefits and risks of robotic rectal surgery[15-17]. Other studies included more than one study from the same institute with overlapping period of assessment, which may cause duplication of results[15,18]. Although meta-analysis of robotic rectal resection have been published, studies included were from non-randomised studies[19,20]. Hence we feel that an up-to-date systematic review on robotic rectal surgery is most appropriate and warranted.

This article aims to compare robotic-assisted rectal surgery with conventional laparoscopic rectal surgery for patients with rectal cancers. The current status of robotic rectal surgery focusing on its efficacy, feasibility and oncological safety will also be discussed.

## MATERIALS AND METHODS

Two reviewers independently (T.M. and K.F.) performed a literature search *via* PubMed, Google Scholar, Cochrane Library and Embase database during the period between January 2007 to November 2013. Search terms such as "robotic surgery", "surgical robotics", "laparoscopic computer-assisted surgery" and "rectal resection" were used. Only english language published studies were considered. In addition, the reference lists of selected articles were searched manually. Abstract publications from conferences were excluded from this review. Published data from robotic rectal surgery using the Da Vinci® Surgical System (Intuitive Surgical, Mountain View, Sunnyvale, CA, United States) were only included in order to reduce clinical heterogeneity and the authors recognise that currently it is the only operating system available.

Inclusion criteria for search include randomised and non-randomised controlled trials, comparison studies, case series and case report. The target population consists of patients aged > 18 years with histologically proven rectal cancers.

This systematic review was conducted according to a guidance from the Centre for Reviews and Dissemination[21] and the Cochrane Handbook[22]. The review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement[23]. Selected articles were screened independently by two reviewers for bias using The Cochrane Collaboration's tool for assessing risk of bias[22].

Two reviewers (T.M and K.F.) extracted data from the manuscripts of selected articles including the study de-

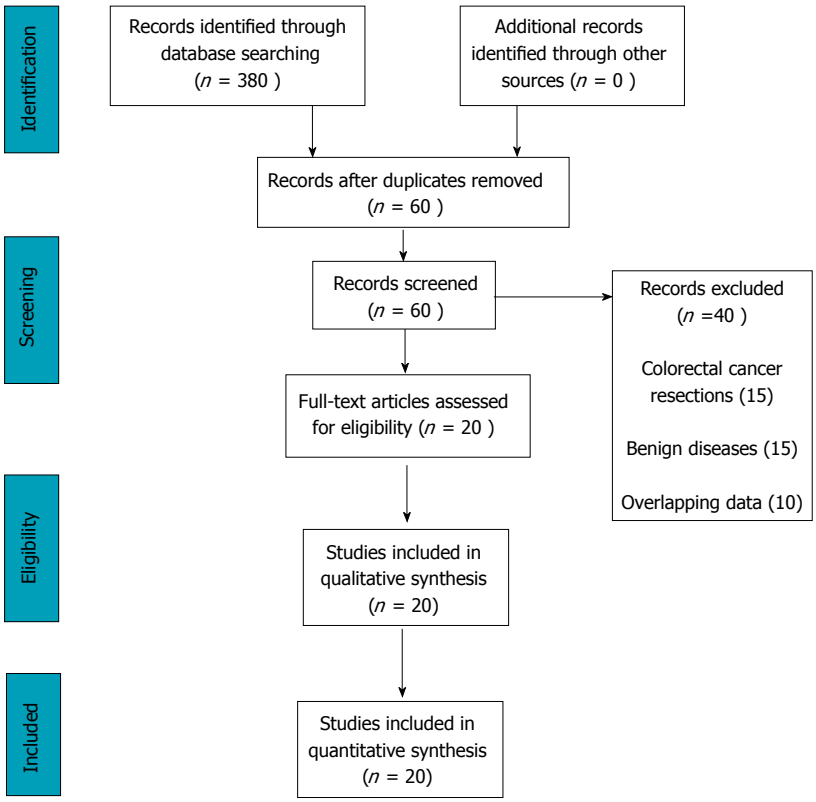


**Figure 1 Systematic review Prisma flow diagram.**

sign, patient demographics, clinical characteristics, site of malignancy, types of intervention, peri-operative details, pathological results, and post-operative outcomes.

## RESULTS

After the initial screen of 380 articles, 60 articles met the predefined inclusion criteria. 15 articles with inseparable data from colonic cancers, 15 articles with benign colorectal disease and 10 articles from the same institutes with overlapping study period were excluded to avoid duplication. 20 studies were selected for review, which comprised of: 13 comparison studies and 7 case series (Figure 1). A large proportion of these studies came from South Korea[24-31] (40.0%) followed by United States[32-36] (25.0%), Italy[37-39] (15.0%), Singapore[40,41] (10.0%) and Turkey[42] (5.0%) and Romania[43] (5.0%) (Table 1).

### *Surgical technique*

There are generally two recognised techniques for Robotic Rectal surgery; the hybrid technique or the total robotic technique. The hybrid technique involves a combination of laparoscopic and robotic techniques to be used in different stages of the operation. The advantage of this method allows a shorter operative time, in particular for rectal cancer operation where the left colon and splenic flexure are mobilised by conventional laparoscopic technique followed by the robotic pelvic dissection[24,27,31,33,34,36-38,40]. Total robotic technique allows the entire operation to the carried out robotically which can either be *via*: (1) single docking technique- which only requires one docking of the robotic cart with repositioning of the robotic arms according to the operative field[25,26,28,39,41,42]; or (2) dual docking technique which requires the operating table to be positioned twice to the desired operative field[30]. Amongst the selected articles, there was 8 Hybrid, 7 Total robotic, 4 combinations of hybrid and total robotic and 1 reverse-hybrid techniques. Study from Park *et al*[35] reported a reverse-hybrid whereby robotic lymphovascular (inferior mesenteric artery) and pelvic dissection is performed before laparoscopic mobilisation of left colon and splenic flexure mobilisation.

### *Clinical outcomes*

**Patient demographics:** A total of 1062 patients were included in the study. The mean age was 61.1 years and 64.0% were male. The average Body mass index BMI was 24.9 kg/m$^2$. Out of 1062 robotic-assisted operations, there were 831 (78.2%) anterior and low anterior resections, 132 (12.4%) intersphincteric resection with coloanal anastomosis, 98 (9.3%) abdominoperineal resections and 1 (0.1%) Hartmann's operation.

**Operative procedures:** The review identified 1062 and 706 robotic and laparoscopic rectal operations respectively (Table 2). Mean operation time in the robotic group was 281.8 min (range, 180.0-528.0) compared with the laparoscopic group 242.6 min (range, 158.1-344.0). 7 out of the 11 comparison studies found robotic rectal surgery to have a significantly longer operative time when

**Table 1 Characteristics of studies on robotic rectal surgery**

| Ref. | Country | Year | Study type | No. of robotic patients | Gender M:F | Mean age (yr) | BMI (kg/m$^2$) | Robotic Technique | Type of operation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | AR/ LAR | ISR | APR | Hartmann's operation |
| Baik *et al*[24] | South Korea | 2009 | Comparison | 56 | 37:19 | 60.0 | 23.4 | Hybrid | 56 | - | - | - |
| Ng *et al*[40] | Singapore | 2009 | Case Series | 8 | 5:3 | 55.0[1] | - | Hybrid | 8 | - | - | - |
| Patriti *et al*[37] | Italy | 2009 | Comparison | 29 | 11:18 | 68.0 | 24.0 | Hybrid | 19 | 5 | 5 | - |
| Bianchi *et al*[38] | Italy | 2010 | Comparison | 25 | 18:7 | 69.0 | 24.6 | Total/hybrid | 18 | - | 7 | - |
| Pigazzi *et al*[32] | United States, Italy | 2010 | Case Series | 143 | 87:56 | 62.0 | 26.5 | Total/hybrid | 80 | 32 | 31 | - |
| Zimmern *et al*[33] | United States | 2010 | Case Series | 58 | 34:24 | 60.9 | 27.5 | Hybrid | 47 | - | 11 | - |
| Baek *et al*[34] | United States | 2011 | Comparison | 41 | 25:16 | 63.6 | 25.7 | Hybrid | 33 | 2 | 6 | - |
| Koh *et al*[41] | Singapore | 2011 | Case Series | 20 | 13:8 | 61.0 | 23.8 | Total | 19 | - | 1 | - |
| Kwak *et al*[25] | South Korea | 2011 | Comparison | 59 | 39:20 | 60.0[1] | 23.3 | Total | 54 | 5 | - | - |
| Leong *et al*[26] | South Korea | 2011 | Case Series | 29 | 23:6 | 61.5[1] | 23.3 | Total | - | 29 | - | - |
| Park *et al*[27] | South Korea | 2011 | Comparison | 52 | 28:24 | 57.3 | 23.7 | Hybrid | 52 | - | - | - |
| Kim *et al*[28] | South Korea | 2012 | Comparison | 100 | 71:29 | 57.0 | 24.0 | Total | 100 | - | - | - |
| Park *et al*[35] | United States | 2012 | Case Series | 30 | 16:14 | 58.0[1] | 27.6 | Reverse-hybrid | 5 | 19 | 6 | - |
| Shin *et al*[29] | South Korea | 2012 | Comparison | 17 | - | - | - | Total/hybrid | 17 | - | - | - |
| Erguner *et al*[42] | Turkey | 2013 | Comparison | 27 | 14:13 | 54.0 | 28.3 | Total | 27 | - | - | - |
| Kang *et al*[30] | South Korea | 2013 | Comparison | 165 | 104:61 | 61.2 | 23.1 | Total | 164 | - | - | 1 |
| Park *et al*[31] | South Korea | 2013 | Comparison | 40 | 28:12 | 57.3 | 23.9 | Hybrid | - | 40 | - | - |
| Stanciulea *et al*[43] | Romania | 2013 | Case Series | 100 | 66:34 | 62.0 | 26.0 | Total/Hybrid | 77 | - | 23 | - |
| D'Annibale *et al*[39] | Italy | 2013 | Comparison | 50 | 30:20 | 66.0 | - | Total | 50[2] | - | - | - |
| Fernandez *et al*[36] | United States | 2013 | Comparison | 13 | 13:0 | 67.9 | - | Hybrid | 5 | - | 8 | - |
| Total | | | | 1062 | 680:382 | 61.1 | 24.9 | | 831 | 132 | 98 | 1 |

[1]median value; [2]TME: Paper did not specify operation. AR: Anterior resection; LAR: Low anterior resection; ISR: Intersphincteric resection; APR: Abdominoperineal resection.

**Table 2 Perioperative and postoperative outcomes**

| Ref. | No. of patients | | Conversion (%) | | Mean OR time (min) | | Blood loss (mL) | | Overall post-op morbidity (%) | | Anastomotic leak (%) | | Erectile dysfunction (%) | | Voiding dysfunction (%) | | LOS (d) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap |
| Baik *et al*[24] | 56 | 57 | 0 | 10.5 | 190.1 | 191.1 | - | - | 10.7 | 19.3 | 1.8 | 7.0 | - | - | - | - | 5.7 | 7.6 |
| Ng *et al*[40] | 8 | NA | 0 | NA | 193.8 | NA | min | NA | 12.5 | NA | 0 | NA | - | - | - | - | 5.0 | NA |
| Patriti *et al*[37] | 29 | 37 | 0 | 18.9 | 202.0 | 208.0 | 137.0 | 127.0 | 26.0 | 32.8 | 6.8 | 2.7 | 5.5 | 16.6 | - | - | 11.9 | 9.6 |
| Bianchi *et al*[38] | 25 | 25 | 0 | 4.0 | 240.0 | 237.0 | - | - | 16.0 | 24.0 | 4.0 | 8.0 | - | - | - | - | 6.5 | 6.0 |
| Pigazzi *et al*[32] | 143 | NA | 4.7 | NA | 297.0 | NA | min | NA | 41.3 | NA | 10.5 | NA | - | - | - | - | 8.3 | NA |
| Zimmern *et al*[33] | 58 | NA | 3.7 | NA | 338.0 | NA | 232.0 | NA | 25.9 | NA | 3.4 | NA | - | - | - | - | 6.0 | NA |
| Baek *et al*[34] | 41 | 41 | 7.3 | 22.0 | 296.0 | 315.0 | - | - | 22.0 | 26.8 | 7.3 | 2.4 | - | - | - | - | 6.5 | 6.6 |
| Koh *et al*[41] | 20 | NA | 0 | NA | 306.0 | NA | - | - | 23.8 | NA | 0 | NA | - | - | - | - | 6.4 | NA |
| Kwak *et al*[25] | 59 | 60 | 0 | 3.4 | 270.0 | 228.0 | - | - | 32.2 | 26.7 | 13.6 | 10.2 | - | - | - | - | - | - |
| Leong *et al*[26] | 29 | NA | 0 | NA | 325.0 | NA | - | - | 37.9 | NA | 10.3 | NA | - | - | - | - | 9.0[1] | NA |
| Park *et al*[27] | 52 | 123 | 0 | 0 | 232.6 | 158.1 | - | - | 19.2 | 12.2 | 9.6 | 5.6 | - | - | 0 | 1.6 | 10.4 | 9.8 |
| Kim *et al*[28] | 100 | NA | 0 | NA | 188.0 | NA | - | - | 11.0 | NA | 2.0 | NA | 36.6 | NA | 6.0 | NA | 7.1 | NA |
| Park *et al*[35] | 30 | NA | 0 | NA | 369.0 | NA | 100.0 | NA | 36.7 | NA | 4.2 | NA | 0 | NA | 0 | NA | 4.0[1] | NA |
| Shin *et al*[29] | 17 | 12 | 0 | 1.0 | 396.5 | 298.8 | 188.8 | 229.2 | 16.7[2] | 20.0[2] | 0 | 0 | - | - | 1.0 | 2.0 | 10.7 | 9.6 |
| Erguner *et al*[42] | 27 | 37 | 0 | 0 | 280.0 | 190.0 | 50.0 | 125.0 | 11.1 | 21.6 | 0 | 8.1 | 0 | 2.7 | - | - | 4.0 | 5.0 |
| Kang *et al*[30] | 165 | 165 | 0.6 | 1.8 | 309.7 | 277.8 | 133.0 | 140.1 | 20.6 | 27.9 | 7.3 | 10.8 | - | - | 2.4 | 4.2 | 10.8 | 13.5 |
| Park *et al*[31] | 40 | 40 | 0 | 0 | 225.0 | 183.7 | 45.7 | 59.2 | 15.0 | 12.5 | 7.5 | 5.0 | A | A | A | A | 10.6 | 11.3 |
| Stanciulea *et al*[43] | 100 | NA | 4.0 | NA | 180.0[1] | NA | 150.0[1] | NA | 30.0 | NA | 9.0 | NA | 3.8 | NA | 7.7 | NA | 10.0[1] | NA |
| D'Annibale *et al*[39] | 50 | 50 | 0 | 12.0 | 270.0[1] | 280.0[1] | - | - | 10.0 | 22.0 | 10.0 | 22.0 | 5.6 | 56.5 | A | A | 8.0[1] | 10.0[1] |
| Fernandez *et al*[36] | 13 | 59 | 8.0 | 17.0 | 528.0[1] | 344.0 | 157.0[1] | 200.0 | - | - | 20.0 | 7.0 | - | - | - | - | 13.0[1] | 8.0[1] |

[1]Median; [2]Overall figures for colorectal resections (not just rectal). OR: Operating room; LOS: Length of stay; A: Erectile and voiding dysfunction was assessed and scored with the International Index of Erectile Function score and/or the International Prostate Symptom score respectively; NA: Not available.

compared to the laparoscopic surgery[25,27,29-31,36,42]. The remaining 4 studies found laparoscopic rectal surgery to be longer but none were statistically significant[24,34,37,39]. Most authors identified the longer time taken with robotic surgery to be due to docking and changing of the robotic arms.

Conversion rates for the robotic group ranges from 0% to 8.0% compared to 1.8% to 22% in the laparoscopic group. Both groups cited reasons for conversion such as obesity, difficulty anatomy, bulky tumour, narrow pelvis, adhesions from previous surgery, equipment malfunction and intra-operative complications (*e.g.*, massive bleeding, rectal perforation). In 10 comparison studies, there were no conversions in the robotic group when

**Table 3 Oncological outcomes**

| Ref. | No. of patients | | Mean follow-up (mths) | | NeoCRT (%) | | Lymph nodes harvested (mean) | | TME grade complete (%) | | CRM +ve (%) | | DRM (cm) | | Robotic Recurrence (%) | 3 yr Robotic Survival (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | Rob | Lap | | DS | OS |
| Baik *et al*[24] | 56 | 57 | 14.3 (both) | | 8.9 | 12.2 | 18.4 | 18.7 | 92.9 | 75.4 | 7.1 | 8.8 | 4.0 | 3.6 | - | - | 7.6 |
| Ng *et al*[40] | 8 | NA | 1.5 | NA | - | - | 12.9 | NA | - | - | 0 | NA | > 2.0 | NA | - | - | NA |
| Patriti *et al*[37] | 29 | 37 | 29.2 | 18.7 | 24.1 | 5.4 | 10.3 | 11.2 | - | - | 0 | 0 | 2.1 | 4.5 | None | 100.0 | 9.6 |
| Bianchi *et al*[38] | 25 | 25 | 10.0 (both) | | 52.0 | 40.0 | 19.7 | 18.2 | - | - | 0 | 4.0 | 2.0 | 2.0 | None | - | 6.0 |
| Pigazzi *et al*[32] | 143 | NA | 17.4 | NA | 65.1 | - | 14.1 | NA | - | - | 0.7 | NA | 2.9 | NA | 1.5 | 77.6 | NA |
| Zimmern *et al*[33] | 58 | NA | 13.2 | NA | 39.7 | NA | 14.1 | NA | - | - | 0 | NA | - | - | 5.2 | - | NA |
| Baek *et al*[34] | 41 | 41 | - | - | 80.5 | 43.9 | 13.1 | 16.2 | - | - | 2.4 | 4.9 | 3.6 | 3.8 | - | - | 6.6 |
| Koh *et al*[41] | 20 | NA | - | - | 9.5 | NA | 17.8 | NA | - | - | 5.3 | - | 3.7 | - | - | - | NA |
| Kwak *et al*[25] | 59 | 60 | 17.0 | 13.0 | 13.6 | 8.5 | 20.0 | 21.0 | - | - | 1.7 | 0 | - | - | - | - | - |
| Leong *et al*[26] | 29 | NA | - | - | 37.9 | NA | 16.0 | NA | - | - | 7.0 | NA | 0.8 | NA | - | - | NA |
| Park *et al*[27] | 52 | 123 | - | - | 23.1 | 8.1 | 19.4 | 15.9 | - | - | 1.9 | 2.4 | 2.8 | 3.2 | - | - | 9.8 |
| Kim *et al*[28] | 100 | NA | 24.0 | NA | 32.0 | NA | 20.0 | NA | - | - | 1.0 | NA | 2.7 | NA | - | - | NA |
| Park *et al*[35] | 30 | NA | - | - | 66.7 | NA | 20.0 | NA | 83.3 | NA | 0 | NA | - | - | - | - | NA |
| Shin *et al*[29] | 17 | 12 | - | - | - | - | 18.4[2] | 15.9[2] | - | - | - | - | - | - | - | - | 9.6 |
| Erguner *et al*[42] | 27 | 37 | - | - | 14.8 | 21.6 | 16.0 | 16.0 | 100.0 | 70.6 | 0 | 0 | 4.0 | 4.0 | - | - | 5.0 |
| Kang *et al*[30] | 165 | 165 | 22.4[1] (both) | | 23.6 | 21.8 | 15.0 | 15.6 | - | - | 4.2 | 6.7 | 1.9 | 2.0 | - | - | - |
| Park *et al*[31] | 40 | 40 | 6.0 | 6.0 | 80.0 | 50 | 12.9 | 13.3 | - | - | 7.5 | 5.0 | 1.4 | 1.3 | - | - | - |
| Stanciulea *et al*[43] | 100 | NA | 24.0[1] | NA | 58.0 | NA | 14.0[1] | NA | - | - | 1.0 | - | 3.0 | - | 2.0 | NA | 90.0 |
| D'Annibale *et al*[39] | 50 | 50 | 12.0 | 12.0 | 68.0 | 56.0 | 16.5 | 13.8 | - | - | 0 | 0 | 3.0 | 3.0 | - | - | - |
| Fernandez *et al*[36] | 13 | 59 | - | - | 77.0 | 54.0 | 16.0 | 20.0 | 69.0 | 73.0 | 0 | 2.0 | - | - | - | - | - |

[1]Median; [2]Overall figures for colorectal resections (not just rectal). Rob: Robotic-assisted surgery; Lap: Conventional laparoscopic surgery; NeoCRT: Neo-adjuvant chemoradiotherapy; TME: Total mesorectal excision; CRM: Circumferential resection margin; DRM: Distal resection margin; DS: Disease free survival; NA: Not available.

compared to the laparoscopic group[24,25,27-29,31,37-39,42].

Intraoperative blood loss was compared in 6 studies in this review[29-31,36,37,42]. Five studies found the laparoscopic group had more blood loss when compared to the robotic group but only two of these studies were found to be statistically significant[29,42].

### Post-operative outcome

The overall post-operative morbidity in both groups was found to be similar with median of 20.0% (range 10.7%-41.3%) in the robotic group compared with 22.3% (range 12.2%-32.8%) in the laparoscopic group (Table 2). These include anastomotic leak, chest infection, urinary tract infection, postoperative ileus, urinary retention, DVT, wound dehiscence and intra-abdominal collection. Anastomotic leak was also assessed separately as it carries a significant morbidity and mortality. It has been postulated that with the advanced technology, robotic assisted surgery may reduce its incidence with better operative vision and a more precise dissection technique. In this review, median anastomotic leak rate was found to be similar with mean of 6.4% (range, 0%-20.0%) in robotic group compared to 7.4% (range, 0%-22.0%) in laparoscopic group. Preservation of the pelvic autonomic nerves during pelvic surgery is important in order to prevent erectile and voiding dysfunctions. In this review, 7 studies[28,31,35,37,39,42,43] assessed erectile dysfunction and found the incidence of complication ranged from 0% to 36.6% in the robotic group compared to 2.7% to 56.5% in the laparoscopic group. Four of these papers were comparative studies, where Patriti *et al*[37] found a higher proportion of erectile dysfunction in the laparoscopic group (16.6% *vs* 5.5% respectively) but this was not significant. Two papers reported sexual and voiding function using the International Index of Erectile Function score (IIEF-5) and the International Prostate Symptom score respectively[31,39]. In the study by Park *et al*[31], patients were asked to complete the questionnaires preoperatively, 3 and 6 mo postoperatively. In terms of erectile dysfunction, the laparoscopic group had a significantly higher incidence than the robotic group. The robotic group also shown a faster rate of improvement when assessed at 3 and 6 mo. However there was no difference found in terms of voiding function. D'Annibale *et al*[39] reported 1-year follow-up assessment of erectile dysfunction and found a significant proportion of sexually active patients in the laparoscopic group (13 out of 23; 56.5%) reported erectile dysfunction when compared with the robotic group (1 out of 17; 5.6%). However this result may need to be interpreted with caution as there were a high non-participation rate in the 30 patients selected in each group (laparoscopic group = 23.3% *vs* robotic assisted group = 40.0%).

Length of stay found the median stay of 7.1 d (range 4-13.0 d) in the robotic procedures compared with median of 9.6 d (range 5-13.5 d) performed by the laparoscopic procedures. Only 2 out of 11 studies showed significantly shorter hospital stay in the robotic group[24,30].

### Oncological outcome

Robotic rectal surgery achieved comparable results with laparoscopic surgery in terms of percentage of CRM positivity, mean distal resection margin (Table 3). All studies documented that rectal cancer patients who

**Table 4 Cost of Robotic rectal surgery**

| Ref. | Country | Year | Study type | No. of rectal cancer patients | | | Average total hospitalisation cost (United States $) | | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Robotic | Laparoscopic | Open | Robotic | Laparoscopic | Open | |
| Baik *et al*[24] | United States | 2011 | Comparison | 41 | 41 | - | 83915 | 62601 | - | 0.092 |
| Kwak *et al*[25] | South Korea | 2011 | Comparison | 59 | 59 | - | Robotic x3 Laparoscopic cost | | NA | NA |
| Leong *et al*[26] | South Korea | 2011 | Case Series | 29 | - | - | Robotic x3 Laparoscopic cost | | - | - |
| Kim *et al*[28] | South Korea | 2012 | Comparison | 100 | - | 100 | 12-15000 | 5000 | - | - |

Rob: Robotic-assisted surgery; Lap: Conventional laparoscopic surgery; NA: Not available.

were preoperatively diagnosed to have T3 or T4 tumour +/- lymph node invasion were given neoadjuvant chemoradiotherapy. Percentage of patients who received neoadjuvant chemoradiotherapy was documented in 11 comparative studies, varying from 8.9% to 80.5% in the robotic group compared with 5.4% to 56.0% in the laparoscopic group[24,25,30,31,34,36-39,42]. The quality of the TME was also assessed. Two studies comparing TME quality after robotic and laparoscopic dissection found the former to be significantly superior[24,42] whereas the study by Fernandez *et al*[36] found the laparoscopic group to be superior but this was not statistically significant. The studies showed there was minimal difference between the number of lymph nodes retrieved with robotic assisted (range, 10.3 to 20.0) and laparoscopic rectal resection (range, 11.2 to 21). Recurrence of cancer from 6 studies ranged from no recorded recurrence to 5.5%. In a study by Kwak *et al*[25], there were no significant differences found between the robotic-assisted group and laparoscopy assisted group in terms of loco-regional recurrence, distant metastasis and total recurrence. Three-year disease free survival ranges from 77.6% to 100% with overall survival between 90% to 97%. The study by Kang *et al*[30] found no difference in 2-year survival between robotic assisted group (83.5%), laparoscopy group (81.9%) and open surgery (79.7%) ($P = 0.855$).

### Learning curve

Within the selected articles, there were only 3 papers which looked into learning curve for robotic rectal surgery[31,32,39]. Pigazzi *et al*[32] found operative time decreased significantly after 20 cases. With intersphincteric resections, Park *et al*[31] found the learning curve plateau after 17 cases by using the moving average method. In one paper the author's opinion was that the numbers of cases require for learning can be as low as two cases if performed by an already skilled laparoscopic surgeon[38]. D'Annibale *et al*[39] found mean operative time decreased from 312.5 min in the first 25 procedures to 238.2 min in the last 10 procedures ($P = 0.002$). Following cusum analysis, this study showed that learning curve in robot group was achieved after 22 cases[39].

### Cost

A review of the selected articles found four studies, which looked into the cost of robotic surgery (Table 4). In two of the studies, the cost of robotic rectal surgery was estimated to be three times more expensive than laparoscopic rectal surgery[25,26]. The remaining two studies found also robotic rectal surgery to be more expensive when compared to laparoscopic and open rectal surgery but the figures in these studies did not show statistical significance[28,34]. Authors also highlighted the fact that the provision of health is different between countries such as in South Korea.

## DISCUSSION

This systematic review suggests robotic-assisted surgery to be feasible and safe. We have selected 20 articles for review out of 380 articles, which met our selection criteria. We deliberately set the inclusion period to be within the past 6 years as it will exclude small case series where authors may not have attained the desired learning curve and also a more recent data-set may give a more accurate reflection of the current practice and capability of the da Vinci robotic systems.

Previous systematic reviews have reported similar outcomes to our study[15,16,18]. They concluded robotic-assisted rectal surgery to be feasible and safe. Similar to our review, conversion rates tend to be lower in the robotic-assisted group when compared to the laparoscopic group. This may have important implications as converted cases are associated with greater morbidity and tumour recurrence[3]. Many authors identified lower conversion rates in the robotic group to be associated with superior visualisation, better exposure and endowrist™ technology.

In our review we found overall complication rates between robotic and laparoscopic group to be similar. These perceived advantages also did not translate to lower anastomotic leaks in the robotic group, which may be due to the fact that the aetiology for anastomotic leak is multifactorial (*e.g.*, patient nutrition, underlying comorbidity, neoadjuvant chemoradiotherapy, surgical technique, blood supply, tension to anastomosis, *etc.*) and therefore an adequately powered study is required. Intraoperative blood loss only resulted in two studies, which found laparoscopic group to have a statistically greater blood loss than the robotic group[29,42].

The short-term oncological outcome using conventional surgical yardsticks for rectal cancer dissection seems to be comparable between the two groups. CRM and distal resection margins are comparable to laparoscopic group. Quality of the TME dissection is important as breach of the TME envelope may increase local and distant recurrence. In this review, only three studies as-

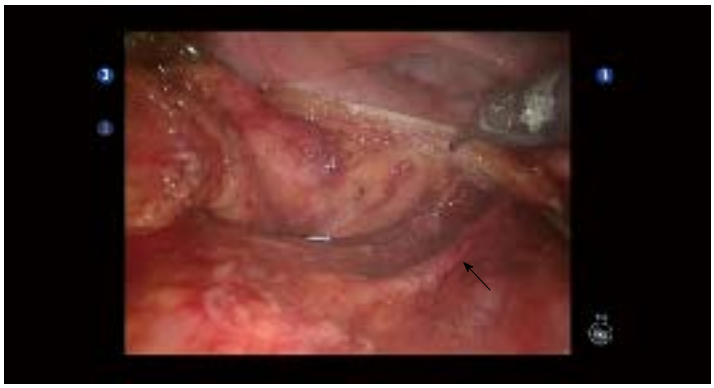

**Figure 2 Robotic pelvic dissection.** High definition 3-D view of the pelvis with the right hypogastric nerve (arrow) identified and protected.

sessed the quality of the TME specimen macroscopically with two comparative studies found robotic dissection to be superior. With emerging data favouring TME *via* minimal invasive approach over open surgery[5,44], robotic surgery may offer additional advantage.

Traditionally long operative times are related with increased morbidity, which is likely to be related to the difficulty of the operation[45]. Robotic surgery has been found to have a longer operative time when compared to laparoscopic or open rectal surgery. Attempts have been made to reduce robotic operating time by adopting the hybrid approach. However this will require the surgeon to be skilled at both robotic as well as conventional laparoscopic surgery. Also the perceived advantage of robotic surgery may be lost during inferior mesenteric artery dissection, which may increase the chance of nerve damage as well as additional cost of laparoscopic instruments. Prolonged operative times are most likely to be related to technical aspects of the operation (time taken to dock and redock the robot as well as changing of robotic arms) rather than the operative difficulty. Indeed the overall complication rates between the robotic and the laparoscopic groups have been shown to be similar in this review, which further supports the theory that longer robotic operative time may not necessarily increase operative morbidity.

Cost of robotic surgery remained to be an important issue. Most papers identified the cost of the robot to be around United States $1.65 to 2 million, disposable robotic instruments costing United States $2000 each as well as the yearly maintenance cost United States $150000[24]. In this review article, it was not possible to include cost-effectiveness analysis studies. Baek *et al*[34] highlighted the fact that caution needs to be taken when interpreting costs as it may differ significantly between hospitals. Different healthcare system between countries will also have an impact on costs. However, maximising the use of the robot by different surgical specialties within the hospital might make savings to the overall running costs.

Identification and preservation of the pelvic autonomic nerves may be better with robotic surgery due to high definition 3-D image, tremor free surgery, surgeon operated camera platform and endowrist™ technology. Common sites of potential pelvic nerve damage leading to sexual dysfunction are: (1) superior hypogastric plexus, leading to ejaculation dysfunction on male patients and impaired lubrication in females; and (2) pelvic splanchnic nerves or the pelvic plexus- leading to erectile dysfunction in men. These perceived advantages may translate to decreased incidence of erectile dysfunction in male patients and urinary dysfunction as the CLASICC trial reported a 41% sexual dysfunction in men after laparoscopic rectal surgery when compared with 23% in the open rectal surgery group[46] (Figure 2). However, in this review although there were some encouraging results to suggest that robotic-assisted surgery is superior to conventional laparoscopic surgery in preventing sexual or urinary dysfunction, the evidence is not entirely clear due to high non-participation rates and possible type II error. Kim *et al*[47] also reported similar results where although the robotic-assisted group reported earlier recovery of erectile, sexual desire and urinary function when compared with the laparoscopic group, there was no difference in long-term follow-up.

In this review, we were unable to draw strong conclusion on the learning curve required for robotic surgery. However the range of 17-25 cases of robotic-assisted rectal surgery from experienced surgeons skilled at both open and laparoscopic surgery are quoted as the number required to achieve competency. The cases selected were very heterogeneous; only few studies used recognised method on assessing learning curve and one of studies were from expert's comment.

Although the da Vinci® robotic platform has produced promising results with at least comparable benefits to laparoscopic colorectal surgery, good quality studies are still required to demonstrate its benefits. The ROLARR (RObotic versus LAparoscopic Resection for Rectal cancer) study is a multicentre international randomised control trial with the primary aim to assess technical ease of robotic rectal operations. The secondary aims are to assess the quality of life, cost-effectiveness analysis and oncological outcome on disease-free and overall survival and local recurrence at 3-year follow-up. The study began recruiting in february 2011 and therefore results will not be available for sometime[48]. Other Robotic rectal surgical clinical trials currently registered on www.clinicaltrials.gov include centres from South Korea[49,50], China[51] and Hong Kong[52].

In summary, from this systematic review, in the au-

thors' opinion we can draw conclusions on the following: (1) robotic-assisted rectal surgery is feasible and safe; (2) it has a lower conversion rate when compared to laparoscopic group; (3) intra-operative blood loss resulted significantly less in the robotic group in 2 of the comparison studies; (4) postoperative morbidity and long-term voiding and sexual functions remain similar in both groups; (5) quality of the TME dissection is significantly better in some studies but nevertheless there were no significant differences found in short-term of oncological outcomes in both groups; and (6) robotic-assisted is more expensive than laparoscopic surgery. Hence the current challenges will be to justify the benefits of robotic rectal surgery over high costs.

## COMMENTS

### Background

The incidence of rectal cancers is increasing owing to the elderly population, westernised lifestyle and other environmental factors. Prognosis in rectal cancer can be related to the quality of surgery such as mesorectal integrity, margin status, and adequate lymph node dissection. Laparoscopic has been proven to reduce hospital stay, less pain and less bleeding but its role in rectal cancer surgery remains controversial due to its steep learning-curve. Da Vinci robotic-assisted rectal cancer surgery may be an effective tool but its effectiveness over laparoscopic surgery is unclear.

### Research frontiers

Robotic-assisted rectal cancer surgery has technical advantages over conventional laparoscopic method such as tremor free surgery, high definition 3-D vision, stable platform and surgeon-control camera. These technological advances seem to be ideally suited for rectal cancer surgery as it may minimize inadvertent pelvic neurovascular injury and achieve good oncological results.

### Innovations and breakthroughs

Conventional laparoscopic rectal surgery has been known to have a steep learning curve owing to 2-Dimensional view, assistant navigated camera and instruments with limited freedom of movement. Robotic-assisted rectal surgery has overcome some of these limitations with 3-Dimensional view, stable platform, surgeon-controlled camera and tremor-free surgery. However further high quality research is required see whether these advances can be translated to benefit patient care.

### Applications

Readers will be able to have an unbiased view on the pros and cons of robotic-assisted rectal surgery. This systematic review has identified current evidence is based on case series and comparative reports and that has demonstrated robotic-assisted rectal surgery is feasible and safe. However as these studies demonstrated potential benefits of robotic surgery are not yet proven and that whether the high cost justify these benefits is still under debate.

### Terminology

Laparoscopic surgery and robotic-assisted surgery are a form of minimal invasive surgery which has advantages over open operations such as less blood loss, faster recovery, less complications and better cosmetic results.

### Peer review

This manuscript is an interesting and well done systematic review on robotic rectal surgery. Authors reported data according to the Prisma guidelines for systematic reviews and meta-analyses. This paper deserves publication.

## REFERENCES


1 **Lacy AM**, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, Pique JM. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008; **248**: 1-7 [PMID: 18580199 DOI: 10.1097/SLA.0b013e31816a9d65]

2 **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]

3 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. 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]

4 **Buunen M**, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy A, Bonjer HJ. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009; **10**: 44-52 [PMID: 19071061 DOI: 10.1016/S1470-2045(08)70310-3]

5 **Jayne DG**, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, Heath RM, Brown JM. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; **25**: 3061-3068 [PMID: 17634484 DOI: 10.1200/JCO.2006.09.7758]

6 **Gaujoux S**, Bretagnol F, Ferron M, Panis Y. Single-incision laparoscopic colonic surgery. *Colorectal Dis* 2011; **13**: 1066-1071 [PMID: 21848732 DOI: 10.1111/j.1463-1318.2010.02404.x]

7 **Kalloo AN**, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, Magee CA, Kantsevoy SV. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; **60**: 114-117 [PMID: 15229442]

8 **Swain P**. Nephrectomy and natural orifice translumenal endoscopy (NOTES): transvaginal, transgastric, transrectal, and transvesical approaches. *J Endourol* 2008; **22**: 811-818 [PMID: 18419222 DOI: 10.1089/end.2007.9831]

9 **Park PO**, Bergström M, Ikeda K, Fritscher-Ravens A, Swain P. Experimental studies of transgastric gallbladder surgery: cholecystectomy and cholecystogastric anastomosis (videos). *Gastrointest Endosc* 2005; **61**: 601-606 [PMID: 15812420]

10 **Weber PA**, Merola S, Wasielewski A, Ballantyne GH. Telerobotic-assisted laparoscopic right and sigmoid colectomies for benign disease. *Dis Colon Rectum* 2002; **45**: 1689-1694; discussion 1689-1694; [PMID: 12473897 DOI: 10.1097/01.DCR.0000037657.78153.A8]

11 **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]

12 **Loulmet D**, Carpentier A, d'Attellis N, Berrebi A, Cardon C, Ponzio O, Aupècle B, Relland JY. Endoscopic coronary artery bypass grafting with the aid of robotic assisted instruments. *J Thorac Cardiovasc Surg* 1999; **118**: 4-10 [PMID: 10384177]

13 **Menon M**, Tewari A, Baize B, Guillonneau B, Vallancien G. Prospective comparison of radical retropubic prostatectomy and robot-assisted anatomic prostatectomy: the Vattikuti Urology Institute experience. *Urology* 2002; **60**: 864-868 [PMID: 12429317]

14 **Cadière GB**, Himpens J, Vertruyen M, Bruyns J, Germay O, Leman G, Izizaw R. Evaluation of telesurgical (robotic) NISSEN fundoplication. *Surg Endosc* 2001; **15**: 918-923 [PMID: 11605106 DOI: 10.1007/s004640000217]

15 **Mirnezami AH**, Mirnezami R, Venkatasubramaniam AK, Chandrakumaran K, Cecil TD, Moran BJ. Robotic colorectal surgery: hype or new hope? A systematic review of robotics in colorectal surgery. *Colorectal Dis* 2010; **12**: 1084-1093 [PMID: 19594601 DOI: 10.1111/j.1463-1318.2009.01999.x]

16 **Kanji A**, Gill RS, Shi X, Birch DW, Karmali S. Robotic-assisted colon and rectal surgery: a systematic review. *Int J Med Robot* 2011; **7**: 401-407 [PMID: 22113977 DOI: 10.1002/rcs.432]

17 **Pucci MJ**, Beekley AC. Use of Robotics in Colon and Rec-

tal Surgery. *Clin Colon Rectal Surg* 2013; **26**: 39-46 [PMID: 24436647 DOI: 10.1055/s-0033-1333660]
18 **Scarpinata R**, Aly EH. Does robotic rectal cancer surgery offer improved early postoperative outcomes? *Dis Colon Rectum* 2013; **56**: 253-262 [PMID: 23303155 DOI: 10.1097/DCR.0b013e3182694595]
19 **Lin S**, Jiang HG, Chen ZH, Zhou SY, Liu XS, Yu JR. Meta-analysis of robotic and laparoscopic surgery for treatment of rectal cancer. *World J Gastroenterol* 2011; **17**: 5214-5220 [PMID: 22215947 DOI: 10.3748/wjg.v17.i47.5214]
20 **Trastulli S**, Farinella E, Cirocchi R, Cavaliere D, Avenia N, Sciannameo F, Gullà N, Noya G, Boselli C. Robotic resection compared with laparoscopic rectal resection for cancer: systematic review and meta-analysis of short-term outcome. *Colorectal Dis* 2012; **14**: e134-e156 [PMID: 22151033 DOI: 10.1111/j.1463-1318.2011.02907.x]
21 **Centre for Reviews and Dissemination (CRD).** Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. York: University of York, 2009: 292
22 **JPT H**, S G. Cochrane Handbook for Systematic Reviews on Interventions, version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011
23 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: 19622552 DOI: 10.1136/bmj.b2700]
24 **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]
25 **Kwak JM**, Kim SH, Kim J, Son DN, Baek SJ, Cho JS. Robotic vs laparoscopic resection of rectal cancer: short-term outcomes of a case-control study. *Dis Colon Rectum* 2011; **54**: 151-156 [PMID: 21228661 DOI: 10.1007/DCR.0b013e3181fec4fd]
26 **Leong QM**, Son DN, Cho JS, Baek SJ, Kwak JM, Amar AH, Kim SH. Robot-assisted intersphincteric resection for low rectal cancer: technique and short-term outcome for 29 consecutive patients. *Surg Endosc* 2011; **25**: 2987-2992 [PMID: 21484533 DOI: 10.1007/s00464-011-1657-6]
27 **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]
28 **Kim JC**, Yang SS, Jang TY, Kwak JY, Yun MJ, Lim SB. Open versus robot-assisted sphincter-saving operations in rectal cancer patients: techniques and comparison of outcomes between groups of 100 matched patients. *Int J Med Robot* 2012; **8**: 468-475 [PMID: 22893623 DOI: 10.1002/rcs.1452]
29 **Shin JY**. Comparison of Short-term Surgical Outcomes between a Robotic Colectomy and a Laparoscopic Colectomy during Early Experience. *J Korean Soc Coloproctol* 2012; **28**: 19-26 [PMID: 22413078 DOI: 10.3393/jksc.2012.28.1.19]
30 **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]
31 **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]
32 **Pigazzi A**, Luca F, Patriti A, Valvo M, Ceccarelli G, Casciola L, Biffi R, Garcia-Aguilar J, Baek JH. Multicentric study on robotic tumor-specific mesorectal excision for the treatment of rectal cancer. *Ann Surg Oncol* 2010; **17**: 1614-1620 [PMID: 20087780 DOI: 10.1245/s10434-010-0909-3]
33 **Zimmern A**, Prasad L, Desouza A, Marecik S, Park J, Abcarian H. Robotic colon and rectal surgery: a series of 131 cases. *World J Surg* 2010; **34**: 1954-1958 [PMID: 20458584 DOI: 10.1007/s00268-010-0591-4]
34 **Baek JH**, Pastor C, Pigazzi A. Robotic and laparoscopic total mesorectal excision for rectal cancer: a case-matched study. *Surg Endosc* 2011; **25**: 521-525 [PMID: 20607559 DOI: 10.1007/s00464-010-1204-x]
35 **Park IJ**, You YN, Schlette E, Nguyen S, Skibber JM, Rodriguez-Bigas MA, Chang GJ. Reverse-hybrid robotic mesorectal excision for rectal cancer. *Dis Colon Rectum* 2012; **55**: 228-233 [PMID: 22228169 DOI: 10.1097/DCR.0b013e31823c0bd2]
36 **Fernandez R**, Anaya DA, Li LT, Orcutt ST, Balentine CJ, Awad SA, Berger DH, Albo DA, Artinyan A. Laparoscopic versus robotic rectal resection for rectal cancer in a veteran population. *Am J Surg* 2013; **206**: 509-517 [PMID: 23809672 DOI: 10.1016/j.amjsurg.2013.01.036]
37 **Patriti A**, Ceccarelli G, Bartoli A, Spaziani A, Biancafarina A, Casciola L. Short- and medium-term outcome of robot-assisted and traditional laparoscopic rectal resection. *JSLS* 2009; **13**: 176-183 [PMID: 19660212]
38 **Bianchi PP**, Ceriani C, Locatelli A, Spinoglio G, Zampino MG, Sonzogni A, Crosta C, Andreoni B. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a comparative analysis of oncological safety and short-term outcomes. *Surg Endosc* 2010; **24**: 2888-2894 [PMID: 20526623 DOI: 10.1007/s00464-010-1134-7]
39 **D'Annibale A**, Morpurgo E, Fiscon V, Trevisan P, Sovernigo G, Orsini C, Guidolin D. Robotic and laparoscopic surgery for treatment of colorectal diseases. *Dis Colon Rectum* 2004; **47**: 2162-2168 [PMID: 15657669 DOI: 10.1007/s10350-004-0711-z]
40 **Ng KH**, Lim YK, Ho KS, Ooi BS, Eu KW. Robotic-assisted surgery for low rectal dissection: from better views to better outcome. *Singapore Med J* 2009; **50**: 763-767 [PMID: 19710972]
41 **Koh DC**, Tsang CB, Kim SH. A new application of the four-arm standard da Vinci® surgical system: totally robotic-assisted left-sided colon or rectal resection. *Surg Endosc* 2011; **25**: 1945-1952 [PMID: 21136096 DOI: 10.1007/s00464-010-1492-1]
42 **Erguner I**, Aytac E, Boler DE, Atalar B, Baca B, Karahasanoglu T, Hamzaoglu I, Uras C. What have we gained by performing robotic rectal resection? Evaluation of 64 consecutive patients who underwent laparoscopic or robotic low anterior resection for rectal adenocarcinoma. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 316-319 [PMID: 23752000 DOI: 10.1097/SLE.0b013e31828e3697]
43 **Stănciulea O**, Eftimie M, David L, Tomulescu V, Vasilescu C, Popescu I. Robotic surgery for rectal cancer: a single center experience of 100 consecutive cases. *Chirurgia* (Bucur) 2013; **108**: 143-151 [PMID: 23618561]
44 **van der Pas MH**, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013; **14**: 210-218 [PMID: 23395398 DOI: 10.1016/S1470-2045(13)70016-0]
45 **Kurmann A**, Vorburger SA, Candinas D, Beldi G. Operation time and body mass index are significant risk factors for surgical site infection in laparoscopic sigmoid resection: a multicenter study. *Surg Endosc* 2011; **25**: 3531-3534 [PMID: 21638185 DOI: 10.1007/s00464-011-1753-7]
46 **Jayne DG**, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. *Br J Surg* 2005; **92**: 1124-1132 [PMID: 15997446 DOI: 10.1002/bjs.4989]
47 **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]
48 **Collinson FJ**, Jayne DG, Pigazzi A, Tsang C, Barrie JM, Edlin R, Garbett C, Guillou P, Holloway I, Howard H, Marshall H, McCabe C, Pavitt S, Quirke P, Rivers CS, Brown JM. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. *Int J Colorectal Dis* 2012; **27**: 233-241 [PMID: 21912876 DOI: 10.1007/s00384-011-1313-6]
49 **Choi GS**. A Trial to Assess Robot-assisted Surgery and Laparoscopy-assisted Surgery in Patients with Mid or Low Rectal Cancer (COLRAR). ClinicalTrails.gov identifier: NCT01423214. Secondary A Trial to Assess Robot-assisted Surgery and Laparoscopy-assisted Surgery in Patients with Mid or Low Rectal Cancer (COLRAR). ClinicalTrails.gov identifier: NCT01423214. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01423214
50 **Park JW**. Clinical Assessment of Laparoscopic and Robotic Surgery for Rectal Cancer-Randomized Phase II Trial. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01591798
51 **Xu J**. A Multicentre, Prospective, Randomised, Controlled, Unblinded, Parallel-group Trail of Robotic-assisted Versus Laparoscopic Versus Open Abdominoperineal Resection for the Curative Treatment of Low Rectal Cancer. ClinicalTrials.gov identifier: NCT01985698. Secondary A Multicentre, Prospective, Randomised, Controlled, Unblinded, Parallel-group Trail of Robotic-assisted Versus Laparoscopic Versus Open Abdominoperineal Resection for the Curative Treatment of Low Rectal Cancer. ClinicalTrials.gov identifier: NCT01985698. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01985698
52 **Law WL**. Randomized Trial on Robotic Assisted Resection for Rectal Cancer. ClinicalTrials.gov identifier: NCT01130233. Secondary Randomized Trial on Robotic Assisted Resection for Rectal Cancer. ClinicalTrials.gov identifier: NCT01130233. Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01130233

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flex-

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

***Units***
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; $CO_2$ volume fraction, 50 mL/L $CO_2$, not 5% $CO_2$; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23243641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5204/g_info_20100312183048.htm.

***Abbreviations***
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

***Italics***
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.
Biology: *H. pylori*, *E coli*, *etc*.

***Examples for paper writing***
All types of articles' writing style and requirement will be found in the link: http://www.wjgnet.com/esps/NavigationInfo.aspx?id=15

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