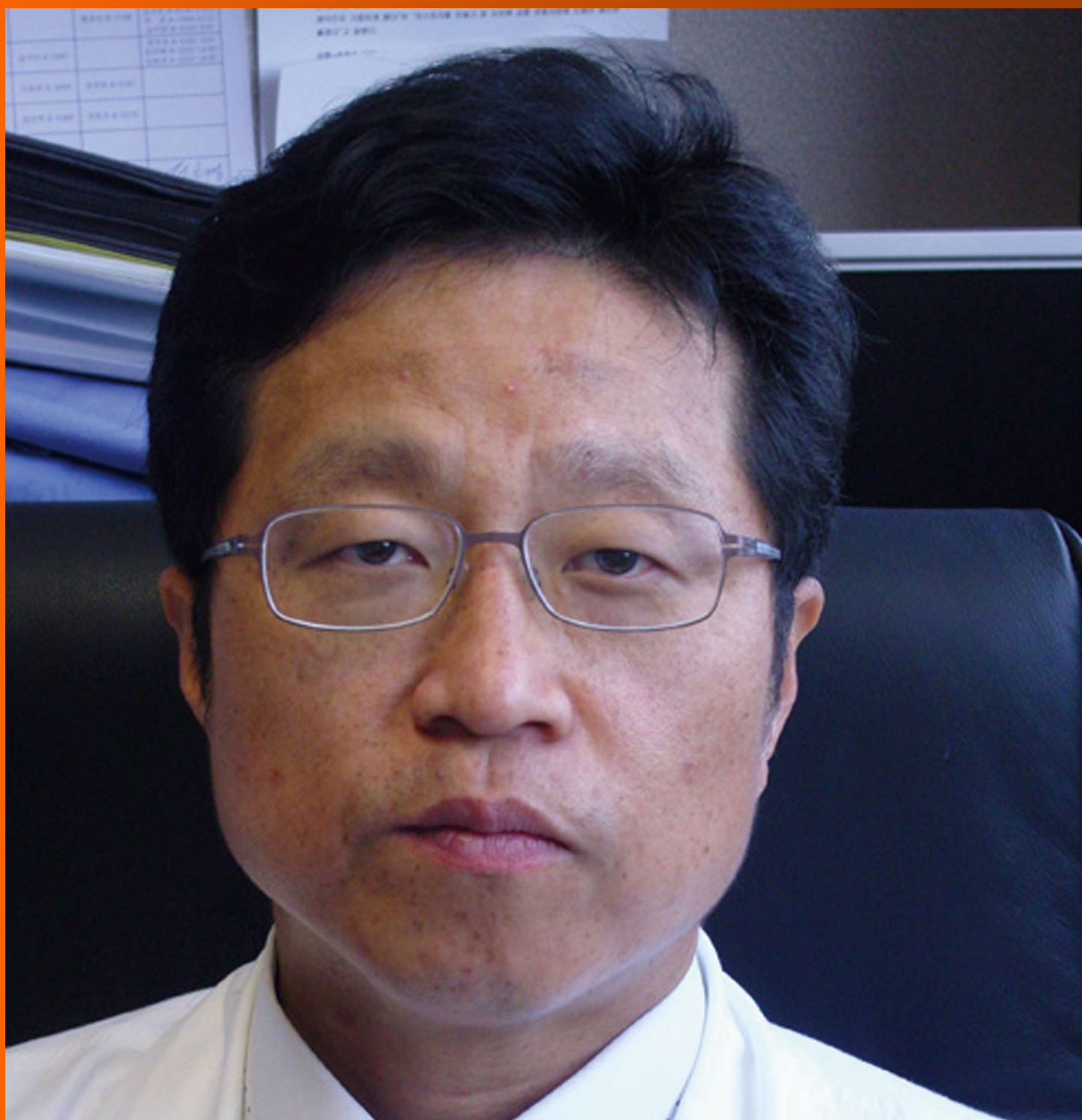


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Quality of life in rectal cancer surgery: What do the patient ask?

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Abstract

Rectal cancer surgery has dramatically changed with

the introduction of the total mesorectal excision (TME), which has demonstrated to significantly reduce the risk of local recurrence. The combination of TME with radiochemotherapy has led to a reduction of local failure to less than 5%. On the other hand, surgery for rectal cancer is also impaired by the potential for a significant loss in quality of life. This is a new challenge surgeons should think about nowadays: If patients live more, they also want to live better. The fight against cancer cannot only be based on survival, recurrence rate and other oncological endpoints. Patients are also asking for a decent quality of life. Rectal cancer is probably a paradigmatic example: Its treatment is often associated with the loss or severe impairment of faecal function, alteration of body anatomy, urogenital problems and, sometimes, intractable pain. The evolution of laparoscopic colorectal surgery in the last decades is an important example, which emphasizes the importance that themes like scar, recovery, pain and quality of life might play for patients. The attention to quality of life from both patients and surgeons led to several surgical innovations in the treatment of rectal cancer: Sphincter saving procedures, reservoir techniques (pouch and coloplasty) to mitigate postoperative faecal disorders, nerve-sparing techniques to reduce the risk for sexual dysfunction. Even more conservative procedures have been proposed alternatively to the abdominal-perineal resection, like the local excisions or transanal endoscopic microsurgery, till the possibility of a wait and see approach in selected cases after radiation therapy.

Key words: Quality of life; Rectal cancer; Laparoscopic surgery; Sphincter preservation; Nerve-sparing

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Core tip: Survival and disease-free survival for patients affected by rectal cancer have overall increased, thanks to the advances in surgery, medical treatments, palliative care and multimodal strategies. This editorial will explore how the growing demand for a better quality

of life has in some way favored the development of new practices and new techniques such as sphincter saving procedures, reservoir techniques, minimally invasive surgery, as long as local treatments or even the possibility of a wait and see approach in highly selected cases.

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INTRODUCTION

Rectal cancer surgery has dramatically changed with the introduction of the total mesorectal excision (TME)^[1-3], which has demonstrated to significantly reduce the risk of local recurrences. Further improvement in local control has been achieved with the implementation of multimodal treatments, specially through the radio-chemotherapy^[4]. Despite a better local control achieved through radiation regimens and proper surgical techniques, the risk for distal failure and systemic disease still represents an issue. Anyway, survival and disease-free survival for patients affected by rectal cancer have overall increased, thanks to the advances in surgery, medical treatments, palliative care and multimodal strategies. This also represents the basis for a new challenge that doctors should face nowadays: If patients live more, they also want to live better. In other words, the fight against cancer cannot be based only on survival, recurrence rate and other oncological endpoints: patients also ask for a decent quality of life. In this regard, rectal cancer is probably a paradigmatic example: We know that its treatment is often associated with the loss or severe impairment of faecal function, alteration of body anatomy, urogenital problems and, sometimes, intractable pain. We also now that post-operative quality of life depends on many factors, some of them related to the disease itself (lower, advanced cancers), some related to the treatments (type of surgery, radiotherapy, stomas, etc.), and all these factors may play a role in reducing the perceived quality of life^[5].

In this effort to improve postoperative short-term outcomes and quality of life-related issues, laparoscopic surgery has rapidly evolved in the last decades, sometimes revolutionizing surgical practice. The role and the dramatic implementation of laparoscopy in the field of colon and rectal surgery also emphasises how the paradigm of cancer treatment is in some way changing: This story tells us about the role that themes like pain, scars, recovery and quality of life might play for patients.

It has been clearly demonstrated that laparoscopic surgery can offer benefits in terms of cosmesis, shorter recovery, shorter hospital stay, less pain, etc.; on the

other hand, the application of laparoscopic surgery to oncological resections encountered many difficulties at the beginning: Concerns were raised regarding the oncological adequacy of laparoscopic resections and lymph nodes yield, the fear for the pneumoperitoneum and the risk for tumor cells implantation on surgical wounds. Such oncological concerns have now been addressed, after many years of clinical trials (COST^[6], COLOR^[7], CLASSIC^[8], Barcelona^[9]), which have demonstrated the non inferiority of laparoscopic resections in the treatment of colon cancer and, more recently, of rectal cancer^[10]. It has also been clearly demonstrated that laparoscopic colorectal resections produce high quality specimens, similar to those obtained with proper open resections and similar results can be achieved by supervised trainee in learning curve settings^[11,12]. But the question is: Why have so many patients decided to enter in clinical trials, when laparoscopic surgery was not proven to give the same oncological results? The answer is probably that people are actually scared of surgery, and the possibility to get short term advantages, less pain, shorter hospital stay and better cosmesis turned out to be attractive, despite the risk for worse oncological outcomes. Actually, if we specifically look into quality of life parameters, literature shows a modest benefit from laparoscopic surgery in the field of colorectal cancer; there are basically two randomized trials and a meta-analysis of them^[13], which failed to demonstrate a clear advantage in term of quality of life in the laparoscopic arm, 2 mo after surgery. The COST study^[14], on the other hand, showed a slightly better overall quality of life in the laparoscopic group two weeks after surgery, without any additional benefit after two months. Possible explanations for the modest benefits in quality of life scores in lap groups from trials, may lay on the substantial lack of proper tools to measure quality of life in patients with cancer. Compared with patients undergoing surgery for benign diseases, cancer patients might perceive postoperative pain, recovery and cosmesis differently. More, most analysis are performed on an intention-to-treat basis, and converted cases, being included in the laparoscopic arms, might mask the benefits in quality of life achieved in the cases completed laparoscopically.

Quality of life after rectal cancer surgery has always been a challenge for surgeons^[5]; the acquisition of the safety of 2 cm disease-free margin or even less^[15], specially in radiated patients, led to a significant improvement of sphincter saving procedures. The possibility to restore intestinal continuity, thus preserving fecal continence is generally considered a key factor for a better quality of life^[16]. Other than the issue of a definitive stoma, the abdominal perineal resections is also impaired by a significant rate of perineal wound complications. This aspect has also become prominent, since the introduction of the "extralevator abdominal perineal resection", first described by Holm *et al*^[17]; this is based on performing the perineal dissection, the patient being turned in a prone jackknife position,

outside the levator plane, rather than along its inner aspect. This approach has demonstrated to reduce the circumferential resection margin positivity and intraoperative perforation rate^[18]. Nevertheless, despite a clear reduction in quality of life after extended APR has not been demonstrated, a significant risk for perineal wound complications has been demonstrated^[19], up to 46.6% of cases, including wound infections, breakdown and chronic perineal pain; however, a conservative management is usually required to face such situations.

On the other hand, low anterior resections with coloanal anastomosis, while preserving sphincters, led to the so called "anterior resection syndrome", characterized by high stool frequency, incontinence, urgency and soiling^[20-23]. A low anterior resection syndrome score (LARS score) has also been created and has been internationally validated recently^[24]; it is a self-administered questionnaire which has demonstrated to be a reliable tool in clinical practice, also considering the high correlation between the LARS score and quality of life.

In order to reduce the anterior resection syndrome, Lazorthes *et al*^[25] and Parc *et al*^[26] described the colonic J-pouch reconstruction; it is based on fashioning a 6-cm side-to-side anastomosis with the terminal distal colon in order to create a new reservoir, that will be then anastomosed to the anus. After its introduction, several studies have demonstrated the overall superiority of the colonic j-pouch in terms of functional results^[27,28], with lower incidence of soiling, urgency and decreased stool-frequency. On the other hand, some studies have also demonstrated that in case of a "straight" coloanal anastomosis, there is a kind of functional adaptation of the pelvic colon and results tend to become similar to the j-pouch 1 year after surgery^[29,30]. More, in case of pre or postoperative radiotherapy, pouch function seems to be significantly impaired, cause of damage to both nerves and sphincters, with high incidence of incontinence and diarrhoea; in these cases benefits from pouches are even less significant^[31,32]. Another kind of colonic reservoir has also been described, in order to face difficult situations like narrow pelvis, fatty mesentery, diverticulitis or inadequate colon length to fashion a j-pouch: The transverse coloplasty pouch, first described by Z'graggen *et al*^[33] and Fazio *et al*^[34]. Several studies have demonstrated that coloplasty may be considered a suitable alternative to j-pouch with similar functional results and a fewer rate of incomplete emptying^[35]. A recent meta-analysis also confirmed that j-pouch or transverse coloplasty allow to achieve better functional results compared to conventional straight anastomosis but this is true only for the first year after surgery^[36].

In this effort to preserve sphincter function, "intersphincteric resection" has also been described for very low rectal cancer instead of the abdominal-perineal resection (APR)^[37,38]. This technique is based on the total or partial resection of the internal sphincter, following the intersphincteric space in order to get a good distal

margin and preserve intestinal continuity, usually through a handsewn coloanal anastomosis. Oncological safety of this procedure has been demonstrated, when proper selection criteria are adopted: No external anal sphincter involvement, no levator plane involvement, at least 1 cm distal margin. When proper selection is obtained, oncological outcome do not differ from APR, in terms of local failure and overall survival^[39]. While the rationale to propose a patient an intersphincteric resection is clearly the possibility to offer him a better quality of life preserving faecal function, some concerns persist cause of the possibility to obtain a poor post-operative continence, specially when a significant portion of the sphincter is resected. Unfortunately a poor faecal function with a high risk of incontinence has been described after the intersphincteric resection, even if an improvement of continence scores is generally registered 12 mo after surgery^[40-42]. Some studies have also specifically looked into the quality of life^[43], showing how a clear deterioration in the faecal incontinence quality of life score is obtained in case of significant impairment of continence; being said, it's a grey zone where surgeons should wonder if a stoma might offer an overall better function. From this standpoint, it should also be argued that colo-anal anastomosis and intersphincteric resections also require the fashioning of a temporary loop ileostomy; this is a further "hot topic" in rectal cancer surgery: It has been demonstrated that ileostomies seem to produce a reduction in quality of life before reversions^[44,45], with decreased social and physical function, cause of the alteration of body anatomy, the risk for peristomal dermatitis, overflow diarrhea and subsequent dehydration, other than for the obvious psychological impact. More, data from literature shows that the ileostomy reversal surgery might be impaired by a significant morbidity, ranging from 9.3% to 45.9%^[46-49] (major morbidity being essentially represented by the risk for postoperative small bowel obstruction and anastomotic leaks). One further problem is that around one third of the ileostomies, intended to be temporary, won't actually be never reverted^[50,51]. Nevertheless, from our experience, loop ileostomy reversal surgery is quite a safe operation, with very low morbidity rate; obviously, adequate selection of patients really needing a diversion is the key point to make it worthwhile to perform the procedure.

Nerve injury during pelvic dissection is another hot topic in rectal cancer surgery, as it may lead to a severe impairment of urinary and sexual function postoperatively^[52]. Nerve-sparing technique is still considered a technical challenge among colorectal surgeons, with no clear consensus on which technique is better to adopt to reduce pelvic nerve injuries. A nerve-preserving technique was first describe by Walsh *et al*^[53] for radical prostatectomy and then applied to rectal surgery. Hypogastric nerves, inferior hypogastric plexus, pelvic sacral nerves and the "nervi erigentes" are the most commonly nerve structures to be damaged during surgery. Risk for nerve injuries should be avoided

through a perfect knowledge of surgical anatomy and relationship between nerves and pelvic organs^[54]; nevertheless, even if a perfect nerve sparing technique is adopted, a complete functional preservation cannot be ensured at the moment^[55]. More, in locally advanced disease, tumor removal is the priority and pelvic nerves need to be sacrificed if necessary. Causes for sexual dysfunctions, in terms of impotency or ability to ejaculate, are sometimes also difficult to determine, as they can also be related to radiotherapy or surgical tractions, even when nerves are recognized and saved. More, erectile dysfunction might also be related to psychological factors and an overall decreased quality of life due to cancer diagnosis. Lindsey *et al.*^[56] suggested the possibility to perform the TME leaving intact the Denonvillier's fascia on the prostate, thus preserving cavernous nerves; this plane is not generally accepted among colorectal surgeons, and we generally believe that it could be considered safe only in case of early tumors not located on the anterior aspect of rectal wall. The magnified view obtained through laparoscopic surgery may play a significant role to help in nerves identification and preservation, but results are not definitive yet^[57,58]. Robotic surgery might combine the benefits from a magnified view and a highly precise dissection, but randomized data are required. The topic of genito-urinary function becomes also more prominent when TME is associated with extended lateral pelvic lymphnode dissection (ELD); this procedure is usually performed in Japan for stage II and III rectal cancer, due to presumed risk of 6.5%-16% to find positive pelvic nodes^[59]. Extended lymphnode dissection is often associated with a tentative pelvic autonomic nerve preservation, nevertheless both the extension of pelvic dissection and the completeness of nerve preservation may vary, depending on tumor stage, location and technical issues. Akasu *et al.*^[60] have demonstrated that while optimal results on sexual and urinary function can be obtain with TME alone, results get significantly worse if pelvic node dissection is added and the degree of dysfunction is directly associated with the extension of the dissection and the degree of preservation of autonomic nerves.

In order to mitigate the sequelae of rectal surgery, transanal local excision and transanal endoscopic microsurgery^[61] have also been described as alternatives in selected cases. It is a local treatment which will allow to take out a small rectal tumor, through a circumferential, full-thickness resection, without the need to enter the abdomen and resect the whole rectum with its lymphatic drainage, thus not fashioning a stoma and avoiding the anterior resection syndrome and a poor quality of life. On the other hand, big concerns still arise regarding the oncological safety of local excision and no clear guidelines currently exist. The most important aspect of the technique is the "full thickness" resection: All the layers adjacent to the lesion need to be excised till the mesorectal fat: Being said, the specimen needs to be a "total biopsy", for further histological assessment.

The major drawback of this technique is the lack of mesorectal lymphnodes clearance; for this reasons a big effort has been made to predict those situations in which the risk to find metastatic mesorectal nodes is high. Several criteria have been described to discriminate "low" and "high risk" rectal tumor. Nascimbeni *et al.*^[62] show a different depth of invasion of the submucosal layer (upper, middle or lower third), correlates with a different risk of finding nodes in the mesorectum (from 3% to 23%); other high risk factors are the grading of the lesion, lymphovascular invasion, the size and a lower location of the tumor. When these high risk factors are identified at the total biopsy, the patient should probably undergo a radical resection within one month from local excision, thus not compromising the prognosis^[63]. Some trials are also investigating the oncological safety of local excision after radiochemotherapy, also in T2 patients^[64]; this latter option, at the moment, should probably be reserved to elderly patients, unfit for surgery or absolutely determined to refuse the risk for a stoma. In this effort to preserve function, quality of life and avoid a mutilating surgery, a "wait and see" approach after preoperative radiotherapy has also been proposed in patients with a complete clinical response; nevertheless, this is still a really debating issue and we should probably look very carefully at this data, at the moment^[65].

Robotic and natural-orifice transluminal surgery are getting more popularity nowadays and probably represent future prospects in rectal cancer surgery. A recent, single institution experience from Park *et al.*^[66], concluded that robotic surgery for rectal cancer failed to offer oncological or clinical benefits over conventional laparoscopy, despite a significant increase in costs. Transanal total mesorectal excision seems to be a promising approach, based on a "bottom-up" dissection to deal with low rectal cancers, specially in narrow pelvis, when traditional laparoscopy may be technically challenging^[67,68]; anyway long-term outcomes, clinical advantages or impact on patients' quality of have not been provided yet.

Randomised, high quality data are still necessary, but new realities are probably not as far, if we consider the development of rectal surgery in the last decades, the new technologies and the importance that patients nowadays give to theme like cosmesis, recovery and quality of life.

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New active drugs for the treatment of advanced colorectal cancer

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Abstract

Newer active drugs have been recently added to the pharmacological armamentarium for the treatment of metastatic colorectal cancer. Aflibercept, a recombinant fusion protein composed of the extracellular domains of human vascular endothelial growth factor receptors (VEGFR) 1 and 2 and the Fc portion of human immunoglobulin G1 (IgG1), is an attractive second-line option in combination with folfox for patients who have failed folfox +/- bevacizumab. Ramucirumab, a human IgG1

monoclonal antibody that targets VEGFR-2, provided similar results in the same setting. Tas-102, an oral fluoropyrimidine, and regorafenib, a multi-tyrosine kinase inhibitor, are both able to control the disease in a considerable proportion of patients when all other available treatments have failed. These new therapeutic options along with the emerging concept that previous therapies may also be reintroduced or rechallenged after regorafenib and Tas-102 failure are bringing new hope for thousands of patients and their families.

Key words: Colorectal cancer; Aflibercept; Ramucirumab; Tas-102; Regorafenib

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Core tip: A brief review dealing with four new active drugs for the treatment of metastatic colorectal cancer covering also the very recent publication of the Tas-102 trial on *New England Journal of Medicine*.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of tumor and represents 8% of all tumors in men and women. CRC is the third leading cause of death in occidental states^[1].

Earlier diagnosis and improved treatments have reduced mortality rate in CRC, but the overall survival (OS) of patients affected by metastatic CRC (mCRC) remains low.

Since 2000, the only useful agent for the treatment of mCRC was 5-fluorouracil. Subsequently, irinotecan

(1996), capecitabine (1998) and oxaliplatin (2002) were introduced, but the most important advancement in the treatment of mCRC was the introduction of targeted therapies such as bevacizumab (2004), cetuximab (2004) and panitumumab (2006).

The selection of first-line therapy remains challenging because the choice of subsequent lines of therapy is dependent on the first administered treatment. Until a few years ago, the only biological therapy that was used as a second-line treatment was bevacizumab, whose target is vascular endothelial growth factor (VEGF)-A. New efficient agents for mCRC treatment have recently been identified; the most promising of these agents are aflibercept, regorafenib, tas-102 and ramucirumab. Aflibercept and ramucirumab are antivascular agents that are useful in second-line treatment settings; tas-102 is a chemotherapeutic agent, and regorafenib acts as multi-tyrosine kinase inhibitor.

Based on the results of the VELOUR study, aflibercept has entered clinical practice. This drug has a wider spectrum of action than bevacizumab and is effective and well-tolerated.

Aflibercept is a recombinant fusion protein composed of the extracellular domains of human VEGF receptors (VEGFR) 1 and 2 and the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept interferes with the growth of tumors *via* inhibition of vascularization by binding VEGF-A and VEGF-B to prevent their interaction with VEGFR. Moreover, aflibercept can bind with high affinity to placental growth factor (PIGF) to enhance the inhibition of VEGFR^[2].

Aflibercept has been evaluated both as a first-line and second-line treatments for mCRC and in second-line settings. In phase 2, randomized, noncomparative, open-label study of aflibercept and modified Folfx6 for the first-line treatment of metastatic colorectal cancer (AFFIRM), aflibercept failed to produce a significant difference in progression-free survival (PFS)^[3]. By contrast, the double-blind phase III VELOUR trial demonstrated that aflibercept plus FOLFIRI as a second-line treatment significantly improved OS (13.5 mo vs 12.06 mo; HR = 0.817, $P = 0.0032$), PFS (6.9 mo vs 4.67 mo; HR = 0.758, $P < 0.0001$) and response rate (RR) (19.8% vs 11.1%) compared with placebo plus FOLFIRI. Of the patients enrolled in this study, 30.4% received bevacizumab as first-line treatment, but this treatment was not associated with decreased clinical benefits^[4], most likely due to the different mechanism of action of aflibercept. Indeed, some authors have suggested that aflibercept can resensitize patients to antiangiogenic treatments by inhibiting PIGF^[5].

The most recently evaluated antivascular drug is ramucirumab, a human IgG1 monoclonal antibody that targets VEGFR-2 and for which good results have been observed in the treatment of gastric cancer^[6]. In the RAISE study, ramucirumab plus FOLFIRI was administered as a second-line treatment in patients affected by mCRC who had been pretreated with bevacizumab. Improvements in both OS (13.3 mo vs

11.7 mo) and PFS (5.7 mo vs 4.5 mo) were observed, consistent with the findings of other trials of the use of antiangiogenic drugs after first-line treatments. In the ramucirumab arm, increases in the frequencies of neutropenia (28% grade 3 vs 15% in the placebo group) and hypertension (11% grade 3 vs 3%) were observed but not grade 3 bleeding or gastrointestinal hemorrhage^[7].

Despite the differences in the design of these two studies, similar survival results were obtained. Because there are no substantial differences in their efficacies and tolerabilities and no predictive biomarkers are available, the choice between these antivascular agents will be quite difficult.

Decisions related to third-line therapies and beyond are less difficult. Relevant research efforts have identified two new drugs, regorafenib and TAS-102.

Regorafenib is a multikinase inhibitor that acts on angiogenesis *via* VEGFR1-3 and TIE2, on the micro-environment through PDGFR- β and FGFR and on cellular proliferation *via* c-KIT, PDGFR, c-RET, B-RAF, and C-RAF^[8]. Two important trials of the use of regorafenib for mCRC have been conducted, the CORRECT and CONCUR trials^[8,9]. The first trial was a multicenter, randomized, double-blind, placebo-controlled, phase III study that enrolled 720 patients with mCRC. They had been heavily pretreated and received 160 mg of regorafenib daily for 3 wk on, 1 wk off plus the best supportive care (BSC) or placebo plus BSC on the same schedule. This trial involved 16 countries and 114 centers. The second trial was a smaller trial that enrolled 200 pretreated Asian patients who were randomized 2:1 to regorafenib or placebo, respectively.

Despite the differences in these studies, both reported increases in OS (HR = 0.77, 95%CI: 0.64-0.94 vs HR = 0.55, 95%CI: 0.395-0.765) and PFS (HR = 0.49, 95%CI: 0.42-0.58 vs HR = 0.311, 95%CI: 0.222-0.435) due to regorafenib. The substantial difference between the results of these trials was probably due to differences in the sample sizes, the number of lines of therapy administered prior to regorafenib and the ethnicities of the enrolled patients. Nearly half of the patients who participated in the CORRECT trial had received at least four lines of chemotherapy, compared to only 38% of the CONCUR patients. The median treatment durations were 7.3 wk in the first trial and 10.6 wk in the second, supporting the hypothesis that the better outcomes reported in the CONCUR trial were due to less pretreatment. The capacity of regorafenib to resensitize cells to subsequent treatments has also been investigated. Twenty-six percent of the patients in the CORRECT trial underwent another therapy after regorafenib. Additional evidence regarding such situations is needed^[8].

Although both studies demonstrated that regorafenib is effective independent of RAS and B-RAF status when used as monotherapy, predictive factors for the treatment response have not been identified. The roles of ECOG PS (*i.e.*, 0 vs 1), lactic dehydrogenase,

neutrophil to lymphocyte ratio, platelet count, the rs2010963 SNP of VEGF-A, ANG-2, interleukin-6 (IL-6), IL-8, PIGF, sTie-1, sVEGFR-1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, M-CSF, SDF-1, TIMP-2, and VWF have been investigated but have not yielded definitive results^[10,11]. The reported toxicities of regorafenib are acceptable and primarily include hand and foot skin reactions, fatigue, diarrhea, hypertension and rashes. Based on the promising results of the CORRECT and CONCUR trials, regorafenib is entering clinical practice.

In addition to molecularly targeted drugs, new chemotherapeutic drugs with "more traditional antitumor activity", such as the new antitumor nucleoside TAS-102, continue to be developed. TAS-102 is a combination of a thymidine-based nucleic acid analogue, trifluridine (FTD), and tipiracil hydrochloride, and the latest of which is a thymidine phosphorylase inhibitor. FTD is a thymidylate synthase inhibitor^[12-14]. FTD also appears to be incorporated into DNA, thereby providing a second mechanism of antitumor activity^[15,16]. The differences in the mechanisms of action of FTD and fluoropyrimidines are supported by the results of preclinical studies indicating that TAS-102 is active and significantly more effective than 5-FU against human cancer cell sublines that are resistant to 5-FU^[17,18]. A double-blind, randomized (2:1), placebo-controlled, phase II study of TAS-102 (given twice daily for 5 d per week with 2 d of rest over 2 wk, repeated every 4 wk) enrolled 169 Japanese patients with mCRC refractory to chemotherapeutic regimens, including fluoropyrimidine, oxaliplatin and irinotecan^[19]. Only one major response was observed in the TAS-102 group, but the disease control rate (DCR; partial response + stable disease) was 43.8% vs 10.5% in the placebo group ($P < 0.0001$). PFS (based on independent reader assessments) was 2.0 mo in the TAS-102 group and 1.0 mo in the placebo group (HR = 0.41, $P < 0.0001$). The median OS was 9.0 mo in the experimental group and 6.6 mo in the placebo group (HR = 0.56, $P = 0.001$). The safety profile of TAS-102 was favorable; no treatment-related deaths were observed, and grade 3 or 4 neutropenia was the most frequently reported toxicity ($\geq 50\%$ of patients). Based on these results, the Refractory Colorectal Cancer Study (RECOURSE) was performed. The RECOURSE was a multicenter, randomized, double-blind, phase III trial in which 800 patients with mCRC refractory or intolerant to all previous chemotherapy regimens available in the setting were randomly (at a 2:1 ratio) assigned to receive TAS-102 (35 mg/m² per dose twice daily) or placebo. The results of this study were recently published^[20] and it indicated that median PFS was 2.0 mo in the TAS-102 arm vs 1.7 mo in the placebo (HR = 0.48, $P < 0.0001$). The objective RRs were 1.6% and 0.4% ($P = 0.286$) in the TAS-102 arm and the placebo arm, respectively. Furthermore, the DCRs were 44% and 16% ($P < 0.0001$) in the treatment and placebo arms, respectively, and the median OS was increased in the TAS-102 arm (7.1 mo vs 5.3 mo; HR = 0.68, 95%CI: 0.58-0.81; $P < 0.0001$). The benefit of TAS-102 in terms

of OS was observed in all of the pre-specified subgroups which included the following three stratification factors: Time from the first diagnosis of metastases to randomization, KRAS status and geographical region. The benefit of TAS-102 treatment after adjustments for the three prognostic factors (time since diagnosis of the first metastasis, ECOG performance status, and the number of metastatic sites) was maintained in a multivariate Cox regression analysis (HR = 0.69, 95%CI: 0.58-0.81). The promising results of this study confirm the role of TAS-102 in the treatment of mCRC patients who are resistant, refractory or intolerant to all standard available therapies.

In conclusion, the second-line setting has been enriched by two new drugs, aflibercept and ramucirumab, with similar efficacies and tolerabilities, but the correct strategy for the use of these drugs is unknown, and no predictive factors have been identified. The landscape for more advanced lines of therapy with regorafenib and TAS102 is also broadening. Our pharmacological armamentarium against metastatic colorectal cancer is becoming richer and smarter each day. Stay tuned for the next exciting news!

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Impact of thiopurines and anti-tumour necrosis factor therapy on hospitalisation and long-term surgical outcomes in ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the large bowel and is associated with a significant risk of both requirement for surgery

and the need for hospitalisation. Thiopurines, and more recently, anti-tumour necrosis factor (aTNF) therapy have been used successfully to induce clinical remission. However, there is less data available on whether these agents prevent long-term colectomy rates or the need for hospitalisation. The focus of this article is to review the recent and pertinent literature on the long-term impact of thiopurines and aTNF on long-term surgical and hospitalisation rates in UC. Data from population based longitudinal research indicates that thiopurine therapy probably has a protective role against colectomy, if used in appropriate patients for a sufficient duration. aTNF agents appear to have a short term protective effect against colectomy, but data is limited for longer periods. Whereas there is insufficient evidence that thiopurines affect hospitalisation, evidence favours that aTNF therapy probably reduces the risk of hospitalisation within the first year of use, but it is less clear on whether this effect continues beyond this period. More structured research needs to be conducted to answer these clinically important questions.

Key words: Immunomodulator; Azathioprine; Anti-tumour necrosis factor; Thiopurine; Ulcerative colitis; Hospitalisation; Surgery; Colectomy; Admission

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Core tip: Longitudinal population data indicates a protective effect of thiopurines on colectomy in ulcerative colitis in the long-term, but there is limited evidence that they reduce hospitalisation. Research on anti-tumour necrosis factor therapy shows a possible short-term protective effect against colectomy, but more data is needed to address any long-term benefits.

Alexakis C, Pollok RCG. Impact of thiopurines and anti-tumour necrosis factor therapy on hospitalisation and long-

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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting bowel condition that presents with recurrent episodes of colonic inflammation, manifesting as periods of prolonged bloody diarrhoea. Despite advances in pharmacological therapies for UC, there is still no known medical cure, and the condition is associated with a considerable risk of surgery^[1]. Moreover, the disease process is often associated with the need for hospitalisation, usually during acute flares. Hospitalisation has been correlated with lower health related quality of life in inflammatory bowel disease (IBD) patients^[2], and is possibly the most costly aspect for healthcare providers in the long-term management of patients with IBD^[3]. As both hospitalization and surgery are objectively identifiable and clinically important events in the natural history of UC, they make attractive clinical endpoints, particularly when addressing the efficacy of UC specific drugs.

The first clinical trials assessing thiopurines in UC are over thirty years old^[4], but these drugs [including azathioprine (AZA) and 6-mercaptopurine (6MP)] are now established as effective steroid sparing agents in the maintenance of remission in UC, and are advocated in national and international guidelines^[5-7]. Over the past decade, the use of anti-tumour necrosis factors (aTNF), including infliximab and adalimumab, has impacted greatly on the management Crohn's disease, and more recently in UC^[8,9] but their role in altering long-term outcomes, in particular surgery and hospitalisation, is less well characterised.

This review focuses on the impact of thiopurines and aTNF therapy on long-term surgical outcomes and hospitalisation in patients with UC. The definition of "long-term" is not easily quantifiable, but for the purposes of the review, we will be primarily considering research that focuses on these two outcomes at one year or later from pharmacological intervention.

SURGERY

Requirement for colectomy is a key endpoint in UC. Some evidence suggests colectomy rates are decreasing. In a large European cohort studied over 30 years, the cumulative probability of surgery at 9 years in UC fell from 14.5% in patients diagnosed between 1979-1986 to 9.1% in patients diagnosed between 2003-2011^[10]. A recent systematic review and meta-analysis indicated that colectomy rates within 10 years of diagnosis have decreased over the past 20 years, with an estimated 10 year risk of colectomy in UC of approximately 15%^[1]. However, the risk of colectomy

within 5 years of diagnosis has not changed significantly over the past 20 years raising a question about the efficacy of contemporary medical management in altering the overall risk of colectomy in the first 5 years of diagnosis, particularly amongst patients with an early onset severe disease phenotype.

It is thus important to try and gauge the impact of both thiopurines and aTNF in long-term surgical outcomes. Table 1 summarises the key literature with regards to both thiopurines and aTNF and their impact on surgical outcomes.

Thiopurines and long-term surgical outcomes

Data from randomised clinical trials addressing risk of surgery and efficacy of thiopurines is limited. Early trials reported conflicting results, but were limited by small patient numbers^[4,11].

A recent Cochrane review comparing AZA or 6MP vs placebo or best treatment in patients with UC included only 6 randomised controlled trials (RCT). Although the review strongly favoured AZA use for achieving clinical remission, long-term colectomy was not considered as a measured endpoint^[12].

A number of large population based studies have attempted to quantify the impact of immuno-modulators on surgery in UC, with more encouraging findings. Kaplan *et al*^[13] reported a population time trends analysis on colectomy rates in a Canadian cohort of UC patients between 1997 and 2009. Over the study period, there was a clear reduction in elective colectomy rates by 7.4% per year, but rates for emergency procedures remained static. Over the same period, the authors reported a doubling of thiopurine usage but were cautious about making inferences about any trend given the absence of a clear inflection point between increased immuno-modulator use and reduced colectomy rates. In a large Canadian population based study from Manitoba including 3752 UC patients with up to 25 years of follow up, a colectomy rate of 10.4% at 10 years was reported^[14]. Almost quarter of the cohort exposed to immuno-modulator had undergone colectomy by 5 years. In a sub-analysis of thiopurine users, patients exposed to more than 16 wk of therapy had a significantly decreased colectomy rate at 2 years (5.6% vs 12.8%), although immuno-modulator use was not included in the final logistic regression analysis calculating risk of early or late colectomy. Similarly, a large Danish registry study of IBD patients showed a reduction in colectomy rates in patients with UC over the 32 year study period. This decrease was in parallel with a significant increase in thiopurine use, although regression analysis did not indicate a significant protective effect of thiopurine exposure on colectomy^[10].

The potential value of prolonged thiopurine exposure was further evaluated by Chhaya *et al*^[15] in a United Kingdom population based cohort study of 8673 patients with UC between 1989 and 2009. After adjusting for confounding factors, the authors found no significant fall in colectomy rates within 5 years of diagnosis during the

Table 1 Summary of key research investigating impact of thiopurines and tumour necrosis factor inhibitors therapy on long-term surgical outcomes in ulcerative colitis

	Ref.	Study design	Population	n	Key findings
Thiopurines	Ardizzone <i>et al</i> ^[11]	RCT comparing AZA <i>vs</i> 5-ASA	Steroid dependent UC	72	No difference in colectomy rates at 6 mo between AZA and 5-ASA groups
	Kaplan <i>et al</i> ^[13]	Population based time trends analysis of colectomy rates	Unselected UC	N/A	Reduction in elective colectomy rates of 7.4% per year Doubling of TP use over the study period Emergency colectomy rates remain static
	Targownik <i>et al</i> ^[14]	Population based analysis of colectomy rates	Unselected UC	3752	10.4% colectomy rate at 10 yr post diagnosis > 16 wk TP therapy associated with reduced colectomy requirement
	Chhaya <i>et al</i> ^[15]	Population based time trends analysis of colectomy rates	Unselected UC	8673	TP use > 12 mo associated with a 71% reduction in risk of colectomy Early TP use not associated with added benefit No significant change in colectomy rates over study period
	Cañas-Ventura <i>et al</i> ^[16]	Retrospective descriptive cohort study of UC patients receiving AZA	Unselected UC	1334	5 yr colectomy rate at 8.8% TP use within 33 mo of diagnosis associated with increased risk of colectomy
aTNF	Sjöberg <i>et al</i> ^[24]	Multi-centre retrospective analysis of IFX rescue therapy	Acute severe UC	211	64%, 59% and 53% colectomy-free survival at years 1, 3, 5 Majority of colectomies within first 2 wk of IFX therapy
	Gustavsson <i>et al</i> ^[26]	RCT comparing IFX rescue therapy <i>vs</i> placebo	Acute severe UC	45	3 yr colectomy free survival 50%
	Laharie <i>et al</i> ^[29]	Head to head RCT comparing IFX <i>vs</i> CSA as rescue therapy	Acute severe UC	115	No significant differences in colectomy rates between two therapies at 3 mo
	Sandborn <i>et al</i> ^[19]	ACT 1 and 2 RCT of IFX <i>vs</i> placebo	Moderate to severe UC	728	Colectomy rate significantly lower in IFX group (10% <i>vs</i> 17%) at 54 wk
	Feagan <i>et al</i> ^[41]	ULTRA 1 and 2 RCT of ADA <i>vs</i> placebo	Moderate to severe UC	963	Very low colectomy rates reported at 52 wk (approximately 4%) No difference in colectomy rates between ADA and placebo
	Reich <i>et al</i> ^[45]	Time trends analysis of colectomy rates following introduction of IFX	Unselected UC	481	19% annual decrease in elective colectomy in biologic era 15% annual decrease in emergency colectomy in biologic era
	Costa <i>et al</i> ^[50]	Meta-analysis of aTNF use in UC	Moderate to severe UC	836	Reduced risk of surgery at 1 yr in patient treated with IFX compared to placebo (OR = 0.55) NNT was 11

UC: Ulcerative colitis; aTNF: Tumour necrosis factor inhibitors; RCT: Randomised controlled trial; AZA: Azathioprine; TP: Thiopurine; 5-ASA: 5-aminosalicylic acid; IFX: Infliximab; CSA: Ciclosporin; ADA: Adalimumab; NNT: Number needed to treat; N/A: Not applicable; ACT: Active ulcerative colitis trials; ULTRA: Ulcerative colitis long-term remission and maintenance with adalimumab.

20 year study period. Also, requirement for thiopurines defined a group of patients with an associated higher risk of colectomy^[15]. Amongst patients treated with thiopurines, use for greater than 12 mo (compared to use \leq 3 mo) was associated with a significant reduction in requirement for colectomy by end of follow up (HR = 0.29, 95%CI: 0.21-0.40). But, early thiopurine use (defined as within 1 year of diagnosis of UC) added no additional reduction suggesting some patients with early onset severe disease were either refractory to thiopurines or had insufficient time to benefit from these drugs before surgery was required.

Most recently, Cañas-Ventura *et al*^[16] described colectomy rates and risk factors for colectomy in a cohort of 1334 Spanish UC patients drawn from a national IBD registry. All patients had had a minimum exposure to immuno-modulator therapy (AZA at median dose of 150 mg/d or 6-mercaptopurine at a median dose of 75 mg/d) of at least 3 mo. The 5 years cumulative risk of colectomy for the cohort was 8.8%, and regression analysis demonstrated an increased risk

of colectomy in patients receiving immuno-modulator therapy within the first 33 mo of diagnosis *vs* those started after this time (HR = 4.9, 95%CI: 3.2-7.8).

Data from "real world" single centre retrospective studies are limited and conflicting in their reporting of the effect of thiopurine therapy on surgery. Williet *et al*^[17] reported medication usage in 151 unselected UC patients (median follow up 58 mo) and their subsequent risk of needing colectomy. In this study, exposure to thiopurine therapy was not associated with an increased risk of colectomy risk in regression analysis. In contrast, data from a Japanese single centre study of 222 UC patients followed for up to 11 years indicated a significant protective effect of thiopurine treatment on colectomy (HR = 0.2, 95%CI: 0.08-0.67), although the sub-analysis only included hospitalised patients^[18].

In summary, there is limited data from prospective controlled trials and retrospective observational studies to support a protective effect of thiopurine therapy in reducing the overall risk of colectomy. This is inherently related to the design of most studies that focus on non-

surgical short-term measures as primary outcomes. Longitudinal population based data is possibly more supportive of the protective role of thiopurine therapy against colectomy, and sufficient exposures may be required to reduce this risk, but this might not be always possible in patients with an early onset severe disease phenotype.

aTNF therapy and long-term surgical outcomes

The Active Ulcerative Colitis Trials (ACT 1 and ACT 2) published in 2005 by Rutgeerts *et al.*^[18] showed the potential benefit vs placebo of the aTNF agent, infliximab (IFX), on clinical and endoscopic responses in 728 outpatients with moderate-to-severe UC. Colectomy data from this cohort was later reported in 2009^[19]. The analysis indicated a cumulative incidence of colectomy of 10% in the IFX group compared to 17% in the placebo group (HR of 0.59, 95%CI: 0.38-0.91) pointing to a protective effect against colectomy. However, the median follow up was only 6.2 mo and there was a significant study drop-out rate, nor was the indication for colectomy clearly defined. In contrast, a placebo-controlled study by Järnerot *et al.*^[20] in 2005 looking at IFX therapy in 45 patients with fulminant UC reported a 29% colectomy rate in the treated arm at the end of the trial (90 d) vs 67% in the placebo arm^[20]. The wide discrepancy in colectomy rates between the 2 studies reflects differing patient subtypes enrolled in both trials, namely chronic non-acute severe cases vs acute severe colitis patients, and this is considered further below.

Acute severe UC: Several small retrospective single centre observational studies exist recording colectomy rates following aTNF treatment in acute severe UC^[21-23]. Colectomy was required in 37%-53% of patients, although there was considerable heterogeneity in the patient subgroups and follow up periods (6-22 mo) between the different studies. A large Swedish multi-centre retrospective analysis of 211 aTNF-naïve patients with acute severe UC treated with 5 mg/kg IFX as “rescue” therapy reported colectomy free survivals of 64%, 59% and 53% at years 1, 3 and 5 suggesting a considerable long term protection against colectomy in this group of patients^[24]. However, in this study 64% of all the colectomies (*i.e.*, IFX failures) in the first year occurred within the first 2 wk possibly suggesting a subgroup of patients with more severe disease in whom IFX cannot alter risk of colectomy. More recently, accelerated aTNF induction regimes have been shown to reduce very early colectomy in acute severe UC, although long-term colectomy free survival does not appear to be improved with this strategy^[25].

Gustavsson *et al.*^[26] prospectively reported similar 3 years colectomy-free survival rates of 50% in the treated arm of the original 45 patients with acute severe UC entered into an earlier RCT by Järnerot *et al.*^[20], although some patients had further IFX rescue treatments in follow up and there were differing rates of immuno-modulator use in the treatment and placebo

arms, making interpretation of this study difficult^[26]. Of particular note, mucosal healing at 3 mo was strongly inversely related to the need for colectomy, with a colectomy rate of 0% in those who achieved mucosal healing at 3 mo, compared to 50% in patient who did not. The importance of achieving mucosal healing with respect to reducing the need for colectomy in UC patients treated with IFX has been further highlighted in a number of other studies including a sub-analysis of the original ACT trials^[27,28].

The available evidence suggests a protective effect of aTNFs in reducing colectomy rates in patients with acute severe UC in the short-term. However, this effect does not appear to be superior to “rescue” therapy with ciclosporin. The results of the CYSIF trial, a randomised open labelled trial comparing ciclosporin vs IFX in 115 patients with acute severe UC (who failed to respond to 5 d of intravenous corticosteroid therapy), showed no significant differences in colectomy free survival at 98 d in either group (25.9% vs 26.3% respectively)^[29]. In contrast, results from the United Kingdom national IBD audit indicated a significantly higher emergency colectomy rate in acute severe UC patients “rescued” with ciclosporin compared to IFX (35% vs 19%), although only colectomies performed in the same index admission were considered and may reflect selection bias^[30]. Meta-analyses on this subject have not established superiority of either therapy in the context of acute severe UC^[31,32]. Moreover, Laharie *et al.*^[33] has recently presented (in abstract) the long-term follow up data from the original CYSIF trial participants that indicates no significant differences in long-term colectomy-free survival between ciclosporin and IFX (5 years colectomy-free survival 61% ± 7% in ciclosporin group vs 65% ± 7% in IFX group)^[33]. The full analysis is awaited, along with the findings of CONSTRUCT, a United Kingdom based trial on the same topic^[34].

Moderate to severe UC: The term moderate-to-severe UC includes a heterogeneous population of colitic patients including steroid-dependent UC and steroid-refractory UC, making comparison of studies more difficult.

Following the ACT 1 and ACT 2 trials, a number of smaller uncontrolled single centre retrospective observational studies on the effect of aTNF therapy on colectomy rates beyond 6 mo have been published^[35-38]. All had follow up periods of at least 12 mo. In these “real life” descriptions of aTNF use, there was considerable variation in the colectomy rates, from 2.7% at 42 mo to 53.3% at 12 mo. However, patient numbers in these studies were limited and there was significant disparity in patient demographics, disease extent, and severity. Reinisch *et al.*^[39] published the results of the extension study from the original ACT trials in 2012. Patients who had achieved benefit from IFX in ACT 1/2, were offered a further 3 years of treatment. Those on 5 mg/kg doses had the option to increase the dose to 10 mg/kg if the investigators felt response had been lost. From 229

patients accepted into the 3 year extension study, there were only 2 colectomies (< 1%). This result should be treated with caution regarding the long-term benefits of aTNF therapy since it can be argued that those patients who survived without colectomy beyond the early stages of diagnosis have inherently less aggressive disease. Secondly, by virtue of their early response in ACT 1 and 2, these patients may have more responsive disease. Additionally, up to half of the original ACT 1 and 2 patients in the treatment arm were also on immuno-modulator therapy, which may have provided additional benefit in reducing the need for colectomy.

The ULTRA 1 and ULTRA 2 trials were randomised placebo controlled trials of Adalimumab (ADA) for the induction and maintenance of remission in moderate to severe UC^[9,40]. In 2014, Feagan *et al.*^[41] published the hospitalisation and surgical outcomes from this cohort. Interestingly, no differences in the colectomy rates between treatment and placebo arm during the 52 wk follow up was found. However, overall reported colectomy rates were only 4%-5%, and the authors acknowledged that this surprisingly low rate meant the study was insufficiently powered to assess for differences in surgical outcomes. Again there was a large proportion of patients on concomitant immuno-modulator therapy in both treatment and placebo arms (37% vs 35%). In a subsequent meta-analysis of 5 RCTs comparing ADA or IFX against placebo (including both ACT and ULTRA trials), both were equally efficacious in achieving clinical remission at 52 wk compared to placebo, but unfortunately no colectomy data was considered in the comparison^[42].

In a retrospective study of 48 Spanish ENEIDA registry patients with either steroid dependent UC or steroid refractory UC treated with ADA, colectomy rates were reported at 22.9% after a mean of 205 d^[43]. Clinical response was determined using the Mayo/partial Mayo scores at week 12, 28 and 54. The only predictor of colectomy was failure to respond to ADA at week 12. However, it was noted by the researchers that there was a high variation of co-medication with other IBD drugs, and that 81% of the cohort had already tried IFX prior to their induction with ADA.

A number of researchers have attempted to determine whether the use of aTNF therapies may alter surgical outcomes using epidemiological methods. Cannom *et al.*^[44] used United States Nationwide Inpatient Sample data combined with census data to estimate surgical rates in the 7 years following the Food and Drug Administration approval for IFX in IBD. No downward trend in surgery was seen over the study period of 1998-2005 in either Crohn's disease or UC, but arguably it was too early to see a noticeable effect of IFX on surgical rates over this relatively short period. Reich *et al.*^[45] performed a time-trends study of colectomy incidence rates in a Canadian subpopulation of UC patients before and after the approval of IFX for UC treatment in 2005. In the biologic era, the annual percentage of both emergency and elective colectomy

rates fell: 18.6% (95%CI: 13.8%-23.3%) and 14.9% (95%CI: 2.18%-25.8%) respectively. This occurred during a period of rapid increase in the proportion of IFX use and no proportional changes in the use of other IBD medications. A relationship between the two was inferred, but the authors accept there may have been other changes in management that could have contributed to declining colectomy rates over this time. Most recently, preliminary data from a very large United States cohort of almost 400000 UC patients admitted to hospital between 1998 and 2011 showed no change in colectomy rates in the era before and after the introduction of aTNF^[46].

Meta-analyses on the subject have helped clarify the clinical question. Recently, Lopez *et al.*^[47] performed a meta-analysis of 5 placebo controlled RCTs^[8,9,40,48,49] assessing efficacy of a variety of aTNF therapies including IFX, ADA and Golimumab in patients with moderate to severe UC. The authors concluded that treatment with aTNF was superior to placebo in achieving the primary endpoints (maintaining remission and achieving mucosal healing), but only IFX had any effect on reducing colectomy rates. However, only 2 studies^[19,41] were included in the analysis of surgery. In overall analysis of both studies, aTNF therapy was not more effective than placebo in reducing the risk of colectomy (RR = 0.87, 95%CI: 0.42-1.81). In subgroup analysis, IFX was superior to placebo in reducing the need for colectomy (RR = 0.64, 95%CI: 0.43-0.97) although follow up was limited to only 6.2 mo. A similar protective effect was not seen for ADA.

An earlier systematic review and meta-analysis of 27 IBD studies was published in 2013 by Costa *et al.*^[50], and included data for 836 UC patients treated with IFX only. Pooled results from 4 RCTs with follow up ranging from 6 to 156 wk (including 3 studies not assessed in the meta-analysis by Lopez) suggested a reduced risk of surgery with IFX (pooled OR = 0.55, 95%CI: 0.40-0.76, number needed to treat = 11)^[19,26,51,52]. However, the analysis was very heavily dependent on the findings from ACT 1 and 2 follow up (91% weighted), and furthermore, a similar protection against colectomy was not seen in the pooled data from the observational studies (although there was considerable heterogeneity in these studies).

In summary, whilst there appears to be a clear benefit of aTNF in inducing clinical remission and achieving mucosal healing in UC patients in the short term, whether this is translated to long-term reduction in surgical risk is less apparent, and data is lacking. Available studies are limited, follow up is short, and patient populations are heterogenous. Similarly, population based studies are also conflicted regarding the role of aTNF therapy in altering the long-term risk of colectomy. No data is available regarding the long term benefits of Golimumab in this respect.

Physicians must also consider the potential detrimental side of aTNF use in this patient group, notably the possible impact of these medications on post-

Table 2 Summary of key research investigating impact of thiopurines and tumour necrosis factor inhibitors therapy on hospitalisation in ulcerative colitis

	Ref.	Study design	Population	n	Key findings
Thiopurines	Actis <i>et al</i> ^[61]	Retrospective study comparing hospitalisation before and after AZA induction	Severe UC	17	Significant decrease in hospitalisation for patients with UC up to 5.8 yr following AZA induction Most of patients were also treated with ciclosporin at AZA induction
	Herrinton <i>et al</i> ^[62]	Population based cohort study of prescribing trends in UC	Unselected UC	5895	150% increase in immuno-modulator use in UC between 1998-2005 Concurrent reduction in UC hospitalisations in the same period by a third
	Vester-Andersen <i>et al</i> ^[63]	Prospective descriptive study of IBD inception cohort	Unselected UC	300	26% exposure to immuno-modulator during follow up Hospitalisation rates decreased from 4.7 d/person-years in year 1 after diagnosis to 0.4 d in year 5 Immuno-modulator therapy found not to be significant in predicting need for hospitalisation
aTNF	Carter <i>et al</i> ^[65]	Medical insurance cost analysis study	Unselected UC	420	UC patients with a prescription for infliximab for > 80% of the study period had less hospitalisation requirement, lower admission costs and shorter inpatient stays
	Oussalah <i>et al</i> ^[37]	Multicentre retrospective study on outcomes in UC patients post aTNF	Unselected UC	191	Estimated hospitalisation-free survival at 1, 2, 3 and 6 yr were 66.7%, 60.2%, 57.1% and 44.6% respectively Earlier use of aTNF predictive of need for hospitalisation
	Sandborn <i>et al</i> ^[19]	ACT 1 and 2 RCT comparing IFX with placebo	Moderate to severe UC	728	Of patients treated with IFX, 84% remained free of hospitalisation at 54 wk, compared to 75% in the placebo group
	Feagan <i>et al</i> ^[41]	ULTRA 1 and 2 RCT comparing ADA with placebo	Moderate to severe UC	963	Significantly reduced all-cause and UC-related admissions at both 8 wk and 52 wk in patients treated with ADA compared to placebo
	Lopez <i>et al</i> ^[47]	Meta-analysis of aTNF in UC outcomes	Moderate to severe UC	964	aTNF therapy was superior to placebo in reducing UC-related hospitalisations, with a relative risk of 0.71 (95%CI: 0.56-0.90)

UC: Ulcerative colitis; aTNF: Tumour necrosis factor inhibitors; RCT: Randomised controlled trial; AZA: Azathioprine; IFX: Infliximab; ADA: Adalimumab; IBD: Inflammatory bowel disease; ACT: Active ulcerative colitis trials; ULTRA: Ulcerative colitis long-term remission and maintenance with adalimumab.

operative complications and/or mortality. In a large study by Ellis *et al*^[53], post-colectomy mortality rates increased significantly between the era before and after the introduction of aTNF use in UC. A recent systematic review suggested increased post-operative complications in patients with Crohn's disease on aTNF therapy^[54]. However, data from other smaller UC cohorts have not indicated similar findings in patients treated with these agents^[55].

Clearly, further work into the long-term protective role of aTNF drugs is required. Equally, the additional benefit of co-administration of TP with aTNF therapy remains largely unexplored. Recent studies addressing this have not shown any additional protection against colectomy, but this strategy warrants further investigation in the future^[56].

HOSPITALISATION

The overall rate of hospitalisation in UC appears to be decreasing. Data from recent population based longitudinal studies indicate a declining trend in UC related admissions^[57,58], although this is not universally reported in all populations^[59,60]. A variety of environmental, demographic and clinical parameters have been implicated as potential risk factors for hospitalisation in patients with UC, although studies into the impact of specific medications on this outcomes are limited. Table 2 summarises the key research in this area.

Thiopurines and hospitalisation

Data regarding the impact of thiopurine use on the risk of hospitalisation is limited. A small retrospective study of 17 patients with severe UC assessed the frequency of admission to hospital before and after the initiation of AZA^[61]. Analysis showed a significant decrease in the number of hospital admissions from a mean of 2.12 ± 0.69 in the preceding 4.2 ± 4.3 years to a mean of 0.12 ± 0.33 in the following 5.8 ± 2.5 years ($P = 0.000$) after initiation of AZA. However, numbers were very small, and 14 of the subjects were also treated with ciclosporin to achieve remission at the time of induction with AZA. A large study from the United States Kaiser Permanente healthcare database between 1998-2005 reported trends in medication use and a variety of key outcomes in a cohort of 5895 UC patients^[62]. Over the study period, immuno-modulator therapy in UC patients increased by 150% (steroid and 5-aminosalicylic acid use also increased over this period but to a much less extent). Over the same period acute hospital admissions were reduced by almost a third. A relationship between these two findings can only be made by inference. However, as the study was performed in an era before United States approval of aTNF agents in UC, there is no confounding by this medication group.

Most recently, Vester-Andersen *et al*^[63] published the hospitalisation rates of a Danish inception cohort of IBD patients including (300 patients with UC) between 2003 and 2011. Forty-seven percent of the UC cohort

had at least one admission to hospital over the follow up period, and admission rates decreased from 4.7 d/person-years in year 1 after diagnosis to 0.4 d in year 5. Twenty six percent of UC had exposure to immuno-modulator therapy in follow up with a median time to exposure of 433 d from diagnosis. In a sub-analysis, however, immuno-modulator exposure was not found to be significant in predicting the need for hospitalisation.

In summary, data is lacking to suggest with certainty that immuno-modulator therapy has a role in avoiding hospitalisation in UC.

aTNF therapy and hospitalisation

The cost of biologic therapy has dramatically shifted the overall healthcare costs in IBD. The recent Dutch COIN study sought to estimate the expenditure of medications, treatments and hospitalisation of large cohort of adult IBD patients including 937 UC patients^[64]. The biggest cost driver was medication, notably aTNFs, with hospitalization and surgery accounting for 19% and < 1% respectively of total costs. Hospitalisation remains costly for healthcare providers, and if medical therapy can reduce the need for admission, this can potentially offset the cost of expensive treatments.

Relatively few retrospective observational studies have looked at hospitalisation rates with respect to aTNF use in UC. Carter *et al*^[65] published the results of a cost analysis based on 420 UC patients' medical insurance claims for IFX treatment in relation to hospitalisation and admission costs. In a sub-analysis whereby patients were categorised by persistent IFX use (defined as having a prescription of IFX > 80% of the time), patients with "persistent" maintenance therapy had less hospitalisation (3% vs 20.4%), lower inpatient costs, and shorter inpatient stays.

In a French multi-centre retrospective analysis of 191 unselected UC patients with varied severity treated with IFX, 36.1% of patients required at least one admission during follow up^[37]. Estimated hospitalisation-free survival at 1, 2, 3 and 6 years were 66.7%, 60.2%, 57.1% and 44.6% respectively. Earlier time from diagnosis to IFX treatment was strongly predictive of need for first hospitalisation. Conversely, a small study from Hungary showed no change in hospitalisation rates in UC patients following the introduction of IFX treatment compared to the pre-IFX era^[66].

A follow up study to ACT 1 and 2 also examined hospitalisation rates^[19]. In the treatment arm, 84% remained free of hospitalisation at 54 wk, compared to 75% in the placebo group. The proportion of patients requiring 1, 2 or more than 2 UC-related admissions was also significantly higher in the placebo group. Similarly, findings from ULTRA study also reported significantly reduced all-cause and UC-related admissions at both 8 wk and 52 wk in patients treated with ADA compared to placebo^[41].

Two meta-analyses have evaluated the impact of aTNFs on rates of hospitalisation^[49,50]. A sub-analysis of hospitalisation by Lopez *et al*^[49], included 964 UC patients

receiving aTNF derived from two RCTs with follow up between 52 and 54 wk. aTNF therapy was superior to placebo in reducing UC-related hospitalisations, with a relative risk of 0.71 (95%CI: 0.56-0.90). In a separate analysis, both IFX and ADA were found to be effective in reducing UC-related hospitalisations, with a number needed to treat of 18 (95%CI: 9-911) and 23 (95%CI: 12-506) respectively. Costa *et al*^[50] also found a 49% (OR 0.41, 95%CI: 0.40-0.65) reduction in risk of hospitalisation in UC patients treated with IFX compared to placebo in analysis of three RCTs not included in the study by Lopes.

In summary, aTNF agents appear to have a potential effect in reducing hospitalisation in patients with UC. Most research on hospitalisation focuses on early admission rates (under a year). There is clear need to further evaluate the impact of these medications on hospitalisation in the longer term.

CONCLUSION

Thiopurines and aTNF therapy form a key part of treatment in patients with UC. Both have established roles in the induction and maintenance of remission. Their role in altering the long-term requirement of surgery and hospitalisation is less clear. Whilst 5 years surgery rates have reduced in Crohn's disease, they remain essentially unchanged in UC^[1]. Thiopurines appear to have a long-term benefit in reducing the need for surgery in UC, although there is a subgroup of UC patients who do not derive benefit from these medications, and require early colectomy. Whereas IFX reduces the need for surgery in the short-term, the evidence that aTNF agents alter the long-term requirement of colectomy is again limited.

The role of thiopurines and aTNFs in reducing hospitalisation is more difficult to interpret in the context of differing models of healthcare provision and changes in other aspects of UC management. However, overall the evidence generally supports their respective roles in reducing acute admissions. Further work is required to evaluate the important question of the long-term benefits of medical therapy on reducing the requirement of for surgery and hospitalisation in UC.

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Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate?

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Abstract

Albumin is the single most abundant protein in the human serum. Its roles in physiology and pathology

are diverse. Serum albumin levels have been classically thought to reflect the nutritional status of patients. This concept has been challenged in the last two decades as multiple factors, such as inflammation, appeared to affect albumin levels independent of nutrition. In general, cancer patients have a high prevalence of hypoalbuminemia. As such, the role of hypoalbuminemia in patients with colorectal cancer has received significant interest. We reviewed the English literature on the prognostic value of pretreatment albumin levels in colorectal cancer. We also consolidated the evidence that led to the current understanding of hypoalbuminemia as an inflammatory marker rather than as a nutritional one among patients with colorectal cancer.

Key words: Hypoalbuminemia; Albumin; Colorectal cancer; Albumin-to-globulin ratio; Cancer survival; Systemic inflammatory response; Glasgow prognostic score

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Core tip: Early studies had shown a prognostic value of hypoalbuminemia in colorectal cancer. The relationship between albumin levels and survival was more consistent when the former was coupled to C-reactive protein, a classic inflammatory marker, in the modified Glasgow prognostic score (mGPS). This relationship also appeared to be independent of nutrition on multivariate analyses. The superiority of mGPS in predicting survival supports inflammation as the major culprit of poorer outcomes. A number of studies showing an association of lower albumin-to-globulin ratios with poorer survival are also in favor of a tilt towards proinflammatory states as the cause of morbidity and mortality. Cancer cachexia is a downstream consequence of the systemic inflammation brought in by colorectal cancer. In this view, albumin is a negative acute phase reactant rather than a nutritional marker. Interventions aimed to halt cancer cachexia should therefore target inflammation.

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BACKGROUND

Albumin is the most abundant protein in the human serum. This monomeric macromolecule constitutes about 60% of the serum proteins by weight, the rest being globulins. It is also present in the interstitial space and body fluids. Albumin is produced by the liver at a rate of 9 to 12 g/d. Its hepatic synthesis is primarily affected by osmotic colloid pressure and inflammatory states, but also, and to a lesser degree, by nutritional status and hormones. The catabolism of this protein is still not completely understood but is postulated to take place in the vascular endothelium^[1,2].

Albumin is the most important contributor to the osmotic colloid pressure. In fact, given its negative charge at normal pH, it retains sodium cations, and therefore water, in the intravascular compartment. It also plays central roles in cellular physiology, including intravascular transport of molecules (like hormones) and lipid metabolism^[1]. A dye-binding method is used to measure serum albumin. Once bound to bromocresol, the complex absorbs light at a different wavelength than unbound bromocresol^[3]. Bromocresol can also bind to other proteins and thus can lead to an overestimation of albumin levels.

Historically, the nutritional status of patients has been evaluated through two approaches: Anthropometric methods and laboratory markers. The former includes physical parameters, such as triceps skin fold to assess fat composition, mid-arm circumference to assess muscle composition, or body mass index^[4]. The latter approach relies on hepatic proteins like albumin, prealbumin and transferrin, which have been believed to be reflective of nutritional status^[5]. Deficiencies in these hepatic proteins were an indicator of malnutrition and prompted at times the use of aggressive nutritional support.

Despite the persistence of the perception among clinicians that albumin is a nutritional marker, the literature in the last two decades has challenged this concept as additional factors were found to impact the serum albumin level^[6]. While reduced food intake can result in hypoalbuminemia, these effects are generally mild. In fact, experimental starvation demonstrated that albumin concentrations may not change for several weeks^[7]. Additionally, inflammation was found to reduce albumin concentration regardless of malnutrition^[8,9].

Among cancer patients, the prevalence of both hypoalbuminemia and malnutrition is common. Those with a malignancy of the gastrointestinal tract also face

the risk of physical interference of the tumor with their feeding, such as a mechanical obstruction. As a result, the role of hypoalbuminemia in patients with colorectal cancer has received significant interest. In this work, we review the English literature on the role of serum albumin levels as a prognostic tool in colorectal cancer. We also present the body of evidence that led to the current understanding of hypoalbuminemia as an inflammatory surrogate rather than nutritional marker among these patients.

ALBUMIN AND CANCER

For the host body, cancer represents a state of high physiological stress, with tumor hypoxia/necrosis and local tissue damage. In an attempt to counteract these changes, the body responds with a systemic release of proinflammatory cytokines and growth factors^[10]. When faced with these stimuli, isolated hepatocytes increase their production of acute-phase proteins, such as C-reactive protein (CRP), and decrease their production of albumin^[11]. This response is often accompanied by a nutritional and functional decline of patients, especially among those with advanced cancer^[12-14].

Babson *et al.*^[15] first described a potential association between cancer and plasma proteins in 1954. The authors demonstrated that tumors act as a trap for plasma proteins and use their degradation products for tumor growth. Their findings were later confirmed by several studies: When serum albumin was either radiolabeled or conjugated with dyes, up to 25% of the dose was accumulated in solid tumors^[16,17]. Albumin therefore appeared to be a possible nutritional source for tumor growth^[17]. Interestingly, evidence points to a physiological anticancer effect of albumin through its antioxidant properties and demonstrated roles in stabilizing DNA replication (among other functions)^[18]. Such characteristics highlight complicated interconnections between albumin and cancer.

The main reason for low albumin levels in patients with cancer remains unclear, yet various mechanisms have been proposed. For instance, cancer cells can produce cytokines, such as interleukin-6 (IL-6), that modulates the production of albumin^[14]. In addition, the presence of hepatic micrometastases may stimulate Kupffer cells to produce cytokines (such as IL-1 β , IL-6 and tumor necrosis factor), which may also affect albumin synthesis. However, the fractional rate of albumin synthesis in cachectic hypoalbuminemic patients with advanced pancreatic cancer was found to be no different compared to healthy controls^[19]. Alternatively, it has also been shown that, in patients with cancer, there is an increase in vascular permeability and hence increase in the albumin flux across the capillary wall towards the extravascular compartment^[20]. This is due to the release of tumor necrosis factor, which may increase microvascular permeability, leading to hypoalbuminemia^[21]. Nonetheless, only small changes in transcapillary escape rates were found among patients

with advanced cancer who had hypoalbuminemia. These rates had little correlation with serum albumin concentrations^[22]. Lastly, a disproportionate increase in albumin degradation without a corresponding increase in synthesis can contribute to hypoalbuminemia. This is evidenced by albumin degradation in sarcoma-bearing mice models compared to controls^[23]. However, using ¹³¹I-labeled albumin, Steinfeld^[24] reported an opposite finding; a reduced albumin degradation in patients with advanced cancer.

In patients with cancer, serum albumin continues to be clinically central to assessing the nutritional status, severity of the disease, disease progression, and prognosis. Moreover, serum albumin level has been found to be an independent prognostic factor for survival in various cancers such as melanoma^[25], colorectal^[7,26], pancreatic^[27], lung^[28], gastric^[29], and breast cancer^[30].

ALBUMIN IN COLORECTAL CANCER

Colorectal cancer is the third most common cancer affecting males and females in the United States, and is the second leading cause in terms of cancer-related deaths^[31]. According to the American Cancer Society, the disease is expected to result in 49700 deaths nationally in 2015^[32]. Most early stage disease is detected on screening colonoscopy. However, patients found to have colorectal cancer after symptoms onset tend to have an advanced disease. For localized disease, tumor resection is the only curative modality. Adjuvant chemotherapy regimens based on oxaliplatin have a demonstrated role in increasing cure rates and reducing chances of recurrence among patients with stage III disease^[33]. For patients with stage IV disease, the 5-year survival continues to be poor (13%) despite advances in therapeutic options^[34].

The prognosis of affected patients is currently best predicted by surgical resection and pathological analysis of specimens. The depth of tumor invasion into the bowel wall, the involvement of regional lymph nodes and the presence of distant metastases are the cornerstone of the tumor node metastasis staging system used in this cancer^[33]. A growing body of literature has investigated laboratory markers as prognostic factors adjunct to pathological staging.

The role of pretreatment serum albumin as a prognostic tool was demonstrated by many studies. Heys *et al*^[7] provided the first documentation of such role. Among 431 patients with localized colorectal cancer, serum albumin was an independent prognostic factor for survival. A remarkable 25% increase in the risk of death was seen for each 0.5 g/dL reduction of serum albumin. While the authors did not investigate the effect of the nutritional status on albumin in the study population, their eloquent discussion on the role of inflammation in hypoalbuminemia was an early sign of a paradigm shift^[7].

As surgery is the mainstay of treatment for localized colon cancer, preoperative hypoalbuminemia later

received considerable attention (Table 1). In a Taiwanese study of 3849 colon cancer patients who underwent curative surgery, hypoalbuminemia predicted higher rates of postoperative mortality for both localized (stage I and II) and regionally advanced cancer. The impact was significant 30 d and 5 years after surgery, and remained significant on multivariate analysis. Further, preoperative hypoalbuminemia was associated with more common wound-healing and anastomotic complications, as well as postoperative pulmonary and urinary morbidities. Interestingly, the study found no statistically significant excess of gastrointestinal or cardiovascular surgery-related morbidity in patients with lower albumin levels^[35]. In another study, albumin levels among patients with preoperative metastatic disease appeared to be lower compared to those who are metastasis-free. Such observation is in favor of a systemic inflammatory response as an etiology of hypoalbuminemia, a response that entails a poorer prognosis. Among patients with advanced disease, albumin levels were more reflective of the tumor size rather than the specific tumor stage, with larger tumors having lower serum albumin levels. The authors suggest that the larger volume of tumor cells translates into a higher production of proinflammatory cytokines, which in turn suppress albumin's hepatic production^[36].

Similar results were found among 260 patients with rectal cancer where hypoalbuminemia was an independent risk factor for poor survival following surgery. In the first thirty postoperative days, however, albumin level had no statistically significant impact on survival^[37]. Of note, we found no studies that assessed whether the impact of preoperative albumin level is essentially equal in the surgical treatment of colon and rectal cancer.

The predictive effect of albumin on survival is also seen in cancers across the gastrointestinal tract. In their systematic review, Gupta *et al*^[38] found that, in an overwhelming majority of 26 out of 29 studies, high levels of albumin were associated with better survival among patients with gastrointestinal cancers. A limitation of such review is the heterogeneity in the way albumin was analyzed along with differences in selection criteria (such as tumor stage). In some studies, the serum level as a predictor of outcomes was treated as a continuous variable, while the majority looked at cutoff values that show differences in survival. In most cases, the cutoff was 3.5 g/dL, the lower limit of serum albumin's normal range. Furthermore, the studies were retrospective, which may have led to patient and treatment selection biases. The outcomes of interest and their measurement were also different across the studies.

Hypoalbuminemia was not consistently a prognostic factor in colorectal cancer. Boonpipattanapong *et al*^[26] showed that hypoalbuminemia, when taken alone, has no statistically significant effect on survival among patients who underwent curative surgery. If combined with the level of carcinoembryonic antigen, a tumor marker that correlates with tumor size, the resulting

Table 1 Pretreatment serum albumin and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Heys <i>et al</i> ^[7]	Retrospective cohort study	ALB's prognostic value in localized and metastatic CRC	431 patients	On multivariate analysis, reduced OS with lower ALB	First report of ALB's prognostic value in CRC
Boonpipattanapong <i>et al</i> ^[26]	Retrospective cohort study	Preoperative CEA and ALB's prognostic value in CRC following curative surgery	384 patients	Combination of CEA ≥ 5 ng/dL and ALB ≤ 3.5 g/dL predicts lower 5-yr OS. No statistically significant association of either alone with survival	Linking a tumor marker (CEA) to a host marker (ALB) can have a prognostic significance
Lai <i>et al</i> ^[35]	Retrospective cohort study	Preoperative ALB's value in predicting postoperative outcomes in CRC	3849 patients	Short-term: More complications related to wounds, anastomosis, lungs and urinary system in low ALB group Long-term: Lower 5-yr OS (60% <i>vs</i> 78%) and 5-yr RFS (73.5% <i>vs</i> 78.9%) in low compared to normal ALB group	No difference in short-term postoperative GI and cardiovascular complications
Cengiz <i>et al</i> ^[36]	Retrospective cohort study	Pretreatment ALB and cholesterol's prognostic value in CRC following curative surgery	99 patients	2.8 RR of death in low compared to normal ALB group. No survival effect for cholesterol on multivariate analysis	No difference in CRC recurrence between low and normal ALB groups
Chandrasinghe <i>et al</i> ^[37]	Retrospective cohort study	Pretreatment ALB's prognostic value in rectal cancer following curative surgery	226 patients	Lower 5-yr OS (47% <i>vs</i> 69%) and RFS (69.7% <i>vs</i> 83%) in low compared to normal ALB group. No differences in 30-d postoperative mortality/complications	First report on ALB's long-term prognostic value in rectal cancer
Gupta <i>et al</i> ^[38]	Systematic review	Relationship between pretreatment ALB and cancer survival	59 studies in total; 29 on GI cancers including 12 on CRC	26 of 29 studies on GI cancers had higher OS with higher ALB on multivariate analysis	Inter-study differences in definition of low ALB (continuous variable <i>vs</i> cut-off points)

ALB: Serum albumin; CRC: Colorectal cancer; OS: Overall survival; RR: Relative risk; CEA: Serum carcinoembryonic antigen; RFS: Recurrence-free survival; GI: Gastrointestinal.

score becomes significant in predicting the 5-year survival in all disease stages^[25]. Their finding, however, had a low power (22%). In other studies, it also was noted that albumin levels were normal among patients with early stages of cancer (stages I and II), which would limit its use in prognostication^[8,14]. These results also indicated that more upstream factors potentially precede changes in albumin levels. As such, studies started to look at albumin's relation to other serum proteins, *i.e.*, globulins.

GLOBULIN

The globulin portion of serum is composed of carrier proteins, immunoglobulins, complement factors and enzymes, almost exclusively synthesized by the liver and plasma cells. The myriad of globulin proteins can be classified into four distinct groups by electrophoresis: α_1 , α_2 , β , and γ ^[2].

Changes in the individual or overall globulin fractions have been clinically used to identify several pathologic states, irrespective of changes in albumin. Generally speaking, increases in overall globulins denoted increases in immunoglobulins such as polyclonal gammopathy, and decreases point to reduced synthesis, *via* malnutrition and congenital immune deficiency, or protein loss due to nephrotic syndrome.

Albumin-to-globulin ratio

As aforementioned, albumin and globulin, individually, can be prognostic indicators for a variety of medical states and conditions. However, it has been hypothesized that the albumin-to-globulin ratio (AGR) has greater clinical significance. This ratio has previously been used as a marker for immunoproliferative diseases and multiple myeloma^[1]. It is a marker of chronic inflammation and it is believed that AGR can be used to predict those at risk for malignancy since carcinogenesis is associated with chronic inflammation^[39,40]. As previously mentioned, a systemic cytokine release in cancer leads to hypoalbuminemia, which in turn results in a low AGR. In a sense, a lower AGR would represent a tilt towards proinflammatory states and therefore involves worse outcomes. Indeed, several studies have demonstrated that a low ratio is associated with increased long-term mortality in cancer patients, including those with gastric^[28], breast^[41], and pancreatic cancer^[26].

The AGR has greater predictive value in patients with gastrointestinal cancer, including colorectal cancer (Table 2). In addition to inflammation, this may be a function of the disease processes causing malabsorption and malnutrition^[42]. A study conducted by Azab *et al*^[43] demonstrated that in colorectal cancer, a low ratio is an independent risk factor for 4-year mortality. Previous studies had shown that low pretreatment albumin was

Table 2 Pretreatment albumin-to-globulin ratio and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Azab <i>et al</i> ^[43]	Retrospective cohort study	AGR's prognostic value in CRC-related mortality	534 patients	75% lower 4-yr mortality in high AGR (> 1.32) compared to low AGR tertile (< 1.03), independent of ALB	Study excluded patients who received preoperative chemotherapy
Shibutani <i>et al</i> ^[44]	Retrospective cohort study	AGR's prognostic value in unresectable metastatic CRC treated with palliative chemotherapy	66 patients	High AGR group had higher OS (HR = 2.25, <i>P</i> = 0.03) and PFS (HR = 2.66, <i>P</i> = 0.03) than low AGR group on multivariate analysis	No statistically significant difference in ORR between high and low AGR groups
Suh <i>et al</i> ^[45]	Retrospective cohort study	Relationship between AGR and cancer incidence among healthy adults	26974 adults (30 ≤ age ≤ 80)	Low AGR (< 1.1) had higher cancer incidence, an OR = 3.28 for CRC development and higher cancer mortality compared to AGR > 1.1	First report on association of low AGR with the risk of cancer incidence and mortality in healthy adults

AGR: Serum albumin-to-globulin ratio; ALB: Serum albumin; CRC: Colorectal cancer; OS: Overall survival; PFS: Progression-free survival; OR: Odds ratio; ORR: Overall response rate.

related to poor outcomes^[7,20,36]. However, Azab *et al*^[43] established that the negative impact of a low ratio was maintained in patients with a normal albumin. It was also found that colorectal cancer patients with high globulins had worse outcomes and this was preserved in patients with normal albumin. Overall, patients with low albumin and high globulins were associated with worse 4-year survival, and the AGR was an independent predictor of long-term mortality in colorectal cancer.

Another study of 66 patients with unresectable metastatic colorectal cancer receiving palliative chemotherapy showed that higher pretreatment AGR was associated with improved disease control rates. Patients with higher AGR also had more favorable progression free survival, a finding that was independent of clinicopathological features on multivariate analysis. The objective response rate in the high-AGR group (44.1%) was higher than the low-AGR one (28.1%) but the difference did not reach statistical significance (*P* = 0.208). However, taken as a whole, the study suggests that palliative chemotherapy is less effective with low pretreatment AGR, a marker of underlying inflammatory conditions^[44].

Interestingly, Suh *et al*^[45] set out to determine if the ratio could identify those at increased risk for the development of malignancy in a large sample of healthy adults (*n* = 28292)^[44]. Not only was a low AGR associated with an increased risk for cancer incidence and cancer mortality, but also higher all-cause mortality^[45]. Given the fact that the authors excluded individuals with major chronic diseases or acute illnesses and those with albumin levels less than 3.2 g/dL, one can infer that a malnutrition leading to hypoalbuminemia was not a determinative factor in a causal pathway to the observed worse outcome. Of interest, the higher incidence of colorectal cancer in the low AGR group was statistically significant. Further, a large genome-wide study of 290659 South Korean individuals demonstrated a strong association between a low AGR phenotype and a single nucleotide polymorphism (SNP) in the gene locus of tumor necrosis factor receptor superfamily member 13 (TNFRSF13B). As this receptor regulates

multiple components of the inflammatory response, the SNP is indicative of a genetic susceptibility to inflammatory states^[46]. The broader implication of both previous studies is that the ratio can identify healthy individuals with inflammation and therefore those at risk for developing cancer. More importantly, the findings suggest that there may in fact be a common inflammatory pathway for carcinogenesis.

Glasgow prognostic score

Besides the relation of albumin to total globulin, a parallel interest arose in individual globulins, specifically those that are classical inflammatory markers such as CRP. Similar to albumin, many articles had demonstrated an association of higher CRP with poorer outcomes. In advanced cancer patients, including patients with colorectal cancer, elevated CRP levels were correlated with poorer cancer and non-cancer survival^[47]. Results, however, are inconsistent as a number of studies showed no survival effect of CRP on multivariate analysis^[48]. Earlier data had also suggested that in many malignancies a rise in CRP was accompanied by a fall in albumin^[47]. These observations led McMillan *et al*^[47] to combine both CRP and albumin into one score, the glasgow prognostic score (GPS).

The original GPS assigned a score of 0 to patients with CRP < 10 mg/dL and albumin > 3.5 g/dL, and a score of 2 for those with both CRP > 10 mg/dL and albumin < 3.5 g/dL. Patients with either abnormality received a score of 1. The authors, however, observed that hypoalbuminemia with a normal CRP was rare and had an excellent prognosis. In a sense, hypoalbuminemia alone once again had no effect on survival. This gave rise to the modified GPS (mGPS) where a score of 1 was reserved for patients with CRP > 10 mg/dL. Regardless of albumin levels, patients with CRP < 10 mg/dL had a score of 0, and those with CRP > 10 mg/dL and albumin < 3.5 g/dL were assigned a score of 2. Both the cancer-specific and overall survival significantly correlated with mGPS^[49]. The implication of such correlation is the idea that a systemic inflammatory responses occurs before hypoalbuminemia. The deve-

Table 3 Glasgow prognostic score and colorectal cancer

Ref.	Design	Objective	Sample size	Findings	Comments
Petrelli <i>et al</i> ^[50]	Systematic review and meta-analysis	Quantification of impact of mGPS on OS in CRC	2227 patients from 9 studies	High mGPS was associated with worse OS (HR = 1.69) and CSS (HR = 1.84)	Studies in meta-analysis did not control for concurrent conditions that may affect mGPS, such as sepsis or medications
McMillan <i>et al</i> ^[51]	Systematic review	Relationship between mGPS and cancer outcome	60 studies with 18 on CRC	Higher mGPS in CRC predicted numerous worse outcomes (<i>e.g.</i> , postoperative infections, toxicity, survival, <i>etc.</i>)	Study looked at all cancer patients. CRC studies were geographically restricted to the United Kingdom and Japan
Richards <i>et al</i> ^[52]	Prospective cohort study	Correlation between parameters of body composition and systemic inflammatory response in operable CRC	174 patients	Elevated mGPS was associated with low skeletal muscle index ($P = 0.001$)	No association seen between skeletal mass index and tumor-related variables such as tumor stage
Read <i>et al</i> ^[55]	Prospective cohort study	Relationship between inflammatory/nutritional prognostic factors and outcomes in advanced CRC	51 patients	High GPS was associated with worse OS (HR = 2.27), while the nutritional status as measured by validated scores was not on multivariate analysis	Small and heterogeneous study population

GPS: Glasgow prognostic score; mGPS: Modified glasgow prognostic score; CRC: Colorectal cancer; OS: Overall survival; CSS: Cancer-specific survival.

lopment of the latter would mark a more advanced inflammatory status and therefore worse outcomes.

The mGPS has been remarkably consistent in predicting survival (Table 3). A recent pooled analysis of nine studies with a total of 2227 colorectal cancer patients showed an association between higher scores and both poorer overall survival and cancer-specific survival across various disease stages^[50]. Another systematic review of GPS/mGPS and cancer-related outcomes demonstrates that the scores are independent prognostic factors among patients with operable disease, inoperable disease and those receiving chemoradiation, not only in colorectal cancer but also across other malignancies. The review listed 18 colorectal studies that outlined widespread prognostic implications independent of a variety of clinical factors, such as tumor stage and emergency presentation. The studies were geographically restricted to the United Kingdom and Japan, with no reports from the United States. The reliability of the GPS/mGPS led the authors to suggest that it should be part of the routine assessment of cancer patients, in conjunction with the currently recommended staging^[51].

Many colorectal cancer patients experience cancer cachexia, an involuntary weight loss that is accompanied by a worsening quality of life and mortality. In a study of 174 patients who underwent surgery for primary colorectal cancer, a systemic inflammatory response as measured by mGPS was a major predictor of cancer cachexia. This association was not seen with the white cell count and the neutrophil-to-lymphocyte ratio, two well-established inflammatory scores^[52]. Such findings are in line with previous data indicating that scores that are based on CRP as a specific marker of inflammation are superior in predicting poorer outcomes among cancer patients^[53]. Despite its multifactorial nature and the multitude of available definitions, cancer cachexia is well predicted by mGPS, suggesting that mGPS can be used as a simple tool to investigate and treat cancer

cachexia^[54].

Read *et al*^[55] compared the impact of nutritional and inflammatory factors on survival among 51 colorectal cancer patients followed over 30 mo. The patient-generated subjective global assessment (PG-SGA) is a validated nutritional assessment tool extensively used in cancer patients. The multivariate analysis revealed that mGPS was a strong predictor of poor prognosis, while the nutritional status as assessed by PG-SGA was not^[55]. Despite its small sample size, the study offers additional evidence that the systemic inflammatory response essentially mediates the observed relationship between the nutritional status and the decline in survival in colorectal cancer.

CONCLUSION

We highlighted how pretreatment serum albumin levels, AGR and mGPS have prognostic values among colorectal cancer patients. Their measurement is relatively cheap, reproducible and widely available, which led many to call for their incorporation into the routine assessment of these patients. The potential of a publication bias to positive associations with survival, although a concern, is less likely given the diversity of study designs and their institutions of origin. Another possible limitation of the listed studies is the combination of colon and rectal cancer into one entity. Evidence exists that the two malignancies have biological distinctions that give rise to differences in their behaviors^[56].

Basic and clinical research results suggest that hypoalbuminemia, malnutrition and cancer cachexia are all consequences of the body's systemic inflammatory response to the malignancy. The superiority and consistency of mGPS in predicting poorer outcomes greatly support such pathophysiology. Also in favor are the studies on AGR, although limited in number. Recent years have seen this literature shift in our understanding

of hypoalbuminemia. Albumin is now seen as the main negative acute phase reactant in humans. We found no studies that investigated clinicians' perceptions of hypoalbuminemia, yet we believe that the view of hypoalbuminemia as a nutritional marker among cancer patients remains to be a common one.

Despite the multitude of studies supporting the prognostic role of mGPS in colorectal cancer prognosis, its use remains at the research level. In the absence of validated controlled trials, the score is yet to be incorporated into clinical treatment algorithms. Future research should clarify its role in patient stratification and thus clinical decisions. Work is also needed to come up with interventions aimed at moderating the inflammatory response in order to halt the slow, yet fatal, progression of cancer cachexia.

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Management of low colorectal anastomotic leak: Preserving the anastomosis

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Abstract

Anastomotic leak continues to be a dreaded complication after colorectal surgery, especially in the low colorectal or coloanal anastomosis. However, there has been no consensus on the management of the low

colorectal anastomotic leak. Currently operative procedures are reserved for patients with frank purulent or feculent peritonitis and unstable vital signs, and vary from simple fecal diversion with drainage to resection of the anastomosis and closure of the rectal stump with end colostomy (Hartmann's procedure). However, if the patient is stable, and the leak is identified days or even weeks postoperatively, less aggressive therapeutic measures may result in healing of the leak and salvage of the anastomosis. Advances in diagnosis and treatment of pelvic collections with percutaneous treatments, and newer methods of endoscopic therapies for the acutely leaking anastomosis, such as use of the endosponge, stents or clips, have greatly reduced the need for surgical intervention in selected cases. Diverting ileostomy, if not already in place, may be considered to reduce fecal contamination. For subclinical leaks or those that persist after the initial surgery, endoluminal approaches such as injection of fibrin sealant, use of endoscopic clips, or transanal closure of the very low anastomosis may be utilized. These newer techniques have variable success rates and must be individualized to the patient, with the goal of treatment being restoration of gastrointestinal continuity and healing of the anastomosis. A review of the treatment of low colorectal anastomotic leaks is presented.

Key words: Anastomotic leak; Colon and rectal surgery; Colorectal anastomosis; Management anastomotic leak; Endoscopic treatment; Surgical complications

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Core tip: The treatment of the leaking colorectal or coloanal anastomosis continues to be challenge for surgeons to manage. This paper presents both older and new techniques in the treatment of low pelvic anastomotic leak, focusing primarily on salvage of the leaking anastomosis.

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INTRODUCTION

Despite advances in modern colorectal surgery, anastomotic leak continues to be a significant cause of morbidity and mortality. Risk of colonic anastomotic leak continues to range between 1.5% and 23%^[1-5], with low colorectal and coloanal anastomoses posing the highest risk^[6]. Leaks also result in increase in hospital costs and increase length of stay^[7,8]. The best treatment for the management of anastomotic leak has not yet been identified, especially in these very low anastomoses^[9].

The presentation of anastomotic leak is widely variable, as is its definition. Some patients present with florid sepsis and peritonitis, while others have a more insidious course with fevers, leukocytosis, and abdominal pain. Management is typically guided by the patient's clinical picture, with operative intervention for the sickest patients, and more conservative interventions for those who are clinically stable. The management of the leaking low colorectal anastomosis has changed over the past several decades. Many new techniques are now available, with the goal being preservation of the anastomosis, and restoration of gastrointestinal continuity with good functional outcome.

OPERATIVE INTERVENTION OF ACUTE LEAK

Traditionally, the treatment of choice for a leaking colorectal or coloanal anastomosis had been resection of the anastomosis with exteriorization of the proximal limb as an end colostomy (Hartmann's procedure). This removes the source of sepsis, but in the majority of cases, leaves the patient with a permanent stoma, with less than 50% of patients ultimately undergoing reversal^[1,10-13]. Hartmann's procedure may be necessary in the patient with diffuse ischemia or necrosis or large dehiscence of the anastomosis at reoperation^[8], but in the recent literature the trend continues to be moving away from resecting the extraperitoneal anastomosis^[2,14,15]. Leaks occurring from intraperitoneal anastomoses continue to have higher rates of resection of the anastomosis than those resulting from extraperitoneal leaks^[2,16].

Many have advocated the use of a "divert and drain" technique for those patients requiring reoperation for a leaking extraperitoneal anastomosis^[2,15-18], consisting of proximal fecal diversion with loop ileostomy, and drain placement into the pelvis, without manipulation of the pelvic anastomosis. This avoids the dangers of reoperation in an acutely inflamed field, and drainage of

the pelvis has been shown to be adequate to control the source of sepsis. Healing rates with this strategy have ranged from 54%-100%^[2,19], without need for further intervention to the leaking anastomosis. Krarup *et al.*^[20] found that patients who had anastomotic salvage with proximal diversion had a 3 fold increase likelihood of stoma reversal, compared to those with resection of anastomosis and end stoma creation in intraperitoneal leaks.

For those patients whose initial surgery was performed laparoscopically, a laparoscopic approach to reoperation may be performed safely at the discretion of the operating surgeon^[14]. In one study 16/18 patients requiring reoperation for anastomotic leak were able to be managed laparoscopically with ileostomy and operative drainage, suggesting that this approach is safe. Eighty percent of these patients were able to undergo subsequent stoma reversal^[14].

Whichever method is utilized for the patient requiring reoperation for anastomotic leak, several points should be taken into consideration. Edden *et al.*^[21] suggest the following principles: "(1) Minimizing the extent of surgical intervention; (2) Shortening the procedure as much as feasibly possible; (3) Adequate abdominal washout; and (4) Proximal fecal diversion should be favorably considered preoperatively with, the relevant actions such as stoma markings".

NON OPERATIVE AND NEWER INTERVENTIONS OF ACUTE LEAK

Reoperation for control of sepsis is rarely necessary in those patients who already have a diverting stoma present at the time of the leak^[2,16,17]. This is likely to be the majority of patients with extraperitoneal anastomoses. In these patients, and those without a stoma who do not require abdominal reoperation for a contained pelvic leak, options for treatment include transanal or percutaneous drainage of the pelvic collection, or newer techniques such as endosponge therapy, endoscopic stenting or endoscopic clip placement.

Transanal drainage through the anastomosis has been a well described technique in management of low anastomotic leaks from low colorectal, coloanal or ileoanal anastomoses. Thorson *et al.*^[22] described proctoscopic placement of a foley catheter into the leaking anastomosis, which was then kept in place and irrigated every 6 h. Approximately 7-14 d later, the cavity decreases in size to allow removal of the catheter and spontaneous healing. Another technique utilizes an exam under anesthesia with placement of a suction drain vs malecot or foley across the anastomosis. The majority of patients (58%) with diverting stomas were able to be managed with transanal drainage, compared with 9% without a diverting stoma. None of these patients required an abdominal intervention for their leak, although 50% required an additional local intervention^[23].

Percutaneous drainage using a computed tomography guided approach has become a common method in the management of contained pelvic leaks^[5,23]. This can be placed either transgluteally or transabdominally depending on the location of the leak. Fistula development, although rare, is a well described complication of percutaneous drainage^[24]. When comparing transanal drainage vs percutaneous drainage, one study found no difference in success rates between the two techniques in patients with ileoanal anastomoses^[25].

A novel technique in transanal drainage is the use of the Heald Silastic Stent. This was initially designed to protect a low colorectal anastomosis as an alternative to diverting ileostomy^[26]. The stent is a 4 cm soft silastic tube with flanges on either end, and is placed within the anal canal below the level of the leak, thus stenting open the anus, and allowing decompression of the anastomotic leak. It can be used alone or in combination with percutaneous drainage^[27,28].

Despite control of acute sepsis with drainage of the collection, there are still many patients whose anastomoses will not heal or who will develop a chronic sinus. This is postulated to occur due to accumulation of mucous and fluid in the presence of a closed anus, converting a presacral abscess into a chronic sinus^[29]. A percentage of these chronic sinuses will heal with time, however, the scarring and fibrosis may lead to worsened bowel function^[30]. Proponents of early intervention and closure of the leaking anastomosis feel that the function of the neorectum will be improved with earlier healing, and less fibrosis. Prevention of the persistent sinus will then lead to better healing, and increase in stoma closure rates^[29,31,32].

ENDOSPONGE

One of the newer techniques in management of the colorectal anastomotic leak is a minimally invasive approach involving the use of an endoscopically placed endoscopic vacuum device. The technique, originally described by Weidenhagen *et al*^[9], utilizes an open pored, polyurethane sponge (B Braun Medical BV, Melsungen, Germany), with an attached evacuation tube which is then connected to a vacuum drainage system. This sponge is placed *via* an introducer sleeve that is fitted over an endoscope and placed through the anastomotic defect and into the pelvic cavity. Position of the sponge into the cavity is verified endoscopically. The sponge is then exchanged every 48-72 h, downsizing the sponge as the size of the cavity decreases^[9,29]. The initial series consisted of 29 patients who underwent endosponge treatment over a median of 34 d, with 28 having healing of the anastomosis^[9]. The endosponge therapy was stopped when the cavity was less than 1 cm in size. Adjuncts to closure included fibrin glue in 9 patients.

Proponents of the endosponge treatment feel that the sponge not only allows for drainage of the cavity, but also stents open the anus to allow unobstructed drainage. The negative pressure of the sponge itself

allows contact with the entire surface of the cavity uniformly, leading to a decrease in size of the cavity with time. Early application of the sponge, when the neorectum is more pliable, is an essential component of treatment, as the defect is more likely to close^[33]. In one series, healing occurred in 89% of leaks treated within 60 d of the original surgery, and in only 50% of those treated more than 60 d out^[34]. Visible vessels in the cavity are a contraindication to treatment^[9], and higher anastomoses make placement of the sponge difficult^[29]. Most authors feel that patients should undergo fecal diversion prior to treatment as there is concern for stool contamination of the defect, and failures tended to occur in those patients who were not diverted^[4,29,34]. This treatment has been applied to patients either with or without preoperative radiation for rectal cancer with success^[4,9,29,34,35].

STENTING

Endoscopic stenting has also been utilized in the management of colorectal anastomotic leak. Covered metal, plastic and biodegradable stents have all been utilized with success^[3,6,35-37]. The stent can only be placed across an end to end anastomosis and the distal end of the stent must be 5 cm or more from the anal verge, so this technique is not an option for very low anastomoses^[35]. Technical success for stent placement has approached 100% in some series, with clinical success 80%-100%^[3,6,35,36], although this has only been in small case series. Up to 40% of patients with covered stents will require stent replacement due to migration^[6,35]. Partially covered stents appear to have less migration than fully covered stents^[37]. They are left in place for up to 50-60 d, and are removed once the anastomosis heals^[6,35]. Endoscopic stenting can be utilized in patients both with and without a stoma, and in combination with percutaneous drainage of an associated cavity^[3,35]. There are also small case series with the use of biodegradable stents made of polyethylene coated polyp-p-dioxanone. Reabsorption of the stents occur at 11-12 wk after placement. The use of these stents in combination with other treatment modalities such as fibrin glue, cyanoacrylate, endosponge and clips resulted in closure of 5 leaks in one series^[37]. The expense of the biodegradable stents and the fact that they require additional anchoring to prevent migration, may limit their use.

ENDOSCOPIC CLIPPING

Another endoscopic therapy is the application of clips to approximate the edges of the leaking anastomosis. Standard clips such as those used to control bleeding or acute perforation, can be used^[38], but these have a low closure force and are limited in size, so are not ideal in closing anastomotic leaks, as the tissue is more scarred and fibrotic, and often irradiated. A newer over the scope clip system using a nitinol clip loaded at the tip of the endoscope (OTSC, Ovesco, endoscopy, Tübingen,

Germany) has the benefit of a larger clip area and increased compression, which allows for full thickness closure^[39]. The wall is anchored with a dedicated grasper and bowel wall is suctioned as the clip is released^[39,40]. In a series of 188 patients with gastrointestinal defects, of which 50 involved the colon and rectum, technical and clinical success with OTSC placement 93.8% and 92.7%, respectively^[41]. Twelve of 15 lower gastrointestinal tract leaks healed using OTSC. Success was higher for leaks than for fistulae. Given that the leaks were treated earlier in the postoperative course, this suggests that timing of application may play a role in the successful closure of the defect. A smaller series of colorectal anastomoses showed healing in 86% of 14 leaks treated with OTSC. Only 2 patients had a diverting stoma at the time of the clip placement^[39]. Indications for the use of the OTSC system are small defects less than 1.5 cm in size and the absence of a pelvic collection^[39]. Percutaneous drains may be utilized to drain a pelvic abscess prior to application of the clip^[40]. A diverting stoma is not felt to be necessary for successful treatment^[40].

Combinations of endoscopic treatment may also have a role in the treatment of anastomotic leak. Endosponge therapy has been used in combination with clips or transanal suturing to close the defect once the abscess cavity had decreased in size^[29]. Fibrin glue injection has also been utilized with endosponge and stenting^[9,36]. If one endoscopic modality fails, additional treatment with other modality is an option. An algorithm for endoscopic closure was proposed by Chopra^[3]. For those patients with a defect greater than 2 cm, diverting ileostomy with endosponge therapy is preferred. Treatment of choice for defects less than 2 cm in size in the mid rectum is endoscopic stenting. The majority of the stented patients do not require diversion, but may require percutaneous drainage of fluid collections. Fibrin sealant is utilized for tiny (less than 3 mm) defects without abscess. For those with abscess only, percutaneous drainage is preferred^[3]. Using this algorithm, 77% of patients had restoration of bowel continuity compared to 57% of surgically managed patients (Hartmann's procedure or diverting ileostomy alone).

Other, newer options for repair of the leaking anastomosis include closure of the defect using a transanal minimally invasive surgery approach and transanal endoscopic microsurgery, but these have been limited to case reports^[13,42].

DELAYED TREATMENT OF ANASTOMOTIC LEAK: THE CHRONIC SINUS

Anastomotic sinuses have been shown to develop in up to 36% of anastomotic leaks, resulting in permanent stoma for many patients^[43]. A small percentage, up to 8% are asymptomatic and found on contrast enema during workup for ileostomy takedown^[2,17]. Up to 63% of patients with chronic anastomotic sinuses will

require multiple interventions^[5,43]. A "watch and wait" approach has been utilized in the treatment of these chronic sinuses, as some will close with time, including all 10 subclinical leaks in one study over a median of 17 mo^[17]. For those that do not heal, there are few options for local treatment, and many will keep their stoma permanently.

Marsupialization of the presacral sinus can be performed utilizing an endoscopic stapler^[44], electrocautery, or laparoscopic electrocautery scissors^[45]. This allows complete drainage of the cavity with incorporation of the sinus tract into the lumen of the bowel. Endoscopic evaluation of the cavity after marsupialization demonstrates epithelialization of the cavity, and allows for reversal of diverting stomas^[44]. This technique has been utilized successfully in colorectal anastomoses as well as ileal pouch anal anastomoses.

Fibrin glue injection, has been utilized successfully in the treatment of chronic presacral sinuses^[46] and as a single case report in combination with endoscopic clip placement in the treatment of chronic fistula^[38]. This technique may have some value in small, narrow tracts, whereas marsupialization may be utilized in large cavities^[43].

Another option is for repair of the chronic sinus through a transanal approach utilizing a flap closure of the defect. Endorectal flap advancement is well described in ileoanal anastomotic sinuses^[47,48]. A small series of patients with persistent leaks after surgery for rectal cancer underwent delayed repair using either a flap (4/6 procedures) or direct closure of the defect. Flaps were created after excising and closing the sinus opening, with a broad endorectal flap in 3 cases, and dermal flap in one^[49]. Of the 5 patients in the series, 4 had successful local treatment, and were able to have subsequent reversal of their ileostomies, even in the face of prior radiation to the rectum.

For those patients failing conservative or local treatment of the leak, reoperation with resection of the leaking anastomosis and re-anastomosis remains the final treatment option^[50]. Patients should be counseled extensively on the risk of reoperation including the possibility of permanent stoma. In one series, all patients were able to have successful reanastomosis. The authors note that this may require full mobilization of the colon, with ligation of the middle colic vessels, and right colon to rectal anastomosis in order to create a tension free anastomosis^[50]. Resection and reanastomosis should be considered the treatment of last resort, and patients who fail to respond to more conservative procedures may end up with a permanent stoma as the final "treatment" of their leak.

CONCLUSION

Newer methods that preserve the colorectal anastomosis are being utilized in the treatment of anastomotic leaks, with improvement in restoration of gastrointestinal continuity. Those techniques that involve early closure of

the leak need further investigation on long term outcome and function, but appear to be promising alternatives in the treatment of leak. The use of defunctioning stomas continue to be common, regardless of the method of treatment; dismantling of the anastomosis with Hartmann's procedure is becoming less common, except in the case of complete disruption or ischemic necrosis. Comparison of functional outcome may prompt surgeons towards earlier closure of the leaking anastomosis as opposed to treatment of a chronic leak or sinus, but further prospective and long term studies are needed.

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Observational Study

Long term recurrence, pain and patient satisfaction after ventral hernia mesh repair

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Abstract

AIM: To compare long term outcomes of laparoscopic and open ventral hernia mesh repair with respect to recurrence, pain and satisfaction.

METHODS: We conducted a single-centre follow-up study of 194 consecutive patients after laparoscopic and open ventral hernia mesh repair between March 2000 and June 2010. Of these, 27 patients (13.9%) died and 12 (6.2%) failed to attend their follow-up appointment. One hundred and fifty-three (78.9%) patients attended for follow-up and two patients (1.0%) were interviewed by telephone. Of those who attended the follow-up appointment, 82 (52.9%) patients had received laparoscopic ventral hernia mesh repair (LVHR) while 73 (47.1%) patients had undergone open ventral hernia mesh repair (OVHR), including 11 conversions. The follow-up study included analyses of medical records, clinical interviews, examination of hernia recurrence and assessment of pain using a 100 mm visual analogue scale (VAS) ruler anchored by

word descriptors. Overall patient satisfaction was also determined. Patients with signs of recurrence were examined by magnetic resonance imaging or computed tomography scan.

RESULTS: Median time from hernia mesh repair to follow-up was 48 and 52 mo after LVHR and OVHR respectively. Overall recurrence rates were 17.1% after LVHR and 23.3% after OVHR. Recurrence after LVHR was associated with higher body mass index. Smoking was associated with recurrence after OVHR. Chronic pain (VAS > 30 mm) was reported by 23.5% in the laparoscopic cohort and by 27.8% in the open surgery cohort. Recurrence and late complications were predictors of chronic pain after LVHR. Smoking was associated with chronic pain after OVHR. Sixty point five percent were satisfied with the outcome after LVHR and 49.3% after OVHR. Predictors for satisfaction were absence of chronic pain and recurrence. Old age and short time to follow-up also predicted satisfaction after LVHR.

CONCLUSION: LVHR and OVHR give similar long term results for recurrence, pain and overall satisfaction. Chronic pain is frequent and is therefore important for explaining dissatisfaction.

Key words: Female; Ventral/surgery; Herniorrhaphy/methods; Laparoscopy; Male; Pain; Patient satisfaction; Postoperative complications/epidemiology; Recurrence; Hernia

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Core tip: This is an observational and retrospective study of laparoscopic and open ventral mesh repair involving both incisional and non-incisional hernias. The principal outcome measures were recurrence, abdominal pain and satisfaction. Of the original cohort of 194 patients, 153 patients (78.9%) were examined individually with a mean follow-up period of 51 mo. Our results demonstrate an overall recurrence rate of 16.1% and we discuss the potential reasons. Excluding clinical recurrence, 13.7% suffered from chronic pain and 55.3% were satisfied with the outcome. Laparoscopic and open ventral mesh repair are comparable with respect to outcome measures.

Langbach O, Bukholm I, Benth JŠ, Røkke O. Long term recurrence, pain and patient satisfaction after ventral hernia mesh repair. *World J Gastrointest Surg* 2015; 7(12): 384-393 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i12/384.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i12.384>

INTRODUCTION

Benefits and pitfalls^[1] have been documented for both the mesh-reinforced open and laparoscopic approaches to incisional and ventral hernioplasty. Most papers

suggest that laparoscopic ventral hernia mesh repair (LVHR) results in a shorter hospital stay, fewer wound complications and better cosmetic results compared to open ventral hernia mesh repair (OVHR)^[2]. Favourable outcome of hernia surgery is often measured by the absence of recurrence and pain^[3]. Chronic pain due to sensations of stiffness and foreign body reaction to the mesh, are adverse effects of mesh implantation^[4,5]. Recurrence rates after LVHR and OVHR vary considerably and are related to surgical methods and skills, patient characteristics and length of follow-up^[6]. The recurrence rate appears to reach peak incidence level after two years, with only small additional recurrences appearing later on^[7].

The purpose of the present follow-up study was to compare laparoscopic and open mesh repair for incisional and non-incisional hernias in terms of complications, recurrence, pain and patient satisfaction with the outcome. As the study is of explorative character, no adjustments were made for multiple hypothesis testing.

MATERIALS AND METHODS

We conducted a follow-up study of all patients undergoing mesh repair for incisional and non-incisional hernia at Akershus University Hospital, Norway between March 2000 and June 2010. Follow-up examinations were carried out by one surgeon and one study nurse. Data from medical records and clinical examinations were recorded. The recorded hernia operation is referred to as the index mesh repair.

We enrolled 194 consecutive patients, of whom 94 had been treated with laparoscopic mesh repair and 100 with open mesh repair including 11 conversions. Of these, 27 patients had died and 12 patients failed to attend their follow-up appointment without providing an explanation. There was no significant difference between the patient characteristics of eligible and non-eligible patients. One hundred and fifty-three patients attended their follow-up appointment and two patients were interviewed by telephone. Of the patients who attended their follow-up appointment, 82 (52.9%) had received a laparoscopic mesh repair while 73 (47.1%) patients had undergone open mesh repair, including 11 conversions from laparoscopic surgery due to intestinal injuries or technical problems (Figure 1). These 11 patients are included under open surgical procedures in tables and text, *i.e.*, as per protocol. The patients were examined at various points after surgery as presented in Table 1. Median follow-up was 48 mo (9-88 mo) after LVHR and 52 mo (12-115 mo) after OVHR. Comorbidity was classified according to Charlson^[8].

Postoperative complications were classified according to Dindo *et al*^[9]. Postoperative complications were recorded as minor (Clavien I + IIIa) or major (Clavien IIIb + IV).

Late complications (> 30 d after surgery) were recorded using medical records.

Pain was assessed by a 100 mm visual analogue

Table 1 Patient and hernia characteristics (n = 155)

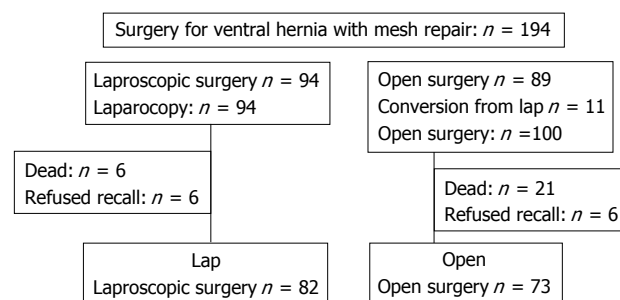
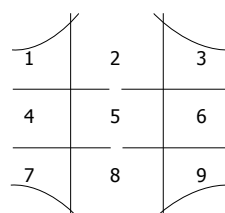
Characteristics	Laparoscopic	Open	P value
Age (yr), mean ± SD	56.5 ± 14.9	57.2 ± 11.6	0.76
Gender: Male	34 (41.5)	34 (46.6)	0.52
BMI (kg/m ²), mean ± SD	30.7 ± 6.2	29.7 ± 5.3	0.29
ASA class			0.64
I	13 (15.9)	13 (17.8)	
II	62 (75.6)	55 (75.3)	
III	7 (8.5)	5 (6.8)	
Charlson index score			0.41
Score 0	25 (30.5)	16 (21.9)	
Score 1	14 (17.1)	19 (26.0)	
Score 2	16 (19.5)	19 (26.0)	
Score 3	16 (19.5)	12 (16.4)	
Score 4, 5, 6	11 (13.4)	7 (9.6)	
Type of co-morbidity			0.64
Hypertension/congestive heart disease	23 (28.0)	19 (26.0)	
³ COPD	16 (19.5)	12 (16.4)	
Diabetes	5 (6.1)	5 (6.1)	
Neurological disease	2 (2.4)	1 (1.4)	
Multimorbid	0	3 (4.1)	
Miscellaneous	8 (9.8)	10 (13.7)	
Smoking	28 (34.1)	26 (35.6)	0.85
Hernia type			0.96
Incisional	66 (80.5)	59 (80.8)	
Non-incisional	16 (19.5)	14 (19.2)	
Recurrent hernia	15 (18.3)	13 (17.8)	0.94
Hernia area (cm ²) ± SD	57.5 ± 56.9	44.9 ± 52.9	0.17
¹ Incisional hernia			0.41
Small/medium < 70 cm ²	44 (67.7)	41 (74.5)	
Large ≥ 70 cm ²	21 (32.3)	14 (25.5)	
² Non-incisional hernia			0.003
Small/medium < 13 cm ²	6 (40.0)	13 (92.9)	0.06
Large ≥ 13 cm ²	9 (60.0)	1 (7.1)	
Hernia location			0.40
Midline	74 (90)	67 (92)	
Others	8 (10)	6 (8)	
Mesh size (cm ²), mean ± SD	235.1 ± 113.4	184.5 ± 124.3	0.03
Follow up (mo), median, range	48 (9-88)	52 (12-115)	0.006

¹Missing value in laparoscopic group, 4 patients; Missing values in open group; ²Missing value; laparoscopic group; ³Chronic obstructive pulmonary disease. Data are numbers with percentages in brackets unless otherwise indicated.

scale (VAS) ruler anchored by word descriptors at each end to calculate the patient's impression of pain^[10]. Chronic pain was defined as pain above 30 mm in the last 30 d^[11]. During the examination, we asked about maximum abdominal wall pain in the last 30 d, and maximum abdominal wall pain associated with sedentary and moderate physical activities like climbing stairs, outdoor walking, gardening. The clinical examination focused on pain by palpating the abdominal wall in nine areas (Figure 2). Duration of surgery was divided into two categories by the median in each surgical group.

Hernia characteristics

We adopted the classification by Muysoms *et al.*^[12] which distinguishes between non-incisional and incisional hernias and which classifies recurrent hernias of any origin as incisional. Hernia area was calculated by the formula: $p/4 \times A \times B$, where A and B are the two diagonals. Due to small numbers of patients in the

**Figure 1** Consort diagram.**Figure 2** Sectoral map of the abdominal wall.

small-sized non-incisional and incisional categories, we constructed a small and medium sized hernia group and a large sized hernia group in both categories. Incisional hernia size was categorised into ordinal variables as small/medium sized (< 70 cm²) and large sized hernias (≥ 70 cm²). Non-incisional hernia size was categorised into ordinal variables as small/medium sized (< 13 cm²) and large sized hernias (≥ 13 cm²) (Table 1). Hernia locations were defined by sectoral mapping of the abdominal wall^[13].

Operative technique

The types of surgical approach and mesh selected were based on the surgeon's preferences and experience. In laparoscopic mesh repair, the access to the abdominal cavity was established with open introduction of a 12 mm trocar. Capnoperitoneum was established with a pressure of 12 mmHg. Two or three additional abdominal trocars, 5 or 10 mm, were positioned on the surgeon's side or on the contralateral side if appropriate. Adhesions were detached with scissors and occasionally with LigaSure® or ultracision. Fatty tissue on the inner abdominal wall was removed. The hernia sac was not routinely removed. The defect was measured. The mesh was introduced through the 12 mm trocar and placed over the defect with a minimum of 5 cm hernia overlap using tacks or transfacial non-absorbable sutures according to the surgeon's preferences. The mesh did not necessarily cover the entire scar with a 5 cm overlap.

In open mesh repair, the incision was made over the hernia thus exposing the hernia content. The hernia sac was removed if possible. The peritoneum or posterior rectus sheet was dissected from the rectus muscle. The posterior sheet was not routinely closed with running absorbable sutures. The mesh was anchored in a retromuscular position with running non-resorbable trans-

Table 2 Perioperative characteristics (*n* = 155)

	Laparoscopic	Open	<i>P</i> value
Operative time, min, mean \pm SD	117 \pm 54	92 \pm 44	0.002
Emergency hernia operation	0	12 (16.4)	
Preoperative antibiotics	30 (36.6)	33 (45.8)	0.24
Postoperative antibiotics	12 (14.6)	17 (23.3)	0.17
Postoperative stay, d, median (IQR)	2 (1-3)	2 (1-4)	0.67
No. of trocars, median (range)	3 (3-6)	-	-
No. of tacks	28 (10-70)	-	-
Mesh types			
Polypropylene	0	27 (38.0)	
Marlex	0	7 (9.9)	
Bard composix	20 (25.0)	5 (7.0)	
Parietex composite	39 (48.8)	9 (12.7)	
Proceed	7 (8.8)	1 (1.4)	
TiMESH	2 (2.5)	1 (1.4)	
Unknown	0	6 (8.5)	
Unknown	0	6 (8.5)	

Data are numbers with percentages in brackets unless otherwise indicated. IQR: Interquartile range.

facial sutures and seeking to achieve a 5 cm overlap. The anterior rectus sheet was not routinely closed. Neither intraperitoneal onlay mesh technique with Kugel patch nor mesh plug repair was applied. For small umbilical and epigastric hernias, the mesh was placed as described, but with minor modifications. Drains were used as per the surgeon's preferences. Adhesions were graded according to Mazuji *et al.*^[14]. In the OVHR cohort, the adhesion score could not be established due to deficient reporting.

For the purpose of examining the association between intraperitoneal adhesions and complications, the grading was dichotomised into adhesions involving, or not involving, the intestine.

Recurrence

Clinical recurrence was determined at follow-up by physical examination and was defined as a detectable gap in the abdominal wall with or without bulging of viscera. Patients with signs of clinical recurrence were intentionally examined by magnetic resonance imaging or computed tomography scan. There were three false positive cases, two after OVHR and one after LVHR. Four patients with clinical recurrence, did not attend for radiology examination. Information received of ventral hernia mesh repair after the index operation was registered as recurrence. Overall recurrence was therefore defined as clinical recurrence, corrected for false positive cases together with information of ventral hernia mesh repair after the index operation.

Statistical analysis

The analysis was performed on a per protocol basis. Data in text and tables are given as mean \pm SD, median (minimum-maximum) and frequency (percentage), as appropriate. For postoperative stay, we have chosen interquartile range instead of standard deviation due to some instances of extreme values^[15]. Categorical variables were compared by the χ^2 -test and the Fisher

exact test as appropriate. Comparison of continuous variables was performed using Student's *t*-test. Non-parametric variables were handled and comparisons of median values were performed using the Mann-Whitney *U*-test and the Median test. Variables associated with postoperative complications, hernia recurrence, pain and overall satisfaction at the *P* < 0.1 level in bivariate analyses, were included in multivariate logistic regression models. The results were presented as odds ratios (ORs) with a 95%CI estimated by a multivariate model unless otherwise stated. All tests were two-tailed with a significance level of 0.05. The analyses were performed using the SPSS version 22 (SPSS Inc., Chicago, IL United States).

RESULTS

Patient and hernia characteristics are presented in Table 1. The groups were similar with regard to age, gender, body mass index (BMI), comorbidity and smoking habits. Thirty-four point eight percent of the patients were smokers, 18.1% had chronic obstructive pulmonary disease (COPD) or asthma and 27.1% had hypertension and/or congestive heart disease. The observation time after open surgery was longer than after laparoscopic surgery. Laparoscopic surgery was more time-consuming compared to open hernia mesh repair (*P* = 0.002) (Table 2). There were 18 (22.0%) minor and seven (8.5%) major complications after LVHR and 22 (30.1%) minor and eight (11.0%) major complications after OVHR (*P* = 0.39) (Table 3). Six patients had two types of complications. Prolonged operative time was associated with an increased rate of minor complications after LVHR (*P* = 0.02), but not after OVHR (*P* = 0.28). Wound infection (*P* = 0.05, OR = 2.74, 95%CI: 0.99-7.65) and seroma (*P* = 0.01, OR = 3.65, 95%CI: 1.25-10.72) were more pronounced after OVHR. In the LVHR cohort, operative time > 108 min. was a predictor for postoperative complications in the crude model (OR = 3.96, 95%CI: 1.44-10.9). The presence of intraperitoneal adhesions involving the intestine (OR = 3.0, 95%CI: 1.1-8.2) or incisional hernias (OR = 8.4, 95%CI: 1.0-67.9) was a predictor for postoperative complications only in the crude model. In the OVHR cohort, large incisional hernias were not associated with postoperative complications in general (OR = 1.71, 95%CI: 0.46-6.32). In multivariate analysis only prolonged operative time was a predictor of postoperative complications (*P* < 0.03, OR = 1.02, 95%CI: 1.00-1.04) (Table 3). The need for postsurgical intervention was not different between the two groups (*P* = 0.58).

Recurrence

We discriminated between clinical recurrence and overall recurrence at follow-up. Ten patients had surgery for recurrence in the follow-up period, six of these had no recurrence at follow-up. The frequency of recurrence judged clinically, was 10 (12.2%) after LVHR and 15 (20.5%) after OVHR. Information received of hernia

Table 3 Perioperative, postoperative and late complications

	Laparoscopic	Open	P value
Postoperative complications - grading			0.39
Minor (I - IIIa)	18 (22.0)	22 (30.1)	
Major (IIIb-IV)	7 (8.5)	8 (11.0)	
Postoperative complications - type			0.17
Wound infection	6 (7.3)	13 (17.8)	0.05
Seroma	5 (6.1)	14 (19.2)	0.02
Deep infection	1 (1.2)	1 (1.4)	
Pneumonia	2 (2.4)	1 (1.4)	
Unclassified infection	3 (3.7)	4 (5.5)	
Subcutaneous bleeding	4 (4.9)	2 (2.7)	
Substantial pain	6 (7.3)	3 (4.1)	
Others	2 (2.4)	2 (2.7)	
Intraoperative complications - type			0.14
Enterotomy	0	4 (5.5)	
Colotomy	1 (1.2)	0	
Late complications - type			0.24
Subileus/ileus	3 (3.7)	0	
Deep infection	1 (1.2)	2 (2.7)	
Substantial pain	4 (4.9)	3 (4.1)	
Hematoma	0	1 (1.4)	
Seroma	4 (4.9)	2 (2.7)	
Wound infection	1 (1.2)	4 (5.5)	
Others	-	2 (2.7)	

Data are numbers with percentages in brackets unless otherwise indicated.

surgery for recurrence after the index mesh repair, confirmed an overall recurrence rate of 14 (17.1%) after LVHR and 17 (23.3%) after OVHR ($P = 0.33$) (Table 4). In univariate analysis, hernia size, BMI, numbers of trocars and length of postoperative stay were associated with recurrence (Table 5). Variables thought of as confounders, namely gender, age, BMI and COPD, were adjusted for in multivariate analysis. There was no difference between incisional and non-incisional hernias with respect to recurrence. In the multivariate model, BMI, number of trocars and length of postoperative stay were independent predictors of recurrence (Table 6). In the OVHR cohort, univariate analysis showed that smoking, postoperative complications in general and length of postoperative stay were factors associated with recurrence (Table 7). In multivariate analysis, only smoking (OR = 4.18, 95%CI: 1.22-14.38) was an independent predictor of recurrence in the crude and adjusted model (Table 8). Gender, BMI and COPD did not change the associations. Wound infection and seroma were not factors associated with recurrence.

Pain

There was no difference in reported pain or pain on palpation between the two surgical groups, calculated with the adjustment factors of clinical recurrence, age, BMI, gender, chronic obstructive pulmonary disease (Table 9). Clinical recurrence was associated with maximum reported pain in both surgical cohorts, but only after LVHR during sedentary (OR = 5.78, 95%CI: 1.11-30.05) and physical activity (OR = 14.22, 95%CI: 1.75-116.05). Adjusting for clinical recurrence, BMI, age and COPD, it was found that after LVHR, female

gender was associated with maximum reported pain (OR = 7.37, 95%CI: 1.36-39.85). In addition, young age and low BMI were factors associated with pain during sedentary and physical activity (Table 10). In the OVHR cohort, there was no association between pain and gender, age and BMI, but with hernia recurrence (OR = 18.04, 95%CI: 1.80-181.09) ($P < 0.05$). Among subjects without clinical recurrence, 13 patients (18.3%) vs eight patients (15.4%) experienced chronic pain in the LVHR and OVHR cohorts respectively ($P = 0.53$). In multivariate regression analysis, clinical recurrence (OR = 11.67, 95%CI: 2.00-68.24) and history of late complications (OR = 5.47, 95%CI: 1.11-27.09) were factors associated with chronic pain in the LVHR group (Table 11). Together with female gender, age, COPD and smoking (adjustment factors), these covariates could explain 41% of the variance on the dependent variable.

In the OVHR cohort smoking was associated with chronic pain in the crude model (OR = 3.85, 95%CI: 1.24-11.99) but not in the adjusted model (OR = 3.81, 95%CI: 0.95-15.34) (Table 12). In the whole model, clinical recurrence, female gender, postoperative complications, late complications and admission time, could only explain 30.7% of the variance on the dependent variable.

Patient satisfaction

Satisfaction among patients after hernia surgery was established by "yes/no" responses to whether they experienced abdominal wall pain or discomfort. Of 152 patients reporting their symptoms, 49 patients (60.5%) were satisfied with LVHR and 35 patients (49.3%) were satisfied with OVHR ($P = 0.17$). Absence of chronic pain (OR = 7.4, 95%CI: 1.43-38.46), age over 60 years (OR = 7.16, 95%CI: 1.37-37.42) at hernia surgery and shorter time to follow-up (OR = 1.83, 95%CI: 1.11-3.05) was associated with satisfaction after LVHR (Table 13). Absence of clinical recurrence was associated with satisfaction only in the crude model (OR = 7.81, 95%CI: 1.54-40.00). These covariates, including female gender and late complications, could explain 55.7% of the variance on the dependent variable. In the OVHR cohort, no clinical recurrence (OR = 20.00, 95%CI: 2.15-200.00) and absence of chronic pain (OR = 5.56, 95%CI: 1.24-25.00) were associated with satisfaction (Table 14). Covariates, including admission time and late complications, could explain 45.7% of the variance on the dependent variable.

DISCUSSION

In the present study, patients who had undergone open mesh repair experienced a higher frequency of wound complications compared to the laparoscopic group, thus supporting previous studies^[2]. The higher frequency of enterotomy in the open surgery group is due to perioperative bowel injuries during laparoscopy, and conversion to open surgery. There were, however, no differences between the two groups with regard

Table 4 Overall recurrence after hernia surgery

	Recurrence LVHR		Recurrence OVHR		P value
	No	Yes	No	Yes	
Clinical recurrence ¹	72 (87.8)	10 (12.2)	58 (79.5)	15 (20.5)	
Hernia surgery after index mesh repair ²	-	4 (4.9)	-	2 (2.7)	
Overall recurrence	14 (17.1)		17 (23.3)		0.33

¹Correction for 3 false positive recurrences; ²No detectable recurrence at follow up. Percentages are given in brackets. OVHR: Open mesh repair; LVHR: Laparoscopic mesh repair.

Table 5 Predictors for overall recurrence after laparoscopic mesh repair univariate analysis

	Yes	No	P value
Gender male/female	7/7	27/41	0.48
Age at hernia surgery, yr; mean ± SD	52 ± 14	57 ± 15	0.24
Period of follow-up, mo ± SD	46 ± 15	46 ± 17	0.94
Charlson index			0.79
0	6 (24.0)	19 (76.0)	
1	2 (14.3)	12 (85.7)	
2	2 (12.5)	14 (87.5)	
3	3 (18.8)	13 (81.3)	
4, 5, 6	1 (9.1)	10 (90.9)	
COPD	3 (18.8)	13 (81.3)	0.84
Smoking	5 (17.9)	23 (82.1)	0.89
BMI (kg/m ²); mean ± SD	34 ± 6	30 ± 6.0	0.05
BMI (kg/m ²); (%) 18.5-24.9	1 (8.3)	11 (92.7)	0.38
BMI (kg/m ²); (%) 25.0-29.9	3 (12.0)	22 (88.0)	
BMI (kg/m ²); (%) 30.0-39.9	10 (22.2)	35 (77.8)	
Hernia type			0.59
Incisional	12 (18.2)	54 (81.8)	
Non-incisional	2 (12.5)	14 (87.5)	
Recurrent hernia	2 (13.3)	13 (86.7)	0.67
Hernia area, cm ² , mean ± SD	80 ± 58	53 ± 56	0.11
Hernia area, both types < 58 cm ²	5 (9.8)	46 (90.2)	0.04
Hernia area, both types ≥ 58 cm ²	8 (27.6)	21 (72.4)	
Incisional hernia area < 70 cm ² , n ¹	6 (13.6)	38 (86.4)	0.15
Incisional hernia area ≥ 70 cm ² , n	6 (28.6)	15 (71.4)	
Non-incisional hernia area < 13 cm ² , n	0	6	0.40
Non-incisional hernia area ≥ 13 cm ² , n	1 (11.1)	8 (88.9)	
No. of trocars, median, (range)	4 (3-6)	3 (3-5)	< 0.001
Operative time, min, mean ± SD	142 ± 63	112 ± 51	0.07
Postoperative stay, d, mean ± SD	4 ± 4	2 ± 1	0.001
Preop antibiotics	8 (26.7)	22 (73.3)	0.08
Surgeons experience			0.69
Less experient	7 (15.6)	38 (84.4)	
Experient	7 (18.9)	30 (81.1)	
Mesh			0.47
Goretex	3 (25.0)	9 (75.0)	
Parietex	7 (17.5)	33 (82.5)	
Bard	3 (15.0)	17 (85.0)	
Other	0	9	
Postoperative complications	5 (20.0)	20 (80.0)	0.64
Postoperative antibiotics	3 (25.0)	9 (75.0)	0.43
Late complications	2 (15.4)	11 (84.6)	0.86
Hernia belt	11 (22.0)	39 (78.0)	0.14

¹Missing value with recurrence; missing value without recurrence. Data are numbers with percentages in brackets unless otherwise indicated. COPD: Chronic obstructive pulmonary disease.

to overall postoperative complication rates and post-operative stay, which is somewhat surprising.

In the present study, the overall recurrence rates

Table 6 Predictors for overall recurrence after laparoscopic mesh repair multivariate analysis adjusted model

	OR (95%CI)	P value
Hernia area ¹	5.55 (0.74; 41.47)	0.095
No. of trocars	4.32 (1.55; 12.05)	0.005
Operative time ²	0.32 (0.03; 2.94)	0.313
BMI	1.21 (1.05; 1.41)	0.010
Postoperative stay	1.79 (1.10; 2.89)	0.018
Preop antibiotics	0.74 (0.12; 4.57)	0.742

¹Hernia area < 58 cm² small, reference category > 58 cm² large; ²Operative time < 108 min reference category. BMI: Body mass index; OR: Odds ratio.

Table 7 Predictors for overall recurrence after open mesh repair-univariate analysis

	Yes	No	P value
Gender male/female	9/8	25/31	0.55
Age at hernia surgery, yr, mean ± SD	57 ± 11	57 ± 12	1.0
Period of follow-up, mo ± SD	56 ± 26	57 ± 30	0.91
Charlson index			0.86
0	3 (18.8)	13 (81.3)	
1	6 (31.6)	13 (68.4)	
2	4 (21.1)	15 (78.9)	
3	3 (25.0)	9 (75.0)	
4, 5, 6	1 (14.3)	6 (85.7)	
COPD	3 (25.0)	9 (75.0)	0.88
Smoking	10 (38.5)	16 (61.5)	0.02
BMI, kg/m ² , mean ± SD	31 ± 6.0	29 ± 5.1	0.25
BMI (kg/m ²) (%)18.5-24.9	2 (20.0)	8 (80.0)	0.80
BMI (kg/m ²) (%) 25.0-29.9	5 (19.2)	21 (80.8)	
BMI (kg/m ²) (%) 30.0-39.9	10 (27.8)	26 (72.2)	
Emergency operation	3 (25.0)	9 (75.0)	1.0
Hernia type			1.0
Incisional	14 (23.7)	45 (76.3)	
Non-incisional	3 (21.4)	11 (78.6)	
Recurrent hernia	2 (15.4)	11 (84.6)	0.72
Hernia area, cm ² , mean ± SD	39 ± 56	47 ± 52	0.60
¹ Incisional hernia area < 70 cm ²	11 (26.8)	30 (73.2)	0.48
Incisional hernia area ≥ 70 cm ²	2 (14.3)	12 (85.7)	
Non-incisional hernia area < 13 cm ²	2 (15.4)	11 (84.6)	0.21
Non-incisional hernia area ≥ 13 cm ²	1	0	
Mesh area, cm ² , mean ± SD	186 ± 112	184 ± 131	0.97
Operative time, min, mean ± SD	97 ± 65	90 ± 36	0.56
Preop antibiotics	8 (24.2)	25 (75.8)	0.70
Surgeons experience			0.98
Less experient	6 (23.1)	20 (76.9)	
Modest experient	11 (23.4)	36 (76.6)	
Mesh			0.63
Goretex	4 (26.7)	11 (73.3)	
Polypropylene	5 (19.2)	21 (80.8)	
Unknown	0	6	
Other	5 (23.8)	16 (76.2)	
Postoperative complications	11 (36.7)	19 (63.3)	0.02
Seroma	5 (35.7)	9 (64.3)	0.22
Wound infection	4 (30.8)	9 (69.2)	0.48
Postoperative antibiotics	7 (52.9)	10 (47.1)	0.05
Late complications	5 (35.7)	9 (64.3)	0.22
Postoperative stay, d, mean ± SD	8 ± 19	2 ± 2	0.02
Hernia belt	5 (15.6)	27 (84.4)	0.54

¹1 missing value with recurrence; 3 missing values without recurrence. COPD: Chronic obstructive pulmonary disease.

were 17.1% after laparoscopic mesh repair and 23.3% after open mesh repair ($P = 0.33$). The median time from

Table 8 Predictors for overall recurrence after open mesh repair-multivariate analysis adjusted model

	OR (95%CI)	P value
Smoking	4.18 (1.22; 14.38)	0.002
Postoperative complications	2.36 (0.49; 11.45)	0.287
Postoperative antibiotics	1.36 (0.25; 7.43)	0.722
Postoperative stay	1.18 (0.89; 1.57)	0.254

OR: Odds ratio.

hernia surgery to follow-up was only four months longer in the open mesh repair group and would probably have no impact on recurrence. Even though our recurrence rates were high after both LVHR and OVHR, the mean follow-up time was longer than in many other studies. The great variation of follow-up time among different studies could affect recurrence rates. There are also other factors to consider: Our study involved mandatory examination of all patients. Patients who report no symptoms of recurrence in mailed questionnaires can easily be misdiagnosed. Finally, we need to consider that relatively small numbers of patients are followed-up in some of the previously conducted studies^[16].

A Cochrane review reported a recurrence rate of only 4.2% after open hernia mesh repair (15/326), but the follow-up time was relatively short (< 2 years in four of nine studies included)^[1]. The review included both incisional and ventral hernia. Lauscher *et al.*^[17] reported a recurrence rate of 13.3% in 90 patients 18 mo after open incisional hernia mesh repair.

Comparing laparoscopic ($n = 119$) and open ($n = 106$) hernia mesh repair, a retrospective study from the Cleveland clinic, showed a 5-year recurrence rate of 28% in the open mesh repair group and 29% in the laparoscopic mesh repair group. There were both incisional and non-incisional hernias included^[18]. Eker *et al.*^[16] reported recurrence rates of 14% and 18% after open and laparoscopic incisional hernia repairs. They conducted a large randomized controlled multicentre trial with a mean follow-up period of 35 mo. Of 194 patients in our study, 146 (75%) completed the follow-up. There are very few studies with a follow-up longer than 5 years. It is suggested that the threshold for recurrence is 5 years after ventral hernia surgery^[18].

The mechanisms underlying recurrence could be due to infection, lateral detachment of the mesh, inadequate mesh fixation, inadequate overlap and mesh shrinkage^[19]. Schoenmacker reported a 7.5% shrinkage rate and no difference in recurrence after comparing one group with double crown of tacks to another group with tacks and sutures^[20]. Another retrospective study reported a shrinkage rate of 6.7% after LVHR and the use of ePTFE (Dualmesh) with double crown fixation and sutures evaluated by CT scans^[21]. In our laparoscopic group, there was no association between mesh/hernia area ratio and overall recurrence ($P = 0.45$). Smoking was a predictor for overall recurrence after OVHR both in the crude and the adjusted model. There was no

association between smoking and overall recurrence after LVHR. The finding that smoking is a risk factor for developing incisional hernia after laparotomy is in accordance with Sorensen and others^[22]. Smoking has also been found to be a risk factor for recurrence, after both open suture repair^[23] and laparoscopic hernia mesh repair^[24].

The rate of seroma was higher after OVHR, but was not associated with overall recurrence. For laparoscopic mesh repairs, increasing the number of trocars was associated with overall recurrence. Large hernia areas ($> 58 \text{ cm}^2$) had more recurrences ($P = 0.095$), an observation which agrees with those of others^[16]. After OVHR, postoperative complications in general were associated with overall recurrence only in the crude model.

Pain

We did not find any difference in abdominal pain between the cohorts. Clinical recurrence was a causative and predictive factor for pain after both LVHR and OVHR. Other factors also modulate the notion of pain, but could only be confirmed after LVHR. In our study it was found, that after adjusting for recurrence, female gender, low BMI and young age were all factors associated with higher levels of reported pain. This gender difference across different diseases, has recently been reported^[25].

The use of tacks vs sutures or the number of tacks used, had no implication on abdominal wall pain in the laparoscopic group. Muysoms *et al.*^[26] reported more patients with abdominal wall pain (VAS $> 10 \text{ mm}$) after sutures and tacks (31.4%) compared to tacks in a double circle shape (8.3%). This was registered three months after LVHR. Wassenaar *et al.*^[27] found no correlation between number of tacks and pain three months after LVHR.

The terms mild, moderate and severe pain have been discussed in several publications^[10,19,28]. The cut-off value for differentiating between moderate and severe pain can differ among studies, but seems to be fairly consistent, particularly on the intercept between mild and moderate pain. This is also the case for the numerical rating scale^[10]. Liang *et al.*^[30] looked at the relationship between chronic pain and other clinical characteristics in 122 patients after LVHR and found that 17.2% of the patients experienced chronic abdominal pain 24 mo after hernia surgery. He assessed patient experience on a 10-point numerical scale. Unfortunately, he did not specify the cut-off value on the numerical rating scale; only the patients' own rating. Eriksen *et al.*^[31] reported that less than 10% had VAS pain scores > 5 six months after LVHR. Setting the cut-off value at 10 mm on the VAS, we found that 39.5% reported pain after LVHR and 43.1% after OVHR. The difference between our results and those reported by others, is their lack of precise criteria for the definition of chronic pain. Furthermore, there is great variation in the time from operation to clinical follow-up in many studies. Excluding recurrence, 13 patients (18.3%) and eight patients (15.4%) reported chronic pain after LVHR and

Table 9 Predictors for abdominal wall pain measured on the visual analogue scale in relation to type of hernia surgery

	Laparoscopic <i>n</i> = 81	Open <i>n</i> = 72	OR ¹ (95%CI)	<i>P</i> value
Maximum pain reported, mean ± SD	16.7 (20.8)	18.6 (20.8)	1.40 (0.42-4.68)	0.58
Maximum pain on palpation, mean ± SD	12.9 (20.2)	12.1 (20.2)	0.78 (0.26-2.32)	0.66
Pain on average, mean ± SD	3.3 (10.3)	2.4 (6.4)	0.85 (0.49-1.47)	0.56
Pain during sedentary activities, mean ± SD	6.5 (17.9)	4.0 (15.4)	0.61 (0.31-1.22)	0.16
Pain during work activities, mean ± SD	9.8 (17.9)	7.7 (15.4)	0.68 (0.24-1.89)	0.46

¹Refers LVHR. Factors adjusted for: Clinical recurrence, age categories, BMI categories, gender, COPD. LVHR: Laparoscopic mesh repair; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index.

Table 10 Predictors for pain after laparoscopic mesh repair and open mesh repair

	Maximum pain OR (95%CI) ²	Average pain OR (95%CI) ³	Pain, sedentary OR (95%CI)	Pain, work OR (95%CI)
¹	LVHR	LVHR	LVHR	
Gender	7.37 ² (1.4-39.9)	NA	NA	NA
Age	19.77 ³ (3.4-115.5)	NA	3.71 ³ (1.1-12.6)	7.04 ³ (1.5-33.0)
BMI	14.56 ⁴ (2.4-90.0)	5.03 ⁴ (1.4-18.3)	7.24 ⁴ (1.5-35.1)	9.73 ⁴ (1.3-73.0)
COPD	NA	NA	NA	NA
Clinical recurrence excluded				
LVHR	32.04 (2.82-363.22)	NA	5.78 (1.11-30.05)	14.22 (1.75-116.05)
OVHR	18.04 (1.80-181.1)	NA	NA	NA

¹Refers to LVHR when OVHR is excluded; ²Refers male; ³Refers age > 60; ⁴Refers BMI > 30; Only significant values (*P* < 0.05) are presented. (1) Pain after LVHR and OVHR relative to gender, age, BMI, COPD. Adjusted for recurrence; and (2) pain after LVHR and OVHR relative to no clinical recurrence. Factors adjusted for: Gender, age, BMI, COPD, clinical recurrence. OVHR: Open mesh repair; LVHR: Laparoscopic mesh repair; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index.

Table 11 Predictors for chronic pain after laparoscopic mesh repair-multivariate analysis (*n* = 81)

	OR (95%CI)	<i>P</i> value
Clinical recurrence	11.67 (2.00-68.24)	0.006
Late complications	5.47 (1.1-27.09)	0.037
Gender (refers female)	0.42 (0.10-1.98)	0.274
Age > 60 yr	0.23 (0.03-1.51)	0.125
COPD	2.39 (0.52-11.10)	0.265
Smoking	1.38 (0.37-5.11)	0.629

COPD: Chronic obstructive pulmonary disease; OR: Odds ratio.

Table 12 Predictors for chronic pain after open mesh repair-multivariate analysis (*n* = 71)

	OR (95%CI)	<i>P</i> value
Clinical recurrence	1.20 (0.24-6.06)	0.828
Smoking (crude model)	3.86 (1.24-12.00)	0.020
Smoking (adjusted model)	3.81 (0.95-15.33)	0.060
Hernia size > 70 cm ²	0.84 (0.13-5.53)	0.852
Gender (ref female)	0.30 (0.07-1.35)	0.116
Postoperative complications	3.59 (0.76-16.88)	0.106
Late complications	1.16 (0.20-6.87)	0.869
Postoperative stay	1.08 (0.75-1.57)	0.668

OR: Odds ratio.

Table 13 Predictors for satisfaction after laparoscopic mesh repair-multivariate analysis (*n* = 79)

	OR (95%CI)	<i>P</i> value
Chronic pain ¹	0.14 (0.03-0.70)	0.017
Age > 60 yr	7.16 (1.37-37.42)	0.020
Gender (ref female)	2.69 (0.72-10.05)	0.142
Time to follow up	0.55 (0.33-0.90)	0.019
Clinical recurrence (crude model)	0.13 (0.03-0.65)	0.013
Clinical recurrence (adjusted model)	0.13 (0.02-1.11)	0.062
Late complications	0.39 (0.07-2.23)	0.289

¹Chronic pain at hard labour activities. OR: Odds ratio.

Table 14 Predictors for satisfaction after open mesh repair-multivariate analysis (*n* = 71)

	OR (95%CI)	<i>P</i> value
Chronic pain ¹	0.18 (0.04; 0.81)	0.025
Age > 60 yr	0.05 (0.01; 0.47)	0.008
Gender (ref female)	0.26 (0.05; 1.37)	0.111
Time to follow up	0.71 (0.49; 1.03)	0.073

¹Chronic pain at hard labour activities. OR: Odds ratio.

OVHR respectively.

Satisfaction

Percent of 60.5 the patients were satisfied after LVHR

and 49.3% after OVHR. Excluding clinical recurrence, 66.2% and 60.7% were satisfied after laparoscopic and open hernia surgery respectively, there being no other significant difference. Factors other than recurrence will therefore have an influence on patient satisfaction.

The equality of long term satisfaction rates between LVHR and OVHR has been confirmed by others^[32]. Liang *et al*^[30] used a 10-point numerical scale to assess satisfaction after laparoscopic ventral hernia repair. He set the cut-off value for satisfaction to ≥ 7 . In his study, 74.5% of patients were satisfied with the outcome. Chronic pain and recurrence were associated with reduced overall satisfaction.

In our study, absence of chronic pain was the most important factor for satisfaction after LVHR. Old age at hernia surgery also predicted satisfaction, while clinical recurrence was predictive only in the crude model. Longer follow-up was associated with discontent in our study and could be due to increased rate of recurrence, though this is not proven.

Chronic pain and clinical recurrence was associated with discontent after OVHR.

Eriksen *et al*^[31] also found that pain was associated with dissatisfaction after laparoscopic ventral hernia repair ($P < 0.001$). They had however no recurrences. Gronnier *et al*^[11] found that almost 83% were satisfied more than 2 years after open hernia mesh repair. A recurrence rate of 6.1% at the repair site could explain the higher rate of satisfaction compared to our results (20.5% recurrence rate/49.3% satisfaction rate).

There are obvious limitations to our study. The study population is relatively small and our retrospective analysis on the basis of medical records and the heterogeneity of ventral hernia type and location, calls for careful interpretation of results. The study does however also benefit from some clear advantages: Nearly 79% of the original cohort attended for examination at follow-up. Also, the study was conducted at a single institution with an established examination protocol, and interviews were conducted by a single experienced doctor.

In conclusion, there was no difference in long term recurrence, pain and overall patient satisfaction after open and laparoscopic mesh repair. We demonstrated a relatively high frequency of hernia recurrences. We could also demonstrate that the two techniques had different predisposing factors for recurrence. High BMI was the most important cause of recurrence after LVHR, while smoking was the most important factor after OVHR. Hernia recurrence is associated with more pain, but pain without recurrence is also quite frequent. The absence of chronic pain is the most important factor for patient satisfaction after ventral hernia surgery.

COMMENTS

Background

No precise data on the incidence and prevalence of non-incisional and incisional hernias are available, but the reported incidence rates for incisional hernia after laparotomy are between 9% and 20%; this represents one of the most common complications after abdominal surgery. Non-incisional and incisional hernias are treated with surgery for cosmetic reasons, but mainly to relieve pain and discomfort, prevent respiratory or skin problems and resolve incarceration or strangulation. The surgical and patient reported outcomes vary according to surgical skills and method, type and size of hernia, type of mesh

and the length of follow-up. Patient characteristics are also important.

Research frontiers

The ultimate goal in ventral hernia surgery is to improve and restore the patients' quality of life. This is achievable with emphasis on the patients' reported outcomes. Surgical approach, mesh considerations and surgical outcome will benefit from well designed studies with sufficiently long follow-up and examination of all participants.

Innovations and breakthroughs

This is the first report from Norway that compares the outcome of laparoscopic and open ventral hernia mesh repair. It is a retrospective observational study with a mixture of non-incisional and incisional hernias, but the authors were able to examine nearly 80% of the original cohort and 92% of those that were still alive at long-term follow up.

Applications

The results presented in this study confirm that laparoscopic and open mesh repair involve complications and pitfalls that put significant demands on surgical skills. The recurrence rate could most likely be lowered in the hands of experts. The selection of patients for open or laparoscopic repair could also benefit from surgical skills of a high standard and better knowledge of the many aspects of hernia disease.

Terminology

The term ventral hernia often refers to a primary hernia which has not been caused by earlier surgery. The authors use the term to refer to both incisional and non-incisional hernias located in the anterior abdominal wall.

Peer-review

This single-centre study has undergone peer-review by colleagues with a science background both at preparation stage and during the follow-up examinations. The results were discussed and revised internally throughout this process.

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Gallstone ileus with multiple stones: Where Rigler triad meets Bouveret's syndrome

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Abstract

A 53-year-old man with multiple medical conditions presented to the emergency department with complaints of vomiting, anorexia and diffuse colicky abdominal pain for 3 d. A computed tomography scan of the abdomen and pelvis showed radiographic findings consistent with Rigler triad seen in small proportion of patients with small bowel obstruction secondary to gallstone impaction. In addition there was a gastric outlet obstruction, consistent with Bouveret's syndrome. The patient underwent an exploratory laparotomy and enterotomy with multiple stones extracted. The patient had an uneventful post-surgical clinical course and was discharged home.

Key words: Rigler triad; Gallstone ileus; Bouveret's syndrome; Small bowel obstruction

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Core tip: Gallstone ileus is an uncommon cause of small bowel obstruction. The classic finding of Rigler triad is often seen. Bouveret's syndrome is a subset of gallstone ileus, and usually presents with gastric outlet obstruction as opposed to small bowel obstruction. We present a case where there were multiple stones, each causing obstruction in different locations. Clinicians need to be aware of the possibility of multiple stones when deciding treatment options.

Gaduputi V, Tariq H, Rahnamai-Azar AA, Dev A, Farkas DT. Gallstone ileus with multiple stones: Where Rigler triad meets Bouveret's syndrome. *World J Gastrointest Surg* 2015; 7(12): 394-397 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i12/394.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i12.394>

INTRODUCTION

Bouveret's syndrome is an uncommon form of gallstone ileus, caused by a gall stone which has migrated into the duodenal bulb from a bilioduodenal fistula comprising only 1%-3% of all cases. It is a rare cause of gastric outlet obstruction. The gallstone usually obstructs the distal part of the small intestine where the lumen is narrowest. It rarely obstructs the duodenum. Bouveret's syndrome presents as a distinct variety of gallstone ileus because of how proximal the obstruction is^[1,2]. It is known to occur more commonly in elderly women due to the increased incidence of gallstone disease and can cause significant mortality in patients with multiple medical comorbidities. The pathophysiology of this syndrome stems from the increase in gallbladder intraluminal pressure due to obstruction which in turn leads to local ischemia and necrosis. This enables the gall stone to penetrate the wall of the gallbladder and enter into the intestines^[3].

CASE REPORT

A 53-year-old man with multiple medical conditions including diabetes mellitus type 2, hypertension and end stage renal disease on renal replacement therapy, presented to the emergency department with vomiting, anorexia and diffuse colicky abdominal pain for 3 d. He denied having ever smoked, consumed alcohol or used illicit drugs. In the emergency department he was afebrile and hemodynamically stable. His abdomen was distended, soft, non-tender with no rigidity, but with hypoactive bowel sounds. Laboratory results revealed an elevated white blood cell count of 20 k/uL, serum bicarbonate of 32 mEq/L, serum chloride of 88 mEq/L, serum blood urea nitrogen 36 mg/dL, creatinine 6.4 mg/dL, serum lipase of 38 and normal liver function tests.

A computed tomography (CT) scan of abdomen and pelvis showed findings consistent with Rigler triad seen in gallstone ileus: (1) Signs of small bowel obstruction; (2) pneumobilia; and (3) ectopic gallstone. Both the pneumobilia and ectopic gallstone are seen in the scout (Figure 1), with the pneumobilia more clearly seen in the axial cuts (Figure 2). The small bowel obstruction as well as the large stone in the left lower quadrant with a transition point in the bowel caliber are seen on lower abdominal cuts (Figure 3). What was unusual in this case was the extent of gastric outlet obstruction in comparison to the small bowel distention. On closer inspection a smaller stone fragment was noted in the duodenum (Figure 4), leading to a secondary Bouveret's syndrome.

The patient underwent an exploratory laparotomy at which time distended proximal small bowel up to distal jejunum was seen. A large gallstone was noted here measuring 6 cm × 4 cm, while another gallstone was noted in proximal jejunum just beyond the duodeno-

jejunal flexure measuring 2 cm × 2.5 cm. Enterotomy was performed and 2 gallstones were removed. No other lesion was identified in the small bowel. The gallbladder was palpated, but no definite stone was felt. The patient had an uneventful post-surgical clinical course.

DISCUSSION

Leon Bouveret first reported two cases of gastric outlet obstruction due to gallstones, in 1896 in the "Revue Medicale"^[1,2]. Gallstone ileus is the cause in about 1%-4% of all cases with intestinal obstruction. Bouveret's syndrome is a rare subset of gallstone ileus comprising of about 1%-3% of cases^[2,3]. Bouveret's syndrome is more prevalent in women with reported median age of presentation being 74 years. The gender difference in prevalence is explained by the higher incidence of gallstone disease in women, likely due to the cholestatic effects of estrogen^[2]. The case we presented was unusual in regards to the gender and age of presentation.

The pathophysiology includes perforation of the wall of biliary system by a stone usually larger than 2.5 cm and subsequent passage into the bowel with impaction usually in the terminal ileum^[4]. Around 1% of gall stone cases develop bilio-enteric fistulas including cholecystoduodenal (60%), cholecystocolic (17%), cholecystogastric (5%), choledochoduodenal (5%) fistulas^[1]. Most common symptoms include vomiting (87%), abdominal pain (71%), hematemesis (15%), weight loss (14%), and anorexia (13%). Common signs may include abdominal tenderness (44%), dehydration (31%), abdominal distension (26%)^[2]. Our case was unique as the patient had two stones, first in the distal duodenum causing gastric obstruction (Bouveret's syndrome) and another larger stone in the left lower quadrant causing ileus of small bowel.

The Rigler triad consisting of small-bowel obstruction, pneumobilia and an ectopic gallstone is virtually pathognomonic for gallstone ileus. However, it is present on conventional radiographs in only about a third of gallstone ileus cases^[5]. This triad of findings is more readily apparent on CT scans. CT scan also provides information about the presence of a fistula; the degree of inflammation in the surrounding tissue; the degree of bowel obstruction; the size, number and locations of the occluding gallstones. However, approximately 15% to 25% of gallstones are not able to be visualized on CT scans, as they are isoattenuating. Such stones can be visualized with magnetic resonance cholangiopancreatography^[4,5].

The first successful endoscopic extraction was described in 1985 by Bedogni *et al*^[6]. Endoscopy in tandem with extracorporeal shockwave lithotripsy^[7] or endoscopic electrohydraulic lithotripsy^[8] and percutaneous approaches should be considered before surgical options, as most patients with Bouveret's

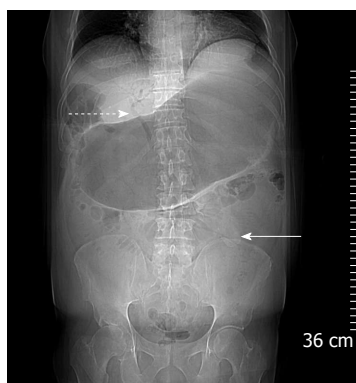


Figure 1 Scout film. Pneumobilia (dotted arrow) and ectopic gallstone (solid arrow). Marked gastric distention, with small bowel obstruction less clearly seen.

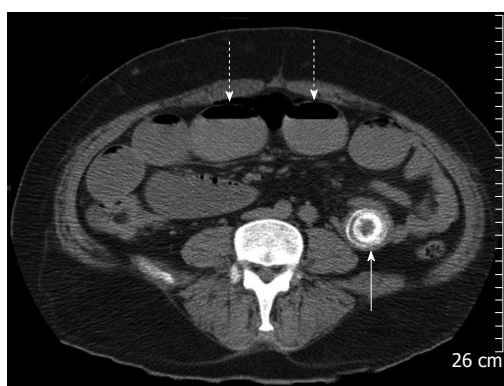


Figure 3 Small bowel obstruction with multiple dilated loops with air fluid levels (dotted arrows), ectopic gallstones in left lower quadrant is seen (solid arrow).

syndrome make for poor surgical candidates^[9]. Laser lithotripsy is also an alternative, non-invasive therapeutic option to surgical treatment in old or high-risk patients with Bouveret's syndrome^[10]. Indications for open surgery are stone size greater than 2.5 cm, residual stones in gall bladder, multiple stones in intestinal lumen, sepsis, perforation, stricture and failure of endoscopic approach^[1]. In patients who require surgery, common options include enterolithotomy with or without intestinal resection and gastrostomy^[11]. Cholecystectomy should be offered to prevent recurrences^[12]. Our patient was not a candidate for endoscopic therapy due to the presence of multiple gallstones in separate locations.

In conclusion, gallstone ileus is an uncommon diagnosis and is usually identified by the Rigler triad seen on imaging. Bouveret's syndrome is a rare subset of this that presents with gastric outlet obstruction. Clinicians should be aware of the possibility of multiple stones being present in the gastrointestinal tract, as is this is critical to choosing the right form of treatment.

COMMENTS

Case characteristics

A 53-year-old man with vomiting and abdominal pain for three days.

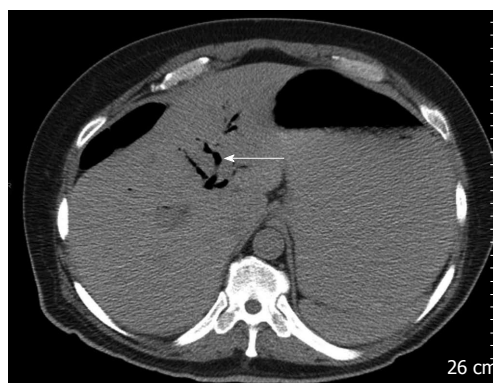


Figure 2 Pneumobilia clearly demonstrated.

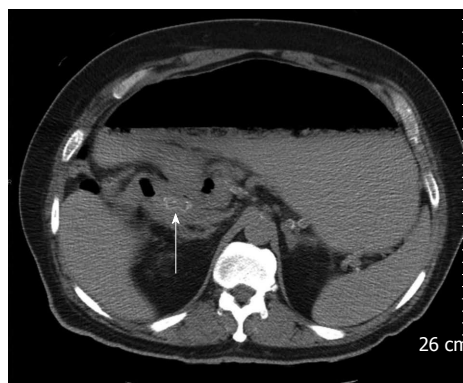


Figure 4 Stone fragment in duodenum leading to gastric outlet obstruction (Bouveret's syndrome).

Clinical diagnosis

The clinical diagnosis was small bowel obstruction.

Differential diagnosis

Other diagnoses included other types of gastrointestinal obstruction, as well as various causes of peritonitis.

Laboratory diagnosis

Lab values were significant for a raised white cell count, as well as a metabolic alkalosis seen in the electrolytes.

Imaging diagnosis

X-rays revealed a gastric outlet obstruction, and computed tomography scan showed small bowel obstruction as well, and the presence of multiple obstructing stones.

Pathologic diagnosis

Pathology was consistent with a gallstone in the gastrointestinal tract.

Treatment

Treatment for this patient was a laparotomy after fluid resuscitation, with an enterotomy and multiple stone removal.

Related reports

Other reports discuss various treatments for gallstone ileus, depending on stone location and other factors.

Term explanation

Gallstone ileus refers to an ectopic location of a gallstone in the gastrointestinal

tract; Rigler triad refers to the classic finding of pneumobilia, small bowel obstruction and ectopic gallstone; Bouveret's syndrome refers to the subset of gallstone ileus where the stone causes a gastric outlet obstruction.

Experiences and lessons

This case highlights the possibility of there being multiple stones causing obstruction in different areas, something which is important to be aware of when deciding which treatment option to use.

Peer-review

The authors describe a nice case of a patient with multiple obstructions caused by a gallstone including the special case of a gastric outlet obstruction.

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Total laparoscopic removal of accessory gallbladder: A case report and review of literature

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Abstract

Accessory gallbladder is a rare congenital anomaly occurring in 1 in 4000 births, that is not associated with any specific symptoms. Usually this cannot be diagnosed on ultrasonography and hence they are usually not diagnosed preoperatively. Removal of the accessory gallbladder is necessary to avoid recurrence of symptoms. H-type accessory gallbladder is a rare anomaly. Once identified intra-operatively during laparoscopic cholecystectomy, the surgery is usually converted to open. By using the main gallbladder for liver traction and doing a dome down technique for the accessory gallbladder, we were able to perform the double cholecystectomy with intra-operative cholangiogram laparoscopically. Laparoscopic cholecystectomy was performed in 27-year-old male for biliary colic. Prior imaging with computer tomography-scan and ultrasound did not show a duplicated gallbladder. Intraoperatively after ligation of cystic artery and duct an additional structure was seen on its medial aspect. Intraoperative cholangiogram confirmed the patency of intra-hepatic and extra-hepatic biliary ducts. Subsequent dissection around this structure revealed a second gallbladder with cystic duct (H-type). Pathological analysis confirmed the presence of two gallbladders with features of chronic cholecystitis. It is important to use cholangiogram to identify structural anomalies and avoid complications.

Key words: Gallstones; Cholangiogram; Laparoscopic cholecystectomy; Accessory gallbladder; Duplicated gallbladder

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Core tip: Accessory gallbladders are a rare anatomic anomaly, that classically goes unnoticed. These are often not diagnosed preoperatively in patients undergoing cholecystectomy. We present a 27-year-old male

scheduled for gallbladder removal for biliary colic. Intra-operatively, following ligation of cystic artery and duct, an additional structure was noted, and intraoperative cholangiogram confirmed a second gallbladder with an associated accessory cystic duct. Pathological analysis confirmed the presence of two gallbladders with features of chronic cholecystitis. Recognizing and understanding the presentation of accessory gallbladders can prevent the pitfalls of surgery with anatomical abnormalities, as well as offering the appropriate management.

Cozacov Y, Subhas G, Jacobs M, Parikh J. Total laparoscopic removal of accessory gallbladder: A case report and review of literature. *World J Gastrointest Surg* 2015; 7(12): 398-402 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i12/398.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i12.398>

INTRODUCTION

Multiple gallbladders are a rare congenital biliary variance occurring in 1 per 3800-5000 people^[1]. We present a case of an accessory gallbladder not discovered by preoperative ultrasound or computer tomography (CT) imaging. The accessory gallbladder was discovered intraoperatively and a total laparoscopic cholecystectomy of both the main and accessory gallbladder was performed. We used the main gallbladder for liver retraction and did a dome down technique for accessory gallbladder dissection. To date, 20 cases of duplicated gallbladder removal by laparoscopic means^[2-4]. We present a successful case of laparoscopic removal of H-type accessory gallbladder, as well as a review of literature.

CASE REPORT

A 27-year-old male was worked up for biliary colic. Ultrasound of the abdomen and CT of the abdomen revealed cholelithiasis (multiple subcentimeter stones), and they did not show any structural abnormalities. Liver enzymes were within normal range. The patient was scheduled for an elective laparoscopic cholecystectomy. Intra-operatively cystic artery and duct of the main gallbladder were ligated and divided after obtaining a critical view. During dissection of the gallbladder from the liver bed, an additional structure was seen on its medial aspect (Figure 1). At this time, the main gallbladder was still bound to the liver edge at the fundus, allowing the use of the gallbladder to retract the liver. Subsequent dissection revealed an accessory gallbladder, with an accessory cystic duct and accessory cystic artery (Figure 2). The accessory gallbladder was then dissected with a dome down technique, from the gallbladder fundus towards the neck, and the accessory cystic duct and artery were identified. An intraoperative cholangiogram was performed through the accessory cystic duct to delineate the anatomy.

No stones or filling defects were identified, the intra-hepatic and extra-hepatic biliary ducts were patent, and contrast confirmed the accessory cystic duct draining into the common bile duct, with contrast then entering the duodenum. Chromic endoloop were tied around the accessory cystic duct and transected. The main gallbladder was then dissected from the liver bed. The whole procedure was completed laparoscopically without any additional ports. The patient was discharged home on post-operative day one. Pathology confirmed a main gallbladder measuring 8 cm × 3 cm showing cholelithiasis with chronic cholecystitis and an accessory gallbladder 1.5 cm × 1.5 cm in dimensions with mild chronic cholecystitis. This accessory gallbladder was of the H-type, or ductular type, per the Harlaftis classification.

DISCUSSION

True incidence of duplicated gallbladders is difficult to calculate, as the gallbladder anomalies are often asymptomatic and goes undiscovered. Incidence is deduced from cadaveric studies^[5]. The first report of an accessory gallbladder was in 1674 during an autopsy by Blasius. It was not until 1911 that Sherren first documented a case of double accessory gallbladder in a living human^[5,6]. This anatomic anomaly occurs during the third and fourth week of embryological development. The anatomical variations of accessory gallbladders have been classified by several authors, with Harlaftis's classification being widely used in the literature. Harlaftis classifies gallbladder anomalies into 3 types (Figure 3).

Type 1, or the split primordial group, has only one cystic duct draining into the common bile duct^[7]. Sub classification of type 1 includes a septated, V-shaped, or Y-shaped duplicated gallbladder. The septated subtype grossly presents as a single gallbladder with an indentation at the fundus and has only one cystic duct. This morphology likely represents an incomplete resolution of the solid stage of the development of the gallbladder^[7]. The V-shaped subtype of duplicated gallbladder refers to gallbladders that are joined at the neck level, draining into a single cystic duct as well. The Y-shaped subtype duplicated gallbladder, has a separated cystic duct that joins together with the main cystic duct to become a shared, single "common" cystic duct that later joins the common bile duct^[1,6,8]. This morphology likely represents an out-pocketing of the cystic duct which subsequently develops into a definitive second gallbladder. These gallbladders are usually close in proximity, commonly sharing a single gallbladder bed.

Type 2, or the accessory gallbladder group, has more than one cystic duct draining into the biliary tree. Here, each subtype consists of a main gallbladder with a main cystic duct and an accessory gallbladder with an accessory cystic duct. The main and accessory cystic ducts drain independently into the biliary tree. Sub classification of type 2 accessory gallbladders includes H or Ductular type and trabecular type. In H or

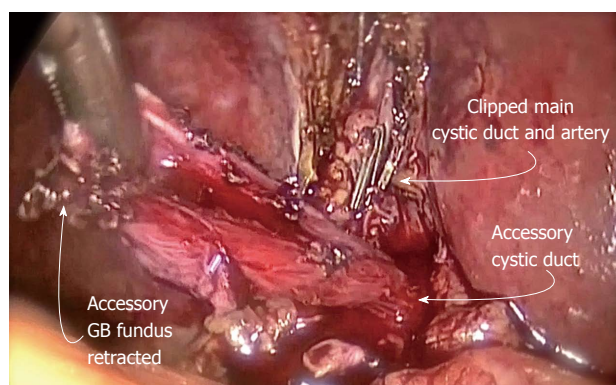


Figure 1 The accessory gallbladder shown here is dissected of the shared liver bed with the main gallbladder. Clips are placed on the divided main cystic duct and artery. GB: Gallbladder.

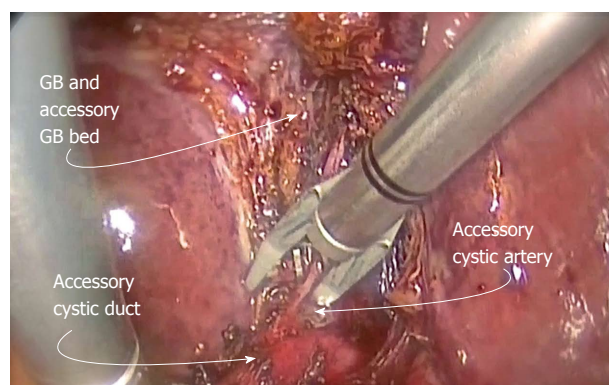


Figure 2 Further dissection of the accessory gallbladder revealed the accessory cystic artery, which helped in the identification of the cystic structure as an accessory gallbladder. The accessory cystic artery is dissected off the accessory cystic duct situated below, clipped and divided. A cholangiogram through the accessory cystic duct was performed. GB: Gallbladder.

Type I : Split primordial gallbladders



Type II : Accessory gallbladders

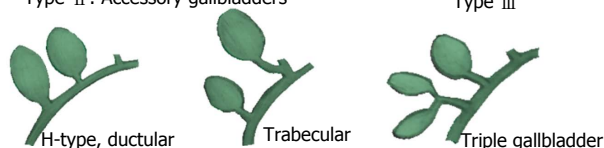


Figure 3 Harlaftis's classification of anatomical variations of accessory gallbladders.

ductular type the accessory cystic duct connects to the common bile duct. In the trabecular type the accessory cystic duct connects to the left or right hepatic duct. Our case represents the H or ductular type accessory gallbladder with the accessory cystic duct inserting into the common bile duct distal to the main cystic duct. A review of 148 cases of accessory gallbladders found that H-type accessory gallbladder was the most common variant accounting for nearly half of the reports^[8]. Van Steenberg *et al*^[9] reported a trabecular type accessory gallbladder identified preoperatively with an endoscopic retrograde cholangiopancreatogram, which showed the accessory gallbladder to be intrahepatic. Cholangiography showed the accessory cystic duct draining into the intrahepatic right hepatic duct. Post-operative pathology report noted both gallbladder walls to be fused together^[9]. Anomalies of type 2 have been reported by several authors, including a laparoscopic cholecystectomy converted to open of an accessory gallbladder draining into the left hepatic duct^[2], an accessory gallbladder arising from the left hepatic duct, which was found on pathology to harbor adenocarcinoma^[8]. There are two more reports of carcinoma found in the accessory gallbladder^[10,11].

Type 3 accessory gallbladders include gallbladders

with anatomical anomalies that do not fit either type 1 nor type 2. These are rare examples of triple gallbladders and other anomalies. Triple gallbladders are rare in humans and were mainly deduced from feline dissections. Roeder *et al*^[12] described triplication of the gallbladder with two of the gallbladders surgically removed, one showing acute cholecystitis and cholelithiasis and the second containing papillary adenocarcinoma. The third gallbladder was demonstrated by T tube cholangiogram but not identified during the operation and was assumed to be intrahepatic^[12]. Schroeder *et al*^[13] described a triple gallbladder in a 38-year-old male, of which two were identified preoperatively, and the third (or second accessory GB) was found intraoperatively. All final histopathology report noted cholelithiasis and chronic inflammation. The entire case was performed laparoscopically^[13].

Accessory gallbladder may be missed on routine preoperative imaging^[2,3,14]. Ultrasound and computerized tomography do not provide sufficient visualization of biliary anatomy to reliably detect double accessory gallbladders^[14,15]. Oral cholecystography has been studied and results showed this imaging modality misses 30%-66% of double gallbladders^[15-17]. Hence, it is important to thoroughly investigate biliary anatomy intraoperatively to identify an accessory gallbladder, noting that these may vary in position. The H-type accessory gallbladder has been reported in the literature as intrahepatic, subhepatic, within the gastrohepatic ligament, and adjacent to the primary gallbladder as seen in this case report^[16,18].

When an accessory gallbladder is found intraoperatively both gallbladders should be removed to avoid complications^[3,5,14,16,19]. If the accessory gallbladder is not removed, patients can return with biliary symptoms^[2,14,20,21]. Reinisch *et al*^[22] revisited a 73-year-old patient 17 years following laparoscopic cholecystectomy due to acute cholecystitis of the accessory gallbladder, not detected during the index operation^[22]. The accessory gallbladder is prone to the same pathology as the

primary gallbladder including cholecystitis, empyema, cholecystocolic fistula, torsion, papilloma, and carcinoma^[3,5,11,12,16,23-25]. Before removing the accessory gallbladder, intraoperative imaging is imperative to outline the biliary anatomy and avoid injury to the biliary tree^[16]. The superior imaging test is an intraoperative cholangiography^[3,14,26-28]. Studies have shown that intraoperative cholangiography reduces the degree of bile duct injury by approximately thirty percent during cholecystectomy, and we believe this would apply in cases of accessory gallbladders as well, although this has not been documented for these cases specifically^[14,21].

It is important to note that the complications and pathology of multiple gallbladders relies on many anecdotal publications. There is not yet a standardized approach when such case is encountered, though there is an agreement among authors that removal of the accessory gallbladder should be attempted, cholangiography is warranted, careful dissection with recognition of the accessory cystic artery and duct aids in recognizing the accessory gallbladder, and the laparoscopic approach, if possible, is an appropriate method of removal of the accessory gallbladder. Final diagnosis is completed with histopathological evaluation, to differentiate from other biliary lesions.

Multiple gallbladders are a rare congenital abnormality that may be missed on routine imaging. Intraoperative identification and subsequent removal of the accessory gallbladder is necessary to avoid recurrent biliary symptoms. Total laparoscopic removal can be performed safely. By using the main gallbladder for liver retraction, the accessory gallbladder can be dissected using dome down technique. Intraoperative cholangiogram should be performed to define biliary anatomy. There is no evidence at this time to remove an incidental accessory gallbladder, and we recommend removal only in association with main gallbladder disease destined for cholecystectomy.

COMMENTS

Case characteristics

Patient had right upper quadrant discomfort for several months, associated with fatty indigestion.

Clinical diagnosis

Patient was suspected to have biliary colic.

Differential diagnosis

On the authors' differential diagnosis were biliary colic due to cholelithiasis, sphincter of oddi dysfunction, chronic/subacute cholecystitis.

Laboratory diagnosis

Patient's basic metabolic and liver function panels were all within normal limits.

Imaging diagnosis

Ultrasound and computer tomography scan were only positive for wall thickening and cholelithiasis, otherwise negative.

Pathological diagnosis

Pathology confirmed a main gallbladder measuring 8 cm × 3 cm showing

cholelithiasis with chronic cholecystitis and an accessory gallbladder 1.5 cm × 1.5 cm in dimensions with mild chronic cholecystitis.

Treatment

Patient was scheduled for elective cholecystectomy.

Related reports

None of the report describes the technique for a total laparoscopic approach for double gallbladder.

Term explanation

ERCP: Endoscopic retrograde cholangiopancreatogram.

Experiences and lessons

Biliary anatomy has great diversity, and as surgeons, it is better to make themselves familiar with this great variability, for the authors' to be better and safer surgeons.

Peer-review

The authors described interesting case of laparoscopic cholecystectomy for accessory gallbladder. It is important to know the anomalies of biliary tract including accessory gallbladder in order to avoid injury of the biliary tree during cholecystectomy.

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Laparoscopic management of a two staged gall bladder torsion

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Abstract

Gall bladder torsion (GBT) is a relatively uncommon entity and rarely diagnosed preoperatively. A constant factor in all occurrences of GBT is a freely mobile gall bladder due to congenital or acquired anomalies. GBT is commonly observed in elderly white females. We report a 77-year-old, Caucasian lady who was originally diagnosed as gall bladder perforation but was eventually found with a two staged torsion of the gall bladder with twisting of the Riedel's lobe (part of tongue like projection of liver segment 4A). This together, has not been reported in literature, to the best of our knowledge. We performed laparoscopic cholecystectomy and she had an uneventful post-operative period. GBT may create a diagnostic dilemma in the context of acute cholecystitis. Timely diagnosis and intervention is necessary, with extra care while operating as the anatomy is generally distorted. The fundus first approach can be useful due to altered anatomy in the region of Calot's triangle. Laparoscopic cholecystectomy has the benefit of early recovery.

Key words: Gall bladder torsion; Gangrenous gall bladder; Perforated gall bladder; Two staged torsion of the gall bladder; Laparoscopic cholecystectomy

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Core tip: Gall bladder torsion is a rare surgical entity that should be considered in a case of suspicious acute cholecystitis not responding to conservative management. Delay in diagnosis and treatment may lead to gall bladder gangrene, gall bladder perforation,

biliary peritonitis or septicaemia. The condition is seldom recognized preoperatively due to its clinical resemblance to acute cholecystitis. We report a 77-year-old, Caucasian lady who was originally diagnosed as gall bladder perforation but was eventually found to have a two staged torsion of the gall bladder with twisting of the Riedel's lobe. This dual entity has so far not been reported in literature.

Sunder YK, Akhilesh SP, Raman G, Deborshi S, Shantilal MH. Laparoscopic management of a two staged gall bladder torsion. *World J Gastrointest Surg* 2015; 7(12): 403-407 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v7/i12/403.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v7.i12.403>

INTRODUCTION

Gall bladder torsion (GBT) is a process, in which there is a mechanical organo-axial torsion that occurs along the gall bladder's longitudinal axis involving cystic pedicle, with a pre-requisite of freely mobile gall bladder. Wendel^[1] first described gall bladder torsion in 1898. Thereafter over 300 cases have been reported in literature and only few were operated laparoscopically. However till date, there has been no report in literature regarding a "two-staged torsion" along with a "tornado" like twisting of the Riedel's lobe.

GBT commonly occurs in the geriatric population, with 85% of patients above 60 years of age. It is found more frequently in the white race with female to male ratio of 3:1^[2]. As this entity is rare and its symptoms overlap with those of acute cholecystitis, it is difficult to diagnose preoperatively^[3,4]. Timely intervention may prevent the morbidity and mortality associated with GBT. We present here a rare case of a two staged gall bladder torsion masquerading as a perforated gall bladder.

CASE REPORT

A 77-year-old, thin, Caucasian lady presented with acute pain in the right upper abdomen, radiating to the back for 4 d. There was no history of fever, jaundice or similar complaints in the past. On general examination, she was afebrile with a pulse rate of 96/min. She also had scoliosis. Her abdomen was soft, tenderness and guarding was present in right hypochondrium and Murphy's sign was positive.

There were no signs of peritonitis. Laboratory investigations showed WBC 14000/cu mm and normal liver function tests. The CT scan showed a peripherally enhancing fluid collection along the segment 5 and 6 of the liver (Figures 1 and 2), and no gall bladder was seen in the gall bladder fossa. A diagnosis of gall bladder perforation with a subhepatic collection was made.

The patient was advised laparoscopic cholecy-



Figure 1 Axial section showing peripherally enhancing fluid density area seen along the segment 5 and 6 of the liver.



Figure 2 Coronal section showing peripherally enhancing fluid density area seen along the segment 6 of the liver. The gall bladder is not seen in the gall bladder fossa.

stectomy but she refused surgery. She was managed conservatively with bowel rest, intravenous fluids, injectable antibiotics and analgesics. The patient did not improve and had increased WBC counts. After 4 d, she gave consent for surgery.

Intraoperatively, we found thick peritoneal folds arising from the pylorus and the hepatic flexure that were pulled into the region of Calot's triangle along with the Riedel's lobe. The gall bladder was adherent to the lateral abdominal wall (Figures 3-5). However, it was still unclear whether these pulled in structures contained the hilar structures or the cystic pedicle. As the anatomy was grossly distorted, we used the fundus first approach to avoid any injury to the hilar structures (Figure 6). After adhesiolysis, the gall bladder was found to be gangrenous till its neck. The gall bladder itself was rotated through 360° in the anticlockwise direction around the fixed cystic pedicle and its neck. There also was a band like adhesion between the neck and the Riedel's lobe (Figure 7). After releasing this band, we noticed a remnant 90° anticlockwise rotation. This was also derotated (Figure 8). The cystic duct was found to be unusually long and twisted (Figures 8 and 9). The common bile duct (CBD) was kinked, pulled anteriorly and was lying close to the anterior edge of the liver. The cholecystectomy was

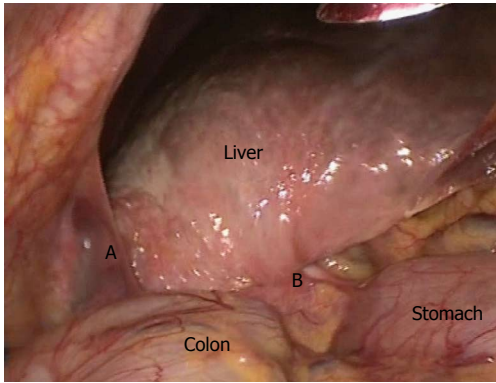


Figure 3 Laparoscopic view showing distorted anatomy. A: Adhesions between the gall bladder and the lateral abdominal wall; B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

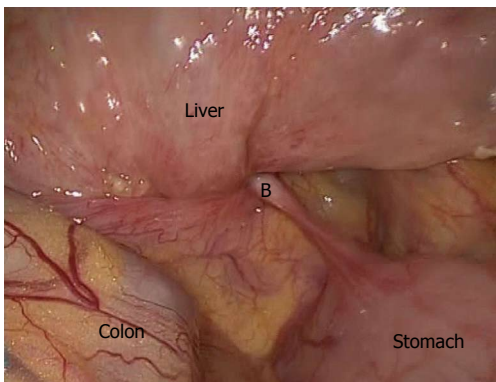


Figure 4 Zoomed in view of Calot's region. B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

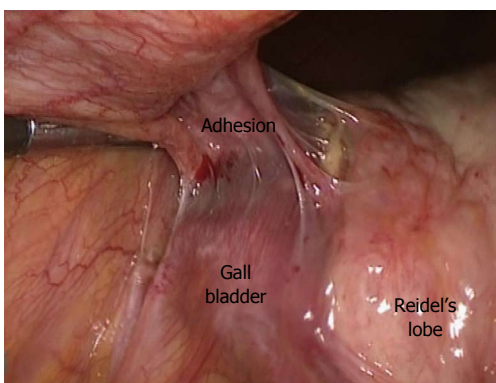


Figure 5 Adhesions between the gall bladder and the lateral abdominal wall.

thereafter safely completed.

In our case, the gall bladder may have undergone a two staged torsion. The first stage is a 90° anti-clockwise rotation during the initial period of symptoms. This might have been followed by the adhesive band formation between the neck and the anomalous Riedel's lobe. Subsequently, the gall bladder might have undergone the second stage of a 360° anti-clockwise rotation, this time taking the Riedel's lobe and the peritoneal folds (arising from the pylorus and

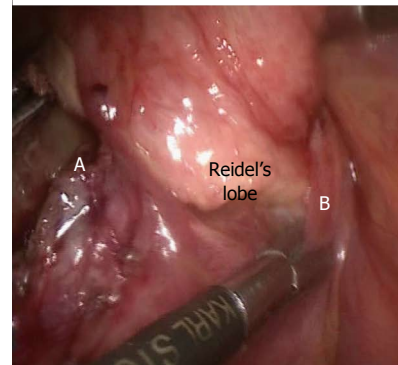
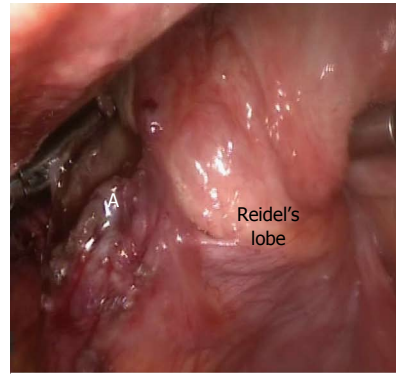


Figure 6 Rotated Riedel's lobe. A: Gangrenous fundus of the gall bladder; B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

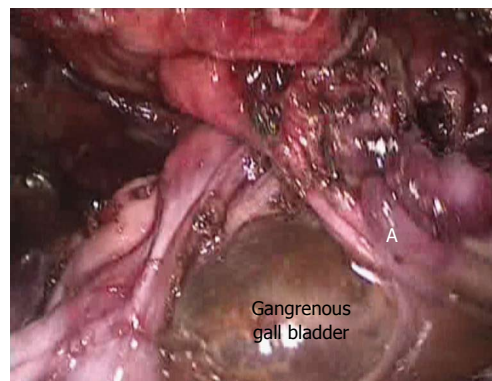


Figure 7 Gangrenous gall bladder after adhesiolysis. A: Adhesive band between the neck of the gall bladder and the Riedel's lobe.

the hepatic flexure). The delay in surgery may have led to the adhesions between the gall bladder and its surrounding structures after undergoing torsion.

An intra-operative cholangiogram was done and it was normal. The gall bladder was removed in an endo-bag through umbilical port. It did not contain any calculi. The histopathology report showed features of gangrenous gall bladder. Postoperatively, the patient improved and was discharged after three days.

DISCUSSION

GBT has been reported in patients ranging from 2 to 100 years old patients^[5,6], more frequently in elderly white females. Loss of fat and elasticity

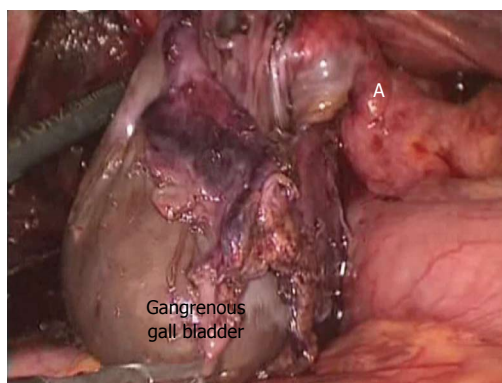


Figure 8 Gall bladder found gangrenous till its neck.

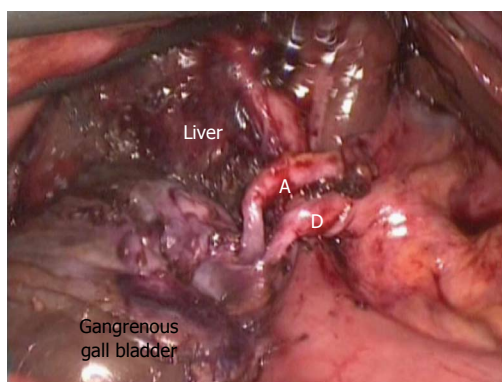


Figure 9 After derotation, the gall bladder in its normal position with the long and twisted cystic artery (A) and cystic duct (D).

may be responsible for its occurrence in the elderly population^[7].

Gross classified the congenital floating gall bladder into two types. In type 1, the gall bladder and cystic duct are attached to the inferior surface of the liver *via* mesentery and in type 2, only the cystic duct is attached to the liver^[8].

The pre-requisite for torsion is a “floating” gall bladder, where the entire organ is covered with peritoneum and is connected to the porta by a cystic pedicle enveloped in peritoneum. Torsion can also occur when the neck, or, along with the neck, part of gall bladder body is attached to the liver with a long pedicle. Several precipitating factors have been proposed as intense peristalsis of the neighbouring organs, blunt trauma to the abdomen, tortuous atherosclerotic cystic artery and kypho-scoliosis. Gall bladder stones are found only in 20%-33% of patients. Clockwise rotation of the gall bladder can occur due to intense stomach peristalsis or anti-clockwise due to transverse colon peristalsis^[7]. But, there are no strong evidences to support these factors. Peristalsis is a continuous phenomenon, with up to 5% of the population have floating gall bladder^[2,9]. In our case, there was a two staged torsion along with twisting of the Riedel's lobe. To cause this type of torsion, an abnormally large force may be required and source of this force needs to be

evaluated, as the above said precipitating factors do not seem to be the culprit.

Surgeons should have a high index of suspicion for GBT in acute cholecystitis patients, who fail to improve with conservative management. These patients should be considered for further careful imaging studies and prompt surgical intervention is required.

However, our patient presented with features of acute cholecystitis and on further imaging (CT scan), it was diagnosed as gall bladder perforation. Eventually, on laparoscopy, we found GBT with partially twisted Riedel's lobe with the gall bladder being loosely adhered to the surrounding structures due to delay in surgical intervention.

GBT is difficult to diagnose pre-operatively because it is rare and the presentation is similar to that of acute cholecystitis^[10,11]. Very few cases have been diagnosed precisely on pre-operative imaging^[12]. The classical findings of GBT on ultrasound are a large “floating gall bladder”. On CT scan, presence of the gall bladder outside its normal position, an echogenic conical structure (twisted mesentery) and a prominent cystic artery to the right of gall bladder, GBT should be borne in mind^[4,13,14]. MRI abdomen may accurately visualize the twisted cystic duct than any other imaging modality^[15]. In very few cases, CT abdomen showed hugely enlarged gall bladder with its unusual shape and configuration^[14]. GBT has been treated mostly by open surgical approach in past with few case reports using the laparoscopic approach. Laparoscopy adds the advantage of clearing the diagnostic dilemma and faster recovery.

As the anatomy is not very clear in GBT, one should be careful while dissecting in the region of the Calot's triangle, as chances of CBD injury are high due to distorted anatomy. The fundus first approach can be useful due to distorted anatomy in the region of Calot's triangle. The overall mortality in gall bladder torsion is approximately 5%^[16].

Gall bladder torsion is an uncommon surgical entity that should be considered in a case of suspicious acute cholecystitis not improving on conservative management. Delay in diagnosis may lead to gall bladder gangrene, gall bladder perforation, biliary peritonitis, or septicaemia. Such complications may obscure the preoperative diagnosis of GBT. A rare possibility of an accompanying twisted Riedel's lobe alters the anatomy and makes dissection cumbersome. Laparoscopic cholecystectomy is more feasible and safer than open approach.

COMMENTS

Case characteristics

A 77-year-old Caucasian lady with right upper quadrant pain since 4 d.

Clinical diagnosis

Her abdomen was soft with tenderness and guarding in the right hypochondrium and Murphy's sign was positive.

Differential diagnosis

Acute cholecystitis, gall bladder perforation.

Laboratory diagnosis

WBC count 14000/cu, the other laboratory reports were within normal limits.

Imaging diagnosis

The computed tomography scan showed a peripherally enhancing fluid collection along segments 5 and 6 of the liver and no gall bladder was seen in the gall bladder fossa.

Pathological diagnosis

Final Histopathological report was suggestive of gangrenous gall bladder.

Treatment

Laparoscopic cholecystectomy.

Related reports

Gall bladder torsion (GBT) is a rare entity, mostly seen in the geriatric population, masquerading as acute cholecystitis. In this case, it presented as gall bladder perforation. A two staged torsion was seen probably due to delayed surgical treatment.

Term explanation

In GBT, there is a mechanical organo-axial torsion that occurs along its longitudinal axis involving the cystic pedicle, with a prerequisite of a freely mobile gall bladder.

Experiences and lessons

This entity is seldom diagnosed preoperatively. It mimics acute cholecystitis. The dissection in the region of Calot's triangle must be done carefully due to the distorted anatomy.

Peer-review

This is uncommon case for laparoscopic cholecystectomy.

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