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REVIEW

Sentinel node navigation surgery for gastric cancer: Overview and perspective

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Abstract

The sentinel node (SN) technique has been established for the treatment of some types of solid cancers to avoid unnecessary lymphadenectomy. If node disease were diagnosed before surgery, minimal surgery with omission of lymph node dissection would be an option for patients with early gastric cancer. Although SN biopsy has been well ascertained in the treatment of breast cancer and melanoma, SN navigation surgery (SNNS) in gastric cancer has not been yet universal due to the complicated lymphatic flow from the stomach. Satisfactory establishment of SNNS will result in the possible indication of minimally invasive surgery of gastric cancer. However, the results reported in the literature on SN biopsy in gastric cancer are widely divergent and many issues are still to be resolved, such as the collection method of SN, detection of micrometastasis in SN, and clinical benefit. The difference in the procedural technique and learning phase of surgeons is also varied the accuracy of SN mapping. In this review, we outline the current status of application for SNNS in gastric cancer.

Key words: Sentinel node navigation surgery; Gastric cancer; Micrometastasis; Minimal surgery; Review

Core tip: The sentinel node (SN) technique has been established for the treatment of some types of malignancies to avoid over invasive surgery. However, SN navigation surgery in gastric cancer has not been yet universal due to the complicated lymphatic flow from the stomach. The results reported in the literature on SN biopsy in gastric cancer are widely divergent and many issues are still to be resolved, such as the collection method of SN, the accuracy of SN mapping, detection of micrometastasis in SN, and clinical benefit. SN mapping should be promising tool for indicating minimally invasive surgery of gastric cancer.

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INTRODUCTION

Gastric cancer is the fourth most common cancer in the world, accounting for approximately 989600 new cases each year and 738000 deaths in the world[1,2]. Recently the proportion of gastric cancer at an early stage has been increasing because of the advances in the screening system, such as endoscopic investigation[2]. In fact, almost half of the patients in Japan who undergo surgery for Depth of tumor invasion (T) 1 gastric cancer[3]. Patients with T1 or T2 gastric cancer have superior prognosis when curative resection was carried out, due to the low rate of node involvement and distant metastasis compared with patients with advanced stage. Thus, in contrast with standard radical gastrectomy with Extent of lymph node dissection (D) 2 lymphadenectomy for gastric cancer, limited lymph node dissection, such as D1+ was often selected for patients with early gastric cancer. Theoretically, lymphadenectomy is unnecessary for patients without nodal metastases. Thus, early and accurate identification of lymph node metastasis is pivotal in making the subsequent surgical decisions. Considering the problem of postoperative morbidity and mortality after gastrectomy with extended lymphadenectomy, D2 lymph node resection is considered to be an over invasive surgery for patients with Lymph node metastasis (N) 0 gastric cancer in Western countries[4]. However, to date, the effective tools to diagnose pre- or intra-operatively the N0 status remains undefined.

The sentinel node (SN) technique has been established in the management of some types of cancers to avoid unnecessary lymphadenectomy[5-7]. SN is defined as the first lymph node to receive cancer cell drainage from the primary tumor, and the lymph node to which cancer cells metastasize initially. In 1992, Morton *et al*[5] reported that the SN was successfully detected by dye injection into cutaneous melanoma. Since then, SN biopsy has been well ascertained in the treatment of breast cancer and melanoma[8]. Minimally invasive surgery such as limited lymph node dissection and reduced the extent of resection based on SN mapping is termed SN navigation surgery (SNNS). This surgery may prevent the complications of the patient and serve as a useful tool for avoiding an over invasive surgery. However, SNNS of gastric carcinoma has not been universal due to the complicated lymphatic flow from the stomach and skip metastasis, which are sometimes recognized in gastric cancer[9-11]. In this review, we outline the current status of SNNS in gastric cancer and provide the future perspective.

STUDY STRATEGY

Data source and search strategy

Literature searches of electronic PubMed, Embase, and the Cochrane Library were performed in English-language articles to identify articles published until September 2014 that described SNNS in gastric cancer. The terms "gastric carcinoma", "gastric cancer", "sentinel", "mapping", "navigation surgery" were utilized. The abstracts were reviewed, and articles that were not associated with to the specific topic were excluded. Duplicate references as well as repeated publications were discarded. All of the studies that were considered to be eligible were retrieved and the final selection was based on the full article.

Study selection

We included randomized and controlled clinical trials or experimental studies (excluding case reports). Studies were considered without restrictions on duration of follow-up. First, the titles were screened and appropriate studies were selected. Of these studies, the full text was acquired. A total of 108 articles meeting this criteria were identified.

CONCEPT AND INDICATION OF SNNS FOR GASTRIC CANCER

The SN technique is derived from the concept that the tumor-bearing status of the SN reflects that of the remaining nodes. If this theory is established, negative metastasis in the SN indicate no other lymph node metastasis. Patients who undergo standard gastrectomy with D2 lymphadenectomy often suffer a variety of complications, such as diarrhea, reflux, dumping syndrome, termed postoperative syndrome. Extended lymph node removal also shows a significantly higher rate of mortality and a longer hospital stay than those underwent D1 lymphadenectomy in Western countries[12]. Thus, redundant extended lymph node dissection should be prevented to keep the patient's quality of life. The proportion of lymph node metastasis in gastric cancer relies on the depth of cancer infiltration across the layers of the stomach (termed TNM staging): it is found in 2%-18% of T1 and in about 20% of T2 tumors. On the other hand, the majority (more than 90%) of the patients with early gastric cancer survive 5-year and pathological data have suggested that the greater part of lymph nodes resected do not show nodal involvement[13].

The SN concept for gastric cancer surgery was first suggested by Japanese studies at the beginning of the 21st century[14-16]. The preliminary data showing a high degree of sensitivity and diagnostic accuracy by the use of an intraoperative radiation technique with a gamma probe was reported in 2002[17]. Another study presented that SN biopsy using indocyanine green (ICG) can predict the lymph node status with a high degree of accuracy[15]. In general, SN mapping and biopsy is performed in patients with clinical T1 or T2 tumors, primary lesions less than 4 cm in diameter, and clinical N0 gastric cancer. A recent study demonstrated 90.9% of patients with T1 tumors and 88.2% with T2 tumors had stained SLNs as compared to only 68.8% of patients with T3 tumors, sentinel node mapping in T1 and T2 gastric cancers may be useful in the decision-making process with regard to the extent of lymphadenectomy[18]. As well as other type of malignancies, SN mapping would exclude in the cases with positive lymph node metastasis ascertained by preoperative image including ultrasonography and computed tomography[11,19].

RESEARCH

Surgical techniques for SN mapping in gastric cancer

Tracer: As a means of identifying the SN, a dye-guided or radio-guided method has been conducted mainly for SN mapping. Dye or radioisotope colloid was usually injected around the primary tumor, and subsequently, the stained lymph node or lymph node uptake of RI was identified, respectively. Patent blue, lymphazurin, and the ICG are preferably selected in intraoperative time. Dye-guided method has been widely used due to the cost effectiveness and has benefit to detect the lymphatic vessels as well as lymph nodes. However, it has been reported that the dye-guided method is not suitable for patients with a dense adipose tissue, which would cause a high false-negative rate[20]. Recent studies described ICG dye is more suitable for SN due to its high accuracy rate[21]. But meanwhile, its disadvantage of poor visibility compared with blue node was often pointed out[22].

To overcome this problem, a noble attempt to use infrared ray electronic endoscopy (IREE) combined with ICG has been studied and developed[23]. IREE (Olympus Optical, Tokyo, Japan) can illuminate not only SLNs but lymphatic vessels that were not found by ICG injection alone. As compared to visual observation of ICG, lymph nodes identified as SNs by IREE combined with ICG showed higher sensitivity and accuracy. ICG fluorescence imaging has been reported to be innovative in that SN can be identified through a dense adipose tissue[24]. In the meanwhile, in order to observe the ICG infrared or fluorescence of the lymph nodes and lymph vessels, dark operating room is indispensable.

On the other hand, in the case of the radio-guided method, technetium-99m tin colloid, technetium-99m sulfur colloid, and technetium-99m antimony sulfur colloid is generally used as radioactive tracers[20]. It has been detected using a gamma probe during surgery by injecting through endoscopy so far. The radio-guided method has several benefits over the dye-guided method such as objectivity to see from its quantity, and identification of SLNs, even in patients with a dense adipose tissue. Furthermore, it is suitable for laparoscopic surgery due to the longer time of its stay in the lymph nodes. However, it has several subjects such as requirement of special facilities and high cost of radioactive substances. Consequently, considering of the advantages and disadvantages in both methods, a dual-tracer method is currently regarded as the most reliable to obtain a more precise identification rate of true SN and avoid confusion[20,25,26]. Recently, a hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) was established to enable gamma cameras to capture precise anatomical structures in CT images for SN mapping in various types of malignancies[27,28]. Application of SPECT/CT may develop the identification and the localization of SNs before gastric cancer surgery.

Injection site of the tracer: To conduct SN mapping by using a tracer, two kinds of methods have been mainly chosen; a method of injecting dye to the submucosal layer around the tumors under endoscopic examination, and a method of injecting to the serosal membrane at the site of primary tumor during surgical procedures. In fact, the dye is injected into the submucosa or serosa with 0.5 mL into the four quadrants around the tumor and 2.0 mL (150 MBq) of technetium-99m colloid solution is generally injected the day before surgery into four quadrants of the submucosal layer of the tumor using an endoscopic puncture needle[17]. Several studies have reported that there is no difference in the SN number and identification rate between the serosal and submucosal injection method[29,30]. In the meanwhile, the submucosal layer injection method has been predominantly used due to the reliability and rationality of a submucosal injection using an endoscope. This method may also be useful in laparoscopic surgery, because tumor cannot be palpable during an operation.

Collection method of SN: In general, there have been two types of methods to collect the SN sampling procedures for gastric cancer. One is the picked-up method to remove only hot node or staining lymph nodes that is currently used to assess breast cancer and melanoma. Another method is a lymphatic basin dissection (LBD)[31]. The gastric LBs were deemed to be distributed in the subsequent five directions along the main arteries: left gastric, right gastric, left gastroepiploic, right gastroepiploic, and posterior gastric artery area[32]. LBD is recognized as a sort of focused lymph node dissection involving stained lymphatic vessels and lymph nodes for early gastric cancer with keeping a safety area to avoid recurrence[33]. There is the possibility that SN basins contain true-positive nodes, even in the false-negative case. A recent report described that the accuracy rate of LN metastasis in LBD group was 92.3%, whereas that in the pick-up method group was 50%[34]. The fact that identified lymph node metastasis was completely involved into the lymphatic basin suggests that there is a limit to the sensitivity of the pickup method currently. Given the complexity of this procedure in laparoscopic surgery, it would be unsuitable for clinical applications. Considering the concept of SN biopsy, the picked-up method is more suitable rather than LBD. However, high accuracy rate of lymph node metastasis in LBD would cause an idea that LBD may be the first choice for the patients with early gastric cancer[10,35].

Detection of cancer cells in lymph nodes

It has been reported that reverse transcriptase polymerase chain reaction (RT-PCR) is the most sensitive method for determination of micrometastasis, while Morton *et al*[5]

Table 1 Cinical trials that validated the importance of sentinel lymph node surgery for gastric cancer in a current decade

Ref.	Year	*n*	Detection rate (%)	Sensitivity (%)	Main results
Kitagawa *et al*[19]	2014	397	97.50	93.00	The proportion of false negatives was 46% (13/28) after a learning period. False negatives remained at 14% (4/28) even by examining additional sections of GNs by paraffin section
Stojanovic *et al*[60]	2013	137	98.20	100	Highly successful mapping and biopsy of SLNs, as well as highest sensitivity was demonstrated and IHC study might enable "ultra staging"
Dong *et al*[61]	2012	23	100	100	SLN-guided minimally invasive surgery could be safely performed in EGC according to feasible criteria
Park do *et al*[62]	2011	68	91.20	100	Simultaneous ICG and (99m)Tc-ASC-guided laparoscopic sentinel basin dissection is an effective tool for gastric cancer SN mapping
Kelder *et al*[34]	2010	212	99.50	97.00	LBD dissection based on IREE is a safe method of nodal dissection in patients with T1 or limited T2 tumors
Tajima *et al*[22]	2009	56	96.40	T1; 97.2 T2 or T3; 72.2	SN mapping guided by ICG fluorescence imaging is useful for predicting the metastasis in lymph nodes in gastric cancer with cT1-stage cancer
Rino *et al*[63]	2007	43	93.00	100	SN mapping seems sufficient in T1 or T2 gastric cancer
Morita *et al*[66]	2007	53	100	82	The accuracy of the SNNS procedure for detecting SNs in patients with early gastric cancer was 96% at the occult metastasis level
Ichikura *et al*[67]	2006	80	100	93	Dissecting the lymph node stations only where the tracers are distributed is recommended for patients with no metastatic SNs
Zulfikaroglu *et al*[64]	2005	32	97	100	SLN biopsy using gamma probe in gastric cancer is a feasible procedure with high sensitivity and accuracy

SLN: Sentinel lymph node; EGC: Early gastric cancer; ICG: Indocyanine green; LBD: Lymphatic basin dissection; IREE: Infrared ray electronic endoscopy; SNNS: Sentinel node navigation surgery.

examined lymph node metastasis by routine hematoxylin and eosin (HE) staining or immunohistochemical staining. It is important to prove the first lymph node detected by the dye-guided or radio-guided method is the true SN to which cancer cells metastasize initially. Osaka *et al*[36] reported that a lymph node detected by the dye-guided method should be the true SN by RT-PCR analysis of micrometastasis, and concluded that an appropriate minimal surgery with SN navigation using this dye-guided method would be made available for patients with early gastric cancer. Another study presented that RT-PCR using carcinoembryonic antigen (CEA) mRNA showed higher sensitive rate compared with immunohistochemistry for identifying micrometastasis of LN[37]. They also indicated minimally invasive surgery would be acceptable if SNNS is conducted for cT1 and cN0 gastric cancer. Shimizu *et al*[38] described that a newly established RT-PCR for the expression of cytokeratin (CK) 19, CK20 and CEA was acceptable for the intraoperative identification of micrometastasis, compared with HE staining and immunohistochemistry with anti-cytokeratin antibody in lymph nodes in patients with cT1 or cT2N0 gastric cancer. In the meanwhile, they also mentioned, if a false-negative finding was not entirely excluded, selective lymph node dissection with LBD was ideal even in patients with negative SN by RT-PCR.

Validation of SNNS for patients with gastric cancer

Despite the development of SNNS, there is still controversy with respect to the application of SN mapping in gastric cancer. Some investigators have reported the usefulness of SNNS in gastric cancer, while some studies report the limitation of SNNS. To date, a large number of single-institutional studies have demonstrated satisfactory results of SN detection. In these reports, the SN detection rate was 90%-100%, and metastasis detection sensitivity was 85%-100% (Table 1). In accordance with these results, two prospective multicenter trials to verify the SN theory in early gastric cancer were conducted. A study group of the Japan Society of SNNS conducted a multicenter prospective trial of SN mapping and analyzes the validity of SNNS using the dual-tracer method with a radioactive colloid and isosulfan blue dye[19]. Twelve institutions with established SN mapping protocol and experienced surgical staffs participated. Three-hundred and ninety-seven patients with clinical cT1N0M0 or cT2N0M0 single tumor with the diameter of the primary lesion less than 4 cm, were enrolled. The SN detection rate was 97.5% and sensitivity of detection of regional lymph node metastasis was 93.0%, which were comparable to previously reported data of SN mapping[39]. The accuracy of metastatic status based on SN evaluation was 99.0%. The plan on the future SNNS study group, clinical study of reduction surgery for negative cases is initiated intraoperative SN for early gastric cancer from this result. On the basis of these findings, randomized controlled trial to compare individualized gastrectomy based on intraoperative SN biopsy data with conventional distal/total gastrectomy is under construction. In future studies, appropriate indications for function-preserving gastrectomy might be individually determined according to the SN mapping concept.

On the other hand, to verify the feasibility and accuracy of diagnosis utilizing SN, Japan Clinical Oncology Group (JCOG) carried out a multicenter clinical trial, JCOGO302[40]. Patients with T1 gastric cancer and less 4 cm tumor size were enrolled. Injection

Table 2 Cinical trials that served to focus on the limitation of sentinel lymph node surgery for gastric cancer in a current decade

Ref.	Year	*n*	Detection rate (%)	Sensitivity (%)	Main results
Miyashiro *et al*[40]	2014	440	97.80	46% of false negative rate	The proportion of false negatives was 46% (13/28) after a learning period. False negatives remained at 14% (4/28) even by examining additional sections of GNs by paraffin section
Ryu *et al*[41]	2011	2684	87.80	97.50	A meta-analysis of feasibility studies showed SNB in gastric cancer may not be clinically applicable due to the unsatisfactory sensitivity and heterogeneity among practicing surgeons
Wang *et al*[11]	2011	2128	93.70	76.90	The reliability of SNLB in EGC is currently not comparable to SNLB in breast cancer or melanoma
Becher *et al*[8]	2009	27	100.00	83.00	The negative predictive value is 75% and clinical use of SN mapping for gastric cancer was not recommended
Yanagita *et al*[56]	2008	133	98.50	100.00	Micrometastasis and ITCs should be removed, especially during SN navigation surgery
Tonouchi *et al*[65]	2005	37	94.60	75.00	During laparoscopic SN mapping there is a high risk of false negativity with SNs located in the right pericardial region

GN: Green node; EGC: Early gastric cancer; ITCs: Isolated tumor cells; SNB: Sentinel node biopsy; SNLB: Sentinel lymph node biopsy; ITCs: Isolated tumor cells.

of 4-5 mL indocyanine green dye was conducted from the serosal side of the stomach around the initial tumor. The detection rate of green nodes was 97.8%. But the rate of false-negative was 46.4%, which was unexpectedly high, and 7 of 13 false-negative cases were diagnosed positively metastasized beyond the lymphatic basin. Recently, the study of meta-analysis studies was performed examining the sensitivity of SN biopsy for patients with gastric cancer[41]. Two thousand six hundred and eighty-four cases of 46 papers of SN biopsy-related gastric cancer were reported for 2001 and 2009. SN identification rate and sensitivity were 87.8% and 97.5%. Negative and positive predictive values were 91.8% and 38.0% respectively. By subgroup analysis, sensitivity of SN was shown to rely on the number of picked-up SN. They concluded SN mapping in gastric cancer is not clinically applicable for limited lymph node dissection due to its insufficient sensitivity and practical differences between surgeons. In the meanwhile, as a result of the examination of the 2128 cases paper of 38 study has been carried out[11]. SN detection rate, sensitivity, negative predictive value and accuracy was 93.7%, 76.9%, 90.3%, and 92.0%, respectively. Combined tracer, submucosal injection method, laparotomy, and immunohistochemical staining revealed a significantly better sensitivity and detection rate. Although the SN mapping is feasible, they concluded that further examinations are necessary for investigating the best technique and standard protocol. These studies that served to refer the limitation of sentinel lymph node surgery in gastric cancer are summarized in Table 2.

As described previously, the results reported in the literature on SN biopsy in gastric cancer are widely divergent. Many authors from Asia reported an accuracy of more than 98%[17,31], in particular in early stages (T1-T2), whereas in Western countries the accuracy was about 80%, with the false negative SLN rate ranging from 15% to 20%[8,42,43]. This extreme variance in results may be explained by the difference in the procedural technique and learning phase of surgeons in these studies. The accurate detection in the case of skip metastases is inadequate even using the LBD method, and the SN jumped the first lymph node level in about 20% of cases, in accordance with the results of the larger Eastern series[44]. Regarding the utility of SLN navigation in an attempt to detect the nodal basin, many issues are still to be resolved and further studies are recommended before this method can be introduced into daily practice.

In order to evaluate whether SN concept is suitable for clinical use, the study regarding the follow-up results including recurrence and survival is essential. In the case of breast cancer, meta-analysis of the literature for studies concerning clinically node-negative breast cancer patients presented the axillary recurrence rate was 0.3%-0.6%[45]. Patients with SN micrometastases or isolated tumor cells do not reveal a worse disease-free survival (DFS) or overall survival (OS) compared with SN negative cases. A significant shorter DFS and OS were shown in patients with macrometastatic disease in the SN[46]. A large, nonrandomized cohort study demonstrated SN biopsy in patients with melanoma more than 1.0 to 4.0 mm in thickness demonstrated improved DFS and regional recurrence-free survival[47]. Despite the advancement of follow-up findings in the prospective randomized studies for precise assessment of SNNS in breast cancer and melanoma, there are small amount of studies in the individual institute referring the recurrence or survival in patients with gastric cancer who underwent SNNS. The majority of reports presented no cases of postoperative metastasis or recurrence was found[33,48-50]. Yano *et al*[51] reported the one of 180 patients (0.8%) developed recurrence at the anastomosis, not at lymph node. A study examined additional RT-PCR analysis for patients with gastric cancer who were determined node-negative intraoperatively. The 3-year survival in group showing positive by RT-PCR (66.7%) is shorter than that showing negative (90%). They concluded the focused SN protocol by using RT-PCR can be applied for an intraoperative approach to determine the extent of lymphadenectomy. To acquire the clinical benefit of SNNS in gastric cancer, prospective multicenter randomized trial to assess outcome and survival of SN biopsy is necessary.

CONCLUSION

In the near future, preserving the function of a residual digestive organ and quality of life in postoperative patients will be more highlighted. SNNS is one of the most attractive tools to detect the clinical undetectable lymph node metastasis of gastric cancer, which may lead to individualized less invasive surgical approach. Despite a large number of studies have made an attempt to validate the feasibility and accuracy of SLN in gastric cancer, the results are still varied, which may due to the different protocol and surgical technique. Thus, for the confirmation of clinical applicability of SNB in early gastric cancer, multicenter phase Ⅲ trial considering these issues should be urgently needed. Recently, SENORITA trial, which comparing the conventional laparoscopic gastrectomy versus laparoscopic SN biopsy with the organ and function preserving surgery of early gastric cancer is ongoing (NIH study trial registration number NCT01804998; Clinical Trials. gov). Another Multicenter phase III trial is also in progress (NIH study trial registration number NCT01544413; ClinicalTrials. gov). All things to do the laparoscopic sentinel lymph node biopsy are ascertained by checklist and evaluated the performance complement. Accumulation of these recent clinical trials (NIH study trial registration number NCT00489515, NCT01926743; ClinicalTrials. gov) may contribute the application of SNNS in gastric cancer in practice.

For the clinical use of the SNNS in gastric cancer to avoid unnecessary lymph node dissection, negative diagnosis of metastatic lymph node should be confirmed intra-operatively before resection of the stomach. Accordingly, highly accurate intraoperative diagnostic techniques are to be explored[52]. To apply SNNS as a practically acceptable method in the same manner as breast cancer and melanoma, there are many issues to be resolved. To begin with, the protocol of SN biopsy should be generally valid. Although SN biopsy has the high accuracy to detect metastatic lymph node, a technique of surgical procedure and pathologic evaluation has been performed in a specialized center and could not be standardized in a wider range of clinical institutions. Subsequently, extensive experience is necessary for developing the technical skill to attain a high accurate degree, which means that the accuracy of the technique relies on the individual surgeon[53]. To overcome these obstacles, standardization of SN mapping technique, using improved tracer, and guideline to evaluate the positiveness of SN specimen should be planned to incorporate SNNS in routine practice.

One possible strategy to validate the conception of SNNS in gastric cancer would be the advancement of rapid intra-operative histopathology. Commonly, frozen lymph node specimen divided into two or four sections is examined using HE staining. The JCOG0302 trial showed the unreliability of frozen section investigation with only one plane and intraoperative diagnosis using SN biopsy could be applied with requirement of multiple planes of specimen[40]. The diagnostic accuracy will increase depending on the number of slices. On the contrary, an enlarged sample number also causes several problems such as a time consuming, increasing workload of the surgeons and pathologists and economic burden. As previously described, in order to reduce the false-negative rate, the usefulness of the diagnostic tools to detect micrometastases using molecular-based diagnostic methods, including RT-PCR method has been reported[37,54,55]. Because of time consuming to obtain the finding of micrometastases by conventional RT-PCR method, conventional RT-PCR procedure has reported to be unpractical for rapid diagnosis during surgery[37,38]. Thus, new method reducing the time required to obtain results of micrometastasis may facilitate the practical use of this technique in the future[56]. One-step nucleic acid amplification assay, an automated system that uses the reverse-transcription loop-mediated isothermal amplification method for gene amplification, may be an ideal to replace the histological examination with a quick and simple molecular approach[57]. Since RT-PCR is not necessary for this assay, results are obtained within 30 min for one LN.

Another strategy to validate the conception of SNNS in gastric cancer would be an enhancement of sensitivity and accuracy of the dye-method to the degree of the combined method. Dye-method is a simple method that can be performed in a general hospital without the approved area for injection of radioactive colloid and special equipment. IREE and ICG fluorescence imaging may contribute to the achievement of this scheme. However, there is one problem that these detection systems have gray scale imaging and require a darkroom. Therefore, it is difficult to perform SN biopsy under the view of SN in the same time. Recent studies presented Hyper Eye Medical System can be used under room light with the ability to detect color and near-infrared rays simultaneously[58,59]. By using this system, surgery can be continued concurrently under the guidance of ICG fluorescence because this system is acceptable under room light. Such novel diagnostic examination and technologies could conquer the current problems of practical application of the SNNS.

In conclusion, there remain many issues to be defined to use SNNS in clinical practice. If these obstacles would successfully be settled, SN mapping should be promising tool for indicating minimally invasive surgery of gastric cancer.

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ORIGINAL ARTICLE

Retrospective Study

Vascular Z-shaped ligation technique in surgical treatment of haemorrhoid

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Abstract

AIM: To present the effectiveness of minimal invasive vascular zet ligation in the surgical treatment of haemorrhoidal disease (HD).

METHODS: Among 138 patients with 2nd-4th grade internal HD having several complaints and operated at our hospital between 2003-2013; 116 patients who regularly attended 1-year control were included in the study. Operation times, postoperative early period pain, satisfaction score, complications and relapse details were obtained from computer records retrospectively. Visual Analogous Scale (VAS) scores were used for patient satisfaction on the 3rd, 7th and 21st days. Technique; fixed suture which is constituted by the first leg of the Z-shaped suture (to pass by the mucosa and muscular layer) was put in the pile root in order to ensure vascular ligation and fixation. The second leg of the Z-shaped suture is constituted by mobile suture and it passes by the pile mucosa and submucosa which prolapses 5-10 mm below the first suture.

RESULTS: Seventy-five of the patients (65%) were male, 41 of them (35%) were female and their age average was 41. The mean operation time was 12 ± 4.8 min. VAS/satisfaction score was found as 2.2/4.3, 1.8/4.0, 1.2/4.4 respectively on the 3rd, 7th, and 21st days. Four of the patient (3.5%) had relapse.

CONCLUSION: This technique is an easily applicable, cost efficient way of operation which increases patient satisfaction.

Key words: Haemorrhoids; Haemorrhoidectomy; Z ligation

Core tip: The non surgical and surgical therapy of symptomatic hemorrhoidal disease, cannot achieve the same results at each patient. The vascular Z suture technique, is an innovative technique employed in the surgical therapy of symptomatic haemorrhoid of 3-4 degree. This technique is reducing significantly the complications which are annoying both the postoperative patient and the surgeon. The product of ten years experience and development, this technique has a facile application and increases the postoperative life quality of the patient. The most distinctive and highest qualities of this technique are embed in the shortness of the operation time, easy applicability and reduction in the postoperative bleeding and pain symptoms of the patient as well as a shorter recovery period.

Gemici K, Okuş A, Ay S. Vascular Z-shaped ligation technique in surgical treatment of haemorrhoid. *World J Gastrointest Surg* 2015; 7(1): 10-14 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i1/10.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i1.10

INTRODUCTION

Haemorrhoidal disease (HD) is one of the oldest diseases known by mankind. In 1888, Fredrick Salmon defined the surgical technique which is a combination of excision and ligation for haemorrhoids[1]. Today, Milligan-Morgan (Open method) and Ferguson (Closed method) haemorrhoidectomy are commonly used in symptomatic grade 3, 4 HD in particular[2]. The conventional haemorrhoidectomy which is used in the treatment of third and fourth grade haemorrhoids has severe morbidity and long recovery times[3]. Towards the middle of this century, there was a tendency towards non-operative methods because conventional haemorrhoidectomy operations were more painful and they wear away at the patient[4]. In United States, nearly 58% of the patients above years of age are estimated to have this disease and one-third of these are exposed to surgical intervention[5]. Since there is no smooth muscles on the walls of the vascular structures that constitute HD, it was shown that they were sinusoidal structures and haemorrhages resulted from perisinusoidal arteriolar. Three theories were suggested as of the twelfth century, which are namely varicose veins theory, vascular hyperplasia and anal cushions' slide out theory. Thompson's anal cushions' slide out theory with detailed anatomic studies has been the most accepted theory. The treatment contains diet arrangement, medical treatment, non-operative treatment and operative treatment. Sclerotherapy, Infrared coagulation, rubber band ligation and radiofrequency ablation can be listed among the most commonly used non-operative treatments. The most commonly used operative methods are conventional haemorrhoidectomy, stapler haemorrhoidectomy, plication and doppler-guided haemorrhoidal artery ligation (DGHAL)[6]. Being a treatment method which does not contain tissue excision and necrosis, Vascular Z ligation technigue (VZLT) ensures vascular ligation, fixation and mucopex by a single suture. This study of ours aims to define this technique and present its effect on the postoperative morbidity and recovery process in the surgical treatment of HD.

MATERIALS AND METHODS

Among 138 patients with 2nd-4th grade internal HD having several complaints and operated at our hospital between 2003 and 2013; 116 patients who regularly attended 1-year control were included in the study. The patients were explained the informed patient consent which involved extensive information about the operation made and presented alternative methods and their permissions were obtained.

The patients were operated under spinal anaesthesia without applying preoperative enema by applying 1 g cefazolin IV in gynaecological position. The technical drawing of the process can be seen in Figures 1 and 2. The first leg of the Z-shaped suture is constituted by the fixed suture. Fixed suture passes by the mucosa and muscular layer from the root of the enlarged and prolapsed sinusoidal network. The second leg of the Z-shaped suture is constituted by the mobile suture; it is put such that it passes by the piles mucosa and submucosa which prolapses 5-10 mm below the first suture. 3/0 round 26 mm polyglactin (vicryl®Ethicon) was used as suture material. This process was applied on nearly three to four piles. Fixed suture ensures vascular ligation and fixation, mobile suture hangs up the venous piles.

Operation times, preoperative early period Visual Analogous Scale (VAS), satisfaction score and complications were obtained from the computer records retrospectively. The most commonly used one for the pain score was VAS (0 = no pain, 10 = intense pain), and numeric scale (0 = not satisfied and 5 = very satisfied) were used as the satisfaction score. Numeric scores were applied on the patients on the 3rd, 7th and 21st days. While complications such as haemorrhage, infection, urinary retention and incontinence were question in the acute period, anal stenosis was questioned in the 3rd month. The patients' complaints were questioned at the monthly controls and they were evaluated for recurrence. Haemorrhage, pain and new pile formation were considered relapse.

Statistical analysis

All data was recorded in SPSS® for Windows (version 21-Chicago, IL, United States) for analysis. The statistical review of the study was performed by a biomedical statistician and statistical review is performed before the submission. The statistical methods of this study were reviewed by M. Sinan IYISOY from Selcuk University, Faculty of medicine, Department of Medical statistics.

RESULTS

Seventy-five of the patients (65%) were male, 41 of them

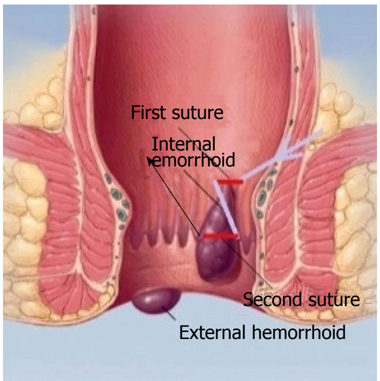

Figure 1 Vascular Z ligation technique application.

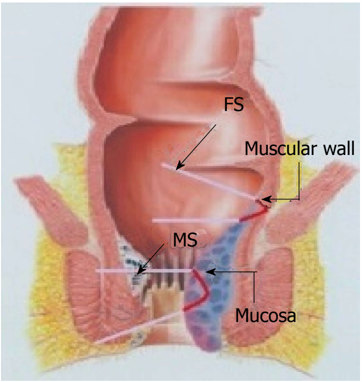

Figure 2 Coronal plane of the Vascular Z ligation technique suture.

Figure 3 Image before the operation.

(35%) were female and their age average was 41. The demographic and other characteristics of the patients can be seen in Table 1. Third grade haemorrhoid was found in 63 (54%) of the patients.

The most frequent complaint of the patients (41 patients) was haemorrhage only. The number of patients who had anal itching (Patients with soiling) and discomfort was 15 (Table 2). The mean operation time was 12 min, and follow-up time was 13 mo.

The preoperative image of the patient with Grade 4 HD can be seen in Figure 3 and the postoperative one can be seen in Figure 4. The VAS pain score of

Table 1 The basic features of the patients

	n (%)	Median (range)
Gender		
Female	41 (35)	43 (19-55)
Male	75 (65)	38 (18-65)
Hemoroit grade		
Grade 2	11 (10)	
Grade 3	63 (54)	
Grade 4	42 (36)	

Table 2 The operative time and complaints of the patients

	Mean (range)	Pain (%)	Hemorrhage (%)	Pain + Hemorrhage (%)	Soiling (%)
Complaints		24 (21)	41 (35)	36 (31)	15 (13)
Operative time	12 min (3-23)				
Follow-up time	13 mo (8-19)				

the patients on the third day was 2.2 while it regressed to 1.2 on the twenty-first day. None of our patients required narcotic analgesics. Satisfaction score was beyond 4 between the third and twenty-first days. Five of our patients developed acute haemorrhage which did not require surgical treatment and blood transfusion and could be kept under control by medical treatment in 1 wk on average. Eight of our patients who mostly consisted of males and developed urinary retention were only attached urethral catheter and followed and they recovered in three days on average. No anal stenosis was observed in any of the patients in the controls in the third month (Table 3). Four of our patients developed relapse. There were grade 2 haemorrhoid in all patients which developed relapse. Three of them had symptoms of pain and haemorrhage and one of them had only haemorrage. Earliest relapse occured in three months and the only symptom was rectal haemorrhage. The other relapses occured in 5th, 7th, 12th months.

Patients with relapse recovered by medical treatment and there was no need for reoperation.

DISCUSSION

The purpose of most methods which have been developed until today for the surgical treatment of HD is based on things such as reducing the blood flow of haemorrhoids, keeping excess haemorrhoidal tissue away and fixing the remaining mucosa and anoderm on the tissue below[7]. The treatment of the symptomatic haemorrhoids which did not give response by change in diet and medical treatment is usually made by non-operative or operative methods. Before planning an interventional process for the treatment of HD, it is essential to determine indication whole and complete. In a study which was done in Cleveland, the correct

Table 3 The postoperative feature of the patients

	n (%)	3rd day (range)	7th day (range)	21st day (range)
VAS		2.2 (1-6)	1.8 (1-4)	1.2 (1-4)
SS		4.3 (2-5)	4.0 (2-5)	4.4 (2-5)
Acut hemorrhage	5 (4.3)			
Infection	2 (1.6)			
Urinary retention	8 (6.9)			
Anal stenosis	0			
Recurrence	4 (3.5)			

VAS: Visual analog scale; SS: Satisfaction score.

diagnosing rate of surgeons in benign perianal pathologies was found as 70.4%. This study is an important one in that it shows misdiagnosis and wrong treatment in 29.6% of the patients[8]. It has been reported that it is wrong not to immediately apply surgical treatment to the patients with haemorrhoidal prolapsus only[9]. Non-operative methods can be applied to the patients with symptomatic grade 1, 2 and selected grade 3 HD. Surgical treatment can be preferred in the HD where these treatments fail or complications emerge. Surgical treatment might vary based on the physiopathology of HD. While haemorrhoidectomy method is preferred in the HD which emerges upon the slide out of the anal cushion, stapler haemorrhoidopexy can be preferred in the HD which is accompanied by rectal mucosa prolapsus. If HD emerges as a result of arteriovenous hyperperfusion in the haemorrhoidal pile, these patients can be applied DGHAL technique as the surgical treatment[6]. As a result of eighteen prospective randomized studies, it was found that haemorrhoidectomy was the most effective method in the surgical treatment of HD. However, high complication (particularly such as pain, urinary retention, haemorrhage) rates and long-term job loss are the most important problems[10].

Although minimal invasive VZLT that we used in our study is an operative method, vascular ligation, fixation and mucopexy are ensured by a single suture without making tissue excision. VZLT is similar to DGHAL technique with the suture which is put on the root of haemorrhoid, and it is similar to rubber band ligation in collecting the piles. However, severe septic complications can emerge dependent on the necrosis tissue which generates in the distal of the band in the rubber band ligation technique. The success rate of rubber band ligation at 1-2 degree HD is 65%-75% and new bandings can be required in the later periods[11]. No severe septic complication was observed in our study. Vacuum effect can sometimes draw anoderm into the band during rubber band ligation application and severe pains can emerge as a result. In our technique, it is less likely to take anoderm inside because mobile suture is passed through by seeing the mucosa. In our technique, while applying fixed suture on the root of the haemorrhoid, no expensive tool is required as in the DGHAL technique. Giordano *et al*[12] reported an average operation time of

Figure 4 Image after the operation.

32 (23-47) min in their study which added mucopexy to the DGHAL technique[12]. Twelve minutes on average is enough for the devascular ligation, fixation and mucopexy process of VZLT. VZLT is an invasive technique as much as non-operative treatment methods. While non-operative treatment methods are mainly applied on internal grade 1-2 HD, VZLT can be applied on all grades of internal HD. But, how come does our technique ensures sufficient mucopexy in grade 4 internal HD without excision? Through the decongestion (diminution) in the distal by the fixed suture (vascular ligation). Five to ten mm hanging process of the mobile suture ensures sufficient mucopexy in the patients as it can be seen in Figure 4. In non-operative and operative methods, the treatment is mostly based on tissue excision, tissue necrosis or mucopexy. Most of the postoperative complications develop dependent to tissue excision and necrosis[9]. As there is no tissue excision and necrosis in our technique, postoperative complications rate is lower and the emerging complications are less severe.

The treatment of HD varies from change in diet to radical surgery according to the grade of haemorrhoid and symptoms. Although the surgical treatment of HD which does not respond to medical treatment is an effective treatment, it can lead to severe complications. Many technological applications have recently become a current issue in order to reduce these complications. The retrospective nature of the study, the lack of comparison with other techniques and the short follow-up time were the limits of the study. The minimal invasive VZLT that is applied by us has higher postoperative patient satisfaction, lower VAS and complication rate. This technique is an easily learnable, applicable and cost efficient method. Being a minimal invasive method in the surgical treatment of HD, we think VLZT can be safely and effectively applied.

COMMENTS

Background

Many surgical therapy methods were defined due to the unpredictable complications occurred in the surgical post-therapy period of the hemorrhoidal disease. The anatomic structure, physiology of the site and the contamination factors are increasing the unexpected complication ratios. Vascular Z ligation technique (VZLT) is an innovative method developed in order to minimize these complications which are annoying both the patient and the surgeon.

Research frontiers

The background of the surgical therapy of hemorrhoidal disease lays on the fixation of the sagged mucosa and Pake resection. In the VZLT used by the authors, the fixation is ensured by the first sutures while the suspending of the Pake is ensured by the second sutures.

Innovations and breakthroughs

The authors' technique does not involve the sagged Pake resection which is responsible for a large part of the postoperative complication. The innovation of this technique is that the fixation of the mucosa and hanging of the Pake is achieved through minimum sutures.

Applications

VZLT may be safely applied in the surgical therapy of symptomatic hemorrhoidal disease due to its easy applicability and high postoperative patient comfort.

Terminology

Haemorrhoids are normally venous structures located in the anal region. The hemorrhoidal disease occurs as a result of their expansion and sagging. Z a patterned suture is a technique.

Peer review

Haemorrhoidal plication has been used as one of effective surgical treatments for advanced internal haemorrhoids.

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ORIGINAL ARTICLE

Retrospective Study

Results of the open surgery after endoscopic basket impaction during ERCP procedure

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Ethics approval: The study was reviewed and approved by the Afyon Kocatepe University, The Ethical Committee of Medical Faculty.

Informed consent: All the patients in the study gave written informed consent prior to study enrollment.

Conflict-of-interest: The authors declare that they have no conflict of interest.

Data sharing: Technical appendix, statistical code and dataset are available from the corresponding author (SY, drsezginyilmaz@gmail.com).

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Abstract

AIM: To report the results of open surgery for patients with basket impaction during endoscopic retrograde cholangiopancreatography (ERCP) procedure.

METHODS: Basket impaction of either classical Dormia basket or mechanical lithotripter basket with an entrapped stone occurred in six patients. These patients were immediately operated for removal of stone(s) and impacted basket. The postoperative course, length of hospital stay, diameter of the stone, complication and the surgical procedure of the patients were reported retrospectively.

RESULTS: Six patients (M/F, 0/6) were operated due to impacted basket during ERCP procedure. The mean age of the patients was 64.33 ± 14.41 years. In all cases the surgery was performed immediately after the failed ERCP procedure by making a right subcostal incision. The baskets containing the stone were removed through longitudinal choledochotomy with the stone. The choledochotomy incisions were closed by primary closure in four patients and T tube placement in two patients. All patients were also performed cholecystectomy additionally since they had cholelithiasis. In patients with T-tube placement it was removed on the 13th day after a normal T-tube cholangiogram. The patients remained stable at postoperative period and discharged without any complication at median 7 d.

CONCLUSION: Open surgical procedures can be applied in patients with basket impaction during ERCP procedure in selected cases.

Key words: Biliary stone; Endoscopic retrograde cholangiopancreatography; Basket; Impaction; Surgery

Core tip: The impaction or wire fracture of basket is an uncommon but potentially highly dangerous complication during endoscopic retrograde cholangiopancreatography and stone extraction. Although there are several endoscopic approaches to treat the basket impaction they require specialized equipments and experienced clinicians. So surgical approach can be an alternative to endoscopic procedures in selected patients.

Yilmaz S, Ersen O, Ozkececi T, Turel KS, Kokulu S, Kacar E, Akici M, Cilekar M, Kavak O, Arikan Y. Results of the open surgery after endoscopic basket impaction during ERCP procedure. *World J Gastrointest Surg* 2015; 7(2): 15-20 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i2/15.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i2.15

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is mainly indicated for choledocholithiasis as well as pancreatic stones[1,2]. It can be performed to remove the biliary stones when combined with sphincterotomy. Bile duct stones are successfully removed with classical Dormia basket or balloon catheters in 85%-95% of the patients[3]. Mechanical lithotripsy is the second line method for non-extractable stones with conventional basket aside from availability and cost[4,5]. Several types of baskets (mechanic lithotripter or wire baskets) can be used for this purpose[6]. The success rates depend on several factors as size and number of the stones, degree of the jaundice and presence of cholecystitis. Complications of ERCP have been reported to occur in 5%-10% of the cases[7]. Basket related complications can be seen as impaction around a calculus or fracture of the traction wire. Endoscopic basket impaction is a rare and unusual complication that can be seen after an attempt for removal of biliary stones with basket. It is not encountered in classical ERCP complications in textbooks due to its extremely rare occurence. Actually it is a problem of high volume centers. It is defined as inability to withdraw the basket with stone from papillary orifice or seperate the stone from the basket in biliary channel lumen. Since there are only sporadic case reports, the precise treatment is still controversial[8]. At present endoscopic or surgical procedures can be applied for the basket impaction. Non operative maneuvers like extracorporeal shock wave, intracorporeal electrohydraulic lithotripsy, catching the basket tip with a second basket, balloon dilatation of the sphincterotomy area or laser lithotripsy are recommended at high technology units[9-11]. However these procedures require experienced endoscopists and sophisticated technological equipment. Therefore open surgery is still an alternative approach for such patients. In the present study, we reported the results of six patients with endoscopic basket impaction that have been treated with open surgery. To our best knowledge the present report is the largest series so far.

MATERIALS AND METHODS

Patients

This retrospective observational study was carried out between June 2008 and June 2014. A total of 1065 ERCP procedures were performed at our invasive endoscopic procedures unit for choledocholithiasis at this period. The total number of ERCP was 2092. Basket impaction of either classical Dormica basket or mechanical lithotripter basket with an entrapped stone were observed in six patients (0.28%). The mean age of the patients was 64.33 ± 14.41 years and they were all female. The patients were admitted with the right upper abdominal pain. Laboratory findings were consistent with cholestasis and obstructive jaundice. Ultrasonography and magnetic resonance cholangiopancreatography (MRCP) revealed one to seven pieces of biliary stones sizes ranging from 15 mm to 30 mm in diameter and dilated choledochus which had a diameter above 15 mm. A diagnosis of obstructive jaundice secondary to choledocholithiasis was made and the patients were proceeded to an ERCP with planned removal of biliary stone. The median age of our patients was 63 years (range 45-81 years). The periampullary diverticulum was present in four patients. In five patients, impacted basket was Dormia and in one impaction occured with mechanical lithotripter basket. The clinical data and the endoscopic features of the patients are represented in Tables 1 and 2. All patients in the work gave informed consent for the study prior to manuscript preparation.

Table 1 Details of the patients characteristics

Case	Age	LOS	Comorbidity	Surgical procedure	Additional procedure	PO complication
1	59	7	HF	T-Tube placement	Cholecystectomy	None
2	54	8	None	Primary closure	Cholecystectomy	None
3	80	4	None	Primary closure	Cholecystectomy	None
4	67	3	None	Primary closure	Cholecystectomy	Atelectesis
5	81	7	COLD	T-Tube placement	Cholecystectomy	SSI
6	45	9	HT	Primary closure	Cholecystectomy	SSI

LOS: Length of hospital stay; PO: Postoperative; HF: Heart failure; HT: Hypertension; SSI: Surgical site infection; COLD: Chronic obstructive lung disease.

Table 2 Endoscopic features of the patients

Case	Diameter of the choledochus (mm)	Maximum biliary stone size (mm)	No. of stones	Impaction type	Presence of diverticula
1	15	15	1	Dormia	Yes
2	20	20	3	Dormia	No
3	30	30	6	Litotripter	No
4	30	30	1	Dormia	Yes
5	25	20	7	Dormia	Yes
6	20	20	2	Dormia	Yes

Anaesthesia protocol and medication

All patients received fentanyl (1 μg/kg) before the procedure and a single dose of 0.04 mg/kg midazolam intravenously and additional doses of 0.5 mg midazolam until the Ramsey Sedation Score reached 3-4 points. We used the additional doses of midazolam to keep the consciousness to allow communication, while providing the necessary degree of sedation to enable surgical comfort and an adequate quality of recovery with no negative effects on haemodynamics and respiratory parameters. During procedure a routine antibiotic prophylaxis (*iv* cefazolin 1 g) was administered and duodenal peristalsis was reduced by *iv* hyoscine-n-butylbromide.

Endoscopic procedure

Endoscopic procedures and ensuing surgical procedures were performed by one of the three consultant surgeons themselves (SY, TO, YA). Following the demonstration and cannulation of the papilla, a cholangiography was obtained revealing the huge stone(s) (Figure 1). First conventional basket was tried to remove the stone from papilla (Figure 2). If it was unsuccessful and the stone could be seperated from basket than basket was removed and mechanical lithotripter was placed to crush the stone(s). In both instances if the basket

Figure 1 Cholangiography demonstrating the two giant sharp edged stones.

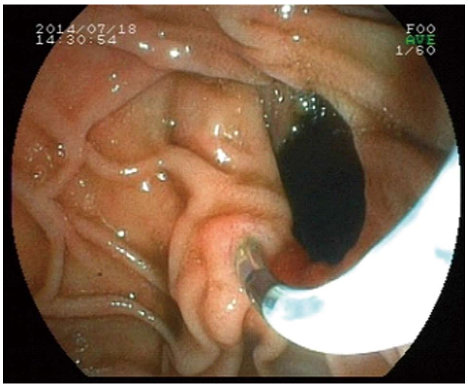

Figure 2 Cannulation through the papillary orifice located near to a big diverticula.

stone complex couldn't be pulled out papillary orifice despite forceful traction or basket couldn't be disengaged from the stone, the diagnosis of basket impaction was verified (Figure 3). The basket impaction occured within the intraduodenal portion of the choledochus in all patients. In this instance the handle site of basket wire was cut with Kirshner cutter, duodenoscope was removed and the patient was transferred to operating room with distal end of the basket emerging from the mouth (Figure 4). In all cases the surgery was performed immediately after the failed ERCP procedure by making a right subcostal incision. The baskets containing the stone were removed through longitudinal choledochotomy (Figure 5). The choledochotomy incisions were closed by primary closure in four patients and T tube placement in two patients. All patients were also performed cholecystectomy additionally since they had cholelithiasis. In patients with T-tube placement it was removed on the 13th day after a normal T-tube cholangiogram. The patients remained stable at postoperative period and discharged without any complication at median 7 d.

Statistical analysis

Since the present study is a retrospective descript

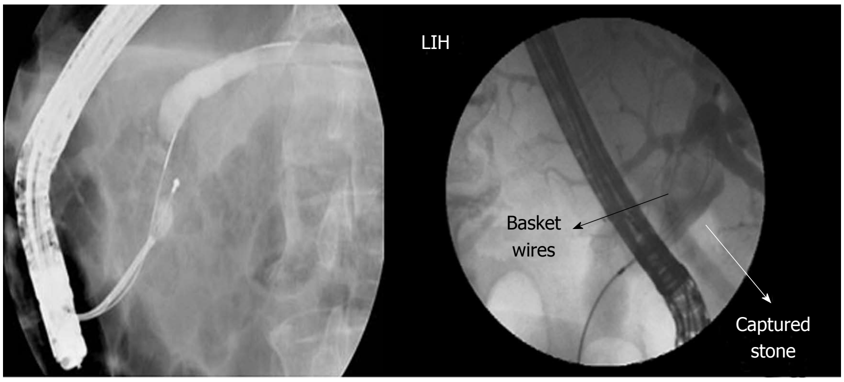

Figure 3 Basket attempts with Dormia to remove the angled (right) and round (left) stones.

Figure 4 Following a failed removal of a stone, the transfer of the patient to the operating room while the cut edge of basket handle emerging from the mouth immediately after the procedure.

Figure 5 Removal of the entrapped basket and stone complex through a ongitudinal choledochotomy incision.

study, we didn't perform any Statistical evaluation.

DISCUSSION

ERCP is an important endoscopic procedure with more than 500000 procedures performed yearly in the United States[7]. Although the precise number in our country is not known, we are performing approximately 300 procedures annually in our centre. Nearly half of these are due to biliary stones. ERCP, sphincterotomy and stone extraction are currently the best method to remove the stones in biliary system[12]. There are several complications including bleeding, perforation sepsis, pancreatitis and cholangitis following ERCP.

Endoscopy clinicians who perform more than 200 ERCP procedures per year (high volume centre) have been shown to have fewer complications than less experienced endoscopists who perform < 200 ERCPs per year[7]. There are several kinds of baskets made from metal wires and available in a variety of sizes and configurations to remove the biliary stones. Basket impaction is relatively rare but potentially quite dangerous complication during ERCP procedure. So far Katsinelos *et al*[13] reported the largest series of basket impaction that is the seven cases within 2715 ERCP procedures[13]. They treated such cases with endoscopic approach in six cases and one case was managed successfully with surgery. In the present study we reported the results of open surgery in six patients with basket impaction out of 2092 ERCP procedures between June 2008-June 2014. The incidence is approximately 0.28% that is quite similar to the rate observed in previous case series (0.26%). Although the incidence is very low, impaction of a basket with an entrapped stone may cause cholangitis, pancreatitis, sepsis and even death, thereby usually requiring open surgery or other specialized endoscopic techniques[12,14,15]. However endoscopic "rescue" interventions mostly require skilled experience and sophisticated endoscopic devices that are not widely available in many endoscopy centres. Additionally failed efforts may deteriorate the patient's clinical condition and even lead to perforation, hemorrhage and severe inflammation around the papilla that make an eventual open surgery more complicated. It can be seen both after conventional Dormia basket or mechanical lithotripter basket usage. Dormia basket may fail in the presence of large stone, in which case mechanical lithotripsy should be the latter choice in the treatment of choledocholithiasis. Mechanical lithotripter is able to crush the biliary stones into pieces so they can be taken out from the papillary orifice with conventional basket easily. However the success rate is low if there are multiple stones and/or calcified stones and the stone size exceeds 20 mm. If the diameter of biliary stone is more than 20 mm than the risk of basket impaction as well as fracture of the basket at the junction between the distal and proximal parts may occur[8]. Once the basket catch the stone, there should be enough space between the stone and biliary channel wall to release the stone from basket in case of failed crushing. By definition basket impaction is expressed as inability to withdraw the basket with stone from papillary orifice or separate the stone from the basket in biliary channel lumen. Since there are only sporadic case reports, the precise treatment is still controversial. At present endoscopic or surgical procedures can be recommended after basket impaction. Endoscopic procedures should be tried if there is adequate experience and specialized endoscopic devices. In such a case extension of the sphincterotomy should be attempted first since the most likely cause of impaction is inadequate sphincterotomy and tissue edema. It can be applied when it is clear that the sphincterotomy can be safely extended. The special equipment required is a duodenoscope with a 4.2 mm working channel[16]. However this can lead to duodenal perforation in inexperienced hands. Percutaneous transhepatic route can also be used in suitable cases by using a goose-neck snare in skilled radiology department[3]. Dilating the papillary orifice is sometimes useful to remove the impacted stone-basket complex with the larger balloon[17,18]. These endoscopic procedures are sophisticated and not widely available everywhere. Basket impaction represents a surgical emergency unless other non operative maneuvers like extracorporeal shock wave, intracorporeal electrohydraulic lithotripsy or catching the basket tip with a second basket are available[9-11,19]. Additionally since our patients required additional surgical procedures for cholelithiasis, open surgery was preferred to treat the current basket impaction problem. In our series all patients also had cholelithiasis thus required cholecystectomy. The basket stone complex was removed through a longitudinal choledochotomy incision. It was repaired with primary closure in four patients and T-tube placement in two patients. In our centre we routinely close choledochotomy incision primarily in patients with previous sphincterotomy. But two patients in the present report were treated with T-tube placement since there are severe inflammation, cholangitis and transmural thickening at the biliary channel. The frequency of diverticula at our 2092 ERCP procedures is approximately 25%, but in the present report we found that 4 patients in 6 basket impaction had duodenal diverticula. This high ratio considered us that the occurence of periampullary diverticula might be a predisposing factor for basket impaction. Small number of patients is our limitation so that the results can not be extrapolated to surgery clinics. However to our knowledge it is the largest series dealing with the open surgery in such patients. So it can suggest an alternative surgical approach besides endoscopic interventions in otherwise healthy patients without comorbidity. In conclusion impaction or wire fracture of basket is an uncommon complication during ERCP and stone extraction. There are several treatment protocols and it should be tailored to the patient's clinical condition, endoscopist's experience and ERCP unit equipment.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is mainly indicated for choledocholithiasis. Endoscopic basket impaction is a rare and unusual complication that can be seen after an attempt for removal of biliary stones with basket during ERCP. It is defined as inability to withdraw the basket with stone from papillary orifice or seperate the stone from the basket in biliary channel lumen. Endoscopic or surgical procedures can be applied for the basket impaction. Non operative endoscopic maneuvers like extracorporeal shock wave, intracorporeal electrohydraulic lithotripsy, catching the basket tip with a second basket, balloon dilatation of the sphincterotomy area or laser lithotripsy are preferable at high technology units. However open surgical procedures can also be applied in selected cases.

Research frontiers

In the present study, the authors reported the results of six patients with endoscopic basket impaction that have been treated with open surgery.

Innovations and breakthroughs

In literature non-operative endoscopic procedures are widely recommended for ERCP-related basket impactions. These procedures require experienced endoscopists and sophisticated technological equipment. However these techniques and endoscopic devices are not widely available in every endoscopy centre. Therefore open surgery is still an alternative approcah for such patients.

Applications

Open surgery by performing choledochotomy can be applied for the patients with basket impaction during ERCP procedure as an alternative to endoscopic interventions in selected cases.

Terminology

ERCP is abbreviation of endoscopic retrograde cholangiopancreatography and is an endoscopic technique to view the biliary and pancreatic channels. It is also used to remove the stones from these channels. Basket impaction is defined as inability to withdraw the basket with stone from papillary orifice or seperate the stone from the basket in biliary channel lumen. It can be treated with open surgery including choledochotomy (incizing the choledochus and removing the stone and basket together) and closing the choledochus by primary closure or T-tube placement.

Peer-review

This paper reported the results of six patients with endoscopic basket impaction that have been treated with open surgery. The results are interesting and encouraging, which provided the practical basis that open surgical procedures could be selected when endoscopic basket impaction occurred.

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CASE REPORT

Hepatic portal venous gas after endoscopy in a patient with anastomotic obstruction

Ai Sadatomo, Koji Koinuma, Rihito Kanamaru, Yasuyuki Miyakura, Hisanaga Horie, Alan T Lefor, Yoshikazu Yasuda

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Ethics approval: This study was approved by the Institutional Review Board of Jichi Medical School for ethical issues.

Informed consent: The patient provided informed written consent prior to submit the manuscript.

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Abstract

A 72-year-old male underwent a laparoscopic low anterior resection for advanced rectal cancer. A diverting loop ileostomy was constructed due to an anastomotic leak five days postoperatively. Nine months later, colonoscopy performed through the stoma showed complete anastomotic obstruction. The mucosa of the proximal sigmoid colon was atrophic and whitish. Ten days after the colonoscopy, the patient presented in shock with abdominal pain. Abdominal computed tomography scan showed hepatic portal venous gas (HPVG) and a dilated left colon. HPVG induced by obstructive colitis was diagnosed and a transverse colostomy performed emergently. His subsequent hospital course was unremarkable. Rectal anastomosis with diverting ileostomy is often performed in patients with low rectal cancers. In patients with anastomotic obstruction or severe stenosis, colonoscopy through diverting stoma should be avoided. Emergent operation to decompress the obstructed proximal colon is necessary in patients with a blind intestinal loop accompanied by HPVG.

Key words: Portal venous gas; Abdominal computed tomography; Colonoscopy; Anastomotic obstruction; Bacterial translocation

Core tip: A rare case of hepatic portal venous gas (HPVG) is reported. Endoscopy through ileostomy leaded the formation of HPVG induced by obstructive colitis. The anastomosis of rectum was totally obstructed after rectum cancer operation. For nine months, the mucosa of ascending to sigmoid colon has changed atrophy for disuse. The patient's condition improved after emergent operation of transverse colostomy. In patients with anastomotic obstruction or severe stenosis, colonoscopy through diverting stoma should be avoided.

Sadatomo A, Koinuma K, Kanamaru R, Miyakura Y, Horie H, Lefor AT, Yasuda Y. Hepatic portal venous gas after endoscopy in a patient with anastomotic obstruction. *World J Gastrointest Surg* 2015; 7(2): 21-24 Available from: URL: http://www.

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INTRODUCTION

Hepatic portal venous gas (HPVG) is a rare radiological sign associated with a wide range of abdominal abnormalities, ranging from benign to life-threatening conditions. Factors leading to gas in the portal vein include mucosal damage caused by necrosis, bowel obstruction, and sepsis[1]. We report a case of HPVG following endoscopy performed through an ileostomy. The patient had severe anastomotic stenosis after low rectal cancer resection leading to a functional blind loop.

CASE REPORT

The patient is a 72-year-old man who underwent laparoscopic low anterior resection of rectal cancer nine months prior to presentation. Five days after the rectal resection with primary anastomosis, he underwent construction of a diverting ileostomy because of an anastomotic leak. The remainder of the hospital course was uneventful after the second operation. Histopathology showed a moderately-differentiated adenocarcinoma with metastases to regional lymph nodes (T3N1M0). Adjuvant chemotherapy including tegafur-uracil (UFT) and leucovorin (UZEL) was administered for 6 mo.

Colonoscopy performed per anus, eight months after resection, revealed severe stenosis at the rectal anastomosis. The pinhole lumen was covered by hard granulation tissue, and the endoscope could not pass through the hole. Following this, colonoscopy was performed through the ileostomy to examine the proximal colon, which confirmed that the anastomosis was completely obstructed and the proximal sigmoid colon mucosa was atrophic and whitish, consistent with chronic ischemic mucosal damage (Figure 1). The procedure was performed in 63 min. The patient complained of mild abdominal pain during the colonoscopy, but the pain improved soon after the examination. Six days after the colonoscopy, he visited his local physician with complaints of appetite loss and slight fever. He was diagnosed with acute enteritis based on laboratory data consistent with inflammation, and treated with oral antibiotics and an intestinal remedy.

Ten days after the colonoscopy, he visited our hospital with a temperature of 40 ℃, blood pressure of 83/49 mmHg, and pulse of 100/min. Physical examination showed mild tenderness in the lower part of the abdomen with no sign of peritonitis. Laboratory data showed a white blood cell count of 8900/mm^3, C-reactive protein of 18.1 mg/dL, metabolic acidosis (PH = 7.374, anion gap of 12), and lactate dehydrogenase level of 1.1 mmol/L. Abdominal computed tomography (CT) scan showed a large amount of HPVG. The transverse, descending and sigmoid colon were dilated with no free air or ascites (Figure 2).

We believe that HPVG was caused by obstructive colitis and septic shock following colonoscopy. An emergency laparotomy was performed, which revealed that the transverse colon was edematous and purple violet (Figure 3). A transverse colostomy was constructed. Stool culture revealed presence of Pseudomonas aeruginosa. The postoperative course was uneventful and he was discharged on the seventh postoperative day. Four months later, ileostomy closure was performed.

DISCUSSION

HPVG was first described by Wolfe and Evens in infants[2] and has been associated with serious underlying diseases and a high mortality rate. HPVG has been reported to be associated with many conditions, such as necrotizing enterocolitis, bowel ischemia, Crohn's disease, ulcerative colitis, graft-*vs*-host disease, bowel obstruction and iatrogenic complications[3]. HPVG has been associated with procedures including endoscopy[4,5], laparoscopy, endoscopic retrograde cholangiopancreatography[6], esophageal variceal band ligation and percutaneous endoscopic gastrostomy tube placement[7].

The diagnosis of HPVG is often made by abdominal CT scans with high sensitivity. It is possible to detect even a small amount of HPVG, leading to the early diagnosis of HPVG. HPVG is not necessarily an indication for surgery, and the prognosis depends on the underlying disease. Allaparthi *et al*[7] reported that the mortality rate of HPVG was 25% to 35%. HPVG associated with bowel necrosis and ischemia usually has a high risk of mortality, so urgent laparotomy is recommended for such patients. Patients with a more equivocal clinical presentation might be treated non-operatively with intensive monitoring[8]. In the present patient, clinical findings indicated that the patient was in septic shock and emergent operation was needed.

Factors that predispose to the development of HPVG include: (1) mucosal damage; (2) bowel distention; and (3) sepsis[1]. Two or three of these conditions often coexist in many patients. Mucosal damage may be secondary to necrotic bowel, ulcerative colitis, or ulcer disease. Intraluminal gas can enter the capillary veins easily through a damaged mucosal barrier. Intraluminal pressures are increased by enema or colonoscopy. An intra-abdominal abscess can contain gas-forming organisms leading to HPVG. In this patient, anastomotic leakage and subsequent stenosis was likely caused by impaired blood flow to the left colon. The colonic mucosa became atrophic because of the absence of

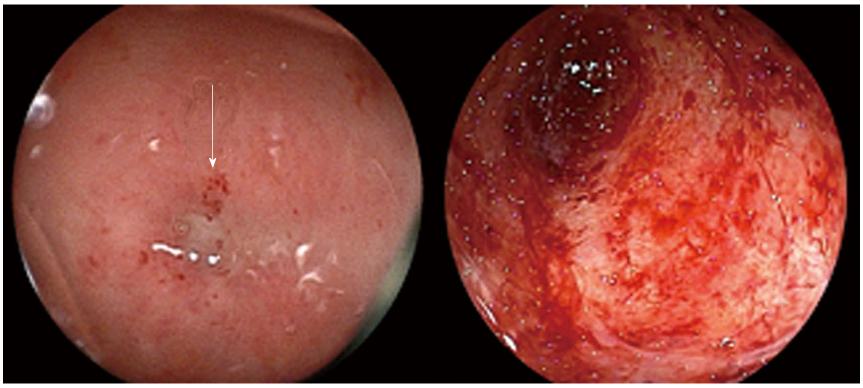

Figure 1 Colonoscopy through the ileostomy showed a tight stricture of the sigmoid colon at the anastomotic site (arrow). The mucosa of the sigmoid colon was severely atrophic (right panel).

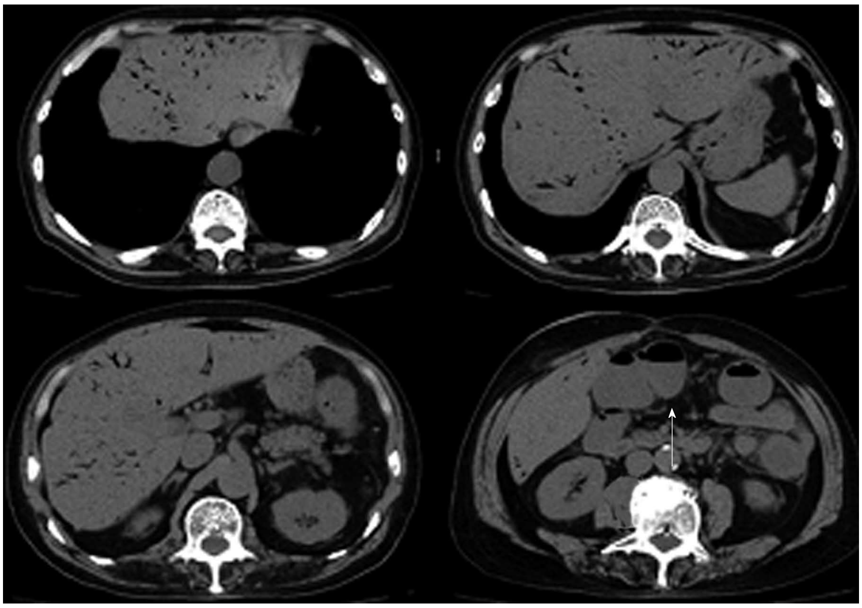

Figure 2 Computed tomography scan of the abdomen showed a marked amount of air throughout the portal venous system. The transverse colon was dilated (arrow).

Figure 3 Intraoperative findings. The transverse colon was edematous.

fecal passage for over 9 mo. A closed loop from the ileocecal valve to the site of the anastomotic stricture became a functional blind loop and intraluminal pressures were increased by the colonoscopy. Although no bacterial blood cultures were obtained, we suggest that HPVG and sepsis were caused by bacterial translocation.

A rectal anastomosis with diverting ileostomy is performed in many patients with distal rectal cancer. In the case of anastomotic obstruction or severe stenosis, the colon proximal to the anastomosis may become a closed loop. Colonoscopy through the ileostomy should be avoided. Emergent surgery to decompress the obstructed bowel is necessary in such patients with a blind loop accompanied by HPVG.

COMMENTS

Case characteristics

Seventy-two years old man presented in shock with abdominal pain and high fevers ten days after colonoscopy through ileostomy.

Clinical diagnosis

Physical examination showed mild tenderness in the lower part of the abdomen with no sign of peritonitis.

Differential diagnosis

Sepsis, gastrointestinal perforation.

Laboratory diagnosis

White blood cells: 8900/mm^3; C-reactive protein: 18.1 mg/dL; metabolic acidosis (PH 7.374, anion gap of 12).

Imaging diagnosis

Abdominal computerized tomography scan showed a large amount of hepatic portal venous gas (HPVG) and dilated transverse, descending and sigmoid colon.

Treatment

Emergent operation of transverse colostomy was done.

Related reports

Some cases of iatrogenic HPVG were reported in English literature and they are named in author's references. This is the first case report of HPVG induced by colonoscopy through ileostomy.

Experiences and lessons

In the case of anastomotic obstruction or severe stenosis, colonoscopy through ileostomy should be avoided.

Peer-review

It is interesting.

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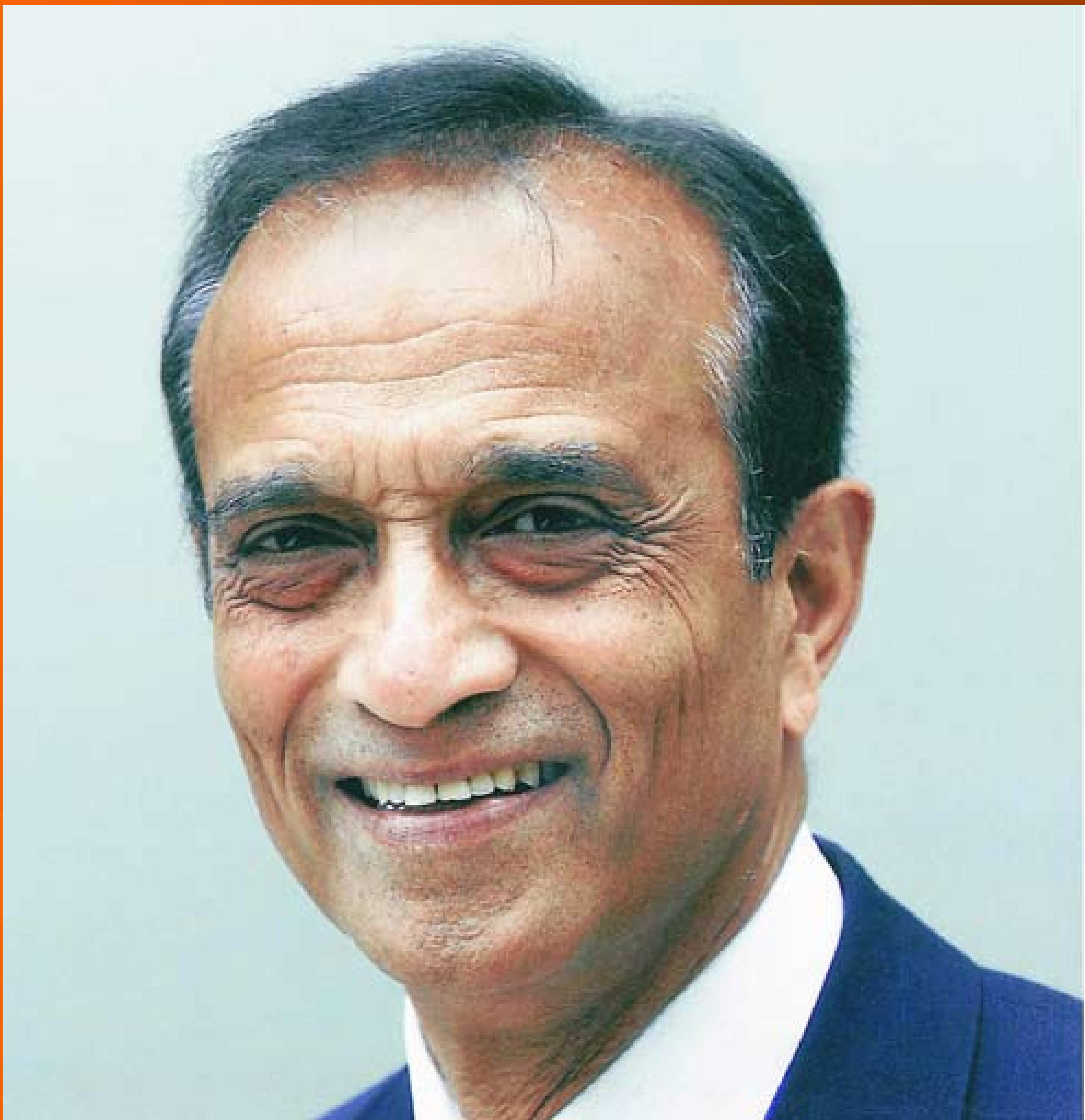

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MINIREVIEWS

Colorectal cancer risk in hamartomatous polyposis syndromes

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Abstract

Colorectal cancer (CRC) is a major cause of morbidity and mortality around the world, and approximately 5% of them develop in a context of inherited mutations leading to some form of familial colon cancer syndromes. Recognition and characterization of these patients have contributed to elucidate the genetic basis of CRC. Polyposis Syndromes may be categorized by the predominant histological structure found within the polyps. The aim of the present paper is to review the most important clinical features of the Hamartomatous Polyposis Syndromes, a rare group of genetic disorders formed by the peutz-Jeghers syndrome, juvenil polyposis syndrome and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes). A literature search was performed in order to retrieve the most recent and important papers (articles, reviews, clinical cases and clinical guidelines) regarding the studied subject. We searched for terms such as "hamartomatous polyposis syndromes", "Peutz-Jeghers syndrome", "juvenile polyposis syndrome", "juvenile polyp", and "PTEN hamartoma tumour syndrome" (Cowden syndrome, Bananyan-Riley-Ruvalcaba). The present article reports the wide spectrum of disease severity and extraintestinal manifestations, with a special focus on their potential to develop colorectal and other neoplasia. In the literature, the reported colorectal cancer risk for Juvenile Polyposis, Peutz-Jeghers and PTEN Hamartoma Tumor Syndromes are 39%-68%, 39%-57% and 18%, respectively. A review regarding cancer surveillance recommendations is also presented.

Key words: Hereditary GI cancer syndromes; Peutz-Jeghers; Juvenile polyposis; Cowden syndrome; PTEN tumor

Core tip: This is a brief review about clinical presentation, diagnosis, molecular features and surveillance recommendations regarding hamartomatous polyposis syndromes: Peutz-jeghers syndrome, juvenil polyposis Syndrome and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes).

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INTRODUCTION

Colorectal polyps may be histologically classified as neoplastic, hyperplastic, hamartomatous or inflammatory. Some of these polyps may develop sporadically or as part of a polyposis syndrome. Hereditary Polyposis Syndromes account for approximately 1% of all cases of colorectal cancer (CRC) and are associated with a broad spectrum of extra-colonic tumors. Each syndrome has its own genetic basis, polyp histology and distribution, clinical features, and malignancy risk.

Taking into account the histological nature of the polyp, the gastrointestinal syndromes may derive from adenomas (familial adenomatous polyposis, MutYH-associated polyposis), from hyperplastic polyps (serrated polyposis syndrome), from hamartomas [Peutz-Jeghers Syndrome (PJS), Juvenile Polyposis Syndrome (JPS), PTEN Hamartoma Tumor Syndrome] or from mixed polyps (Hereditary Mixed Polyposis Syndrome).

Hamartomatous polyp usually appear macroscopically as pedunculated, cherry-red lesions. They vary in size and its characteristic histological structure allows the distinction between a Peutz-Jeghers and Juvenile Polyp[1]. Peutz-Jeghers polyps (Figure 1) are tipically multilobulated with a papillary surface and branching bands of smooth muscle covered by hyperplastic glandular mucosa. A Juvenile Polyp (Figure 2) exhibits a normal epithelium with a dense stroma, an inflammatory infiltrate and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria. For this reason, it might be difficult to distinguish it from an inflammatory polyp.

The clinical significance of the Hamartomatous Polyposis Syndromes lies on their association with colorectal and other extracolonic malignancies (gastrointestinal, urogenital, breast and thyreoid)[2]. Thus, knowledge of their genetic basis and clinical expressions help establish diferential diagnosis and allow the construction of screening, surveillance and treatment recomendations, that should differ from the general population.

Genetic data and prevalence of PJS, JPS and PTEN Hamartoma Tumor Syndrome (Bannayan-Riley-Ruvalacaba and Cowden Syndromes) are presented in Table 1.

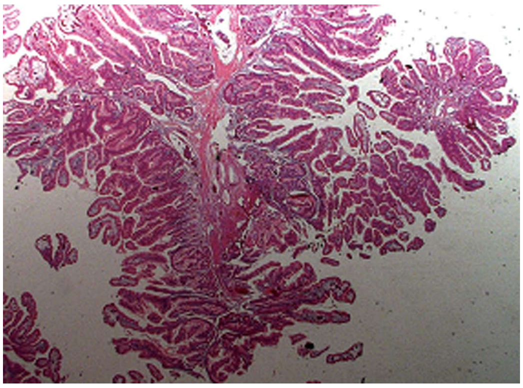

Figure 1 Histological features of a Peutz-Jeghers polyp. Note that they are typically multilobulated with a papillary surface and branching bands of smooth muscle covered by hyperplastic glandular mucosa.

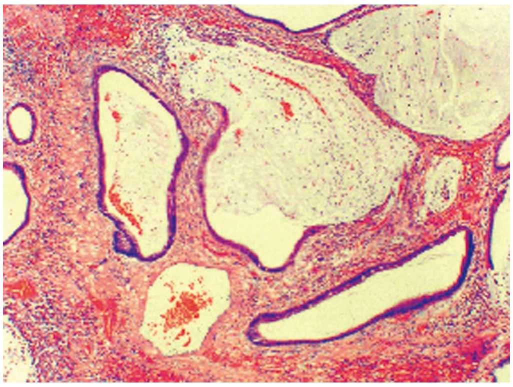

Figure 2 A Juvenile Polyp exhibiting a normal epithelium with a dense stroma, an inflammatory infiltrate and a smooth surface with dilated, mucus-filled cystic glands in the lamina propria.

Table 1 Genetic features and prevalence of pure Hamartomatous Polyposis Syndromes

Syndrome	Mode of inheritance	Gene	Incidence
Juvenile Polyposis	AD	*SMAD4/DPC4* *BMPR1A*	1:100 to 1:160 thousand
Peutz-Jeghers	AD	*STK11/LKB1*	1:60 mil a 1:300 thousand
BRRS	AD	*PTEN*	Rare
Cowden	AD	*PTEN*, *SDH* and *KLLN* epimutations	1:200 thousand

BRRS: Bannayan-Riley-Ruvalacaba syndrome; AD: Autosomal dominant; *SDH*: *Succinate dehydrogenase* (B and C subunits); *KLLN*: *p53 target* gene.

The aim of the present paper was to review the most important clinical features of the Hamartomatous Polyposis Syndromes, focusing on their potential to develop neoplasia, especially colorectal. This review was based on a literature search in order to retrieve the most recent and important papers (articles, reviews, clinical cases and clinical guidelines) regarding the subject. We searched for terms such as "hamartomatous polyposis syndromes", "PJS", "JPS", "juvenile polyp", and "PTEN hamartoma tumour syndrome" (Cowden

Figure 3 Mucocutaneous pigmentation in Peutz-Jeghers Syndrome.

Table 2 Clinical features and colon cancer risk in Hamartomatous Polyposis Syndromes, according to literature series

Syndrome	Main clinical features polyp distribution	Increased risk of other tumors	Colon cancer risk
Juvenile Polyposis	Juvenile polyps Distribution: large bowel (mainly), small bowel, stomach	Gastric and colorectal	39%-68%
Peutz-Jeghers	Peutz-Jeghers polyps Typical melanotic oral and dermic pigmentations Distribution: small bowel, large bowel, stomach	Gastric, small bowel, pancreas, colorectal, ovary, uterus, breasts, sex cords	39%-57%
PTEN	Mucocutaneous tumors (multiple trichilemmomas) Distribution: Small bowel, large bowel, stomach	Breast, thyroid, retina and uterus cancer	18%

syndrome, Bananyan-Riley-Ruvalcaba).

Table 2 presents the main clinical features and the reported malignancies described in association with these syndromes, revealing how heterogeneous this group is regarding polyp distribution and neoplasia risks.

The Hereditary Mixed Polyposis Syndrome is not discussed here cause this entity encompass polyps with distinct histologies (adenomas, serrated, hyperplastic, juvenile, mixed juvenile-adenomatous or hyperplastic adenomatous)[3]. In the same context, other syndromes where hamartomatous polyps are present (Multiple endocrine neoplasia type 2B, Gorlin, Neurofibromatosis type 1, Birt-Hogg-Dubbé and Cronkhite-Canada) have not either been included in this revision.

PJS

History and genetics

The association of mucosal pigmentation and gas trointestinal polyposis was first described by the English Sir Jonathan Huchinson in 1896. Although this condition has received many denominations throughout time, it was only after the work of the Dutch Peutz[4] (1886-1957) in 1921 and the American Jeghers[5] (1944), who firmed the disease features, that this association was nominated PJS.

Gastrointestinal polyps from PJS present distinct features from those found in other Hamartomatous Syndromes, such as the presence of a muscular component infiltrating the conective tissue in a pattern of ramification. Although a good pathologist should be able suggest the diagnosis based on histology, the establishment of a hamartomatous polyposis syndrome should be based on molecular features, as clinical manifestations may differ slightly.

PJS is inherited by an autosomal-dominant gene that is responsible either by the polyposis and the pigmentation. Nevertheless, some isolated cases have been reported. The genetic mutation occurs in a supressor gene that codifies the serina/threonina kinase (LKB1 ou STK11), located in chromossome 19p13.3[6]. Germline mutations of this gene lead to hamartoma formation, and other somatic mutations may transform hamartomas into adenomas and subsequently carcinomas[7]. The multiple mutations identified in gene LKB1 are responsible by the phenotypic variability of PJS, including the development of aggressive cases and other that never developed cancer.

Clinical features

PJS is characterized by the triad mucocutaneous melanic pigmentation, intestinal polyposis and familial history. Diagnostic criteria of PJS include two or more hamartomatous polyps in the gastrointestinal tract *or* one confirmed Peutz-Jeghers polyp with a family history of PJS or typical perioral pigmentation[8].

The pigmentation is manifested by dark black or blue spots around the lips, eyes and extremities (hands and feet), but are also found in the neck, thorax and perineum. They are formed by smooth melanin deposits in a round or oval shape, rarely confluent, with a 1 cm maximal diameter (Figure 3). They may appear since the neonatal period or even after the begining of the gastrointestinal symptoms[9].

The most important clinical manifestations are

Table 3 Cumulative cancer risk by site and age in Peutz-Jeghers Syndrome (Hearle *et al*[18])

Cancer/Age	20 yr	30 yr	40 yr	50 yr	60 yr	70 yr
All cancers	2	5	17	31	60	85
Gastrointestinal	-	1	9	15	33	57
Breast	-	-	8	13	31	45
Gynecological	-	1	3	8	18	18
Pancreas	-	-	3	5	7	11
Lung	-	-	2	4	13	17

secondary to the polyps, that may affect the small bowel (70%-95%), colon (27%), stomach (25%) and colorectum (24%-50%); the jejunum is more commonly involved than duodenum and ileum[10]. Gastrointestinal symptoms usually develop during the second and third decades, with abdominal pain resulting from hiperperistalism or polyp invagination. PJS polyps may may also cause obstruction, prolapse through the rectum, bleeding and anemia. Isolated polyps may rarely develop in the absence of other clinical features and are not associated with gastrointestinal cancer risk[11].

Risk of malignancy

Since its classical description in 1944[5], numerous cases of PJS associated with gastrointestinal (duodenum, jejunum, pancreas, stomach and colon) or extra-intestinal carcinomas (breast, ovary, cervix, thiroid, lung, pancreas and testicles) have been reported[2]. The supposed carcinogenesis is based on the controversial idea that the hamartomas may develop carcinomas as adenomatous and malignant alteration have been described in hamartomas[12,13].

It's been estimated that lifetime risk of any gastrointestinal cancer approaches 70% (mainly colorectal at 39% and pancreatic at 36%). Additional tumors (breast, sex chord in females, adenoma malignum of the cervix, Sertoli cell tumors of the tests, *etc.*) increase patient's lifetime risk to near 90%[14,15].

In a Dutch group of 133 PJS from 54 families, Van Lier *et al*[16] found 37% cancers, and CRC was the most common malignancy (14%). Compared to the general population, this report confirms a 9 fold increased cancer risk, a higher risk among women (20 fold) compared to men (5 fold), a 3.5 fold increased mortality rate and that gastrointestinal cancers develop at young age. In a recent paper, Beggs *et al*[17] reported a high rate of extracolonic tumors such as gastric (29%), small bowel (13%), pancreatic (36%), breast (54%), ovarian (21%), lung (15%), cervical (10%) and uterine/testicular (9% each).

In another paper[18], CRC turned to be the most common luminal gastrointestinal cancer (17/40) among 419 patients with 297 documented mutations, with a cumulative risk of 3%, 5%, 15% and 39% at ages 40, 50, 60 and 70 years, respectively (Table 3). The risk of developing cancer at any site was four fold that observed in the general population.

In females with PJS, the risk of breast cancer was also increased six fold over the population and is comparable to the BRCA mutations.

Similarly, in a metanalysis to evaluate the risk of many tumors, Giardiello *et al*[19] grouped 107 men and 106 women from 79 families, and reported estimated cumulative cancer risks of 54% for breast, 39% for colorectal, 36% for pancreas, 29% for stomach and 21% for ovarian cancer by 64 years of age.

Management of PJS is based on the treatment of symptomatic benign conditions, large polyps and surveillance of malignant tumors. For this reason, endoscopic resection of polyps larger than 1.5 cm is advisible, even in asymptomatic patients. Patients scheduled to a conservative follow-up must undergo periodic examination after 30 years of age, with bienal evaluation of superior and inferior digestive tract, anual pelvic, testicular and abdominal ultrasound (mainly for pancreas) and anual mammography after 25 years Family member should be equally examinated[20].

JPS

Genetics and history

JPS is a rare genetic disease that exhibits incomplete penetrance and heterogeneity, with positive familiar history appearing in only 20% to 50% of patients. There were described germinative mutations in the *SMAD4* (*MADH4*) (chromosome 18q21.1) and in the *BMPR1A* (chromosome 10q 21-22) genes[21,22]. The genetic mutations have not been identified in all cases of JPS. *SMAD4* mutations are more common and predispose to polyposis in the upper digestive tract[23]. *BMPR1A* mutations are found in 40%-100% of families without *SMAD4* mutation.

Pathological features of polyps in children were described many years ago, at the same time when the term juvenile polyp was coined by Horrilleno *et al*[24] in 1957. But it was Morson in 1962 who established those polyps as hamartomas[25], and McColl *et al*[26] in 1964 defined the JPS as a distinct entity.

Clinical features

When discovered as isolated sigmoid or rectal lesions during infancy, Juvenile polyps may cause bleeding, hematochezia, intussusception, or even self-amputation (Figure 4). In this cases, the risk of malignization is very low. Once recognized, they should undergo endoscopic resection.

On the other hand, development of JPS is much more less frequent, being characterized by numerous hamartomatous polyps in the intestine and other parts of the gastrointestinal tract. Diagnostic criteria include: (1) more than 5 juvenile polyps in the colorectum; and (2) multiple juvenile polyps throughout the gastrointestinal tract or one or more polyp and a positive family history of juvenile polyposis[27-29].

During infancy, the polyposis may affect all the digestive tract, and the prognosis is dependent on this

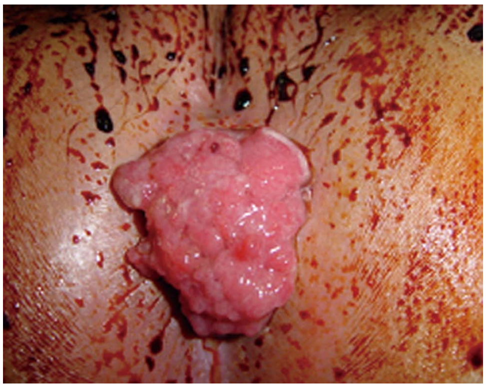

Figure 4 Prolapsed polyp through the anus in a patient with Juvenile Polyposis.

involvement (referred as JP of infants). These cases are not associated with familiar history[28]. Within the other forms of the disease, the polyposis may appear during the second or third decades, more rarely (15%) in adults. Within the gastrointestinal tract, the most affected sites are the colorectum (98%), stomach (14%), jejunum/ileum (7%) and duodenum (2%)[29]. Similarly, in 262 patients with PJS, Höfting *et al*[30] reported colorectal, gastric and intestinal lesions in 98%, 13.6% and 8.8% of them, respectively.

Some patients may refer familar history suggesting an autosomal dominant pattern of inheritance[31]. Some congenital abnormalities have been described in 15%-20% (midgut malrotation, cardiac anomalies, cleft palate, supranumerary teeth, macrocephaly, hydrocephalus, polydactyly, mesenteric lymphangioma, *etc.*), mainly in patients not referring familiar history. *SMAD4* mutations are associated with JPS and hereditary hemorrhagic telangiectasia, and some carriers may present symptoms from both conditions. Conective tissue disorders have been documented in approximately one-fifth of these patients, such as enlarged aortic root, aortic and mitral insufficiency, aortic dissection and others[32].

Risk of malignancy

Carcinomas from many locations have been reported within a wide variation of lifetime cumulative cancer risk[33,34]. The estimated lifetime risk of gastrointestinal cancer in JPS family members varies from 9% to 50%[22]. Although most of these tumors consist of colon cancer, tumors arising in the stomach, upper gastrointestinal tract and pancreas have also been reported. The estimated risk for CRC is 17%-22% by age 35[35] and a lifetime risk of gastric and duodenal cancer of 10%-21%[15,36].

Specialized centres have reported adenomatous features or adenomas associated with juvenile polyps in 2 a 15% of the patients, suggesting a possible histogenical mechanism to carcinogenesis[33,37,38]. Otherwise, it is not known if those adenomas are formed through a total conversion of a juvenile polyp or if they represent "*de novo*" lesions.

Isolated juvenile polyps should be endoscopically or surgically excised, depending on location. In PJS patients, regular endoscopic examinations is considered a more conservative approach after 15 years of age. There is a tendency to manage the patient according with symptoms severity and polyp features (number, accelerated growing and displasia). In the case of few polyps, polypectomy is indicated. A prophylactic colectomy (Ileal-rectal anastomosis or pouch surgery has been advocated by others, especially in patients with adenomatous features, displasia and a strong history of CRC[39,40].

Some studies showed that up to half of patients required a completion proctectomy after initial total colectomy. Annual endoscopic surveillance of the rectum and ileal mucosa is advisable after surgery in order to detect recurrent polyps. First-degree relatives must be screened by colonoscopy from the second decade of life up to the age of 70[15,22,31].

PTEN HAMARTOMATOUS TUMOR SYNDROME

Genetics and clinical features

PTEN Hamartomatous Tumor Syndrome (PHTS) groups patients diagnosed with either Cowden (CS) or Bannayan-Riley-Ruvalcaba syndromes (BRRS). Both are inherited in an autosomal dominant pattern and develop due to mutations of the *PTEN* gene (phosphatase and tensin homolog), a tumor suppressor gene located on 10q23.3. PTEN mutations have been recently found in only 25% of CS patients. Other patients were described as having SDH gene mutations (succinate dehydrogenase B and C) or KLLN epimutations in 10% and 30% of the cases, respectively[41].

While BRRS is usually diagnosed during infancy, CS prevails in adults. Mucocutaneous features allow early recognition of CS, manifesting before the neoplastic changes. They appear in 80% of the patients and are represented by multiple facial triquilemomas, oral mucosa papilomatosis and hand queratosis (Figure 5). Colorectal polyps are small, sessile and asymptomatic, being found in 35%-65% of patients[42].

Cowden's syndrome should be screened for the development of various cancers, such as thyroid (10%), breasts (30%-50%), endometrium and colorectal. Less than 10% of patients develop Central Nervous System tumors[43].

BRRS is characterized by intestinal polyposis (45% of patients) associated with dermatological lesions (pigmented macules of the glans penis)[44]. Extraintestinal manifestations have been described such as macrocephaly, subcutaneous lipomas, vascular malformations, high birth weight and central nervous system anomalies[45].

Cancer risks in PHTS

CRC risk in PHTS has been evaluated in the past few years. In a study of 127 patients with PTEN mutations

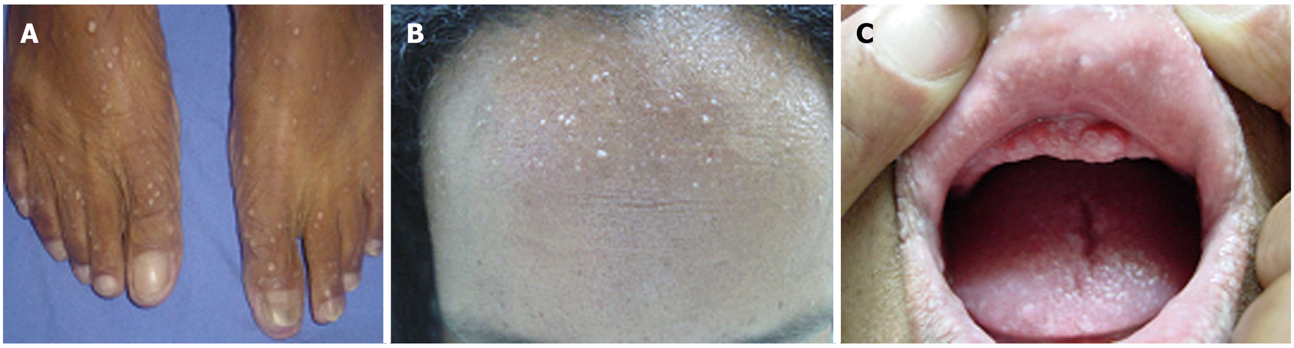

Figure 5 Feet queratosis (A), multiple facial triquilemomas (B) and oral mucosa papilomatosis (C) in a patients with Cowden's Syndrome.

Table 4 Recommendations for screening and surveillance according to the literature[17,40,48-51,53]

Syndrome	Screening	Work-up	Interval
Peutz-Jeghers	18-25 yr	Endoscopy (upper/lower)	2-3 yr
	25 yr	MRI and mammography	Annual
	10 yr	Testicular examination	Annual
	30 yr	MRI or CT (pancreas)	1-2 yr
Juvenile Polyposis	15-18 yr	Upper endoscopy	1-3 yr
		Colonoscopy	1-3 yr
		Upper endoscopy and video capsule endoscopy for HHT	3 yr
PTEN	After 25 yr	Colonoscopy	3-5 yr
		Mamography/thyroid US	Annual

US: Ultrasound; CT: Computorized tomography; MRI: Magnetic resonance imaging; HHT: Hereditary hemorrhagic telangiectasia.

(62 colonoscopies), Heald *et al*[46] found a wide spectrum of polyps and 13% CRC diagnosed in patients under 50 years of age. In a multi-national cohort of 3399 patients with CS (368 with PTEN mutations), Tan *et al*[47] reported a significantly increased incidence of CRC (10 fold), breast (20 fold), thyroid (50 fold), endometrium (40 fold), kidney (30 fold) and melanoma (8 fold).

In a group of 156 patients from 101 families with PTEN mutations, Nieuwenhuis *et al*[48] reported a cumulative risk of 70% for benign gastrointestinal polyps and 18% for CRC at age 60, respectively. This three to four-fold increase in CRC risk led the authors to recommend colonoscopy after 40 years of age.

Recommendations for screening and surveillance

Besides rare, recognition and screening of any Hamartomatous Polyposis Syndromes is a great deal for the patient, as these disorders may manifest important complications due to polyp bleeding or intestinal obstruction. Family members at risk should be fully evaluated after the second decade of life even if they are asymptomatic.

Once diagnosis is established, upper and lower endoscopic investigation (as well as radiological images) should be performed every 2 to 5 years[42,46]. Moreover, especial attention should be driven to extraintestinal malignancies at risk such as breasts, thyroid, uterus and others[47].

Gastrointestinal surveillance aims to reduce the polyp burden, its complications and cancer development. Furthermore, polyp management may reduce surgical intervention and prevent resection or emergency surgery, as demonstrated for PJS[49]. As the chance of malignant degeneration of colonic polyps has also been recognized in all hamartomatous polyposis syndromes, screening colonoscopy should be advised for all patients. Current recommendations for screening and surveillance according to recent publications[17,40,48,50,51] are resumed in Table 4.

Surveillance of the breast, colon and rectum and the small intestines should be established for PJS patients[51]. After comparing surveillance programs already published, Beggs *et al*[17] proposed to postpone the gastrointestinal screening till the late teens, with repeated exams each three years till 50 years of age (and each 1-2 years thereafter). Colonoscopy should be performed every 2-5 years from 25 years of age.

Recommendations regarding JPS families include colonoscopy every 1-2 years starting at 15-18 years and upper endoscopy with a 1-2 year interval from 25 years of age[22,52]. The group from the St. Mark's Hospital[53] showed that colonic polyps predominated in the right colon and that carpeting disease represents a special concern. They recommend upper and lower gastrointestinal endoscopy every 1-3 years starting at 12 years. Moreover, they advise annul full blood count and cardiovascular examination and screening for HHT (hereditary-hemorrhagic telangiectasia) symptoms (mainly A-V malformations) in *SMAD4* mutation carriers.

Finally, PTEN-mutations carriers are suggested to perform dermatological examination, neurological, psychological testing, and thyroid ultrasound from the late teens. After 30 years, women should undergo annual mammogram, endometrial examination and transvaginal ultrasound[47]. Biannual colonoscopy is advised after 40 years of age[48].

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ORIGINAL ARTICLE

Retrospective Study

Long-term survival following radiofrequency ablation of colorectal liver metastases: A retrospective study

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Abstract

AIM: To retrospectively evaluate the long-term survival of patients that received radiofrequency ablation (RFA) therapies of colorectal liver metastases.

METHODS: In 2005 to 2008, RFA of 105 colorectal liver metastases (CRLM) were performed on 49 patients in our institution. The liver metastases were evaluated, both before and after ablation therapies, with contrast enhanced computerised tomography and contrast enhanced ultrasonography. Histological evidence of malignant liver metastases was obtained in the few instances where contrast enhanced ultrasonography gave equivocal results. Accesses to the CRLM were guided ultrasonically in all patients. The data obtained from records of these ablations were retrospectively analysed and survival data were compared with existing studies in the literature.

RESULTS: 1-, 2-, 3-, 4- and 5-year survival rates, when no stringent selection criteria were applied, were 92%, 65%, 51%, 41% and 29% respectively. To explore the impact of the number and size of CRLM on patients' survival, an exclusion of 13 patients (26.5%) with number of CRLM $\geqslant$ 5 and tumour size $\geqslant$ 40 mm resulted in 1-, 2-, 3-, 4- and 5-year survival rates improving to 94%, 69%, 53%, 42% and 31% respectively. It is of note that 9 of 49 patients developed extra-hepatic metastases, not visible or seen on pre-treatment scans, just after RFA treatment. These patients had poorer survival. The development of extra-hepatic metastases in nearly 20% of the patients included in our study can partly account for modestly lower survival rates as compared with earlier studies in the literature.

CONCLUSION: Our study underscores the fact that optimum patients' selection before embarking on RFA treatment is vitally important to achieving a superior outcome.

Key words: Colorectal cancer; Liver metastasis;

Radiofrequency ablation; Long-term survival; Ablation success

Core tip: The current study corroborates the consensus in the literature which proposes that adequate patients' selection before radiofrequency ablation (RFA) therapy is vitally important to achieving a satisfactory ablation success. To the best of our knowledge, the consensus proposed that patients with more than 5 hepatic metastases and tumour size of more than 40 mm are probably unsuitable for RFA. Furthermore, inadvertent inclusion of patients with extra-hepatic metastases for RFA treatment of colorectal liver metastases is an important factor that can influence negatively the overall patients' survival.

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INTRODUCTION

Cancers constitute a great economic burden in the western world. Colorectal cancer is the third most common cancer across the world and is ranked the second most frequent cause of cancer associated mortality in the industrialised countries[1,2]. Around 50% of colorectal cancer patients will eventually develop liver metastases[2-5]. So, effective control of colorectal liver metastases (CRLM) has the potential of improving patients' survival.

The traditional mode of treating CRLM has been surgically with quoted 5 year survival rate varying from 24% to 58% in carefully selected patients[3,5-7]. Surgical resection has some significant inherent drawbacks; mortality can be as high as 10% peri-operatively and up to 37% of patients undergoing hepatic resection could end up with profound morbidity[3]. Resection of several hepatic metastases has the potential of leaving behind a significant low hepatic reserve. Resection of metastatic lesions in the liver close to vital structures such as major vessels cannot be safely carried out[3].

Radiofrequency ablation (RFA) as one of the techniques to achieving local control of CRLM has received intense attention in recent years. Development and incessant improvement of RFA techniques as a treatment modality of CRLM aim to reaching similar patients' survival as in surgical treatment with fewer complications[3]. The main goal of this study was to retrospectively evaluate the long-term survival of patients that received ablation therapies of CRLM in our institution compared with earlier studies in the literature with the intention to ascertain optimum quality control of our applied RFA technique.

MATERIALS AND METHODS

Wealth of data for this study originated from the electronic patient chart database, picture archiving and communication system (PACS) and records of RFA therapy. From 2005 to 2008, ablations of liver metastases were performed at the Aalborg University Hospital on 49 patients (32 men and 17 women) who had colorectal cancer. The demography of the patients is presented in Table 1 and is essentially similar to other studies in the literature[6,8,9]. It was not possible, at the time of diagnosis, to establish in all patients whether the liver metastases were synchronous or metachronous with the primary tumour. Twenty patients (40.8%) received at least one additional session of RFA therapy due to either local tumour recurrence or development of new liver metastases.

Because the institution was only modestly experienced in the ablation technique in 2005-2008, strict and well defined inclusion criteria were not clearly outlined before embarking on CRLM ablation therapy. The pre-RFA scans were evaluated according to the best clinical practice, and none of the included patients had any clear signs of extra-hepatic metastases. However, we saw some non-specific lung nodules in the pre-RFA scans of some patients, where some of these nodules later turned out to be metastases. Patients were accepted for ablation therapy irrespective of numbers and sizes of the liver metastases. All patients had resection of their colorectal primary tumour and received chemotherapy in oncologic regime.

A grand total of 105 liver metastases were primarily ablated (Table 1). A significant proportion of patients (82%) had ≤ 3 liver metastases, 8 patients had 4-7 liver metastases and only one patient had 8 liver metastases at the time of diagnosis. The largest size of a single ablated lesion was 70 mm.

Lesions' evaluation: Pre- and post-ablation

The diagnoses of colon tumour and hepatic metastases were established with the aid of contrast enhanced computerised tomography (CECT). In most cases, hepatic metastases were also confirmed by contrast enhanced ultrasonography (CEUS) to aid the planning of RFA procedures. Histological evidence of malignant liver metastases was obtained in the few instances where CEUS gave equivocal results. Two consultant radiologists with several years of experience evaluated CECT and CEUS in all patients.

The same protocols as for pre-treatment diagnostic imaging evaluation were repeated for follow-up post treatment. Post treatment imaging assessments were carried out at 1 mo and thereafter 3 monthly post-ablation treatments if there were no evidences of recurrence or new metastases.

Table 1 Demography of patients who had colorectal liver metastases ablation therapy and lesions' characteristics *n* (%)

Total number of patients (*n*): 49	No. of women: 17
Mean age: 65 yr	No. of men: 32
	No. of patients
Age distribution	
≤ 50 yr	3 (6)
51-79 yr	44 (90)
≥ 80 yr	2 (4)
Total number of liver metastases ablated: 105	
Average numbers of metastases per patient: 2.3	
No. of liver metastases ablated	
≤ 3	40 (82)
4-7	8 (16)
≥ 8	1 (2)
Maximum size of metastases ablated	
Size of metastases	
< 10 mm	3 (6.1)
11-30 mm	31 (63.3)
31-39 mm	6 (12.2)
≥ 40 mm	9 (18.4)

Evaluation of ablation success

We defined primary ablation success in terms of lack of abnormal hepatic contrast enhancement (in CECT and CEUS) at 1 mo post treatment imaging. Enhancement at the border of earlier site of ablation was termed local tumour recurrence (LTR). Newly discovered abnormally enhancing lesions in follow-up imaging that were neither clear in the pre-treatment scanning nor related to earlier ablation sites, were dubbed new hepatic metastases (NHM). Presence of LTR or NHM or both qualified patients for additional session(s) of RFA.

Radiofrequency ablation technique

RFA were guided ultrasonically in all patients. Vast majority of liver ablations were carried out percutaneously. In few cases where liver metastases could not be reached safely percutaneously or because of limited visualization, RFA were carried out under ultrasound guidance following laparotomy. All patients had ablations under local and general anaesthesia. During percutaneous ablations, patients were positioned appropriately to ensure the best visualization of target lesions in the liver. In few cases, CEUS were utilized to increase the confidence of tumour visibility under ablation therapy.

The size of each metastasis to be ablated dictated the choice of RFA electrode. In a small sized tumour (< 3 cm), single internally cooled electrode (Cool-tip™ Ablation Electrodes, ACT2530, Covidien, CO, United States) was utilized. In a large sized tumour (≥ 3 cm), either a single electrode with repeated overlapping ablations or cluster electrode with 3 electrodes contained in a single applicator (Cool-tip™ Ablation Electrodes, ACT2015, Covidien, CO, United States) was used. Each electrode was powered by the attached generator (Cool-tip™ Ablation Generator E series, Covidien, CO, United States) and tissue temperature around the tip of the electrode placed appropriately in the tumour was continuously monitored. Each electrode in the target tissue was powered continuously for 12 min and average final tissue temperature reached was 65 ℃.

Statistical analysis

The manuscript was supervised by a co-author, Jens Brøndum Frøkjær, with extensive statistical expertise.

RESULTS

A total of 105 liver metastases were ablated. Twenty-eight piont six percent of patients (14 of 49) received ablation therapies at a time frame less than one month after the detection of CRLM. Thirty-eight piont eight percent (19 of 49) and thirty-two piont seven percent (16 of 49) respectively had treatment 1-3 mo and > 3 mo after diagnoses of liver metastases.

Overall survival results

Primary ablation success was achieved in 95.2% (100 of 105) of CRLM at first month post-ablation treatment. To put in another way, only 4.8% of ablated tumours had local recurrence at 1 mo following ablation therapy. However, 15 new liver metastases were diagnosed within one month after liver ablation treatment. The range of survival from dates of diagnosing CRLM was 10 to 93 mo (median survival of 28.5 mo and mean survival of 35.5 mo). Only 18.4% (9 of 49) of patients survived beyond 93 mo. 1-, 2-, 3-, 4- and 5-year survival rates were respectively 92%, 65%, 51%, 41% and 29% (Figure 1).

Survival results after application of strict exclusion criteria

To explore the impact of number and size of CRLM on patients' survival, we re-analysed our data based on introduction of certain hypothetical exclusion criteria; exclusion of patients with number of CRLM ≥ 5 and tumour size ≥ 40 mm. This is in accordance with the recently introduced recommendation[10-14]. Following the introduction of these criteria, thirteen patients (26.5%) were excluded, resulting in the improvement of 1-, 2-, 3-, 4- and 5-year survival rates as depicted in Table 2.

Sub-analysis showed that 9 of 49 patients developed extra-hepatic metastases, not visible on pre-treatment scans, just after RFA treatment. These patients had poorer survival.

DISCUSSION

Colorectal cancer (CRC) is ranked the third commonest malignancy in the world[1,2]. Large proportions of patients with CRC are susceptible to developing liver metastases[15,16]. Uncontrolled secondary malignant liver lesions, including CRLM, are among the major sources of mortality and morbidity in patients diagnosed with CRC[10]. CRLM is invariably fatal if left untreated[17,18].

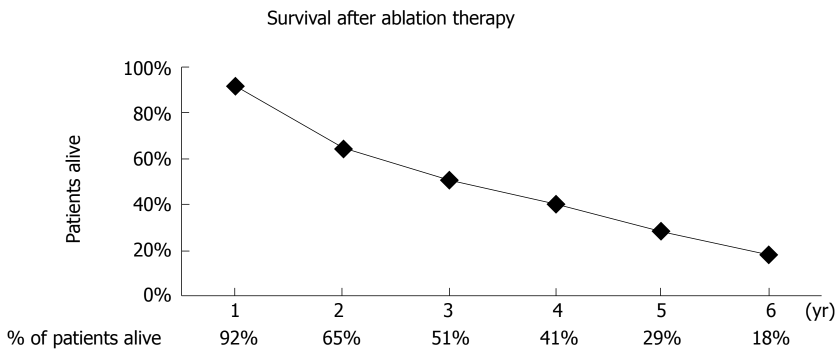

Figure 1 Five-year survival curve calculated from the date of diagnosing colorectal liver metastases (*n* = 49).

Table 2 Patients' survival after application of strict selection criteria (*n* = 36, tumour size < 40 mm)

Years	1	2	3	4	5
% of patients alive	94	69	53	42	31

Table 3 Patients' survival following ablation therapy compared with earlier studies in the literature

Year	Survival (%)			
	Current study (*n* = 49)	Sørensen *et al*[8] (*n* = 100)	Solbiati *et al*[6] (*n* = 99)	Vogl *et al*[7] (*n* = 603)
1	92	95	98	94
2	65	78	-	77
3	51	63	69.3	56
4	41	50	-	-
5	29	44	47.8	37

The dismal quoted median survival of untreated CRLM is 12 mo[17].

Management of colorectal liver metastases

To improve patients' survival, a number of treatment modalities have been developed. Surgical resection is widely acknowledged as the gold standard of treating secondary liver malignancy[6,15,17,19,20]. It is argued that surgical resection can effectively cure liver metastases[5,21] and that local recurrence rate is low as well as increased chance of long disease-free interval[15,18]. Improvements in patients' assessment and surgical techniques have been suggested as the factors that improved the patients' survival following surgical excision of CRLM in recent years[22]. However, more than 70% of patients with CRLM are not suitable candidates for surgery at the time of diagnosis due to diverse factors such as co-morbidity, unfavourable tumour stage, limited liver reserve and proximity of liver lesions to vital structures[3,5,7,21]. So, a different modality of treatment had to be advanced.

Some local treatments of CRLM that have been tried include RFA, microwave ablation, cryotherapy and percutaneous ethanol injection[8,23,24]. RFA is widely accepted as a promising alternative to achieving local control of CRLM because of associated fewer complications[16,25-27]. In other words, mortality and morbidity are comparably insignificant and efficacy of tumour ablation in patients treated with RFA is impressive[8,21,24]. RFA is also deemed to be a safe and effective procedure[11,12,19,28]. Despite the numerous benefits of RFA, it is not without some shortcomings. One of the undesirable entities that could negatively impact success rate following liver ablation therapy is local tumour recurrence. The factors that have been attributed to hepatic tumour recurrence following RFA are large sizes and multiplicity of CRLM. It is advocated that the number of CRLM ablated per patient should be at most 5[9,11,14]. Some studies also proposed that patients with more than 4 to 5 metastatic liver lesions are probably unsuitable for RFA therapy[10,26]. The ideal size of CRLM to be targeted for ablation is still a subject of much discussion. Some suggested that the largest size of CRLM to be ablated should be ≤ 30 mm[4,10,11,21] while others were of the opinion that the largest size should be ≤ 40 mm[13,14,28]. The inferential consensus from the above statements is that the maximum numbers of CRLM per patient should be ≤ 5 and each with size of ≤ 40 mm to achieve a high ablation success[4,10,12-14]. It is immediately clear that strict patients' selection largely determines the degree of success in RFA treatment of CRLM.

Evaluation of the present study

In our study, 1-year survival rate of 92% is favourably comparable to other three selected studies in the literature (Table 3). Our 5-year survival rate of 29%, without applying strict exclusion criteria, is apparently on the lower side as compared with other RFA therapy studies. This impression would definitely appear less gloomy if the comparison is made with the 5-year survival rate (ranging from 24% to 58%) in patients treated mainly with surgical resection[3,5,6]. Adam *et al*[29] reported even lower 5-year survival rate of 18% when survival was estimated in connection with resection of CRLM in patients who had extra-hepatic metastases. Considering the nature of our studies in which patients were not strictly selected, our estimated 5-year survival rate might not be absolutely unsatisfactory. In most of the earlier studies, patients were meticulously selected. As noted earlier, we did not apply stringent criteria to patients' selection in 2005. Eighteen percent of our patients had at least four CRLM and a similar proportion had an individual tumour size of at least 40 mm. It should be noted that 2% of our patients had eight CRLM. It is reasonably obvious that the results of our patients' overall survivals would have been modestly better if we applied the generally agreed principle that at most 5 tumours[9,11,14] and individual tumour size $\leqslant$ 40 mm[4,11-13,28] be considered for RFA therapy to substantially minimize the risk of local tumour recurrence and thereby improving patients' survival. This is partly supported by a modest improvement in our results following the application of hypothetical strict exclusion criteria (Table 2).

It is of note that 9 of 49 patients in our study developed extra-hepatic metastases, not visible or seen on pre-treatment scans, just after RFA treatment. These patients had the worst overall survivals and this can partly explain why the overall survivals of our patients were modestly lower. It is immediately clear that optimum patients' selections resulting from initial careful patients' assessment and meticulous pre-RFA evaluation have profound influence on patients' survival. It is probable that paying limited attention to strict patients' selection could account for some of the disappointing results seen at other institutions introducing RFA technique.

To moderate the tumour recurrence rate in connection with RFA, technique has to be continuously improved. As modestly experienced as our institution was in 2005-2008, our RFA technique was quite effective. A staggering 95.2% primary ablation success rate was accomplished at first month post-ablation treatment. This figure is comparable to the one (93.1%) reported by Solbiati *et al*[6].

Limitations of the current study

The potential downside of our study is the difficulty we encountered in providing convincing data to establish a guideline for optimum patients' selection before embarking on RFA treatment of CRLM. The major reason for this probable shortcoming is the small number of patients included in the study. Forty-nine (49) patients that underwent RFA of CRLM between the years 2005 and 2008 were preliminary included in the study to allow for 5 year follow-up and estimation of preliminary survival rates. Other patients that received similar treatment after 2008 are being followed closely and data originating from this are being collated for future large study and publication. Besides, we chose to have our preliminary data published to excite interest in further research with the possibility of establishing widely acceptable optimum guidelines for performing minimally invasive treatment of CRLM. The success emanating from such research, in no doubt, will have a positive impact on myriads of patients across the world diagnosed with CRLM.

Number and sizes of CRLM as well as the presence of extra-hepatic metastases are among the most important factors that influence the outcomes of patients treated with RFA. Even though our study did not convincingly establish precise inclusion criteria, it underscored the fact that optimum patients' selection before embarking on RFA treatment is critically important to achieving a superior outcome. We are of the opinion that further research is necessary to outline widely accepted criteria for selecting patients for RFA therapy.

COMMENTS

Background

Colorectal cancer is a common cancer worldwide and ranks second among the cancers that frequently cause deaths globally. A significant proportion of patients diagnosed with colorectal cancer are prone to developing the spread of the disease to the liver. The spread of the disease to the liver is one of the reasons for the prevalence of high mortality and morbidity associated with colorectal cancer. Effective controls of the cancer at the primary site (colorectum) as well as the metastatic spread to the liver are extremely important in improving patients' survival.

Research frontiers

To improve patients' survival, a number of treatment modalities have been extensively explored. Surgical resection is widely acknowledged as the gold standard of treating metastatic liver disease. In addition, other treatment modalities that have been developed include radiofrequency ablation, microwave ablation, cryotherapy and percutaneous ethanol injection.

Innovations and breakthroughs

In recent years, attention has been shifted away from treatment of metastatic liver cancers with surgical resection due to the inherent risks associated with surgery and the fact that more than 70% of patients were unsuitable for surgery at the time of diagnosing metastatic colorectal cancer. Radiofrequency ablation, a procedure that is deemed safe and effective, is a widely accepted alternative for controlling metastatic liver disease because of associated fewer complications compared with surgical resection.

Applications

One of the undesirable entities that could negatively impact the success rate following liver radiofrequency ablation therapy is local tumour recurrence. In order to prevent local tumour recurrence and thereby improving patients' survival, guideline for optimum patients' evaluation and selection pre-treatment should be established. In our study, the authors explored the impacts of various factors that have been attributed to tumour recurrence following radiofrequency ablation of metastatic liver cancer. The published data will, in no doubt, excite interest in further research with the possibility of establishing widely acceptable optimum guidelines for performing minimally invasive treatment of metastatic liver cancer. The success emanating from such research will have a positive impact on myriads of patients across the world diagnosed with metastatic colorectal cancer.

Terminology

Metastasis is the spread of cancerous cells from a primary site of origin to other parts of the body. Metastatic colorectal liver cancer is therefore, the spread of cancerous cells from the colorectum to the liver. Radiofrequency ablation of metastatic liver cancer is a minimally invasive treatment modality in which metastatic tumours in the liver are thermally destroyed by introducing high frequency electric current from a generator to the tumour *via* the electrode(s) inserted through the skin, under imaging guidance, to the tumour in the liver.

Peer-review

The manuscript is well written.

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CASE REPORT

Respiratory distress due to malignant ascites palliated by hyperthermic intraperitoneal chemotherapy

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Author contributions: de Hingh IHJT performed the surgical operation; van den Houten MML and van Oudheusden TR wrote the manuscript; Luyer MDP, Nienhuijs SW and de Hingh IHJT critically reviewed the manuscript for intellectual content.

Ethics approval: The study was reviewed and approved by the Catharina Hospital Institutional Review Board.

Informed consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Conflict-of-interest: The authors declare no conflict of interest.

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Abstract

Malignant ascites is a common symptom in patients with peritoneal cancer. Current assumption is that an increased vascular permeability and obstruction of lymphatic channels lead to the accumulation of fluid in the abdominal cavity. This case report describes a severely symptomatic patient with malignant ascites. The previously healthy 73-year-old male was presented with abdominal distention causing respiratory distress. Computed tomography revealed large amounts of ascites, a recto-sigmoidal mass with locoregional lymphadenopathy and an omental cake. Biopsy taken during colonoscopy revealed an adenocarcinoma of the colon with signet cell differentiation. A widespread peritoneal carcinomatosis was found during a diagnostic laparoscopy. The extent of peritoneal disease rendered the patient not suitable for cytoreductive surgery with curative intent. The ascites proved to be refractory to ultrasound-guided paracentesis; thus, a decision was made to perform palliative hyperthermic intraperitoneal chemotherapy without cytoreductive surgery. Consequently, ascites production stopped, and the respiratory distress was relieved thereafter. The postoperative recovery was uneventful. Ascites recurred eight months later, and a second hyperthermic intraperitoneal chemotherapy procedure was performed. The patient was still alive at the time of writing, 16 mo after the initial diagnosis.

Key words: Ascites; Intraperitoneal chemotherapy; Palliative hyperthermic intraperitoneal chemotherapy; Peritoneal carcinomatosis; Colorectal cancer

Core tip: Malignant ascites can cause debilitating symptoms in patients with peritoneal cancer. This report describes a patient with severe respiratory distress caused by malignant ascites from peritoneal colorectal carcinomatosis. The patient was successfully treated with hyperthermic intraperitoneal chemotherapy without cytoreductive surgery. Our results suggest that hyperthermic intraperitoneal chemotherapy without cytoreductive surgery should be considered in patients with symptomatic ascites, even when their prognosis is dismal.

van den Houten MML, van Oudheusden TR, Luyer MDP, Nienhuijs SW, de Hingh IHJT. Respiratory distress due to malignant ascites palliated by hyperthermic intraperitoneal chemotherapy. *World J Gastrointest Surg* 2015; 7(3): 39-42 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i3/39.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i3.39

INTRODUCTION

Malignant ascites (MA) is a pathologic accumulation of fluid in the peritoneal cavity caused by intraperitoneal disseminated cancer cells[1,2]. About 40% of patients with peritoneal carcinomatosis (PC) secondary to colorectal cancer (CRC) develop MA[3]. In these patients, progressive abdominal distention eventually causes debilitating symptoms such as pain, nausea, anorexia, vomiting, and fatigue. In addition, ascites may hinder patients' breathing, causing dyspnea[4]. The presence of MA is considered to be a grave prognostic sign, and in many patients, treatment is aimed only at palliation of symptoms. However, the first-line therapy with diuretics and paracentesis has shown varying efficacy[1,2]. Consequently, hyperthermic intraperitoneal chemotherapy (HIPEC) has been advocated as an alternative treatment for refractory ascites[5-8].

The current report describes a patient with severe respiratory distress caused by MA from peritoneal colorectal carcinomatosis. The patient was successfully palliated using HIPEC.

CASE REPORT

A previously healthy 73-year-old man was admitted to a regional hospital with a 3-wk history of debilitating abdominal distention, obstipation, dyschezia, anorexia, and dyspnea. A computed tomography (CT) scan showed large amounts of ascites (Figure 1), a large rectosigmoidal mass with locoregional lymphadenopathy, and an omental cake, but no systemic metastases. These findings were highly suggestive of PC of colonic cancer. Biopsies taken during the colonoscopy confirmed the presence of a mucinous adenocarcinoma in the proximal rectum.

At the time of referral to our hospital, the patient was wheelchair bound and short of breath. A diagnostic laparoscopy was performed in order to determine the possibility of HIPEC with curative intent. The results revealed widespread peritoneal metastases (Figures 2 and 3) affecting all abdominal regions, adding up to a peritoneal cancer index of 34. Radical resection of all metastases was deemed impossible, disqualifying the patient from HIPEC with curative intent. To alleviate symptoms, 10 L of ascitic fluid was drained, and a colostomy was performed for fecal diversion. The patient felt immediate relief, but a day later, recurrent fluid production caused severe respiratory distress. An ultrasound-guided paracentesis was performed, temporarily alleviating symptoms. However, ascites production remained unmanageable with the production rate of 10 L every 24 h. In an effort to stop the ascites production, a laparoscopic HIPEC without cytoreductive surgery, was performed. Saline was heated to 41–42 ℃ and perfused intra-abdominally, followed by administration of mitomycin C (35 mg/m^2) circulating for 90 min. Postoperatively, the peritoneal cavity was drained with three catheters that were removed 48 h after surgery as per protocol. The postoperative stay was uneventful, and the patient was discharged after 12 d. The malignant ascites and resulting symptoms disappeared. Subsequent pathologic investigation confirmed the presence of a mucinous adenocarcinoma with signet cell differentiation in the peritoneal deposits.

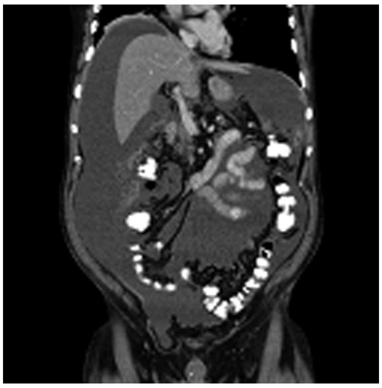

Figure 1 Abdominal computed tomography scan at the first presentation demonstrating voluminous ascites throughout the abdominal cavity.

Palliative chemotherapy (FOLFOX/bevacizumab) was started four weeks later. Recurrent ascites occurred 8 mo after the HIPEC. Ultrasound-guided paracentesis provided insufficient relief. Given the positive response to the initial HIPEC, this procedure was repeated with oxaliplatin as the intraperitoneal agent. The patient was still alive 16 mo after the diagnosis and continues to receive palliative chemotherapy.

DISCUSSION

Approximately 10% of CRC patients develop peritoneal cancer in the course of their disease[9]. In a select group of patients, cytoreductive surgery and HIPEC are the treatment modality of choice, which offer long-term survival, or in some cases, a cure[10]. These results can only be achieved when complete cytoreduction of all visible tumors is obtained[9]. Consequently, patients unfit for major surgery, with systemic metastases or wherein complete cytoreduction cannot be achieved, have a dismal prognosis. In these patients, treatment is aimed at palliation of symptoms, including those caused by ascites.

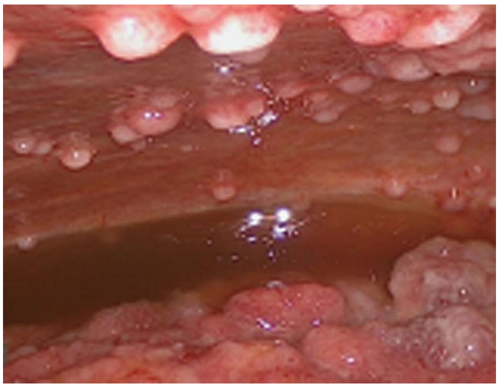

Figure 2 Intra-abdominal view showing ascites and confluence of tumor deposits.

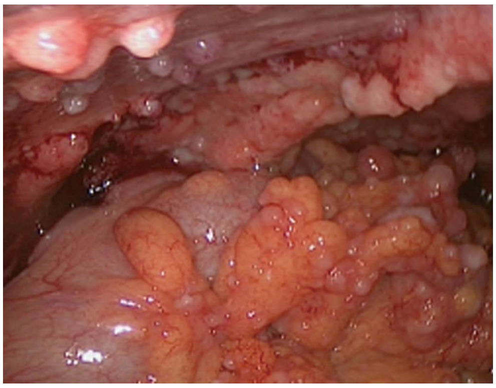

Figure 3 Intra-abdominal view of large tumor deposits.

MA is a common symptom in patients with PC[1-3]. The pathophysiology of MA is multi-factorial and remains to be fully elucidated. The current view is that an increased vascular permeability and obstruction of lymphatic channels lead to the accumulation of fluid in the abdominal cavity[1,2,11,12]. Ultrasound-guided paracentesis and fluid analysis are used to distinguish a benign origin from a malignant cause. CT may aid in the diagnostic work-up and reveal the primary source of malignancy[2].

Several palliative treatment modalities can be used in the management of MA. Paracentesis alleviates abdominal distention and subsequent symptoms, yet improvements are short-lived, as ascites often reaccumulates within 72 h, as was the case in our report[2]. Diuretic therapy appears to be effective in controlling MA when the serum-ascites albumin gradient is > 1.1 g/dL[13]. Although diuretic therapy has been effective in patients with ascites due portal hypertension secondary to liver metastases, its use in patients with PC is likely to be less effective[14]. Systemic chemotherapy for the treatment of ascites in CRC patients has not yet been assessed. However, MA usually presents itself in the terminal stage of disease when available chemotherapeutic regimens have already been deployed[1]. Therefore, systemic chemotherapy is likely to play a minor role.

In patients with MA refractory to the first-line treatment modalities, HIPEC may provide symptomatic relief. In a case series by Valle *et al*[6], 52 patients with PC-related ascites were treated with palliative HIPEC without cytoreductive surgery. This strategy appeared to be successful in all but one patient. As the survival is highly dependent on complete cytoreduction, the reported median survival of only 98 d is not surprising. Ideally, ascites caused by peritoneal cancer should be treated with complete cytoreduction and HIPEC. Unfortunately, Randle *et al*[8] found that complete macroscopic reduction can only be achieved in 15% of MA patients. The presence of MA is, therefore, a grave prognostic sign, as it is indicative of incomplete cytoreduction after surgery and HIPEC and worse overall survival. On the other hand, palliative HIPEC appeared to be highly successful in controlling MA, with 93% of patients being palliated even when complete cytoreduction was not possible. Both patient series suggest that HIPEC, without complete tumor debulking, can be a valid option for palliating MA, offering symptomatic relief with low complication rates and a short hospital stay[6,8].

In conclusion, this case report describes the successful palliation of MA by HIPEC in an elderly patient with severe symptoms. Although the prognosis of patients not suitable for curative treatment is dismal, alleviating the debilitating symptoms such as MA with HIPEC as a sole procedure should be considered.

COMMENTS

Case characteristics

A previously healthy 73-year-old man presented with abdominal distention, dyspnea, obstipation, dyschezia, and anorexia.

Clinical diagnosis

Upon physical examination, the patient showed dullness to percussion over the abdomen and shallow breathing.

Differential diagnosis

Portal hypertension, peritonitis, portal vein occlusion, abdominal malignancy.

Imaging diagnosis

Computed tomography showed large amounts of ascites, a large rectosigmoidal mass with locoregional lymphadenopathy, and an omental cake, but no systemic metastases.

Pathological diagnosis

Biopsies taken during a colonoscopy and the pathologic investigation after a diagnostic laparoscopy confirmed the presence of mucinous adenocarcinoma with signet cell differentiation in the rectum and peritoneal deposits.

Treatment

The patient was treated with hyperthermic intraperitoneal chemotherapy without cytoreductive surgery.

Related reports

Two case series previously described similar cases, with palliation of ascites in the majority of patients.

Term explanation

Cytoreductive surgery refers to the removal of visceral organs and peritoneal surfaces in order to treat peritoneally metastasized cancer.

Experiences and lessons

Hyperthermic intraperitoneal chemotherapy without cytoreductive surgery should be considered when managing symptomatic malignant ascites, even when the prognosis is dismal.

Peer-review

This is case report about hyperthermic intraperitoneal chemotherapy in carcinomatosis can be reported because is a new tool for these patients.

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CASE REPORT

Successful emergency resection of a massive intra-abdominal hemophilic pseudotumor

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Informed consent: The patient gave his verbal consent for reporting this case.

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Abstract

An intra-abdominal pseudotumor is a rare complication of hemophilia. Surgical treatment is associated with high morbidity and mortality rates and reported cases are scarce. We present a 66-year-old Caucasian male suffering from severe hemophilia type A treated for 10 years with Factor Ⅷ. Major complications from the disease were chronic hepatitis B and C, cerebral hemorrhage and disabling arthropathy. Twenty-three years ago, retro-peritoneal bleeding led to the development of a large intra-abdominal pseudotumor, which was followed-up clinically due to the high surgical risk and the lack of clinical indication. The patient presented to the emergency department with severe sepsis and umbilical discharge that had appeared over the past two days. Abdominal computed tomography images were highly suggestive of a bowel fistula. The patient was taken to the operating room under continuous infusion of factor Ⅷ. Surgical exploration revealed a large infected pseudotumor with severe intra-abdominal adhesions and a left colonic fistula. The pseudotumor was partially resected *en bloc* with the left colon leaving the posterior wall intact. The postoperative period was complicated by septic shock and a small bowel fistula that required reoperation. He was discharged on the 73rd hospital day and is well 8 mo after surgery. No bleeding complications were encountered and we consider surgery safe under factor Ⅷ replacement therapy.

Key words: Hemophilia A; Hemophilic pseudotumor; Colonic fistula; Factor Ⅷ replacement therapy; Surgery in hemophilic patient

Core tip: We present a patient suffering from hemophilia A complicated by a large intra-abdominal hemophilic pseudotumor. This condition is rare and there is no consensus for treatment. Emergency resection was required because of bowel complications and septic shock. Based on our experience, we recommend elective surgery prior to complications under appropriate factor

Ⅷ replacement therapy.

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INTRODUCTION

Hemophilia A is a congenital disease with an estimated incidence of 10 to 20 cases for 100000 males[1]. Spontaneous bleeding and hemarthrosis are the most frequent complications. Hemophilic pseudotumors are less common, found in severe cases of hemophilia (1%-2%) and mainly located in the limbs[1,2]. Pseudotumors consist of encapsulated, chronic, slowly expanding hematomas. Abdominal pseudotumors are rare and their management is still controversial. Replacement therapy is often the first therapeutic approach. However, surgery is the most effective and the only definitive treatment[2] even though it is associated to high morbidity and mortality rates[3]. Therapeutic alternatives include radiotherapy, percutaneous drainage, embolization and external radiation[2]. We describe our experience in the surgical management of a large intra-abdominal hemophilic pseudotumor.

CASE REPORT

Our patient is a 66-year-old Caucasian male with severe hemophila type A complicated by arterial hypertension, chronic hepatitis B and C, a cerebral hemorrhage 20 years ago and many spontaneous bleeding episodes causing disabling diffuse arthropathy. His medical treatment includes recombinant factor Ⅷ concentrate 2000 IU (Refacto AF®, Pfizer) twice a week for the past 10 years, spironolactone 25 mg once a day and painkillers.

At the age of 44, an intra-abdominal bleeding episode led to the development of an intra-abdominal hemophilic pseudotumor, which was treated conservatively as it was asymptomatic. Follow-up by annual abdominal computed tomography (CT) showed stability of the tumor with no sign of complication. A year prior to the current episode, the patient was hospitalized for intra-tumoral bleeding with hemorrhagic shock that responded to conservative treatment.

This most recent event started when the patient was admitted to the emergency room for sepsis, recent onset of diarrhea, vomiting and abdominal distension. Physical examination showed abdominal distension without guarding, no bowel sounds and spontaneous fecal discharge from the umbilicus (Figure 1). The laboratory tests were significant for C reactive protein 300.9 mg/L, white blood cell count 17490/L, hemoglobin 10.8 g/dL, platelets 429000/μL, prothrombin time 15.7 s (normal 8.6-13.8 s), factor Ⅷ 59% (after factor Ⅷ replacement). Abdominal CT showed air within the tumor (Figure 2). The patient was brought to the operating room. A bolus of 2000 U factor Ⅷ infusion (Refacto AF®, Pfizer) was given before incision followed by continuous infusion of factor Ⅷ (6000 U per day). Abdominal exploration through a midline incision revealed severe adhesions between the pseudotumor and the small and large bowel. There was no peritonitis. The cyst was filled with stools and old clots and a fistula between the left colon and the tumor was found. Intra-operative management consisted of left hemicolectomy *en bloc* with the cyst. The posterior cyst wall was left *in situ* because of involvement of the aorta, inferior vena cava and right ureter. A terminal colostomy was performed, including a Hartmann pouch. Hemostasis was achieved easily. The abdomen was closed after saline irrigation, and 3 drains were left in place. The total operative time was 353 min and the patient was transfused 6 units of red blood cells.

In the immediate postoperative period, the patient was given a continuous infusion of 6000 U/d of factor Ⅷ in order to maintain factor Ⅷ levels between 30% and 40%. On the 3rd postoperative day, he developed a small bowel fistula complicated by intra-abdominal sepsis that required surgical re-exploration. A T-tube was inserted in the fistula site and later served as a feeding jejunostomy.

On the 55th postoperative day, the patient underwent a negative re-exploration because of an inflammatory syndrome with abdominal CT scan findings of portal venous gas and intestinal pneumatosis. He recovered well postoperatively, and quickly resumed enteral feeding. He was discharged to a rehab facility on the 73rd postoperative day.

The patient had no bleeding complication during his hospital stay. Eight months after surgery, he is well.

DISCUSSION

Hemophilia is a group of inherited blood coagulation disorders. The mutation is located on the X chromosome, therefore only men are afflicted and women are carriers. Depending on the remaining level of factor Ⅷ activity, hemophilia A is classified as mild (> 5%), moderate (1%-5%) or severe (< 1%)[1]. Most common complications are spontaneous bleeding into joints and muscles[4].

Hemophilic pseudotumors are rare complications of hemophilia occurring in approximately 1% to 2% of patients suffering from severe hemophilia[1,2]. The pseudotumor is caused by recurrent bleeding episodes into bone or soft tissue leading to the formation of an encapsulated mass of clotted blood and necrotic tissue. In children, pseudotumors are most likely to occur in the limbs or jaw bone, whilst in adults they

Figure 1 Preoperative state.

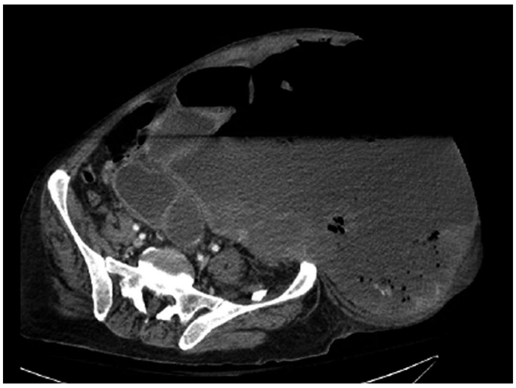

Figure 2 Abdominal computed tomography on admission.

predominantly arise in large muscles of the abdomen, pelvis or thigh. They have also been reported to affect the lung, the abdomen or the wall of the stomach[4].

Reports in the literature of patients suffering from intra-abdominal hemophilic pseudotumors are scarce. Reports of successful emergency resections are even scarcer, which makes our case noteworthy. Pseudotumors are painless except during episodes of acute bleeding but can lead to symptoms due to their mass effect[5]. Indeed, as the tumor enlarges, growing pressure on adjacent structures leads to bowel ischemia and/or fistula[5], as described in our case. Erosion into an artery or spontaneous rupture of the tumor can lead to massive bleeding[4].

There is no consensus for the treatment of intra-abdominal hemophilic pseudotumors because of their rarity. Minimizing complications and preserving the function of the affected tissue or organ is the primarily goal. Reluctance to treat surgically is linked to the risk of bleeding. As a result, several other treatment modalities have been attempted, such as radiotherapy, percutaneous drainage, embolization and external radiation[2]. Most authors do not recommend aspiration of the cyst[4]. Indeed, the cyst contents are too thick to permit complete drainage and its aspiration increases the risk of sepsis, relapse or chronic fistula.

When surgery is considered, one should aim for complete resection but it is not possible in all cases. Indeed, both major neurovascular involvement and anatomy distortion caused by the cyst often prevent safe resection[4,5]. Common indications for surgery include evidence of enlargement of the pseudotumor, hemodynamic deterioration or gastro-intestinal complications.

The risk of surgical bleeding can be minimized by judicious administration of factor Ⅷ at induction, during and after surgery under the close supervision of hemophilia specialists. Frequent monitoring to maintain adequate levels of factor Ⅷ makes surgical option safe even when faced with a major hemophilic pseudotumor. In our case, continuous factor Ⅷ replacement therapy was proven effective in preventing bleeding complications during the 3 laparotomies and during the patient's prolonged hospitalization. There are several reports in the literature in favor of surgery in hemophilic patients with continuous or interrupted[1] infusion of clotting factors with minimal risk of hemorrhage.

The particularly large size of the cyst (over 30 cm in diameter) and the duration of its evolution made the resection hazardous in the present patient. The fact that surgical long-term outcome was favorable despite the patient's complications and emergency context should encourage elective resection.

We report a rare case of successful emergency resection of a large abdominal hemophilic pseudotumor. Abdominal surgery in a hemophilic A patient is feasible without hemorrhagic complications under continuous factor VIII replacement therapy. Elective resection of an abdominal hemophilic pseudotumor should be considered prior to the development of major complications.

COMMENTS

Case characteristics

A hemophilic patient known for a large intra-abdominal hemophilic pseudotumor presenting with abdominal distension, umbilical fecal discharge and vomiting.

Clinical diagnosis

Physical examination showed signs of severe sepsis and abdominal distension without guarding.

Differential diagnosis

Peritonitis, intestinal obstruction, pseudotumor infection, bowel fistula.

Laboratory diagnosis

C reactive-protein (300.9 mg/L), white count (17490/L), hemoglobin (10.8 g/dL), platelets (429000/μL), prothrombin time (15.7 s), factor VIII (59%).

Imaging diagnosis

Abdominal computed tomography showed air within the pseudotumor.

Pathological diagnosis

Pathological analysis of the surgical specimen confirmed the diagnosis of large bowel fistula into the hemophilic pseudotumor.

Treatment

Emergency exploratory laparotomy was performed. The pseudotumor was resected *en bloc* with the left colon because of the presence of a large bowel fistula.

Related reports

Few cases of successful resection of intra-abdominal hemophilic pseudotumors have been reported. The treatment of those tumors is still controversial.

Term explanation

A hemophilic pseudotumor is a chronic slowly expanding hematoma. An intra-abdominal hemophilic pseudotumor can lead to severe complications such as massive bleeding or bowel fistulas.

Experiences and lessons

Our case describes the management of a complicated intra-abdominal hemophilic pseudotumor requiring an emergency resection. The patient was discharged after 73 d and 2 further exploratory laparotomies due to complications. The authors recommend resection before complication, under appropriate factor VIII replacement therapy.

Peer-review

In this report, the authors described a patient with a hemophilic intraabdominal pseudotumor.

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CASE REPORT

Incarcerated amyand hernia

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Author contributions: Ciftci F and Abdulrahman I designed, organized and wrote the report and were attending doctors for the patients; Ciftci F performed surgical operations; all authors read and approved the final manuscript.

Ethics approval: The study was reviewed and approved by the Safa Hospital Institutional Review Board.

Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

Amyand's hernia is a rare condition defined by the inclusion of the appendix vermiformis within the hernia sac. Its incidence among cases of groin hernia is less than 1%. The clinical manifestation of incarcerated inguinal hernia generally masks the symptoms and signs of acute appendicitis, which renders preoperative diagnosis difficult. In this study, we present two cases of Amyand's hernia that were diagnosed preoperatively. The patients were taken for operation with the prediagnosis of ıncarcerated inguinal hernia. We evaluated these cases along with data from prior studies.

Key words: Incarcerated hernia; Appendectomy; Amyand

Core tip: Amyand's hernia is a seldom surgical pathology whereby there is inclusion of the appendix vermiformis within the groin hernia sac. Its incidence among cases of groin hernia is less than 1%. The clinical presentation of incarcerated inguinal hernia generally masks the symptoms and signs of acute appendicitis, which renders preoperative identification difficult. Owing to the rarity of the condition there is yet no general consensus pertaining the diagnosis and management approach. Arguments continue as to whether to do or not appendectomy and where to employ a mesh during operation. In this paper we share our experience in the diagnosis and treatment of this rare condition by presenting two cases of Amyand's hernia one having acute appendicitis and the other gangraneous appendicitis.

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INTRODUCTION

Amyand's hernia may present with the inflammation of the appendix vermiformis enclosed in its sac, albeit rarely. The disorder comprises less than 1% of all inguinal hernia cases and 0.2% of appendicitis

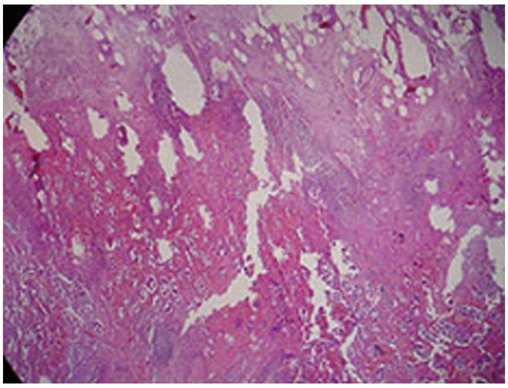

Figure 1 Hernia sac with appendicitis.

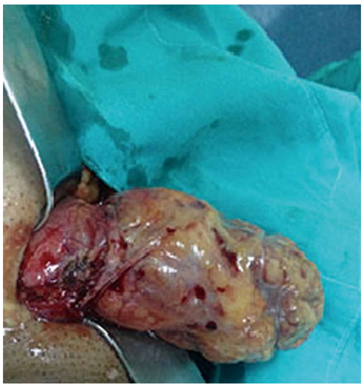

Figure 2 Pathological view for acute gangrenous appendicitis.

cases. Consensus has yet to be reached regarding the risk involved in herniorrhaphy with prosthetic material subsequent to the resection of the inflammed appendix and regarding the necessity of resecting an uninflammed appendix. Due to the rarity of this condition, management of Amyand's hernia varies amongst different clinicians and can even vary for the same clinician over time. The presence of an inflammed appendix vermiformis in the sac of an inguinal hernia is referred to as Amyand's hernia. The condition was first described by an English surgeon named Claudius Amyand in an 11-year-old male patient after finding a perforated appendix in the sac of the inguinal hernia. The disorder has since carried Amyand's name. The incidence of the presence of an uninflammed appendix vermiformis in the sac of an inguinal hernia is estimated to be 0.13%, but it is even rarer to find an inflammed appendix in an inguinal hernia sac[1,2]. Routinely found within the sac of an inguinal are the omentum, small intestine or urinary bladder. Aside from these conditions, Meckel's diverticulum (Littre's hernia), part of the wall of the intestine (Richter's hernia), or inflammed or uninflammed appendix vermiformis (Amyand's hernia) may be included in the sac of an inguinal hernia[3,4]. In this paper, we aim to discuss our cases along with data from current studies.

CASE REPORT

Case 1

A 27-year-old male patient reported to our emergency clinic with complaints of pain, swelling and loss of appetite for the past 10 h of an inguinal hernia that had been present for 3 years. There was tenderness at the right lower quadrant. Neither defence nor rebound tenderness was present. Air-fluid levels attributable to the small bowel could be appreciated on a direct X-ray of the abdomen. The patient had not experienced any loss in appetite and could break wind. He had no fever, and his white blood count was 12000/mm^3. He was operated on for irreducible hernia and perioperatively, the cecum was found to be within the hernia sac (Figure 1). As expected in Amyand's hernias, a sliding hernia formed part of the sac wall, and the appendix was slightly edematous and gangrenous, presumably due to impaired blood circulation. An appendectomy was accomplished, the stump was embedded, and the cecum was retrieved from the sac. Part of the hernia sac was resected, and the peritoneum was covered, after which non-tensile plication with prolen was accomplished. A prolen mesh (15 cm × 10 cm) was spread to reinforce the herniorrhaphy region. The patient was discharged from the hospital without complications on the second postoperative day. In a follow-up one week later, the right inguinal region looked to be healing well. The pathology examination reported an acute gangrenous appendicitis. There was active intense inflammation with neutrophilic leucocytes predominance that infiltrates tissues surrounding the appendix and distruct all layers of the appendix wall (Figure 2).

Case 2

A 24-year-old male patient reported with increased swelling and pain for the last 3 h in his inguinal hernia that had been present for 2 years. An attempt to reduce the hernia was unsuccessful. The patient's white blood count was within normal range (9800/mm^3), and direct abdominal X-rays revealed nothing noteworthy. In the operation, the appendix was found to adhere to the inner surface of the hernia sac (Figure 3). The pathology looked to be an acute appendicitis with a mixture of inflaming cells on the appendiceal wall, presenting a great deal of eosinophils and few focus of granulomatous lesion (Figure 4). Through the same incision, an appendectomy, herniorrhaphy and prolen mesh reinforcement were accomplished. The patient was discharged from the hospital without complications on the first postoperative day. In a follow-up one week later, the right inguinal region looked to be healing well.

DISCUSSION

The current practical approach includes appendectomy and hernia repair with prolen mesh in cases in which the appendix is intact or inflammed without perforation. However, in the presence of perforation, the proposal

Figure 3 The appendix was found to adhere to the inner surface of the hernia sac in the operation.

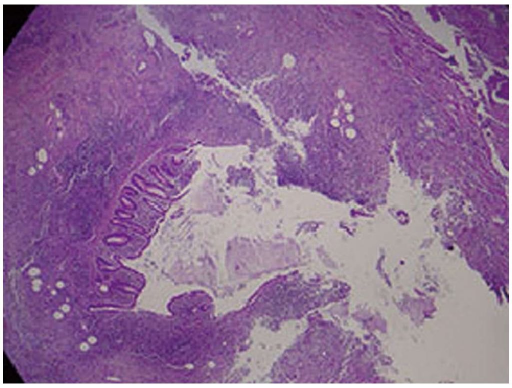

Figure 4 Acute appendicitis with a mixture of inflaming cells on the appendiceal wall.

includes appendectomy and herniorrhaphy without the use of prolen mesh so as to avoid subsequent infection, recurrent hernia and enterocutaneous fistula. The lack of consensus is due, in large part, to a lack of large-scale studies and meta analyses. The absence of typical clinical presentation and manifestation of acute appendicitis in the cases presented above indicates that the appendicitis was the result of extraluminal tension. The disorder is generally right-located due to the malpositioning of the cecum as a predisposing factor. The inflammation of the appendix in an Amyand's hernia of an incarcerated or sliding type may be due to the process of incarceration itself[5]. In cases with chronic hernia adhesions and increased intraabdominal pressure due to contraction of the abdominal wall, the appendiceal mesothelium is squeezed, thereby hindering the perfusion of the appendix. This in turn leads to inflammation and increased bacterial colonization of the appendix[6]. A chronic process is always involved in the disorder's mechanism of development.

Differential diagnoses of Amyand's hernia include incarcerated or strangulated inguinal hernia, inguinal lympadenitis, testicular torsion, acute epididymitis, acute hydrocele and focal panniculitis[6-8]. It is difficult to diagnose Amyand's hernia preoperatively. Patient clinical complaints and laboratory findings are usually inadequate for the diagnosis. Generally, although it is easy to diagnose a hernia, an ultrasonic or tomographic evaluation is needed to ascertain the presence of an inflamed or intact appendix within the hernia sac. These two techniques are not routinely employed in hernia surgery. Nevertheless, there are reports of cases being diagnosed with the aid of tomography prior to an operation[9]. In most instances, however, the diagnosis is made during the operation, as was the case with our diagnoses.

Amyand hernia is an unusual condition involving the presence of different entities, and a preoperative identification enigma, and requiring expertise in two surgical difficulties: symptomatic hernia and appendicitis. Management is surgical, and in a hernioplasty with or without an appendectomy related to intraoperative detection, a routine prophylactic appendectomy is not indicated[10-12].

Sharma *et al*[13] briefly discussed treatment for Amyand's hernia amid 18 patients within a 15-year time period, including appendectomy followed by the Bassini repair, mesh hernioplasty, later reduction of a normal appendix, and Bassini's hernia repair plus a lower midline laparotomy for a pelvic washout. His strategy is dependent on the status of the appendix in the sac.

The management for hernial appendicitis is appendectomy through the herniotomy with primary hernia repair using the identical incision. Lyass *et al*[14] reported delayed wound closure due to retroperitoneal abscess secondary to the appendicular inflammation. Mesh is not recommended in a contaminated abdominal wall defects due to a greater risk of being wounded or of developing an infection or appendiceal stump fistula. Laparoscopic reduction of Amyand's hernia has been studied previously[15].

In our cases, each patient suffered from a right inguinal hernia. Presumably, repetitive reduction led to inflammation of the region, or in the absence of inflammation pressure on the organs causes pain, thus leading patients to feel the need to report to the hospital.

When the appendix enclosed in the hernia sac is inflamed or perforated, complication rates increase. In such cases, repair methods for Amyand's hernia differ from the standard approach. Grafting may be employed in cases in which neither inflammation nor perforation occurs. In other situations, grafting provokes an inflammatory reaction that may lead to complications, such as incision site infection and stump fistula[8,10]. As reported in the literature, a prosthetic mesh should be avoided due to a high risk of infection. Findings regarding the use of prosthetic mesh to repair Amyand's hernia with Losanoff 2-4 have been reported (Table 1) by Priego *et al*[16]. In all cases, an appendectomy was performed *via* the hernia sac, and acute appendicitis was found to be present in four them. A prosthetic mesh was used in 3 cases, and 1 case of wound infection was also found. In the other

Table 1 Losanoff and Basson classifications of Amyand's hernia[19]

	Definition	Surgical management
Type 1	Normal appendix	Reduction, mesh hernioplasty
Type 2	Acute appendicitis No abdominal sepsis	Appendectomy through the hernia, hernioplasty with native tissues, no mesh
Type 3	Acute appendicitis Abdominal sepsis present	Appendectomy through laparatomy, hernioplasty with native tissues, no mesh
Type 4	Acute appendicitis within inguinal hernia Other abdominal pathology Related or unrelated	Manage as with types 1 to 3 hernia investigate or treat second pathology as appropriate

cases, the hernia ring was sutured using propilene. In each of our cases, at the same time that we carried out the appendectomy, we successfully treated the hernia through an inguinal incision anatomically with a propilene mesh. There was minimal abscess formation found in the sac. Both patients were discharged from the hospital with no complications. The patients seemed healthy in a follow-up two years later.

As for the repair of the hernia, several authors recommend delayed repair or suturing repair rather than prosthetic mesh so as to avoid complications arising from potential infection. Further study is required to define the optimal surgical strategy, prognostic factors and risk of hernia recurrence[4,17-20]. In each of our cases, the operation was performed immediately, and minimally abscess formation was found in the sac. We chose simultaneous appendectomy and primary hernioplasty using prosthetic mesh as treatment for these cases. Although mesh is generally not suggested for use with Amyand's hernia, mesh can be used with acute appendicitis in selected cases.

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COMMENTS

Case characteristics

Clinical symptoms include abdominal pain, and new onset swelling in hours around the hernia and loss of appetite.

Clinical diagnosis

Incarcerated amyand hernia, acute gangrenous appendicitis at the same time.

Differential diagnosis

Incarcerated hernia.

Laboratory diagnosis

Laboratory tests showed a leucocytosis for case 1 (12000/mm^3; 4100-11200) and case 2 (9800/mm^3; 4100-11200).

Imaging diagnosis

An abdominal X-ray radiography indicated air-fluid levels.

Pathological diagnosis

Pathology findings indicated acute gangrenous appendicitis.

Treatment

Appendectomy and prolen mesh in use hernia sac repair.

Term explanation

Amyand's hernia is a rare condition defined by the inclusion of the appendix vermiformis within the hernia sac. Its incidence among cases of groin hernia is less than 1%. The clinical manifestation of incarcerated inguinal hernia generally masks the symptoms and signs of acute appendicitis, which renders preoperative diagnosis difficult.

Peer-review

The authors described two cases of Amyand's hernia in two adult male patients. It is an extremely interesting cases series.

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ORIGINAL ARTICLE

Clinical Trials Study

Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors

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Author contributions: Habib N developed the device concept and designed the study; Pai M, Senturk H, Reddy N, Kahaleh M and Brugge W materialized the design concept and designed the study; Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Kaba I and Beckebaum S contributed in patient screening, recruitment and procedures; Pai M, Senturk H, Lakhtakia S, Kaba I and Beckebaum S were responsible for the acquisition of data; Pai M and Habib N done the analysis and the interpretation of data; Pai M and Habib N drafted the manuscript; Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Drymousis P, Kahaleh M and Brugge W did critical revisions of the manuscript and had input of important intellectual content; Pai M and Habib N did the statistical analysis; Pai M and Habib N were responsible for administrative, technical and material support; Habib N had the study supervision.

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Data sharing: Further technical data and device application details are available from Nagy Habib.

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Abstract

AIM: To outline the feasibility, safety, adverse events and early results of endoscopic ultrasound (EUS)-radiofrequency ablation (RFA) in pancreatic neoplasms using a novel probe.

METHODS: This is a multi-center, pilot safety feasibility study. The intervention described was radiofrequency ablation (RF) which was applied with an innovative monopolar RF probe (1.2 mm Habib EUS-RFA catheter) placed through a 19 or 22 gauge fine needle aspiration (FNA) needle once FNA was performed in patients with a tumor in the head of the pancreas. The Habib™ EUS-RFA is a 1 Fr wire (0.33 mm, 0.013”) with a working length of 190 cm, which can be inserted through the biopsy channel of an echoendoscope. RF power is applied to the electrode at the end of the wire to coagulate tissue in the liver and pancreas.

RESULTS: Eight patients [median age of 65 (range 27-82) years; 7 female and 1 male] were recruited in a prospective multicenter trial. Six had a pancreatic cystic neoplasm (four a mucinous cyst, one had intraductal papillary mucinous neoplasm and one a microcystic adenoma) and two had a neuroendocrine tumors (NET) in the head of pancreas. The mean size of the cystic neoplasm and NET were 36.5 mm (SD ± 17.9 mm) and 27.5 mm (SD ± 17.7 mm) respectively. The EUS-RFA was successfully completed in all cases. Among the 6 patients with a cystic neoplasm, post procedure imaging in 3-6 mo showed complete resolution of the cysts in 2 cases, whilst in three more there was a 48.4% reduction [mean pre RF 38.8 mm (SD ± 21.7 mm) *vs* mean post RF 20 mm (SD ± 17.1 mm)] in size. In regards to the NET patients, there was a change in vascularity and central necrosis after EUS-RFA. No major complications were observed within 48 h of the procedure. Two patients had mild abdominal pain that resolved within 3 d.

CONCLUSION: EUS-RFA of pancreatic neoplasms with a novel monopolar RF probe was well tolerated in all cases. Our preliminary data suggest that the procedure is straightforward and safe. The response ranged from complete resolution to a 50% reduction in size.

Key words: Endoscopic ultrasound; Radiofrequency ablation; Pancreas; Cystic neoplasms; Neuroendocrine tumors

Core tip: This manuscript presents a pilot, safety feasibility study with the results of the first in humans endoscopic ultrasound (EUS) guided radiofrequency ablation (RFA) for cystic neoplasms and neuroendocrine tumors of the pancreas with a novel EUS-RFA catheter. EUS-RFA is feasible and well tolerated. EUS-RFA with this novel catheter provides endoscopic treatment option other than surgical resection for pancreatic lesions.

Pai M, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Kaba I, Beckebaum S, Drymousis P, Kahaleh M, Brugge W. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. *World J Gastrointest Surg* 2015; 7(4): 52-59 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i4/52.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i4.52

INTRODUCTION

Incidental pancreatic solid or cystic lesions are diagnosed with increased frequency due to the widespread use of abdominal cross-sectional imaging to investigate unrelated symptoms. In a large single-centre study, pancreatic cysts were diagnosed in 1.2% of 24000 individuals subjected to abdominal cross-sectional imaging[1]. As a result, the majority of these lesions are diagnosed at an earlier stage, before they become invasive and present with jaundice, pancreatitis or abdominal pain[2]. Lesions such as neuroendocrine tumors (NET), mucinous cystadenomas and intraductal papillary mucinous neoplasms have the potential of malignant transformation. This risk is lower with NET, but significantly higher with mucinous lesions[3].

The standard treatment of solid or cystic pancreatic lesions with malignant potential has been surgical resection, with lesions in the pancreatic head requiring a Whipple resection whereas pancreatic tail lesions are treated with distal pancreatectomy. Both types of resection carry significant morbidity and mortality, resulting in unacceptably high risk/benefit ratios for many elderly patients with co-morbidities[4,5]. Currently, patients deemed unfit for major pancreatic surgery are offered cross-sectional imaging surveillance at regular intervals according to the International Association of Pancreatology Guidelines[6]; these guidelines recommend annual imaging for lesions < 10 mm, 6-monthly imaging for cysts 10-20 mm and 3-monthly imaging for lesions larger than 20 mm. However, controversy exists regarding the optimal follow up of patients with primary pancreatic lesions, underlying the need for minimally invasive ablative techniques as alternative to surgical resection.

Radiofrequency ablation (RFA) has been used percutaneously and intraoperatively to treat primary and secondary liver cancers by achieving localized tumor necrosis[7-10]. Endo-biliary application of radiofrequency (RF) has been developed in our unit and used in patients with inoperable bile duct and pancreatic head adenocarcinomas presenting with biliary obstruction[11]. Many alternative techniques of endoscopic ultrasound (EUS)-guided tumor ablation have been described, including RF ablation, photodynamic therapy, laser ablation, and ethanol injection[12].

EUS-RFA could achieve complete ablation of pancreatic cysts with malignant potential in patients unfit for surgery, thus eliminating the requirement for long-term surveillance in this group of individuals. Gaidhane *et al*[13] showed that EUS-RFA of the pancreatic head using Habib EUS-RFA catheter (Emcision Ltd., United Kingdom) through a 19 gauge needle was well tolerated in 5 Yucatan pigs with minimum amount of pancreatitis. The aim of this study is to outline the safety, feasibility, adverse events and early results of EUS-RFA in patients with pancreatic neoplasms using a novel probe.

MATERIALS AND METHODS

Patients

Eight patients were subjected to EUS-RFA of a neoplastic lesion in the head of the pancreas. A novel monopolar RF catheter [Habib™ EUS-RFA catheter, Emcision Ltd., London (CE Marked)] (Figure 1) was placed through a 19 or 22 gauge fine needle aspiration (FNA) needle.

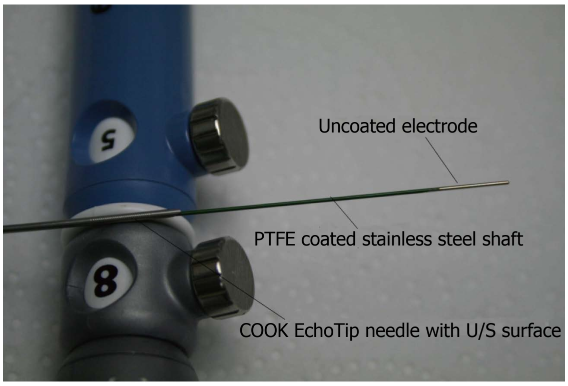

Figure 1 Close up of the Habib™ endoscopic ultrasound-radiofrequency ablation catheter showing uncoated electrode at the tip and the PTFE Coated stainless steel shaft.

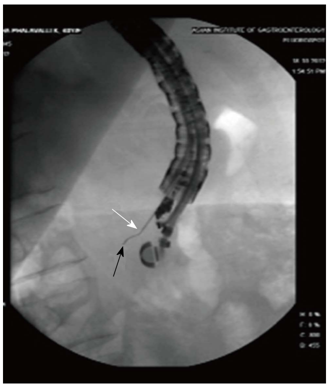

Figure 2 Fluoroscopic view of Habib™ endoscopic ultrasound-radiofrequency ablation catheter (black arrow) protruding out of the endoscopic ultrasound Biopsy needle (white arrow).

Inclusion criteria were age over 18 years, patients with a cystic pancreatic lesions that were not suitable surgical candidates and patients that consented to participate in the study. Exclusion criteria included patients younger than 18 years, patients not consenting to participate in the study, uncorrected coagulopathy and cardiac pacemakers *in situ*.

All patients were investigated with blood tests; haematological, biochemical, tumor markers as well as radiological investigation including computed tomography scan and ultrasound scans. On follow-up, patients had clinical examination, blood tests and cross sectional imaging to assess the pancreatic lesion. The follow-up ranged from 3 to 6 mo. Data are presented as mean plus or minus standard deviations of the mean or median with range. Research was carried out in accordance with the Helsinki Declaration.

Description of device

The Habib™ EUS-RFA is a 1 Fr wire (0.33 mm, 0.013”) with a working length of 190 cm, which can be inserted through the biopsy channel of an echoendoscope. RF power is applied to the electrode at the end of the wire to coagulate tissue in the liver and pancreas. This is a monopolar device and is used in conjunction with a patient grounding/diathermy pad.

Intervention

Habib™ EUS-RFA catheter comes in a dispensing sheath. The catheter is removed from the dispensing sheath and connected to the adaptor cable, which is then connected to the generator. Power in the generator is set to the required wattage we used 5-25 Watts in our patient group). A patient grounding/diathermy pad is applied as close to the operating field as possible, since the catheter is monopolar. We applied the pad on the lower back of the patient. The entire area of the grounding pad should be reliably applied to the patient’s body to avoid skin burns.

The echoendoscope is manoeuvred to obtain proper sonographic visualization of the target lesion. Under EUS control, a 19 gauge biopsy needle (with stylet) is introduced into the target lesion. In pancreatic cystic lesions, effort was made to completely aspirate the cyst before applying RFA. The tip of the needle was positioned near the far end of the lesion. In case of pancreatic NET also, the FNA needle was positioned at the deepest part of the tumor. The stylet is removed from the biopsy needle and Habib™ EUS RFA catheter is gently pushed inside the hollow of the biopsy needle until it cannot be pushed any further. Carefully maintaining this position of the Habib™ EUS RFA probe, the FNA needle is gradually withdrawn by 3 cm in order to disengage contact between the active part of the RF catheter located at the tip and the metallic FNA needle. Fluoroscopy assists in visualization of the RFA probe protruding beyond the tip of the needle (Figure 2). The tip of the probe is floppy, and may take a curved shape in emptied cystic lesons.

RF energy is applied for 90-120 s at the set wattage. In larger lesions, the Habib™ EUS RFA probe and needle is pulled back as one unit and repositioned to ablate near end of the lesion (Figures 3-5). This process can be repeated as many times, as needed to ensure complete ablation of the lesion. In larger pancreatic lesions, repeat puncture with the FNA needle is done in a different axis (after withdrawing the RFA probe, with or without replacing with stylet). The patients were managed post procedure as per standard hospital practice for EUS interventional procedures.

RESULTS

Eight patients [median age of 65 (range 27-82) years; 7 female and 1 male] were recruited in a prospective multicentre trial. Six had a pancreatic cystic neoplasm (four a mucinous cyst, one had IPMN and one a microcystic adenoma). In all six cases, diagnosis was based on imaging reviewed by an expert radiologist. The remaining two cases, had a NET in the head of pancreas (previously documented with diagnostic FNA cytology and not suitable for surgical intervention). The mean size of the cystic neoplasms and NETs were

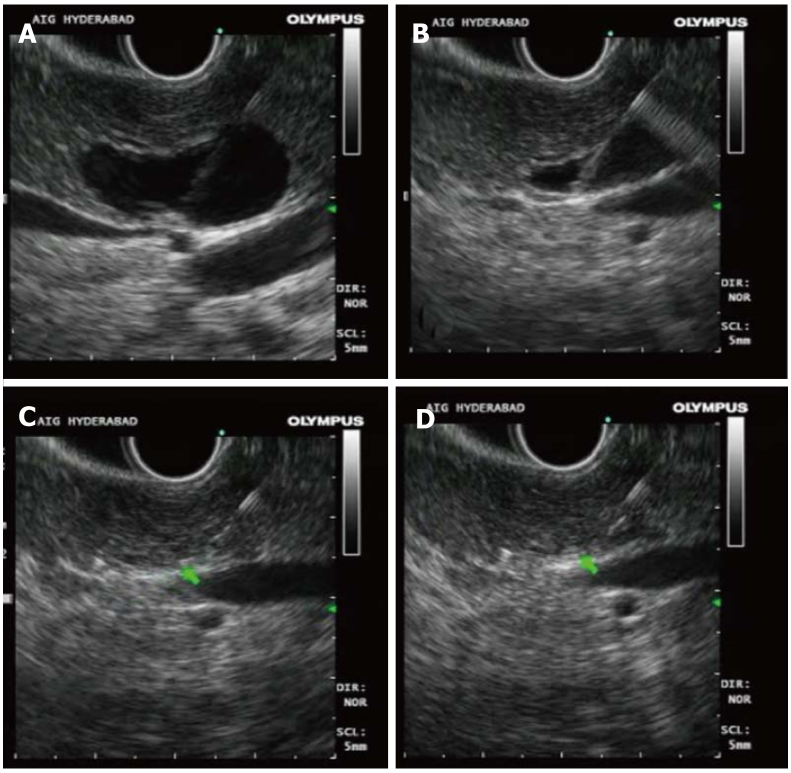

Figure 3 Endoscopic ultrasound pictures of radiofrequency ablation of pancreatic cyst. A: Pancreatic cyst with the biopsy needle in position; B: Aspiration of the pancreatic cyst; C and D: Complete aspiration of the cyst followed by radiofrequency ablation using the endoscopic ultrasound radiofrequency ablation catheter.

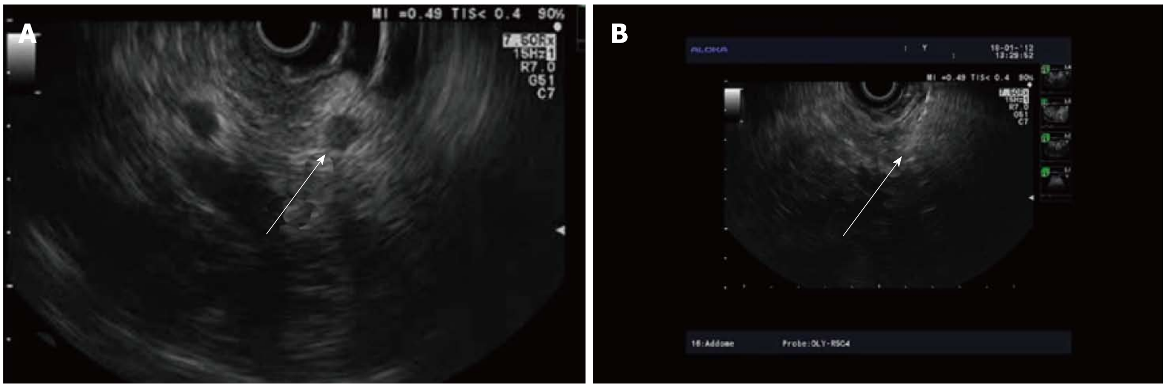

Figure 4 Endoscopic ultrasound Pictures of radiofrequency ablation of pancreatic cyst. A: Pancreatic cyst Pre ablation (arrow); B: Pancreatic cyst aspirated completed and the radiofrequency ablation with in process using the endoscopic ultrasound radiofrequency ablation catheter (arrow).

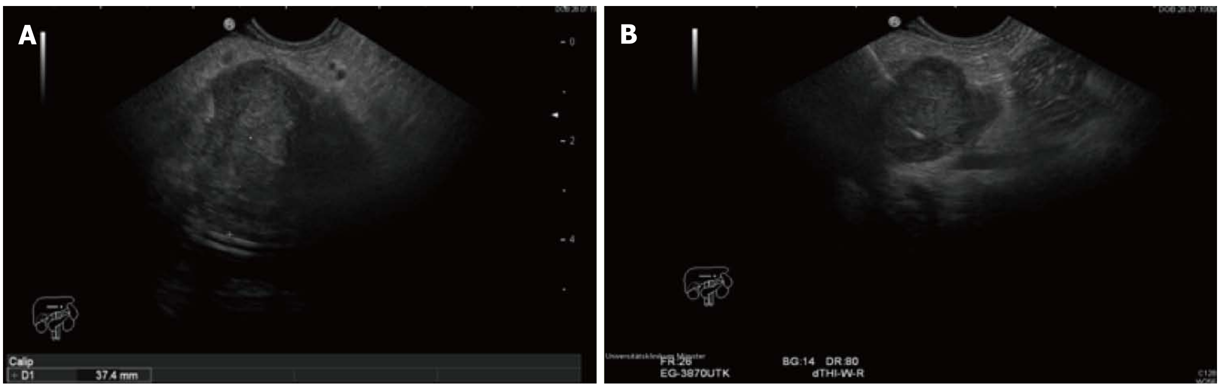

Figure 5 Endoscopic ultrasound radiofrequency ablation of pancreatic neuroendocrine tumors. A and B: Endoscopic ultrasound pictures of the pancreatic neuroendocrine tumors pre and during ablation.

36.5 mm (SD ± 17.9 mm) and 27.5 mm (SD ± 17.7 mm) respectively. RF [Rita (Model 1500X) or ERBE

Table 1 Patient characteristics and procedure specifications

Age	Sex	Diagnosis	No. of RF applications/session	No of sessions	Dead/ alive
5 Watts					
82	F	Mucinous cyst	3	1	Alive
73	F	Mucinous cyst	5	1	Alive
46	F	Microcystic adenoma	5	1	Alive
15 Watts					
40	F	Mucinous cyst	3	1	Alive
27	F	Mucinous cyst	2	1	Alive
20 Watts					
57	F	NET	6	1	Alive
82	F	NET	4	2	Alive
25 Watts					
78	M	IPMN	7	1	Alive

IPMN: Intraductal papillary mucinous neoplasm; NET: Neuroendocrine tumors; RF: Radiofrequency; F: Female; M: Male.

Table 2 Outcome after endoscopic ultrasound radiofrequency ablation of pancreatic cystic neoplasm and neuroendocrine tumors

No.	Diagnosis	Pre ablation size (mm)	Post ablation size (mm)	Adverse events
1	Mucinous cyst	30	10	No
2	Mucinous cyst	40	Cyst not seen	No
3	Microcystic adenoma	20	8	No
4	Mucinous cyst	70	45	Mild pain
5	Mucinous cyst	24	Cyst not seen	Mild pain
6	IPMN	35	17	No
7	NET	15	Change in vascularity	No
8	NET	40	Central area of necrosis 15 mm	No

IPMN: Intraductal papillary mucinous neoplasm; NET: Neuroendocrine tumors.

(Model ICC 200) was applied at 5 watts, 15 watts, 20 watts and finally 25 watts in 3, 2, 2 and one patients respectively over 90 s for each watt setting (Table 1). The median number of applications was 4.5 (range 2-7). Patients with cystic neoplasm and one patient with NET had one session of RFA each, whilst a second patient with NET had two sessions of RFA.

The EUS-RFA was completed in all cases. Amongst the 6 patients with pancreatic cystic neoplasm, the post procedure imaging in 3-6 mo showed complete resolution of the cysts in 2 patients, whilst in 3 patients there was 48.4% reduction [mean pre RF 38.8 mm (SD ± 21.7 mm) *vs* mean post RF 20 mm (SD ± 17.1 mm)] in size (Table 2). Using cross sectional imaging in 2 patients with NET, a change in vascularity and central necrosis after EUS-RFA was demonstrated. There were no episodes of post-procedural pancreatitis, perforation or bleeding within 48 h. Two patients had mild abdominal pain that resolved in 3 d.

DISCUSSION

RFA is a well-recognized, safe and effective modality for the treatment of focal malignant diseases[14,15]. RFA uses high-frequency alternating current to generate thermal energy and thus coagulative necrosis to the tissue[16]. The technique is minimally invasive and has very good tolerability which are the major advantages[17]. RFA is increasingly applied in pancreatic lesions[18], including unresectable pancreatic carcinoma where RFA has an acceptable mortality but high morbidity[16,17,19-21]. In general, adverse events are associated with the duration of ablation. Pancreas is very thermo-sensitive, and when heat is applied on normal pancreas it produces an inflammatory response causing edema and later fibrosis and occasionally cystic transformation[18]. Massive necrosis of the pancreas following RFA have been reported, probably due to sequential ablations done in close proximity at the same session[17,20].

In recent years there have been reports of prospective studies using RFA in locally advanced pancreatic adenocarcinoma. In 2010, Girelli *et al*[22] reported ultrasound-guided RFA during laparotomy in fifty patients with locally advanced pancreatic cancer. In this prospective study the main outcome measures were short-term morbidity and mortality. In thirty four patients the tumor was located in the pancreatic head or the uncinate process and in 16 in the body or tail; median diameter was 40 (inter-quartile range 30-50) mm. Abdominal adverse events occurred in 24% of patients. Half of those were directly associated with RFA (two pancreatic fistulas and four cases of portal vein thrombosis) and were managed conservatively. When the applied heat was reduced from 105 degrees C to 90 degrees C there was a significant reduction in adverse events (ten *vs* two of 25 patients; P = 0.028). Median postoperative hospital stay was 10 (range 7-31) d. The authors concluded that RFA of locally advanced pancreatic cancer is feasible and relatively well tolerated. In another observational study, the same group compared patients with locally advanced pancreatic carcinoma treated with either primary RFA (group 1) or RFA following any other primary treatment (group 2)[23]. In total, 107 consecutive patients were treated with RFA of which 47 patients in group 1 and 60 in group 2. Median overall survival was 25.6 mo and it was significantly shorter in group 1 than in group 2 (14.7 mo *vs* 25.6 mo; P = 0.004). In this study the authors reported that RFA after alternative primary treatment was associated with prolonged survival.

RFA has been proposed by many groups as a strong adjuvant for antitumor response as it induces an immune response targeting tumor antigens[24-26]. *In situ* tumor destruction by RFA provides the immune system with an antigen for the induction of antitumor immunity. Antigen-presenting cells take up antigens in the periphery after which they induce specific immune responses[25]. Wissniowski *et al*[24] reported that RFA can induce a tumor-specific T-cell reaction in the non-reactive neoplasm-bearing host, probably by overcoming immune tolerance and leading to the presentation of otherwise cryptic neoplastic antigens. In another study, ablation of hepatocellular carcinoma (HCC) was found to induce a functional transient activation of myeloid dendritic cells associated with increased serum levels of TNF-α and IL-1β with a sustained antitumoral immune response[26]. Moreover, animals treated with subtotal RF ablation showed significant increases in tumor-specific class Ⅰ and Ⅱ responses to male minor histocompatibility (HY) antigens and tumor regression[27]. Subtotal RF ablation produces an enhanced systemic antitumor immune response and tumor regression which is related to increased dendritic cell infiltration. RFA can also induce a tumor-specific proliferative T cell response and even transplantable protective immunity[28].

Intraoperative RFA uses a larger device with higher energy and is associated with significant morbidity and mortality. However, EUS guided RFA is a more conservative approach and avoids surgical intervention. Goldberg *et al*[29] applied EUS guided RFA to the pancreas of 13 Yorkshire pigs at 285 ± 120 mA for 6 min resulting in discrete zones of coagulation necrosis in the porcine pancreas. Only one of the 13 animals had increased lipase levels and mild focal pancreatitis. No other significant adverse events were observed. A more recent study in 2008 demonstrated the feasibility and efficacy of EUS RFA using a newly developed bipolar ablation probe combining RFA and cryotechnology in 14 pigs. The size of the ablation achieved was related to the duration of ablation; when applied for 900 s there was a high complication rate in the healthy pancreas. Adverse events were less common compared to conventional RFA needles[18]. In a recent study by Kim *et al*[30], EUS-RFA of the pancreas was applied on 10 adult mini pigs. An 18 gauge endoscopic RFA probe was used to ablate the body and tail of the pancreas, with an output power of 50 W for 5 min. On histology, there was a spherical necrotic lesion surrounded by fibrous tissue localized in the pancreatic parenchyma. The mean diameter of the ablated tissue was 23.0 ± 6.9 mm. No major procedure-related adverse events were observed, and all pigs survived without any distressed behavioural pattern for 7 d until autopsy. Another minimally invasive technique for treatment of pancreatic cystic lesions with moderate success is the EUS-guided injection of ethanol into the cyst, with reported efficacy of 33.5%-62% in achieving cyst resolution[31,32]. The adverse events associated with this technique are significant, with a reported risk of severe post-procedural pain and pancreatitis of 4%-20%. Also, the presence of multiple septations within the cyst reduces the efficacy of ethanol injection. Another limitation of ethanol ablation is that this method would not be suitable for treatment of solid pancreatic lesions. A major potential advantage of EUS-RFA of cystic tumors is that it could be done in a minimally invasive way, with the likelihood of fewer adverse events than the alcohol injection because the area of ablation can be assessed and monitored in real-time by EUS.

EUS-RFA using Habib EUS-RFA catheter (Emcision Ltd., United Kingdom) through a 19 gauge needle for ablation of lymphatic and pancreatic tissue, was reported in two animal studies. In the former study[33], EUS-guided RFA ablation of mediastinal lymph nodes was successfully attempted in six pigs. RFA was performed with the ERBE Vaio generator (ERBE, Tuttlingen, Germany) with bipolar settings of 10 watts, effect 2 for 2 min. During the procedure, the probe was visible in all cases. No evidence of ablation effect in the surrounding tissue or at the needle puncture site was seen on gross examination. There was a direct correlation between the probe length and the size of necrosis. In the pancreatic study using the same catheter, five Yucatan pigs underwent EUS-guided RFA of the head of the pancreas[13]. RFA was applied with 6 mm of the probe exposed at 4 watts for 5 min, 5 watts for 0.9 min, and 6 watts for 0.2 min. Then, with 10 mm of the probe exposed in the pancreas, RFA was performed at 4 watts for 4.3 min, 5 watts for 1.4 min, and 6 watts for 0.8 min. Autopsy showed moderate level of pancreatitis, with involvement of 20% of the proximal pancreatic tissue in only one pig. There was minimal tissue damage in the other animals. In this study EUS-guided RFA of the pancreatic head with the monopolar probe through a 19 gauge needle was well tolerated with a minimal amount of pancreatitis.

We have reported in this prospective study the application of RFA *via* the novel Habib EUS-RFA catheter (Emcision Ltd., United Kingdom) for pancreatic cystic neoplasms and NET. The concept of treating pre-malignant asymptomatic pancreatic lesions by means other than surgical resection is appealing, as the latter is associated with major morbidity and some mortality. This study shows that such an approach is feasible and safe. Our patients were discharged hours without any major adverse events. However, it is conceivable that the application of RF energy in the pancreatic parenchyma may be associated with some adverse events. Such adverse events may include (but not necessarily limited to) acute pancreatitis, pancreatic leaks, infection of necrotic pancreatic tissue post treatment and bleeding. Using lower energy also allows for repeating the ablation with low morbidity as per clinical indication. EUS-RFA of pancreatic neoplasms with a novel monopolar RF probe was well tolerated in all patients. These preliminary data results suggest that the procedure is technically easy and safe. The response ranged from complete resolution to a 50% reduction in diameter. Further multicenter experience is required before widespread use of this novel procedure.

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which designed and developed the device. None of the other authors have a conflict of interest or a financial disclosure to declare.

COMMENTS

Background

The aim of this report is to outline the feasibility, safety, adverse events and early results of endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) in pancreatic neoplasms using a novel RF probe. The Habib™ EUS-RFA is monopolar catheter with a 1 Fr wire (0.33 mm, 0.013") with a working length of 190 cm, which can be inserted through the biopsy channel of an echoendoscope. RF power is applied to the electrode at the end of the wire to coagulate tissue in the liver and pancreas.

Research frontiers

This first in human study shows that EUS-RFA with this novel catheter provides an endoscopic treatment option other than surgical resection for pancreatic lesions.

Innovations and breakthroughs

The standard treatment of solid or cystic pancreatic lesions with malignant potential has been surgical resection. Pancreatic resections carry significant morbidity and mortality, resulting in unacceptably high risk/benefit ratios for many elderly patients with co-morbidities. There is an unmet need for minimally invasive ablative techniques as alternative to surgical resection.

Applications

Our results show that the procedure is technically easy and safe. The response in this series ranged from complete resolution to a 50% reduction in diameter. Therefore it might be an excellent alternative for patients that are not suitable surgical candidates.

Terminology

Radiofrequency ablation is the procedure of destructing tissue with the use of heat generated from high frequency alternating current (in the range of 350-500 kHz). It is a widely accepted method of tissue destruction for primary solid organ tumors. It has been used in the management of primary liver and lung tumors in patients that are not suitable surgical candidates and in secondary malignancies as part of the treatment algorithm.

Peer-review

This author congratulated demonstrating wonderful study.

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CASE REPORT

Glucagon receptor gene mutations with hyperglucagonemia but without the glucagonoma syndrome

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Author contributions: Miller HC wrote the paper and analysed genetic data; Kidd M and Modlin IM performed genetic studies; Drymousis P, Vlavianos P and Frilling A contributed to the clinical work up; Cohen P and Dina R conducted the histopathology, Klöppel G reviewed the histology; Frilling A designed the research, analysed data and reviewed and edited the manuscript.

Ethics approval: This study is part of our project R12025: Genetic signature, metabolic phenotyping and integrative biology of neuroendocrine tumors. Ethics approval REC number: 07/MRE09/54.

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Conflict-of-interest: None of the authors have any relevant affiliations or financial involvements to disclose.

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Abstract

Pancreatic neoplasms producing exclusively glucagon associated with glucagon cell hyperplasia of the islets and not related to hereditary endocrine syndromes have been recently described. They represent a novel entity within the panel of non-syndromic disorders associated with hyperglucagonemia. This case report describes a 36-year-old female with a 10 years history of non-specific abdominal pain. No underlying cause was evident despite extensive diagnostic work-up. More recently she was diagnosed with gall bladder stones. Abdominal ultrasound, computerised tomography and magnetic resonance imaging revealed no pathologic findings apart from cholelithiasis. Endoscopic ultrasound revealed a 5.5 mm pancreatic lesion. Fine needle aspiration showed cells focally expressing chromogranin, suggestive but not diagnostic of a low grade neuroendocrine tumor. OctreoScan® was negative. Serum glucagon was elevated to 66 pmol/L (normal: 0-50 pmol/L). Other gut hormones, chromogranin A and chromogranin B were normal. Cholecystectomy and enucleation of the pancreatic lesion were undertaken. Postoperatively, abdominal symptoms resolved and serum glucagon dropped to 7 pmol/L. Although H and E staining confirmed normal pancreatic tissue, immunohistochemistry was initially thought to be suggestive of alpha cell hyperplasia. A count of glucagon positive cells from 5 islets, compared to 5 islets from 5 normal pancreata indicated that islet size and glucagon cell ratios were increased, however still within the wide range of normal physiological findings. Glucagon receptor gene (GCGR) sequencing revealed a heterozygous deletion, K349_G359del and 4 missense mutations. This case may potentially represent a progenitor stage of glucagon cell adenomatosis with hyperglucagonemia in the absence of glucagonoma syndrome. The identification of novel *GCGR* mutations suggests that these may represent the underlying cause of this condition.

Key words: Hyperglucagonemia; Glucagon receptor gene; Mutation; Adenomatosis; Pancreas

Core tip: We identify novel mutations in the glucagon receptor gene in a patient with hyperglucagonemia but no glucagonoma syndrome. Physicians dealing with pancreatic disorders should be aware of this unusual condition.

Miller HC, Kidd M, Modlin IM, Cohen P, Dina R, Drymousis P, Vlavianos P, Klöppel G, Frilling A. Glucagon receptor gene mutations with hyperglucagonemia but without the glucagonoma syndrome. *World J Gastrointest Surg* 2015; 7(4): 60-66 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i4/60.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i4.60

INTRODUCTION

Glucagon cell adenomatosis has been reported by Henopp *et al*[1] as an independent previously unrecognised disease of the endocrine pancreas. Multiple pancreatic neoplasms exclusively producing glucagon, associated with glucagon cell hyperplasia of the islets and unrelated to multiple endocrine neoplasia (MEN) type 1 (MEN 1), p27 MEN or von Hippel-Lindau (VHL) syndromes, are the hallmarks of the condition[2]. To date very few such patients have been reported[1,3,4].

Most patients present with abdominal pain and increased serum glucagon levels but fail to exhibit the characteristics of the glucagonoma syndrome (necrolytic migratory erythema, diabetes mellitus, stomatitis and weight loss)[5]. While macroscopic tumors are evident on imaging in some, numerous microadenomas scattered throughout the pancreas and enlarged islets are the findings in others[1,3,4]. Malignancy has not been identified in any cases reported to date. The underlying cause of glucagon cell hyperplasia and consequent development of glucagon cell neoplasia without the glucagonoma syndrome remains unknown. Yu *et al*[3], Zhou *et al*[6] have proposed that malfunction of the glucagon receptor (GCGR) and/or glucagon may be responsible for the disease after detection of a homozygous missense mutation, c.256C>T (P86S) in the *GCGR* of a patient.

We present another example of hyperglucagonemia without morphological evidence of neoplasia or the glucagonoma syndrome in which we identified *GCGR* mutations which may represent the underlying pathogenic cause of the condition.

CASE REPORT

A 36 years old Caucasian female with no previous medical or known family history was referred to us in 2011 with a 10 year history of non-specific diffuse abdominal pain. She repeatedly underwent complete gastrointestinal diagnostic work-up over a period of 8 years which revealed no pathologic results. In 2009, she had been diagnosed with cholelithiasis on abdominal ultrasound. Upon referral to our centre in 2011, extensive investigations including upper and lower intestinal endoscopy, computerised tomography and magnetic resonance imaging (MRI) were carried out. Apart from the previously diagnosed cholelithiasis, no other pathology was evident. Endoscopic ultrasound (EUS) confirmed calculi in the gallbladder and a mild dilatation of the distal common bile duct. In addition, a 5.5 mm hypoechoic lesion with irregular margins was detected in the pancreatic tail. Fine needle aspiration (FNA) revealed cells focally expressing chromogranin A. The features were suggestive but not diagnostic of a low grade neuroendocrine tumor. Somatostatin receptor scintigraphy showed no foci of increased uptake. While serum gastrin, vasoactive intestinal polypeptide, somatostatin, and pancreatic polypeptide were within the normal range, glucagon was elevated to 66 pmol/L (normal: 0-50 pmol/L). Serum fasting and postprandial glucose was normal. Neuroendocrine tumor markers chromogranin A and chromogranin B were not elevated. At laparotomy, a sub-centimeter lobulated lesion was found at the inferior margin of the pancreatic tail corresponding with the lesion identified on EUS. No further lesions were identified in the remaining pancreas after meticulous bimanual exploration and intraoperative ultrasound. There were no enlarged peripancreatic lymph nodes. The pancreatic tail lesion was enucleated and cholecystectomy performed. A grade 1 pancreatic fistula developed postoperatively and resolved within 2 wk. The further course was uneventful and the patient was entirely asymptomatic. Moreover, she reported that the abdominal pain she experienced over the last decade had completely disappeared. Serum glucagon was assessed 1 mo postoperatively after the pancreatic morphology returned to normal on imaging. It was found to have decreased to 7 pmol/L. Serum glucagon was monitored at regular intervals (see Table 1). At the last follow-up, 31 mo after surgery, the patient remained asymptomatic with a normal MRI result, serum glucagon was 10 pmol/L and insulin was within the normal range.

Histology (H and E) showed features of normal pancreatic tissue. Immunohistochemical examination for glucagon and insulin was undertaken using the technique of Henopp *et al*[1]. Approximately 20% of the islet cells were glucagon positive and 80%

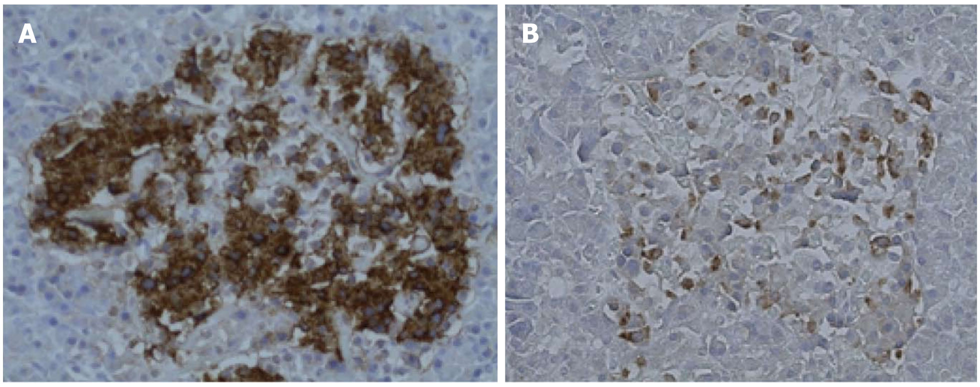

Figure 1 Islet from patient. Immunohistochemistry for A: Insulin; B: Glucagon, x 200 magnification (600 μm at maximum diameter).

Table 1 Serum glucagon levels

Time	Serum glucagon (pmol/L) (normal range: 0-50 pmol/L)
Pre-surgery	
2 mo	66
Post-surgery	
1 mo	7
5 mo	28
6 mo	6
17 mo	15
20 mo	29
31 mo	10

Table 2 Islet size and number of glucagon positive cells in the current case compared to 5 normal pancreata

	Average[1] islet size (μm)	Average[1] number glucagon positive cells	
		Count 1	Count 2
Patient	192	29.2	28.8
Control 1	256	59.8	61.8
Control 2	186	25.6	25.2
Control 3	255	32.2	31.6
Control 4	260	52.4	53.4
Control 5	190	44.6	42.6

[1]Average of 5 pancreatic islets.

insulin positive. Glucagon cell hyperplasia was initially considered (Figure 1). In order to investigate this further, glucagon cell counts were done with 5 islets from 5 normal pancreatic controls and compared to 5 islets from the patient (Table 2). The counts showed that the average islet size and the average number of glucagon positive cells per islet were increased in the patient, however still within the wide range observed in normal pancreatic tissue.

Methods of genetic investigation

A peripheral blood sample was obtained from the patient, her daughter and a healthy individual as a normal control (informed consent obtained). Genomic DNA (gDNA) was extracted using the DNeasy Blood and Tissue Kit according to the protocol (Qiagen, catalogue number: 9506). Polymerase chain reaction (PCR) amplification of exons 2-13 (and most of exon 14) of *GCGR* and the intron:exon borders was carried out using previously described primers[6]. Purified PCR products were sequenced by the W.M. Keck Biotechnology Resource Laboratory at Yale University, New Haven, United States using an automated Applied Biosystems 373A Stretch DNA sequencer (Perkin-Elmer, Norwalk, United States). PCR products were sequenced using forward primers. If ambiguous peaks were evident, the sequence was confirmed with the reverse primers[7]. Bioedit software was used to analyse the sequencing results[8]. Sequencing products were compared to the control sample and the national centre for biotechnology information (NCBI) reference sequences for the human *GCGR*, DNA (NG_016409.1), mRNA (NM_000160.3) and protein (NP_000151.1).

MEN1 sequencing was carried out on gDNA from the peripheral blood. PCR amplification of exons 2-10 of *MEN1* was undertaken using previously described primers[9,10]. The DNA extraction, sequencing and analysis were carried out using the same technique as for *GCGR*. The reference sequence used was NCBI GenBank: U93237.1.

VHL sequencing was carried out on gDNA from the peripheral blood. PCR amplification of exons 1-3 of *VHL* was undertaken using primers previously described[11]. The DNA extraction, sequencing and analysis were carried out using the same technique as for *GCGR*. The reference sequence used was NCBI GenBank: NM_000551.3.

Results of genetic analysis

A heterozygous deletion of 33 nucleotides in exon 11 of the *GCGR* was detected. This corresponded to a K349_G359del in the GCGR with the loss of the following 11 amino acids, KSTLTLIPLLG. There were also 5 heterozygous point mutations including 4 missense mutations, E362K, V368L, K381E, S389N and 1 synonymous mutation (Figure 2). There were no mutations in *MEN1* or *VHL*. No mutations were

```
A  Control   CTGGCCAAGTCCACGCTGACCCTCATCCCTCTGCTGGGCGTCCACGAAGTGGTCTTCGCC   1098
   Patient   CTGGCC---------------------------------GTCCACAAAGTGGTCTTTGCC

   Control   TTCGTGACGGACGAGCACGCCCAGGGCACCCTGCGCTCCGCCAAGCTCTTCTTCGACCTC   1158
   Patient   TTCCTGACGGACGAGCACGCCCAGGGCACCCTGCGCTCCGCCGAGCTCTTCTTCGACCTC

   Control   TTCCTCAGCTCCTTCCAG   1176
   Patient   TTCCTCAACTCCTTCCAG

B  Control   LAKSTLTLIPLLGVHEVVFAFVTDEHAQGTLRSAKLFFDLFLSSFQ   392
   Patient   LA-----------VHKVVFAFLTDEHAQGTLRSAELFFDLFLNSFQ
```

Figure 2 Genetic findings. A: Sequencing results showing a heterozygous 33 nucleotide deletion and 5 point mutations in exon 11 of the *GCGR*; B: Amino acid sequence showing K349_G359del, E362K, V368L, K381E, S389N in the GCGR. Alignments done using Clustal W multiple sequence alignments software[25]. Numbers indicate the position of the last residue shown along the GCGR cDNA/protein.

detectable in the daughter.

DISCUSSION

This case report represents the second case of hyperglucagonemia which has been associated with a specific genetic lesion in the *GCGR.* The case could potentially represent a progenitor stage of an entity leading to glucagon cell adenomatosis.

To date 8 individuals exhibiting characteristics of glucagon cell adenomatosis with hyperglucagonemia but without glucagonoma syndrome have been reported in the literature[1,3,4,6,12,13]. It is a matter of debate whether all cases cited completely fulfil the criteria of glucagon cell adenomatosis as defined by Henopp *et al*[1]. For example, the individual described by Yu *et al*[3] had not only raised serum glucagon levels but also pathologic values of pancreatic polypeptide. The patient reported by Balas *et al*[13] in 1988 had normal serum glucagon levels; however immunohistological findings in the resected pancreas were consistent with glucagon cell adenomatosis. In our patient, although the morphology of the resected pancreatic islets was within the broad range of findings reported in unaffected pancreata, we speculate that a cluster of hyperfunctioning cells might potentially be responsible for the development of hyperglucagonemia. Functional studies would be needed to confirm this theory.

The majority of individuals had glucagon cell adenomatosis, but were asymptomatic with respect to evidence of the glucagonoma syndrome. The results of imaging ranged from no pathologic findings to diffuse pancreatic enlargement associated with multiple tumors of various sizes. Abdominal pain is present in most individuals as was the case in our patient (Table 3). While the case we present exhibited normal uptake on somatostatin receptor scintigraphy, diffusely increased uptake was reported on OctreoScan® in a patient with diffuse pancreatic enlargement and multiple tumors by Henopp *et al*[1]. In our patient the positive staining for chromogranin on FNA was thought to be suggestive of a neuroendocrine tumor. This might reflect the small number of cells obtained from the FNA, with a sampling error leading to a higher proportion of chromogranin positive cells (*e.g.,* if FNA sampling comprised an islet). In comparison to two reported cases which had highly elevated serum glucagon levels, our patient had only slightly increased serum glucagon (Table 3). The lack of standardised serum glucagon reporting in the majority of cases and the small number of patients means it is difficult to tell if the levels in our patient were truly lower than average.

The majority of previously reported patients demonstrated numerous microadenomas expressing almost exclusively glucagon and/or glucagon cell hyperplasia. This observation prompted Henopp *et al*[1,14] to postulate that diffuse glucagon cell hyperplasia might represent a precursor from of glucagon cell neoplasia. In the case described by Yu *et al*[3], 60%-80% of the hyperplastic islet cells stained positive for glucagon but negative for insulin. A similar trend was noted by Henopp *et al*[1]. In our patient, the pancreatic morphology was unusual, nevertheless still within the wide range of physiological findings. Approximately 20% of the islet cells expressed glucagon while 80% expressed insulin. Based on this observation and only mildly increased serum glucagon, we hypothesize that the disease might have been diagnosed at a very early stage prior to evidence of hyperplasic transformation and development of overt morphological evidence of neoplasia/s. While a subcentimeter nodule at the pancreatic tail was evident on EUS and confirmed intraoperatively, standard histology showed regular findings. This scenario resembles a report by Martignoni *et al*[4] of hyperglucagonemia but no microadenomas.

Both of the two previously reported patients for whom follow-up data was available showed increased serum glucagon levels after pancreatic resection in the presence of negative imaging results[1,3]. These findings underline the presumption of disease persistence. Our patient however, had normal serum glucagon levels at 31 mo after surgery (10 pmol/L) (Table 1). Due to the

Table 3 Hyperglucagonemia without the glucagonoma syndrome-review of the literature

	Martignoni *et al*[4]	Henopp *et al*[1] (patient 2)	Yu *et al*[3], Zhou *et al*[6]	Present case
Patient	54, M	43, F	60, F	36, F
Origin	-	-	Persian	Caucasian
Clinical symptoms	Abdominal pain Diarrhea[1]	Abdominal pain	Abdominal pain Constipation	Abdominal pain
Serum Glucagon (pmol/L)	Elevated	Elevated (25-fold)[2]	17011[3]	66
Imaging	Negative	Positive	Positive	Negative (positive on EUS)
OctreoScan®	Negative	-	Negative	Negative
Localization	No focal abnormality	Tail	Uncinate	Tail
Pancreatic pathology	α-cell hyperplasia nesidioblastosis	α-cell hyperplasia, large cystic tumor and small solid tumors, multiple microadenomas	α-cell hyperplasia non-functioning pancreatic NET microglucagonoma microadenoma	Normal pancreatic morphology on standard H and E staining
GCGR	-	-	Homozygous gDNA point mutation	Heterozygous gDNA deletion 5 point mutations
Other Genes	-	Negative for *MEN1*/*VHL* gDNA mutations	-	Negative for *MEN1*/*VHL* gDNA mutations
Relatives *GCGR*	-	-	Brother Negative	Daughter Negative

[1]Mild diabetes was initially suspected but then found to be unlikely; [2]The glucagon levels were only measured postoperatively; [3]Glucagon levels converted to pmol/L from pg/mL. M: Male; F: Female; EUS: Endoscopic ultrasound; GCGR: Glucagon receptor.

genetic predisposition of the disease we cannot exclude the possibility that at some point in the future the disease may recur therefore our patient requires life-long follow up. Any future increases in serum glucagon levels could potentially represent the emergence of alpha cell hyperfunction consistent with the concept of a residual genomic lesion representing a diffuse alpha cell abnormality in the remaining pancreatic islets.

The GCGR is a member of the class B G protein-coupled receptor family, glucagon binding triggers downstream signalling, allowing glucagon to regulate blood glucose levels by stimulating glycogenolysis[15,16]. The knockout mouse for *GCGR* expresses high glucagon levels associated with pancreatic enlargement, glucagon cell adenomatosis and microglucagonomas or glucagonomas at 10-12 mo when compared to their heterozygous littermates[17,18]. Based on these observations, Yu *et al*[3,6] sequenced *GCGR* and the glucagon gene in their patient with hyperglucagonemia, alpha cell hyperplasia and microglucagonoma. They detected a homozygous c.256C>T (P86S) mutation in *GCGR* resulting in lower binding affinity of GCGR P86S to glucagon and hypothesized that this mutation was responsible for the alpha cell hyperplasia and hyperglucagonemia. They showed *in vitro* that the GCGR P86S localized to the plasma membrane but bound glucagon with less avidity than wild type GCGR; a greater glucagon concentration was thus needed to trigger downstream signalling *via* adenylate cyclase activation[6]. Neuroendocrine cells undergoing hyperplastic changes is particularly relevant for MEN1 conditions however they probably also occur in sporadic cases. Very recently Klöppel *et al*[14] identified 3 further patients with germline *GCGR* mutations and glucagon cell adenomatosis unrelated to MEN1 or VHL syndromes. The genetic lesions present in the *GCGR* were not described, however a further 3 patients had glucagon cell adenomatosis in the absence of any *GCGR* mutation[14].

Our case represents the second case with genetic lesions described in the *GCGR* associated with hyperglucagonemia in the absence of the glucagonoma syndrome. The heterozygous K349_G359del and E362K, V368L, K381E, S389N mutations could potentially represent a loss of function mutation in the *GCGR*. Functional studies would be needed to show if these mutations might be the cause of the hyperglucagonemia observed in our patient. All mutations were in exon 11 towards the C terminal end of GCGR. The point mutations appear to represent rather conservative amino acid changes in terms of hydrophobicity. Lysine and glutamate have a positively and a negatively charged R group respectively and the serine to asparagine change represents an alteration from a hydroxyl R group to a carboxamide R group. Site directed mutagenesis studies have noted that D385 is relevant to the specificity of glucagon/GCGR binding[19]. Since this residue is close to the K381E mutation site and adjacent to the glucagon binding site, the alteration in R group may affect glucagon binding. However in the absence of high resolution crystal structure data for the human glucagon receptor (except for the extracellular N terminal domain) and site directed mutagenesis studies for these sites, the effects of these genetic changes cannot be directly inferred[15].

The K349_G359del falls within the 6th transmembrane domain of GCGR, therefore the 11 amino acid deletion could prevent GCGR from inserting into the plasma membrane. This would prevent GCGR binding to glucagon[20]. In structural studies where COS-1 cells were transfected with the rat glucagon receptor gene, truncation mutants lacking any of the different

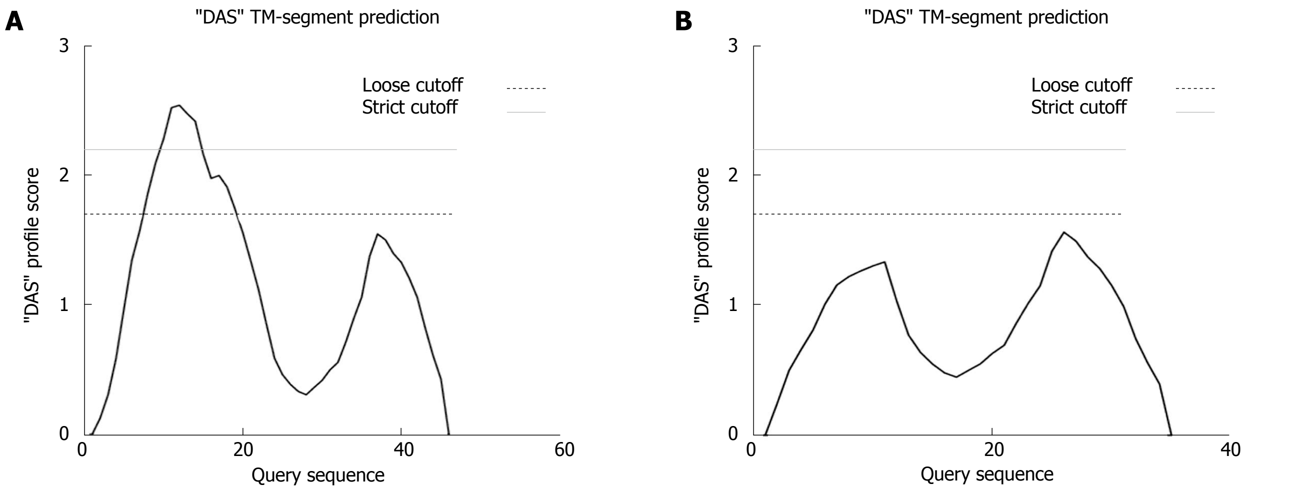

Figure 3 Membrane topology prediction. The loss of 11 amino acids from the glucagon receptor (GCGR) 6th transmembrane domain is predicted to prevent the insertion of GCGR into the plasma membrane. A: Predicted normal GCGR membrane topology; B: Predicted K349_G359del GCGR membrane topology. Software used: MetaTM[22]; input amino acid sequence shown in Figure 2B. DAS: Distributed Annotation System.

transmembrane domains, were not localized to the plasma membrane suggesting that all 7 transmembrane domains are needed for correct membrane insertion[21]. The K349_G359del mutation is predicted by membrane topology prediction software to prevent the GCGR from properly inserting into the plasma membrane[22] (Figure 3). If this was the case, then the GCGR would be miss-localized preventing glucagon binding. This would however need to be confirmed by *in vitro* protein localization studies and assays to check glucagon binding efficiency in the presence of the deletion. In addition, since the mutation in the *GCGR* is heterozygous, there would still be a normal gene copy present which might allow sufficient glucagon signalling via the remaining receptors to give normal function. However, the clinical pathology evident in the presence of hyperglucagonemia seems to suggest that this may not be the case.

The phenotype could potentially represent incomplete dominance leading to the modest elevation of serum glucagon in our patient. Alternatively, it is possible that this individual might have a second mutation in the other copy of the *GCGR* within some of the pancreatic alpha cells which could potentially be causing them to become hyperfunctional.

It has been previously suggested that incretin treatment is associated with the development of alpha cell hyperplasia since pancreata from autopsies of incretin treated persons exhibit alpha cell hyperplasia (and beta cell hyperplasia) and some had glucagon expressing microadenomas[23,24]. A possibility exists that as incretin usage increases, alpha cell hyperplasia may become more prevalent.

In conclusion, we have identified a novel heterozygous K349_G359 deletion and 4 missense mutations in the *GCGR* which appear to be associated with hyperglucagonemia without the glucagonoma syndrome. Physicians dealing with pancreatic disorders should be aware of this very unusual condition. Further study leading to a better understanding of this disease entity would be of benefit to patients. The further usage of *GCGR* sequencing in such individuals should be undertaken to provide additional information on the breadth of the spectrum of mutational abnormalities associated with alpha cell transformation and excess glucagon production.

COMMENTS

Case characteristics
36 years old patient with a 10 year history of non-specific diffuse abdominal pain.

Clinical diagnosis
A sub-centimeter lobulated lesion was found at the inferior margin of the pancreatic tail, no further lesions were identified in the remaining pancreas after meticulous bimanual exploration and intraoperative ultrasound.

Differential diagnosis
Fine needle aspiration revealed cells focally expressing CgA. The features were suggestive but not diagnostic of a low grade neuroendocrine tumor.

Laboratory diagnosis
Serum glucagon was elevated to 66 pmol/L (normal: 0-50 pmol/L). Other gut hormones were within the normal range.

Imaging diagnosis
Endoscopic ultrasound identified a 5.5 mm hypoechoic lesion with irregular margins in the pancreatic tail.

Pathological diagnosis
Histology (H and E) showed features of normal pancreatic tissue. Glucagon cell hyperplasia was initially considered based on glucagon immunohistochemistry. Further investigation revealed that the average islet size and the average number of glucagon positive cells per islet were increased in the patient, however still within the wide range observed in normal pancreatic tissue.

Treatment
At laparotomy, a sub-centimeter lobulated lesion was found at the inferior margin of the pancreatic tail and was enucleated.

Related reports
This is a very rare disease entity. Genetic lesions in the glucagon receptor (*GCGR*) have only been described in one individual in the literature in the context of glucagon cell adenomatosis with hyperglucagonemia but without glucagonoma syndrome. Several additional cases exhibiting the characteristics of glucagon cell adenomatosis with hyperglucagonemia but without glucagonoma syndrome have been published however their *GCGR* mutation status remains unknown.

Experiences and lessons
The authors have identified novel *GCGR* mutations which appear to be associated with hyperglucagonemia without the glucagonoma syndrome. Physicians dealing

with pancreatic disorders should be aware of this very unusual condition.

Peer-review

This is an interesting case of an entity not described before.

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CASE REPORT

Appendiceal tie syndrome: A very rare complication of a common disease

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Author contributions: Awale L, Joshi BR and Rajbanshi S designed the report; Awale L and Joshi BR performed the surgery; Awale L, Rajbanshi S and Adhikary S collected the patient's clinical data; Awale L and Adhikary S analyzed the data and wrote the paper.

Ethics approval: The study was reviewed and approved by the BP Koirala Institute of Health Sciences Institutional Review Committee.

Informed consent: The study participant provided informed written consent.

Conflict-of-interest: None declared.

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Abstract

Acute appendicitis is the most common surgical emergency that we encounter. Adynamic Intestinal obstruction due to appendicitis or its complication may be seen time and often. Mechanical obstruction because of appendicitis is uncommon and even rarer for a closed loop obstruction to occur. Although it was described as early as 1901, very few cases have been reported. We report the case of a 20 years male who presented with generalized colicky pain abdomen, abdominal distension, vomiting and obstipation for three to four days. Vital signs were stable. His abdomen was distended and peritonitic, especially in the right iliac fossa. Rest of the physical examination was unremarkable. Blood tests were normal except for leucocytosis with neutrophilia. An abdominal X-ray finding was indicating a small bowel obstruction. A midline laparotomy was performed. On intraoperative examination, distended loops of small bowel from the jejunum to the distal ileum was observed, and a constricting ring around the terminal ileum created by a phlegmonous appendicitis with its tip adherent to the root of mesentery was found, obstructing an edematous loop of small bowel without signs of ischemia. As the bowel was viable simple appendectomy was done. Postoperatively, he had an uneventful recovery and was discharged after 3 d.

Key words: Appendicitis; Appendicular band; Intestinal obstruction; Mechanical small bowel obstruction; Closed loop obstruction

Core tip: It is safe to say, almost no-one will become a surgeon without seeing or doing appendectomy. It is so common, yet time and often we are deceived by it. As we know, abdomen is a "Pandora's box", we never know what come up sometimes and this is a perfect example. We report a case of mechanical small bowel obstruction due to acute appendicitis that was timely and successfully managed surgically.

Awale L, Joshi BR, Rajbanshi S, Adhikary S. Appendiceal tie syndrome: A very rare complication of a common disease. *World J Gastrointest Surg* 2015; 7(4): 67-70 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i4/67.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i4.67

INTRODUCTION

Acute appendicitis is one of the most common surgical problems that we encounter. Diagnosis is not always so straightforward and can impose a dilemma. Indeed appendicitis is well known to cause mechanical small bowel obstruction because of adhesion. On the contrary, very few cases of mechanical small bowel obstruction developed as a direct result of acute appendicitis have been reported in literature[1,2]. In 1901, Hotchkiss *et al*[3] first reported it but till date only a handful of cases has been reported. The clinical feature of small bowel obstruction may obscure the clinical picture of appendicitis, making its diagnosis further challenging if not impossible. Hence, the preoperative diagnosis is very difficult and is made during laparotomy. Its paucity makes this case interesting.

CASE REPORT

A 20 years young male presented with the four days history of worsening generalized colicky pain abdomen, three days history of abdominal distension and bilious vomiting and three days history of obstipation. There was no history of previous abdominal surgery. On examination he was afebrile and vital signs were stable. His abdomen was distended, with visible bowel loops remarkably in the center abdomen and peritonitic, especially in the right iliac fossa, with exaggerated bowel sound. The rectal examination was normal. Rest of the physical examination was unremarkable. Laboratory parameters were within normal limits, except for the leukocytosis (16800/μL) with neutrophilia. A plain abdominal skiagram (Figure 1) showed dilated jejunal and ileal loops with multiple air-fluid levels indicating a small bowel obstruction.

The patient was kept nil per oral with active nasogastric aspiration. Intravenous fluid, prophylactic intravenous antibiotics and analgesics were started. Meanwhile the patient was planned for emergency laparotomy with a diagnosis of mechanical small bowel obstruction of unknown etiology.

A midline laparotomy was performed. On intra-operative examination, distended loops of small bowel from the jejunum to the distal ileum were observed. These loops were followed distally to reveal a constricting ring around the terminal ileum (Figure 2) created by a phlegmonous appendicitis (as represented in Figure 3) with its tip adherent to the root of mesentery (Figure 4), obstructing an edematous loop of terminal ileum

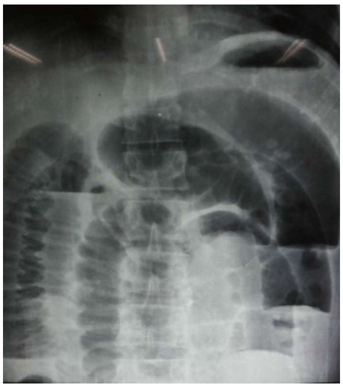

Figure 1 Abdominal radiograph showing multiple distended loops of small bowel with fluid levels.

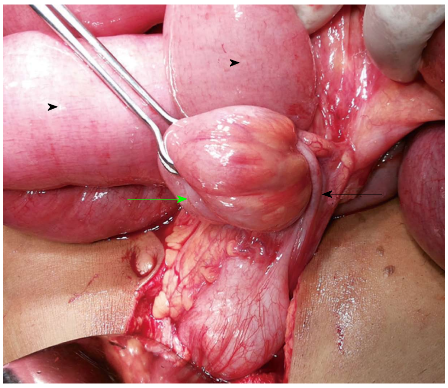

Figure 2 The Appendix (black arrow) encircling the loop of terminal Ileum (green arrow) with dilatation of proximal small bowel (black arrowheads).

without signs of ischemia (Figure 2). As the bowel was viable simple appendectomy was done and the abdomen was closed with a drain in the pelvis.

Postoperatively, he had an uneventful recovery. The drain was removed on the 2nd operative day, and was orally started after around 48 h with the evidence of bowel movement. Subsequently, he was discharged on the 4th postoperative day. Histopathology report of excised appendix revealed acute appendicitis. He was doing well till 2 mo.

DISCUSSION

The first case of intestinal obstruction due to acute appendicitis was described by Hotchkiss[3]. In 1909, Hawks[4] divided the causes into mechanical and septic appendicitis or a combination of both. Appendix is a mobile organ and has variable position. Hence, during appendicitis it has tendency to get adhere to surrounding structures resulting in mechanical small bowel obstruction, and an increased length seems to facilitate the phenomenon[5].

In 2009, Bhandari *et al*[6] classified intestinal obstruction because of appendicitis into four types: adynamic, mechanical, strangulation, and caused by mesenteric ischemia. Adynamic obstruction or paralytic

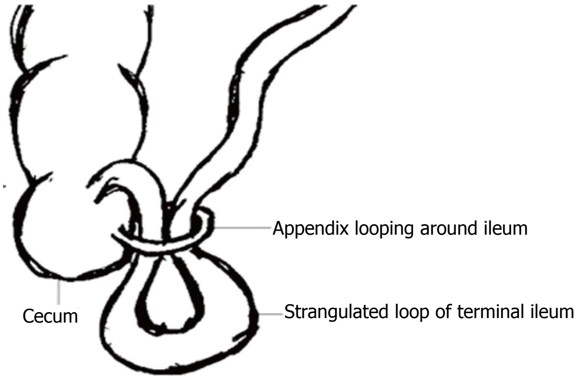

Figure 3 Depiction of Appendix wrapping around loop of Ileum. (Reproduced with permision from Menon *et al*[7]).

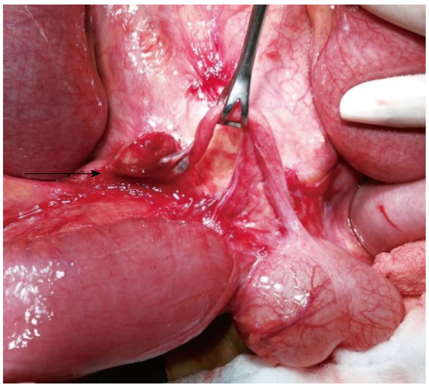

Figure 4 Inflamed and odematous tip of Appendix adherent to the root of mesentry (black arrow).

ileus is undoubtedly the most common type and is due to the appendicular inflammation spreading to the surrounding structures (caecum, small bowel or posterior peritoneum). Strangulation may result from a long standing closed loop obstruction, which can be due to the long appendix constricting around a loop of small bowel, or when it is adhere to surrounding structures and a part of bowel herniates through the gap. In 2005, Assenza *et al*[5] reported only six such cases in the review. Mesenteric ischemia due to appendicitis causing intestinal obstruction is the rarest one.

Among the mechanical causes, the vast majority are due to the formation of appendicular abscess that compresses the loops of small bowel, and postoperative adhesions that occur years after treatment[6]. There are two basic situations where the appendix may also cause a mechanical obstruction[5]; appendicular tip attached to the mesentery surrounding an ileal loop, producing compression of its lumen and the appendicular tip attached to the intestinal serosa, producing the obstruction by direct compression or torsion of a loop. There are only ten cases reported in literature reviewed by O'Donnell *et al*[2], *i.e.*, a loop obstruction caused by the loop of the appendix attached to the mesentery, in the context of acute appendicitis, which is similar to the one in our case.

The paucity of this condition makes it very challenging in making its preoperative diagnosis. In the early inflammation phase, CT (Computerized Tomography) may help to clinch the diagnosis. After resolution of appendicitis, its role is very limited[5-7]. Thorough history and clinical examination, imaging findings and high index of suspicion may help in diagnosis. Diagnostic laparoscopy may be a valuable option.

Treatment is straightforward and depends on intraoperative findings. Appendectomy is sufficient if intervened early, as in our case. It may require small bowel or ileocaecal resection when there is strangulation.

Closed loop and strangulating obstruction of the small bowel are serious lesions that require emergency surgery. An accurate and early diagnosis of intestinal strangulation is essential in patients with small bowel obstruction to minimize the risks of morbidity and mortality. Delayed operation potentially results in high mortality. Preoperative, diagnosis of Appendiceal tie syndrome[7] is always difficult. Early surgical intervention in case of small bowel obstruction can reduce the postoperative risk.

COMMENTS

Case characteristics

A 20 years young male presented with generalized colicky pain abdomen, abdominal distension, bilious vomiting and obstipation.

Clinical diagnosis

Acute abdomen, Mechanical small bowel Intestinal obstruction.

Differential Diagnosis

Congenital anomalous bands, Intestinal malrotation.

Laboratory Diagnosis

Laboratory tests showed a leukocytosis (16800/μL; 4000-11000) rest within normal range (including haemoglobin, haematocrit, creatinine, ABG analysis).

Imaging diagnosis

An abdominal X-ray radiography indicated remarkably multiple air-fluid levels.

Pathological diagnosis

Pathology findings indicated acute appendicitis.

Treatment

Appendectomy.

Related reports

Acute appendicitis, as a cause of mechanical small bowel obstruction is very rare. Long inflamed appendix may lead to this problem. Close loop obstruction by loop of the appendix, in the context of appendicitis, is even rarer. A literature review in 2005 identified only six such cases leading to strangulation.

Term explanation

Appendiceal tie syndrome also called as appendicular band or knot syndrome is an extremely rare surgical entity, in which there is entrapment of bowel loop by the appendix, acting as constricting ring, and may lead to its strangulation.

Experiences and Lessons

Sometimes a very common disease like appendicitis can surprise you with its very rare presentation. But the key thing is the early intervention before it really does the damage, that is, to prevent strangulation.

Peer-review

This manuscript is a well designed with visual materials and will contribute to the literature.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Lymph node pick up by separate stations: Option or necessity?

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Author contributions: Morgagni P, Nanni O, Carretta E and Garcea D designed the study; Morgagni P, Nanni O, Carretta E, Altini M, Saragoni L and Falcini F were responsible for data collection; Morgagni P, Nanni O and Carretta E analyzed and interpreted the data; Nanni O and Carretta E performed the statistical analysis; Morgagni P, Nanni O, Carretta E and Saragoni L drafted the manuscript; all authors read and approved the final version of the paper.

Ethics approval: As anonymized administrative and clinical data were used for this study, it was exempt from formal ethics review.

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Data sharing: Technical appendix, statistical code, and dataset are available from the corresponding author at p.morgagni@ausl.fo.it. Consent was not obtained but the presented data are anonymized and the risk of identification is low.

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Abstract

AIM: To evaluate whether lymph node pick up by separate stations could be an indicator of patients submitted to appropriate surgical treatment.

METHODS: One thousand two hundred and three consecutive gastric cancer patients submitted to radical resection in 7 general hospitals and for whom no information was available on the extension of lymphatic dissection were included in this retrospective study.

RESULTS: Patients were divided into 2 groups: group A, where the stomach specimen was directly formalin-fixed and sent to the pathologist, and group B, where lymph nodes were picked up after surgery and fixed for separate stations. Sixty-two point three percent of group A patients showed < 16 retrieved lymph nodes compared to 19.4% of group B (P < 0.0001). Group B (separate stations) patients had significantly higher survival rates than those in group A [46.1 mo (95%CI: 36.5-56.0) *vs* 27.7 mo (95%CI: 21.3-31.9); P = 0.0001], independently of T or N stage. In multivariate analysis, group A also showed a higher risk of death than group B (HR = 1.24; 95%CI: 1.05-1.46).

CONCLUSION: Separate lymphatic station dissection increases the number of retrieved nodes, leads to better tumor staging, and permits verification of the surgical dissection. The number of dissected stations could potentially be used as an index to evaluate the quality of treatment received.

Key words: Gastric cancer; Lymph node; Separate station pick up; Lymphadenectomy

Core tip: Lymph node retrieval in the operating theater after surgical resection is a common practice in Eastern Asia. When applied in the west, the procedure permits a higher number of lymph nodes to be detected, thus improving tumor staging. In the present multicenter study in which the participating centers used different surgical procedures, patients who were submitted to accurate lymph node pick up showed better survival than those were not. Although we are aware that this procedure cannot improve survival, we believe that it can identify patients submitted to a more accurate treatment.

Morgagni P, Nanni O, Carretta E, Altini M, Saragoni L, Falcini F, Garcea D. Lymph node pick up by separate stations: Option or necessity? *World J Gastrointest Surg* 2015; 7(5): 71-77 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i5/71.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i5.71

INTRODUCTION

Lymph node dissection has always been a subject of great debate. The extension of surgical lymphatic dissection[1], N stage definition in TNM or N ratio classifications[2-4], and the surgeon or pathologist's role in lymph node pick up are widely discussed issues, especially when few lymph nodes are retrieved, as frequently occurs in Western countries. In fact, although a low number of detected lymph nodes may indicate a lack of accuracy by the pathologist, it may also reflect limited surgical lymphatic dissection.

The accuracy of lymph node retrieval has an important impact on staging, and the number of retrieved lymph nodes is generally reported in multicenter studies to underline the kind of lymphatic dissection performed[5,6]. Moreover, the number of positive lymph nodes is related to the overall number of dissected lymph nodes and is considered a significant prognostic factor[2,4,5,7-10].

The main aim of this study was to verify whether immediate pick up and collection of lymph nodes by separate stations in a fresh gastric cancer specimen can improve the number of lymph nodes retrieved. We also evaluated whether an increased number of separate lymphatic stations sent for histological examination can identify patients adequately treated from a surgical point of view. Such an approach leads to better staging and facilitates the choice of subsequent cancer treatments.

MATERIALS AND METHODS

This retrospective study was carried out on 1203 consecutive gastric cancer patients radically resected during the period 2004-2008 in Area Vasta Romagna (AVR), a catchment area of 1100000 inhabitants with a high gastric cancer incidence compared to other Italian regions and western populations. Information on patients was retrieved from the hospital discharge records (HDR) of the seven main AVR hospitals. Patients were identified using the ICD-9 codes of the International Classification of Diseases. Focusing on a radical surgical approach, the sample was limited to patients with a primary diagnosis code of stomach cancer (151.x) and primary or secondary procedure codes of partial gastrectomy (43.6, 43.7, 43.81, 43.89) or total gastrectomy (43.91, 43.99)[11]. Data from the HDR database were merged in a deterministic record-linkage procedure with those from the Regional Death Registry and histological referrals. Prior to the analysis, data were anonymized, assigning a unique identifier code to each patient. Access to data was granted by the Regional Health Authority and the Department of Healthcare Management of AVR hospitals. The study was conducted in compliance with Italian legislation on privacy (Art.20-21, DL 196/2003) and approved by the Ethics Committee of each of the centers participating in the study.

Data from the pathological report of selected patients were reviewed by a surgeon (PM) and the following information was collected in a common database: exact number of lymph nodes removed; dissected stations sent to the pathologist; tumor size; site and macroscopic classification according to Japanese guidelines[2]; Lauren classification; microscopic resection line infiltration; total number of dissected and pathological lymph nodes; and T and N stage according to 7th UICC classification[3].

Patients with documented macroscopic metastases submitted to palliative treatments were excluded from the study, while those with only microscopic involvement not identified by surgeons were included. No information was available on the extension of surgical lymph node dissection and there were no common surgical or pathological guidelines for the 7 general hospitals. After surgery, patients underwent treatment in accordance with the guidelines of the hospital they attended.

Patients were subdivided into two groups to evaluate the correlation between the number of lymphatic stations picked up and the number of lymph nodes retrieved. In group A, only one formalin-fixed specimen per patient was sent to the pathologist who picked up lymph nodes separately from the greater and lesser curvature. Group B comprised patients for whom at least one more lymphatic station was separately removed on fresh stomach specimens and immediately fixed in formalin. Special attention was paid to pathological reports in which more than 6 separate stations were evaluated because in some cases this may indicate that some kind of lymphadenectomy has been performed. Patients with $\geqslant$ 16 lymph nodes dissected were considered as

Table 1 Patient characteristics *n* (%)

	All patients (*n* = 1112)	Group A (*n* = 401)	Group B (*n* = 711)	*P*
Gender				
Female	448 (40.29)	144 (35.91)	304 (42.76)	0.0254
Male	664 (59.71)	257 (64.09)	407 (57.24)	
Age (yr)				
≤ 75	621 (55.85)	176 (43.89)	445 (62.59)	< 0.0001
> 75	491 (44.15)	225 (56.11)	266 (37.41)	
Charlson score				
0	869 (78.15)	312 (77.80)	557 (78.34)	0.5067
1	195 (17.54)	68 (16.96)	127 (17.86)	
≥ 2	48 (4.32)	21 (5.24)	27 (3.80)	
Procedure				
Partial gastrectomy	674 (60.61)	257 (64.09)	417 (58.65)	0.0746
Total gastrectomy	438 (39.39)	144 (35.91)	294 (41.35)	
Lymph nodes				
N0	426 (38.45)	72 (43.22)	254 (35.77)	0.0126
N1	176 (15.88)	67 (16.83)	109 (15.35)	
N2	180 (16.25)	65 (16.33)	115 (16.20)	
N3a	200 (18.05)	63 (15.83)	137 (19.30)	
N3b	126 (11.37)	31 (7.79)	95 (13.38)	
Missing	4	3	1	
No. lymph nodes removed				
< 16	389 (34.98)	250 (62.34)	139 (19.55)	< 0.0001
≥ 16	723 (65.02)	151 (37.66)	572 (80.45)	
T				
T1	232 (20.86)	80 (19.95)	152 (21.38)	0.008
T2	162 (14.57)	59 (14.71)	103 (14.49)	
T3	317 (28.51)	94 (23.44)	223 (31.36)	
T4	401 (36.06)	168 (41.90)	233 (32.77)	
Margin		25	156	
Infiltrated	76 (8.16)	28 (7.45)	48 (8.65)	0.5111
Not infiltrated	855 (91.84)	348 (92.55)	507 (91.35)	
Missing	181			
Lauren classification				
Intestinal	807 (74.24)	291 (75.58)	516 (73.50)	0.4532
Diffuse/mixed	280 (25.76)	94 (24.42)	186 (26.50)	
Missing	25	16	9	

correctly classified on the basis of the new UICC TNM staging system[3].

The potential impact of the number of dissected specimens on survival was investigated by performing a separate sensitivity analysis for patients correctly staged with < 16 or ≥ 16 dissected lymph nodes. Overall survival was considered as outcome measure up to the last follow up on 31st December 2011.

Statistical analysis

We compared patient and tumor characteristics in the two groups using percentages and the χ^2 test. The Kaplan-Meier method was used to estimate long-term survival between groups of patients and the log-rank test was used to compare survival curves. Taking into account all the information collected for the study, we calculated the adjusted hazard ratios and 95%CI using a Cox regression model to evaluate the impact on survival of the number of stations sent to the pathologist and the number of lymph nodes removed. Given the nature of the study design and the endpoints, a prior sample size was not calculated. All tests were two-sided with a significance level of < 0.05. No multiplicity test correction was done. All statistical analyses were performed using SAS 9.3 software for Windows.

RESULTS

One thousand two hundred and three pathological reports of patients submitted to radical resection for gastric cancer from 2004 to 2008 were retrieved from the 7 AVR general hospital databases. Ninety-one (7.6%) patients were excluded because the pathological report described gastric diseases other than cancer or surgical procedures other than radical gastrectomy. Clinical and pathological characteristics of the remaining 1112 patients are presented in Table 1. No significant differences were observed between either group of patients in terms of Charlson comorbidity index, type of gastrectomy performed, infiltrated margins and Lauren classification. Conversely, a significant difference was found with respect to age, gender, T or N stage and number of retrieved lymph nodes.

Relation between the 2 patient groups and retrieved lymph nodes

Group A comprised 401 patients and group B, 711 patients. Considering the number of dissected lymph nodes in the 2 groups, 62.3% of group A patients could not be adequately staged with the TNM classification because of insufficient lymph node retrieval (< 16 lymph nodes). Conversely, in group B (separate dissection), an insufficient number of lymph nodes was retrieved in only 19.4% of patients. This difference was significant (P < 0.0001). As the difference in the number of lymph nodes removed (< 16 *vs* ≥ 16) was not statistically significant in multivariate analysis, this variable was removed from the model by a stepwise procedure (Table 2).

Relation between number of picked up stations and survival

An overall survival of 35.6 mo (95%CI: 31.7-42.7) was observed for the entire case series, with a median follow up of 69 mo. With respect to the number of removed stations, the separate specimen group B showed significantly higher survival rates than the A group [46.1 mo (95%CI: 36.5-56.0) *vs* 27.7 mo (95%CI: 21.3-31.9); P = 0.0001] (Figure 1). Furthermore, in the multivariate model, which included all the available prognostic factors, group A patients showed a higher risk of death than those in group B (HR = 1.24; 95%CI: 1.05-1.46). Of note, the 264 patients in the latter group for whom more than 6 separate stations (4 more than in group A) were considered showed the best survival rates with a median survival of 56.7 mo (95%CI: 44.43-56.7; P < 0.0001).

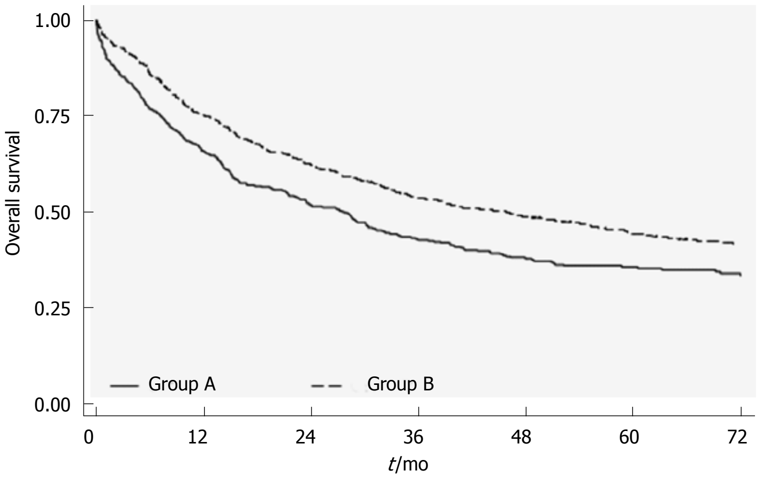


Figure 1 Overall survival of the study groups.

Table 2 Hazard ratios and 95%CI from multivariate Cox regression models

Parameter		HR	95%CI		P
No. specimens sent to pathologist	Group A *vs* Group B	1.239	1.053	1.458	0.0098
Gender	M *vs* F	1.235	1.046	1.457	0.0127
Age, yr	> 75 *vs* ≤ 75	2.190	1.858	2.582	< 0.0001
T	2 *vs* 1	1.202	0.843	1.715	0.3087
	3 *vs* 1	1.957	1.438	2.663	< 0.0001
	4 *vs* 1	3.410	2.518	4.618	< 0.0001
N	+ *vs* -	2.166	1.753	2.676	< 0.0001
Type of procedure	Total *vs* partial	1.327	1.132	1.556	0.0005
Lauren classification	Diffuse-mixed *vs* intestinal	1.256	1.051	1.500	0.0119

HR: Hazard ratios.

Survival in group A patients with a sufficient number of retrieved lymph nodes

In group A, overall survival was significantly higher in patients with < 16 lymph nodes retrieved than in those with ≥ 16 lymph nodes, whereas in the separate specimen group B no difference was observed between patients with < 16 or ≥ 16 lymph nodes (Figure 2). The number of positive lymph nodes in group A patients with ≥ 16 lymph nodes retrieved was twofold higher that of negative lymph nodes ($P < 0.001$). In contrast, group B patients with ≥ 16 retrieved lymph nodes did not show such a different distribution of positive lymph nodes ($P = 0.067$) (Table 3). However, in multivariate analysis the interaction term between group and number of lymph nodes retrieved was not statistically significant, indicating no difference in the risk of death between patients with < 16 or ≥ 16 lymph nodes in either group.

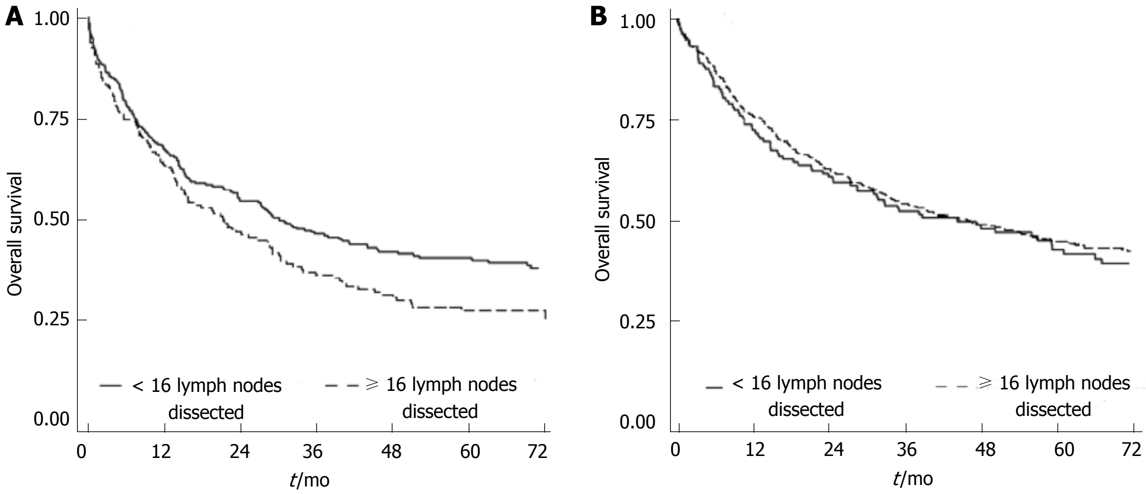
DISCUSSION

The extension of lymphadenectomy and the number of lymph nodes to remove for correct gastric cancer staging is still matter of great debate. The UICC TNM 7th edition classification considers 16 lymph nodes as the minimum number required for N staging[3], independently of lymphatic station dissection. The N ratio classification states that fewer nodes suffice, but even though lower sensitivity has been reported when fewer lymph nodes are dissected, the most effective minimum number has yet to be defined[4].

Lymph node dissection has finally been acknowledged as a crucial practice in the west and several studies have reported better results for patients treated with D2 dissection[12,13]. However, an important problem associated with the type of lymphadenectomy performed is that of non compliance (less extensive dissection than specified) and contamination (more extensive dissection than specified)[14]. All these factors must be taken into consideration when a multicenter study is proposed in order to standardize patients operated on in different institutions and to facilitate the comparison of results.

Increasing interest is being shown in the creation of large international databases to collect information on patients undergoing surgical treatment in different countries. Although an interesting initiative, the different approach taken to lymphadenectomy in different countries could represent a problem. The most widely proposed index to verify the quality of lymphadenectomy and the extension of lymph node dissection is the number of retrieved lymph nodes[5,6], but this alone is probably not enough to confirm the correctness of treatment. In their 1998 multicenter study, Estes *et al*[15] observed a significant survival benefit for patients who had a post-surgery histology report clearly supporting a curative resection compared to those whose histologic documentation was insufficient to support such a conclusion.

The present work focused on patients who were part of a previous retrospective cohort study[16] carried out in 7 hospitals within the same area where there are no common surgical or pathological guidelines. We evaluated the relationship between the number of retrieved lymph nodes, number of dissected lymphatic



	n	Events	Median OS (95%CI)	*P*		*n*	Events	Median OS (95%CI)	*P*
< 16 lymph nodes dissected	250	153	31.10 (23.44-43.97)	0.0194		139	81	47.21 (28.50-66.03)	0.5275
≥ 16 lymph nodes dissected	151	111	21.34 (14.03-29.02)			572	314	46.13 (36.50-56.79)	

Figure 2 Overall survival according to the number of lymph nodes retrieved in each study group. A: The stomach specimen was immediately formalin-fixed and sent to the pathologist. Patients with < 16 lymph nodes retrieved showed better survival when only 2 stations were dissected; B: Lymph nodes were picked up after surgery and fixed for separate stations. No difference in survival was seen in either group (< 16 or ≥ 16 lymph nodes removed) when > 2 stations were dissected.

stations and survival without, however, having any information on surgical lymphadenectomy. Whilst there were some dissimilarities between the 2 groups, *i.e.,* group B included younger patients, more T3 than T4 cases and higher lymph node involvement than group A, all patients were considered radically resected and comparable. We also assessed whether the pathological report could represent a sort of surgical quality index.

Relation between group A patients and retrieved lymph nodes

The first interesting result from our study was that an insufficient number of lymph nodes was obtained in the majority of group A patients. The removal of only one fixed specimen is normal practice in D0 dissection and several authors have reported that D0 and D1 dissections frequently do not permit correct staging[17]. Although we cannot be certain whether a low number of collected lymph nodes was due to insufficient lymphadenectomy or to difficult retrieval from formalin-fixed specimens, we can confirm that an increased number of picked up lymph node stations was correlated with a higher number of retrieved lymph nodes.

Relation between number of lymph nodes and survival

In 2006, Coburn *et al*[18] observed better survival rates in radically resected patients when a higher number of lymph nodes were collected. This result was confirmed for all stages but was more evident for stages I and II. Survival rates in Coburn's study were positively modified by stage migration when the number of lymph nodes was > 15, but multivariate analysis also suggested an independent role for the number of nodes retrieved[18]. In our study, although patients with ≥ 16 lymph nodes removed showed better survival in univariate analysis, this was not confirmed in multivariate analysis.

Relation between dissected stations and survival

Another interesting result from our study was the correlation between the number of dissected lymph node stations and survival. The survival rate of group B patients who had at least one more lymphatic station separately removed was significantly higher than that of group A (P < 0.0001) and increased when 6 or more separate stations were dissected. A description of > 2 stations in the pathological report was identified as an independent prognostic factor in multivariate analysis. Interestingly, this finding was independent of N stage and consequently was not influenced by the Will Rogers phenomenon. Multivariate analysis did not confirm the same independent role of the "> 2 stations" variable when < or ≥ 6 stations were considered [HR = 1.23; P = 0.075 (95%CI: 0.97-1.54)].

The dissection of separate stations only represents a technical procedure and cannot be considered as a therapeutic option designed to improve survival. However, this type of dissection of fresh specimens probably identifies patients treated in centers of excellence in gastric cancer. Thus, survival rates could potentially be improved by lymphadenectomy rather than by post-surgical procedures, and the number of dissected stations could be used as a quality index in multicenter studies.

Table 3 Lymph node status distribution by number of lymph nodes dissected and groups considered in the study *n* (%)

	Group A		Group B	
	< 16 lymph nodes[1] dissected	≥ 16 lymph nodes dissected	< 16 lymph nodes dissected	≥ 16 lymph nodes[2] dissected
Lymph nodes -	132 (76.7)	40 (23.3)	59 (23.2)	195 (76.8)
Lymph nodes +	115 (50.9)	111 (49.1)	80 (17.5)	376 (82.5)
	P < 0.0001		*P* = 0.067	

[1]Information missing for 3 patients; [2]Information missing for 1 patient.

Survival of group A patients with a sufficient number of retrieved lymph nodes

Notably, group A patients with ≥ 16 lymph nodes removed showed significantly worse survival rates than those with < 16 lymph nodes resected. This may have been due to the different distribution of positive lymph nodes in patients with ≥ 16 lymph nodes retrieved in the two study groups. We found a higher number of positive lymph nodes in the ≥ 16 lymph node group, probably because pathological lymph nodes are often larger and easier to remove (Table 3). Although these patients were better staged because an adequate number of lymph nodes were available for TNM classification, they had a poorer prognosis. This suggests that the number of retrieved lymph nodes alone cannot identify correctly treated patients from a surgical point of view. An adequate number of dissected stations must be removed.

Separate lymphatic station dissection of fresh specimens increases the number of nodes retrieved, permitting better staging. This procedure, common in centers specializing in the treatment of gastric cancer, permits a greater quality control of lymphadenectomy and provides more standardized data for large databases. In our experience, ≥ 16 lymph nodes retrieved identified patients with a poor prognosis when stations were not picked up separately, suggesting that the number of lymph nodes removed cannot itself be considered as a quality indicator. Unfortunately, this is a retrospective study and no information was available on the extension of the lymphadenectomy performed or on postoperative therapy. However, our statistical analyses confirmed the above correlations. Thus, although separate station dissection in fresh specimens is a time-consuming procedure and not yet a requisite of the TNM classification, its potential importance cannot be ignored.

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COMMENTS

Background

Lymph node dissection is performed as part of the surgical resection of gastric cancer to stage lymphatic diffusion. In Eastern Asia, separate station lymph node dissection is routinely carried out in the operating theatre immediately after tumor resection, whereas in the West stomach specimens are formalin-fixed *en bloc* and sent to the pathologist for evaluation.

Research frontiers

In the area of gastric cancer, the current research hotspot is how to improve staging accuracy.

Innovations and breakthroughs

Lymph node pick up by separate stations could be an indicator of patients treated at centers of excellence in gastric cancer.

Applications

Accurate lymph node pick up by separate stations leads to better tumor staging and facilitates the choice of subsequent treatments.

Terminology

Lymph node pick up is a procedure performed by a surgeon or pathologist after surgical resection to detect all the lymph nodes in the removed specimen.

Peer-review

An interesting article in its field, focusing on lymph node dissection by separate stations which is a common procedure in East Asia. This manuscript demonstrates that patients with separate lymph node station have better survival than those without.

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CASE REPORT

Pancreatectomy and splenectomy for a splenic aneurysm associated with segmental arterial mediolysis

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Author contributions: Matsuda Y, Sakamoto K and Nishino E designed the report and wrote the paper; Kataoka N, Yamaguchi T, Tomita M, Kazi A, Shinozaki M and Makimoto S provided treatment.
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Ethics approval: The study was reviewed and approved by the Institutional Review Board of Kishiwada Tokushukai Hospital for ethical issues.
Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.
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Abstract

Segmental arterial mediolysis (SAM) is characterized by intra-abdominal, retroperitoneal bleeding or bowel ischemia, and the etiology is unknown. A 44-year-old man complaining of abdominal pain was admitted to our hospital. He had been admitted for a left renal infarction three days earlier and had a past medical history of cerebral aneurysm with spontaneous remission. The ruptured site of the splenic arterial aneurysm was clear *via* a celiac angiography, and we treated it using trans-arterial embolization. Unfortunately, the aneurysm reruptured after two weeks, and we successfully treated it with distal pancreatomy and splenectomy. We recommended a close follow-up and prompt radiological or surgical intervention because SAM can enlarge rapidly and rupture.

Key words: Re-rupture; Segmental arterial mediolysis; Trans-arterial embolization; Spontaneous remission; Splenic artery aneurysm

Core tip: Segmental arterial mediolysis (SAM) related to intra-abdominal, retroperitoneal bleeding or bowel ischemia has a mortality approaching 25%-50%. We treated the splenic artery aneurismal re-rupture associated with SAM after trans-catheter arterial embolization with a distal pancreatomy and splenectomy. We recommend close follow-ups and prompt radiological or surgical intervention because SAM can increase rapidly and rupture.

Matsuda Y, Sakamoto K, Nishino E, Kataoka N, Yamaguchi T, Tomita M, Kazi A, Shinozaki M, Makimoto S. Pancreatectomy and splenectomy for a splenic aneurysm associated with segmental arterial mediolysis. *World J Gastrointest Surg* 2015; 7(5): 78-81 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i5/78.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i5.78

INTRODUCTION

The first case of a distinct arterial lesion in the large abdominal muscular arteries was described by Slavin *et al*[1] in 1976 and was termed segmental arterial mediolysis (SAM) in 1995[1,2]. Alterations of SAM stem from two separate lesions: mediolysis and a tear that separates the outer medial muscle from the adventitia[3]. As a result, sudden hemorrhage due to an aneurysm rupture or dissection occurs in the abdomen, retroperitoneum, or brain[3,4]. Cases of SAM that are complicated by intra-abdominal hemorrhage have mortality rates approaching 25%-50%[5,6]. In this report, we present a case of SAM, which was associated with trans-arterial embolization (TAE) and surgical resection for a splenic artery aneurysm that had enlarged rapidly within a short time period.

CASE REPORT

A 44-year-old man had been previously admitted to the hospital for treatment of a left renal infarction. He was received balloon angioplasty because the ventral branch of the left renal artery had been dissected. Three day after hospital discharge, he returned to the hospital due to complaints of abdominal pain. The pain gradually worsened after discharge. This patient had a past medical history of cerebral aneurysm with spontaneous remission (with no family history). When he arrived, his vital signs indicated hypotension (96/62 mmHg); normal sinus rhythm (81 beats/min); and normal body temperature (36.9 ℃). A physical examination revealed only abdominal tenderness. The laboratory findings indicated inflammation (white blood cell count: 13300/μL, C-reactive protein: 3.133 mg/dL) and no anemia (hemoglobin: 14.4 g/dL, hematocrit: 40.4%). Enhanced computed tomography (CT) demonstrated a 20 mm aneurysm of the splenic artery with extravasation and hematoma accumulated around the retroperitoneum (Figure 1). In addition, the CT scan revealed other aneurysms, which had a string of beads appearance, in the common hepatic, left gastric, gastroduodenal, left renal, and both internal iliac arteries. These aneurysms were not present two weeks earlier (Figure 2).

We confirmed the ruptured site of the splenic arterial aneurysm *via* celiac angiography. The microcatheter was inserted at the distal site of the aneurysm, and the ruptured aneurysm was successfully managed by TAE. After the intervention, the aneurysm was not enhanced, and surgical treatment was avoided (Figure 3). After TAE, we followed up the aneurysms *via* enhanced CT scanning, and there was no extravasation or enlargement. Unfortunately, this patient had abdominal pain again two weeks later because the aneurysm re-ruptured. We performed an emergency operation due to unstable vital signs. Additionally, he underwent distal pancreatectomy and splenectomy because the aneurysm was located within the pancreatic body, and the resection of splenic artery was difficult. The postoperative complications included pancreatic fistula and intra-abdominal abscess. On day 9, he was treated with an antimicrobial agent (Vancomycin: 1 g/d) for 10 d because the abscess culture demonstrated coagulase negative staphylococcus. In addition, we performed abscess drainage for 28 d postoperatively. He was discharged 30 d after surgery.

Histopathology revealed an adventitial-medial junction created by separation of the media from the adventitia and organized thrombi deposited at the site. There was no infiltration of inflammatory cells and no arterial sclerosis (Figure 4).

DISCUSSION

Splanchnic artery aneurysms (SAAs) are relatively rare and most commonly occur in the splenic artery (60%)[7]. Multiple SAAs are very rare (3.6%-15% of patients with visceral aneurysms). When multiple SAAs are present, other disorders, such as SAM, should be suspected[8]. SAM may also be accompanied by coronary arterial lesions or intra-cranial vascular lesions[9]. Michael *et al*[10] reported that the vascular changes completely vanished after treatment of un-ruptured aneurysms. This patient had 6 SAAs in different sites, and we clinically considered that the previous cerebral aneurysm with spontaneous remission was caused by SAM. Uchiyama *et al*[11] suggested that clinical criteria were required because some patients are treated with embolization. Nishikawa *et al*[8] clinically diagnosed their patient with SAM based on the following: (1) multiple SAAs; (2) middle to old age; (3) non-inflammatory, non-atherosclerosis, and non-genetic backgrounds; (4) radiological features demonstrate a bead-like appearance, irregular dilatation and stenosis; and (5) acute vessel remodeling[8].

The differential diagnosis of SAM includes arteriosclerotic disease, infection, connective tissue disorders (*e.g.*, polyarteritis nodosa), congenital disease (*e.g.*, Marfan syndrome), and especially fibromuscular dysplasia (FMD). FMD is primarily observed in young females.

The histological findings in SAM also overlap with FMD. Lie *et al*[12] proposed that SAM might represent a variant of FMD. Slavin *et al*[2] suggested that it might represent a precursor to certain types of FMD. They did not wish to imply that all cases of FMD are preceded by SAM and described that SAM demonstrated a partial to total loss of media with replacement fibrosis and remained a non-specific aneurysm[2]. In this patient, the pathological findings revealed an adventitial-medial junction created by the separation of the media from the adventitia. As a result, we diagnosed SAM based on the clinical and pathological findings.

Treatment of SAM involves embolization, surgical bypass, or resection of the injured arteries. Ryan *et al*[13] described the first case of coil embolization. Since then, successful endovascular management is

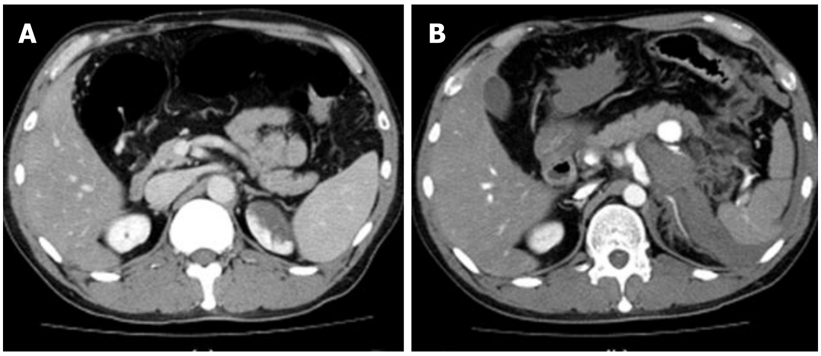

Figure 1 Enhanced computed tomography demonstrated no splenic artery aneurysm two weeks prior to the hospital visit (A) and a 20 mm aneurysm of the splenic artery and hematoma accumulated around the retroperitoneum (B).

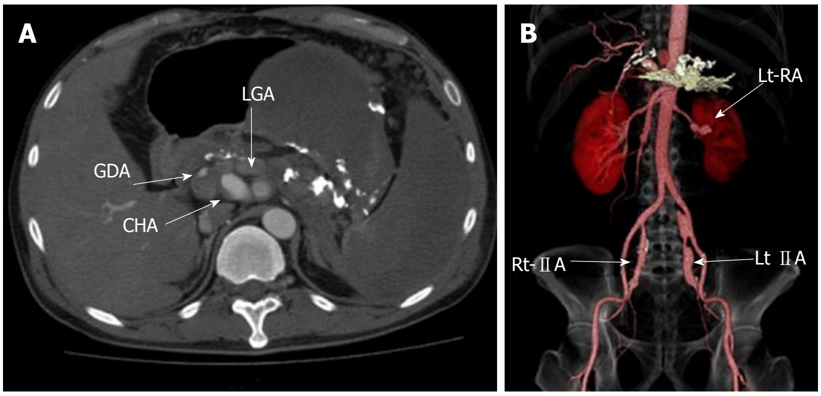

Figure 2 Enhanced computed tomography demonstrated six splanchnic artery aneurysms. GDA: Gastric duodenal artery; LGA: Left gastric artery; CHA: Common hepatic artery; Lt-RA: Left renal artery; Rt-IIA: Right internal iliac artery; Lt-IIA: Left internal iliac artery.

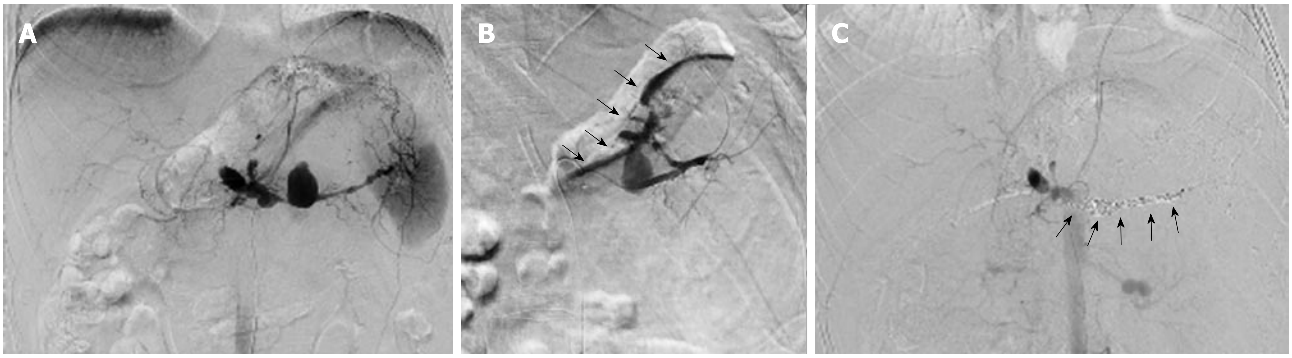

Figure 3 Celiac angiography revealed aneurysms in the splenic, left gastric, and common hepatic arteries (A), splenic angiography demonstrated extravasation from the splenic artery aneurysm (arrow) (B), and successful microcoil embolization of the ruptured splenic artery aneurysm with complete cessation of flow within the aneurysm (arrow) (C).

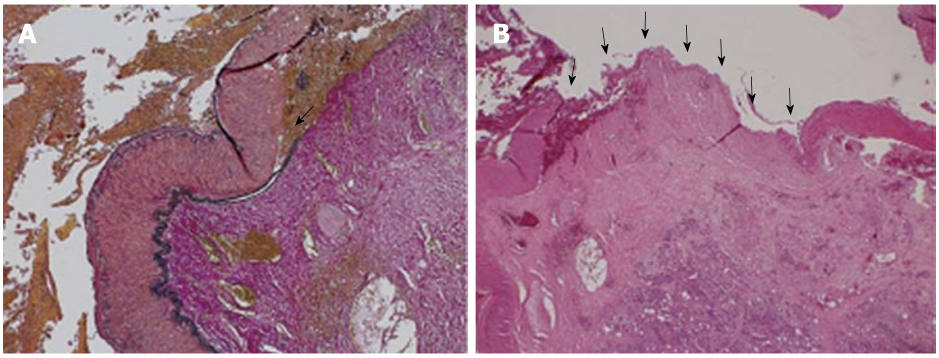

Figure 4 Histopathology revealed an adventitial-medial junction created by separation of the media from the adventitia and organized thrombi deposited at the site. A: Organized thrombi were deposited at the adventitial-medial junction created by the incipient separation of the media from the adventitia (arrow). Elastica Van Gieson stain; magnification × 4; B: Mediolysis can involve the entire medial muscle with preservation of the intima and internal elastica (arrow). The overlying adventitial-medial junction is suffused with fibrin. Hematoxylin Eosin stain; Magnification × 2.

common, and TAE is successful in 88% of attempted cases with no reported mortality. Only 3 cases have reported unsuccessful outcomes with endovascular treatment requiring open surgical intervention[6]. One case had difficulties in the catheterization, and two cases were hemodynamically unstable. We considered that the angiography did not demonstrate extravasation because our patient was hemodynamically unstable. As a result, endovascular management serves as a reliable, minimally invasive treatment option and may also provide a temporary solution before definitive surgery at a later date[6].

Although SAM related to intra-abdominal, retroperitoneal bleeding or bowel ischemia has a mortality rate approaching 25%-50%[5,6], the surgical intervention for re-rupture after TAE was successful in this patient. SAAs (except splenic artery) are followed up with a short time period because the risk of rupture is low.

In conclusion, close follow-up is necessary for SAAs when SAM is suspected. If necessary, radiological or surgical intervention should be promptly pursued because multiple SAAs associated with SAM may increase rapidly and rupture.

COMMENTS

Case characteristics

A 44-year-old male with a history of cerebral aneurysm with spontaneous remission had abdominal pain.

Clinical diagnosis

Segmental arterial mediolysis (SAM).

Differential diagnosis

Arteriosclerotic disease, infection, connective tissue disorders (*e.g.*, polyarteritis nodosa), congenital disease (*e.g.*, Marfan syndrome), and especially fibromuscular dysplasia.

Laboratory diagnosis

White blood cell count was 13300/μL and C-reactive protein was 3.133 mg/dL.

Imaging diagnosis

Enhanced computed tomography demonstrated a 20 mm aneurysm of the splenic artery with extravasation.

Pathological diagnosis

Histopathology revealed an adventitial-medial junction created by separation of the media from the adventitia and organized thrombi deposited at the site.

Treatment

The authors performed distal pancreatectomy and splenectomy because the aneurysm was located within the pancreatic body, and the resection of splenic artery was difficult.

Related reports

Rerupture of a splenic artery aneurysm, associated with segmental arterial mediolysis after transcatheter arterial embolization is rare.

Term explanation

SAM stem from mediolysis and a tear that separates the outer medial muscle from the adventitia.

Experiences and lessons

Close follow-up is necessary for splanchnic artery aneurysms when SAM is suspected.

Peer-review

Good management of an unusual situation.

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CASE REPORT

Thoracoabdominal pseudocyst of pancreas: An rare location, managed by retrocolic retrogastric Roux-en-Y cystojejunostomy

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Author contributions: Kamble RS, Gupta R, Gupta AR evaluated the patient, performed the surgery, designed the paper; Kothari PR guided during surgery and preparation paper; Dikshit KV, Kekre GA, Patil PS collected the data and did literature search.

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Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompaying images.

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Abstract

Pseudocyst formation is a common complication of acute and chronic pancreatitis. Most common site of pseudocyst is lesser sac; mediastinal extension of pseudocyst is rare. Other possibilities of posterior mediastinal cyst must be considered. This patient presented with computed tomography abdomen with thorax showing a large thoraco-abdominal pseudocyst with right sided pleural effusion. It was confirmed to be pancreatic pseudocyst by analyzing fluid for amylase and lipase during surgery. In our patient, the pseudocyst was accessible transabdominaly. Cystogastrostomy was not possible as it was causing twisting of cardio-esophageal junction; we did retrocolic and retrogastric Roux-en-Y cystojejunostomy. Only two such cases were reported in literature.

Key words: Thoracoabdominal pseudocyst; Retrocolic; Retrogastric; Roux-en-Y loop; Cystojejunostomy

Core tip: Thoraco-abdominal pseudocyst is rare location of pancreatic pseudocyst. Other possibilities of posterior mediastinal cyst must be considered. Internal drainage is a definitive management but will be difficult. Retrocolic retrogastric Roux-en-Y cystojejunostomy is feasible option. Only two such cases were reported in literature.

Kamble RS, Gupta R, Gupta AR, Kothari PR, Dikshit KV, Kekre GA, Patil PS. Thoracoabdominal pseudocyst of pancreas: An rare location, managed by retrocolic retrogastric Roux-en-Y cystojejunostomy. *World J Gastrointest Surg* 2015; 7(5): 82-85 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i5/82.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i5.82

INTRODUCTION

Posterior mediastinal cysts can be foregut duplication cyst, pancreatic pseudocyst, lymphatic malformation, cystic teratoma, and cystic neuroblastoma. Pseudocyst formation is a common complication of acute and chronic pancreaitis. Mostly pseudocyst occurs in lesser sac or peripancreatic region. Mediastinal extension of pseudocyst is rare.

We report this case of rare location of pseudocyst *i.e.,* thoraco-abdominal without any ductal communication. About 50 cases of mediastinal pseudocyst has been reported in literature[1]. In our patient, the pseudocyst was accessible from transabdominaly. Cystogastrostomy was not possible as it was causing twisting of cardio-esophageal junction; we did retrocolic retrogastric Roux-en-Y cystojejunostomy.

CASE REPORT

A 10-year-old girl was referred from peripheral center. She was investigated there for dull aching pain in epigastrium, which was for 3 to 4 mo, and pain on right side of chest. She had undergone a computed tomography (CT) scan abdomen and thorax there, which shows 7.3 cm × 4.6 cm × 4.1 cm large loculated collection in posterior mediastinum, right paravertebral region, extending through esophageal hiatus abutting the posterior surface of Right atrium, Inferior vena cava, causing displacement of esophagus. Pancreas was smaller and duct was dilated without any obvious ductal communication (Figures 1 and 2). Patient has also right sided moderate pleural effusion on chest X-ray. She was treated conservatively there. Pleural fluid study was normal, fluid amylase and lipase were within normal limit. Patient referred to us after 2 mo for recurrent abdominal pain. Hematological investigations were normal. Serum amylase and lipase were within normal limit. As possibility of esophageal duplication cyst can't be ruled out we did barium swallow study which revealed lesion is indenting lower esophagus (Figure 3). Ultrasonography showed similar findings about paraesophageal collection, and right sided mild pleural collection. We did magnetic resonance cholangiopancreatography (MRCP), which showed mild dilatation of multiple side branches of pancreatic duct in tail region without any peripancreatic collection with features of resolving pancreatitis and large loculated collection in right paravertebral region, with a tail extending down (Figure 4).

As the radiological investigations didn't demonstrate definitive communication with pancrease or esophagus, nature of cyst could not be confirmed. Hence exploratory laparotomy followed by sos procedure was planed. After optimization, patient is posted for exploratory laparotomy. On exploration, there was no collection in lesser sac or peripancreatic region. Pancreas was firm on palpation. Dissection was done at the esophageal hiatus. On deep palpation, we felt a fluid filled structure at hiatus, structure delineated, cardio-esophageal junction formed one of the cyst walls and fluid was aspirated. Aspirate fluid was deep amber colored and sent for analysis intraoperative, (fluid amylase-1735 somogyi U, fluid lipase-101436 IU). So it was confirmed to be a pancreatic pseudocyst. A 2 cm × 2 cm cyst wall was cut (Figure 5). Then we had two option either gastrocystostomy or jejunocystostomy. We thought of doing gastrocystostomy but it was not possible as it was causing twisting of cardio-esophageal junction. Hence decided to do cystojejunostomy. Roux-en-Y loop of jejunum brought retrocolic and retrogastric up to the cyst and cystojejunostomy done (Figure 6). Cyst wall biopsy was suggestive of pseudocyst of pancreas without any evidence of malignancy. Patient was given somatostatin perioperative period. Post op recovery was uneventful, pleural effusion resolved in 15 d. Patient is on pancreatic enzymes supplementation and is asymptomatic, in regular follow up.

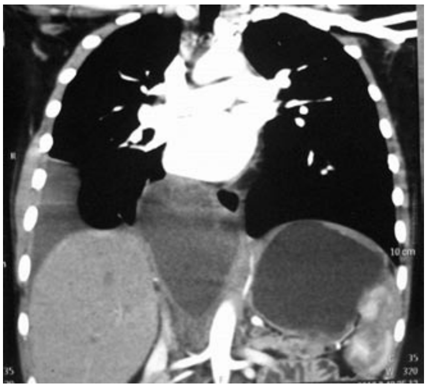

Figure 1 Computed tomography thorax and abdomen showing well defined thoraco-abdominal cyst.

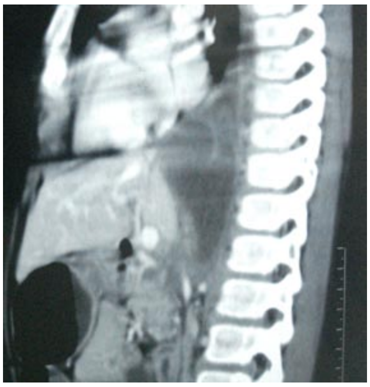

Figure 2 Lateral view of computed tomography thorax and abdomen showing extension of cyst in posterior mediastinum and abdomen.

DISCUSSION

Posterior mediastinal cysts can be foregut duplication cyst, pancreatic pseudocyst, lymphatic malformation, cystic teratoma, and cystic neuroblastoma.

Figure 3 Barium study-showing smooth indentation li lower esophagus with right sided.

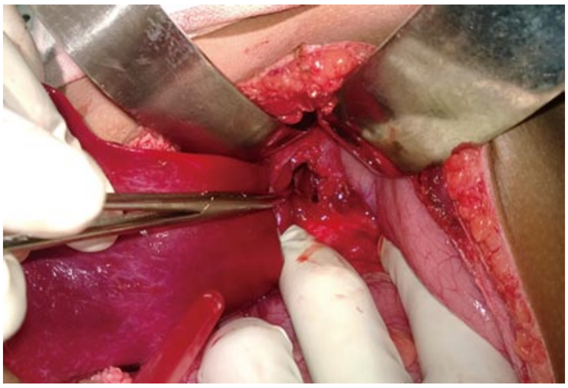

Figure 5 Intra operative photograph showing opening made in the anterior wall of pseudocyst.

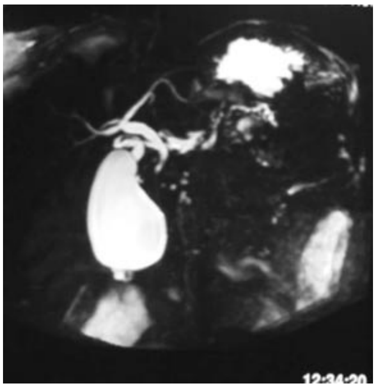

Figure 4 Magnetic resonance cholangiopancreatography, showing mild dilatation of multiple side branches of pancreatic duct in tail region without any peripancreatic collection.

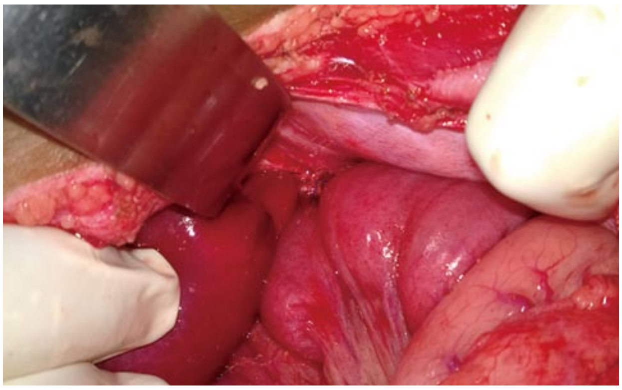

Figure 6 Intraoperative photograph showing completed anastomosis, Roux-en-Y loop seen behind stomach.

Pseudocyst formation is a common complication of acute and chronic pancreatitis. Common site of pseudocyst are lesser sac and peripancreatic region. Thoracic/ mediastinal extension of pseudocyst is a rare. About 50 cases have been reported in literature of mediastinal extension[1]. Mediastinal pancreatic pseudocyst was first described in 1951[2]. In acute pancreatitis, fluid gets collected and due to inflammatory process, it gets walled up with granulation tissue and connective tissue. Pancreatic fluid in retroperitoneal space tracts into mediastinal space through aortic, esophageal hiatus and forms mediastinal, thoraco-abdominal pseudocyst. In our patient, it was a thoraco-abdominal. Most of such patients have pleural effusion. Ectopic pancreatic tissue with formation of pseudocyst is also reported in literature[3].

The most common causes of pseudocyst in children are trauma and infection, other causes are congenital anomalies, drug induced[4]. Anomalous pancreatic duct, anomalous pancreaticobiliary junction, pancreatic divisum, annular pancrease causes recurrent pancreatitis.

Symptoms are mainly due to compression or invasion of adjacent structures by pseudocyst, *i.e.*, chest or abdominal pain, dysphagia, dyspnea, pseudo achalasia, weight loss[1,5].

In absence of any peripancreatic collection/communication, these cysts are difficult to say as a pseudocyst of pancrease. Chest X-ray is not diagnostic but can show pleural effusion. For diagnosis CT is better than Ultrasonography, and MRCP is necessary for ductal anatomy. Endoscopic ultrasound gives more information about pancreas and duct if any communication. Endoscopic ultrasound guided aspiration of fluid and fluid analyses will the definitive diagnostic measure[6].

In all patients primary management of pancreatitis, stabilization of patient is must. Spontaneous resolution pseudocyst occurs in about 50% of case and complications can occur in 5%-40% cases[7]. If any ductal obstruction or communication with cyst is there it should be managed first with ERCP stenting. Surgical options available for management of pseudocyst are internal/external drainage. Internal drainage includes cystogastrostomy, Roux-en-Y cystojejunostomy (open/ laparoscopic/endoscopic). For Mediastinal pseudocyst these options are not available. A newer technique of endoscopic transmural stenting is reported with variable success rate[7,8]. Endoscopic/thoracoscopic aspiration of pseudocyst is also reported[8]. Endoscopic ultrasound is now increasingly being used for transmural endoscopic drainage. Cysto-gastrostomy for complex mediastinal cyst was reported by Sadat *et al*[9].

Only two cases of transdiaphragmatic Roux-en-Y cysto-jejunostomy in adult for mediastinal pseudocyst were reported in literature[10,11]. Kotsis *et al*[10] used thoraco- abdominal approach.

In our patient the nature and etiology of cyst could not be confirmed preoperatively by radiological investigation. Due to presence of major vessels near the cyst and thoraco-abdominal extension of cyst, radiologist could not get a safe window for percutaneous needle aspiration. Endoscopic ultrasound or endoscopic needle aspiration might be helpful, but as such facility was not available at our hospital, diagnostic laparotomy was decided.

On exploration the diagnosis of pseudocyst of pancrease was confirmed. Though the major part was intrathoracic lower part of the cyst in accessible through abdomen. Abdominal part was the most dependent part and cystojejunostomy with Roux-en-Y loop was feasible.

We report this case of rare location of pseudocyst of pancrease, *i.e.*, thoraco-abdominal in 10 years girl managed successfully with retrocolic retrogastric Roux-en-Y cystojejunostomy.

COMMENTS

Case characteristics

Ten years female child had dull aching pain in epigastrium for 3-4 mo.

Clinical diagnosis

Patient had dull aching pain in abdomen, per abdominal examination was normal and had decreased air entry on right side.

Differential diagnosis

Pseudocyst of pancrease, esophageal duplication.

Laboratory diagnosis

Hematological investigations, serum amylase and lipase were within normal limit. intraoperative fluid analysis- fluid amylase-1735 somogyi U, fluid lipase-101436 IU.

Imaging diagnosis

Computed tomography suggested 7.3 cm × 4.6 cm × 4.1 cm size collection in posterior mediastinum, extending through esophageal hiatus likely to be pseudocyst of pancrease or esophageal duplication.

Pathological diagnosis

Cyst wall biopsy was suggestive of pseudocyst of pancreas without any evidence of malignancy.

Treatment

Patient undergone surgery-exploratory laparotomy with retrocolic retrogastric Roux-en-Y cystojejunostomy and postoperative patient is on pancreatic enzymes supplementation.

Related reports

Only two cases of transdiaphragmatic Roux-en-Y cysto-jejunostomy in adult for mediastinal pseudocyst were reported in literature, Kotsis *et al* used thoraco-abdominal approach.

Term explanation

Retrocolic retrogastric Roux-en-Y cystojejunostomy is measure to treat thoraco-abdominal pseudocyst.

Experiences and lessons

In the patient the though the major part was intrathorasic lower part of the cyst in accessible through abdomen and retrocolic retrogastric cystojejunostomy with Roux-en-Y loop was feasible.

Peer-review

The author reported a case who had a pseudocyst locating retoroperitoneo-retormediastinal space and managed by retrocolic retrogastric Roux-en-Y cystojejunostomy. The manuscript is very interesting.

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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Chandra K Pandey, MD, Professor, Department of Anaesthesiology, Sgpgims Lucknow 226014, India

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MINIREVIEWS

Intraoperative blood loss in orthotopic liver transplantation: The predictive factors

Chandra Kant Pandey, Anshuman Singh, Kamal Kajal, Mandeep Dhankhar, Manish Tandon, Vijay Kant Pandey, Sunaina Tejpal Karna

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Author contributions: Pandey CK collected the references, conceived the concept, wrote the manuscript, revised and did the editing works; Singh A, Kajal K, Dhankhar M, Tandon M, Pandey VK and Karna ST wrote the manuscript, revised and did the editing works; all the above authors contributed equally in writing the manuscript, revising and did the editing works.

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Abstract

Liver transplantation has been associated with massive blood loss and considerable transfusion requirements. Bleeding in orthotopic liver transplantation is multifactorial. Technical difficulties inherent to this complex surgical procedure and pre operative derangements of the primary and secondary coagulation system are thought to be the principal causes of perioperative hemorrhage. Intraoperative practices such as massive fluid resuscitation and resulting hypothermia and hypocalcemia secondary to citrate toxicity further aggravate the preexisting coagulopathy and worsen the perioperative bleeding. Excessive blood loss and transfusion during orthotopic liver transplant are correlated with diminished graft survival and increased septic episodes and prolonged ICU stay. With improvements in surgical skills, anesthetic technique, graft preservation, use of intraoperative cell savers and overall perioperative management, orthotopic liver transplant is now associated with decreased intra operative blood losses. The purpose of this review is to discuss the risk factors predictive of increased intra operative bleeding in patients undergoing orthotopic liver transplant.

Key words: Liver transplantation; Intraoperative blood loss; Liver disease

Core tip: Liver transplantation has been associated with massive blood loss and considerable transfusion requirements. The bleeding in orthotopic liver transplantation is multifactorial such as etiology and severity of liver disease, preexisting coagulopathy,

previous abdominal surgeries, preoperative hematocrit, surgical techniques and methods of clamping, experience of surgical team, central venous pressure, the use of antifibrinolytics and procoagulants and use of point of care monitoring during the transplantation. The purpose of this review is to discuss the risk factors predictive of increased intra-operative bleeding in patients undergoing orthotopic liver transplant.

Pandey CK, Singh A, Kajal K, Dhankhar M, Tandon M, Pandey VK, Karna ST. Intraoperative blood loss in orthotopic liver transplantation: The predictive factors. *World J Gastrointest Surg* 2015; 7(6): 86-93 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i6/86.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i6.86

INTRODUCTION

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with decompensated end stage liver disease[1]. Historically, liver transplantation has been associated with massive blood loss and considerable transfusion requirements[2]. With improvements in surgical skills, anesthetic technique, graft preservation and overall perioperative management, OLT is now associated with decreased intra operative blood losses[3,4].

Though the origin of bleeding is multifactorial, technical difficulties inherent to this complex surgical procedure and pre operative derangements of the primary and secondary coagulation system are thought to be the principal causes of perioperative hemorrhage[5]. Intraoperative practices such as massive fluid resuscitation and resulting hypothermia and hypocalcemia secondary to citrate toxicity further aggravate the preexisting coagulopathy and worsen the perioperative bleeding. Blood loss during OLT, however remains highly variable. Rate of blood product transfusion may vary between median of two to 13 packed red blood cells (PRBC) units per patient[6].

Blood transfusion (BT) is an independent predictor of post transplant outcome and is associated with a significant increase in morbidity and mortality[7,8]. Intraoperative blood loss is a predictor of poor short and long-term prognosis immediately after LDLT. Excessive blood loss and transfusion during OLT are correlated with reduced graft survival and increased septic episodes and prolonged ICU stay[9].

The risk of allogenic blood transfusion extends beyond viral transmission and includes allergic reactions, alloimmunization, bacterial sepsis, transfusion related acute lung injury (TRALI), volume overload, graft *versus* host disease (GVHD), renal failure and immunosuppressive effects[10]. Persistence of soluble and cell associated antigens in the circulation of the recipient after allogenic blood transfusion is considered to result in immune down regulation[11]. Significant association between allogenic BT and immune suppression including graft survival, recurrence of malignancies, impaired cell mediated T-cell and natural killer (NK) cell activity and deterioration in liver regeneration has been shown by studies[12].

Preoperative identification of factors predictive of increased intra operative bleeding in patients undergoing OLT is useful not only for availability of blood products and initiation of blood salvage with the most appropriate strategy but also to consider the timing and advisability of transplantation.

From a comprehensive review of literature, we were able to identify the following factors associated with increased risk of intraoperative bleeding during OLT and liver resection.

PREOPERATIVE RISK FACTORS

Etiology of liver disease

The extent of resection and the size of tumor are predictive of perioperative blood transfusion[13]. Cockbain *et al*[14] concluded that hilar cholangiocarcinoma resections are a risk factor for excessive bleeding due to the technical difficulty as these resections may include lymph node dissection, caudate resection, resection and reconstruction of hepatic inflow. On the other hand, OLT for hepatocellular carcinoma (HCC) was found to be negative predictor for massive blood transfusion in a retrospective study by Cywinski *et al*[15].

Severity of liver disease

Assessment of severity of liver disease is most commonly done by Child Pugh Turcotte (CTP) and Model for end stage disease (MELD). Association of severity of liver disease with perioperative blood loss is controversial. Findlay *et al*[16], Massicotte *et al*[17], and Roullet *et al*[18] in their recent study concluded that it is not an independent predictor of bleeding and blood product requirement.

Contradictory to these findings, McCluskey *et al*[19] derived a risk index for the prediction of massive blood transfusion in OLT. In their derived risk index, two of the variables included in calculating the MELD score-preoperative creatinine and International Normalized Ratio (INR) were found to be independent predictors of bleeding, although the MELD score itself was less predictive. In consistence, Mangus *et al*[20] found high MELD scores to a one of the risk factors found to be significantly associated with increased bleeding and transfusion requirements. Frasco *et al*[3] also showed a positive association between MELD score and transfusion requirement during OLT. In 2006, a high MELD scores (> 30) was found to be significantly associated with increased bleeding and transfusion requirements compared to patients with low MELD scores (< 30)[21]. Higher MELD score was found to be highly statistically significant predictor of massive blood transfusion in a recent retrospective study by Cywinski *et al*[15]. Thus, if a MELD score is greater than 30 or patient is Child grade B or C, it is prudent to assume the probability of increased blood loss perioperatively even though studies show conflicting results.

Preexisting coagulopathy

Impaired hemostasis in patients with advanced liver disease is multifactorial. Predominant factors includes impaired coagulation factor synthesis, synthesis of dysfunctional coagulation factors, accelerated consumption of coagulation factors and platelets, splenomegaly causing platelet sequestration and consumption, altered clearance of activated coagulation factors including factors of the fibrinolytic pathway contributing to hyperfibrinolysis, Accelerated intravascular coagulation and fibrinolysis (AICF) and qualitative disorders of platelet function are all contributory[22,23].

Recent advances in the understanding of the coagulopathy in patients with liver disease have led to the concept of the rebalanced theory of hemostasis in these patients as alterations in both anti and procoagulant pathways balance each other in patients with liver disease[24].

It has been shown that correction of coagulation defects before the anhepatic phase is not necessary[25]. There is a relatively poor correlation between bleeding and laboratory indices of coagulation (PT/INR) in patients with chronic liver disease[22,23]. Pre transplant higher INR and lower platelet counts were found to be highly statistically significant predictors of higher intraoperative blood product usage in retrospective study by Cywinski *et al*[15].

Previous abdominal surgery

Cywinski *et al*[15] in their retrospective study reported that higher intraoperative blood product usage was more frequent in patients undergoing OLT with history of previous upper abdominal surgery. This result has been concordant with the results of previous studies by Steib *et al*[4], Palomo Sanchez *et al*[9] in which previous abdominal surgery was independently associated with massive transfusion intra operatively[9]. However, this association was not derived in studies by other investigators[18,26].

Findlay *et al*[16] did not find any significant association between retransplantation and blood usage. These results were similar to previously published results of Motschman *et al*[27].

Preoperative hematocrit

Transfusion requirements depend not only on the intraoperative blood loss but also on the threshold for when transfusions of different products are initiated. Therefore, comparison of intraoperative transfusion requirements from different studies may be inherently biased by inability to account for differences in transfusion triggers and clinical practices. Low starting hemoglobin (Hb) value represents the most important indicator for the need for transfusion as shown by Massicotte *et al*[6]. Despite pre operative hemoglobin being an important predictor of intra operative RBC transfusion in various studies; the cut off threshold for the same has not been clearly reported in them[20]. In a study by Steib *et al*[4], one of the three preoperative risk factor predictive of high blood loss was preoperative low Hb. The investigators concluded that patients with an initial low Hb below 10 gm/dL would require transfusion in order to reach the selected trigger point in their study.

SURGICAL RISK FACTORS

Surgical technique of OLT

The conventional method for liver transplantation requires clamping of both portal flow from the viscera and caval flow from the lower body.

Piggyback hepatectomy (PGB) is a surgical technique increasingly utilized in both DDLT and LDLT. The pseudonym Caval preservation technique is justified because it avoids clamping of the vena cava while maintaining flow from the lower body back to the heart throughout the transplant. Preservation of cardiac preload maintains hemodynamic stability and avoids large infusions of fluid volume, vasopressors, and need for venovenous bypass (VVB). The total duration of warm ischemia time is significantly reduced, as one less anastomosis is required prior to reperfusion.

The conventional method would seem to be associated with lesser blood loss and transfusion requirements because PGB is technically more demanding and time consuming than the conventional approach. However, studies suggest otherwise.

Maguns *et al*[20] concluded that blood loss and blood product usage with PGB technique are similar to or better than those for the conventional technique. It is the preferred method in high-risk patients such as the elderly or those with poor physiologic reserve and may be associated with less perioperative morbidity and mortality.

Previously published studies also concluded that PGB is a potentially superior technique given its benefits of avoiding VVB, maintaining hemodynamic and physiologic stability, decreasing warm ischemia time and association with significantly lower blood loss and transfusion requirements[28]. As summarized by an analysis by the Cochrane database[29], no trial has till date shown superiority of one technique over the other.

Clamping methods

Blood losses during liver resection are usually greatest at the stage of parenchymal transaction. Selective clamping of the vasculature prevents excessive blood loss during this phase. Commonly used methods for clamping are: (1) Complete inflow occlusion (Pringle maneuver) - Method most commonly used. Blood loss associated with this method is lesser than the intermittent method. Greater degree of ischemic injury to the liver parenchyma is however reported with this method; and (2) Intermittent clamping or (ischemic preconditioning technique)-This technique has shown to reduce ischemic injury during liver resection, more so in cirrhotic livers. On a comparative analysis however, intermittent clamping has been shown to be associated with more bleeding than the continuous clamping method[30].

Technical improvement in surgery

Amongst the newer devices available for liver parenchymal transaction, the Cavitron Ultrasonic Surgical Aspirator (CUSA) is universally used[31]. Lesurtel *et al*[32] compared four different techniques of liver transaction in a prospective randomized clinical trial. Techniques compared were - conventional clamp crushing technique, CUSA, Hydro-jet, and a dissecting sealer in 100 non-cirrhotic patients undergoing major liver resections. Significantly reduced resection time, costs along with a significant reduction in intra operative blood loss was seen with the clamp-crashing technique.

Deakin *et al*[26] also concluded that that technical improvement in surgery has led to a threefold reduction in the blood transfusion rate. The changes enumerated were-increased use of diathermy dissection with meticulous suture ligation of vessels difficult to control by diathermy, increase use of VVB and the use of sophisticated coagulation devices like Argon Beam Coagulator. This study was done in the pre PGB technique era and these surgical techniques have more or less become the norm in OLT.

Experience of the surgical team

The experience of the surgical team was found to be an independent predictor of transfusion[33]. Steib *et al*[4] concluded that there is a significant decrease in the number of patients undergoing high blood loss with the progressive experience of the surgical team, but it was not found to be an independent predictor of blood loss and transfusion requirements.

INTRAOPERATIVE MANAGEMENT INFLUENCING TRANSFUSION REQUIREMENTS

Role of central venous pressure

Performance of liver resection under low central venous pressure (CVP) has been extensively studied[34]. Low CVP (defined as a pressure < 5 mmHg) can be attained by volume contraction, vasodilators, forced diuresis, adequate neuromuscular blockade, reduction of respiratory tidal volume and applied PEEP.

Conservative transfusion policy and volume contraction reduces perioperative transfusion requirement by avoidance of fluid overload. Prophylactic correction of deranged routine tests of coagulation results in administration of large volumes of plasma and/or platelet concentrates. Pathophysiological changes in patients with ESLD including portal hypertension and numerous collaterals, increased plasma volume with redistribution of plasma volume to splanchnic bed, and disturbed cardiac function with peripheral vasodilatation, causes rapidly administered fluids and blood products to further increase the portal and central venous pressure. This results in bleeding with surgical trauma probably due to venous congestion[35].

Jones *et al*[36] were the first to show that intra operative blood loss during liver resection correlated almost linearly with the CVP. The safety and benefits of restricted intra operative fluids and low CVP in patients undergoing liver transplant was studied by Schroeder and colleagues. They compared outcome variables of patients with two different fluid policies in two different centers. The target in the intervention group of a low CVP (< 5 mmHg) was achieved by fluid restriction, whereas a normal CVP of (7-10 mmHg) was maintained in the other group in the second center. Decreased transfusion requirements of RBC, FFP and platelets was observed in the low CVP group as compared with the normal CVP group[37].

The maintenance of a low CVP intra operatively in cirrhotic patients undergoing liver resection was not associated with any significant increase in mortality and morbidity. Significantly reduced intraoperative transfusion of blood and blood products along with decreased hospital stay was observed in the low CVP group. There was no derangement in postoperative hepatic and renal function in the study group[38].

Hashimoto *et al*[39] studied the effect of prophylactic phlebotomy and withdrawal of calculated amount of blood (0.7% of the patient's body weight) *vs* no withdrawal of blood in a randomized prospective study of healthy donors scheduled for partial liver resection for LDLT. At the beginning of parenchymal transection CVP was significantly lower in the phlebotomy group [median 5 (range 2-9) cm H_2O *vs* 6 (range 2-13) cm H_2O) as compared with controls. Post operative outcomes were comparable between the groups[39].

In another study in liver transplant recipients, Massicotte *et al*[35] achieved a low CVP by volume contraction and intraoperative phlebotomy. Expansion of blood volume post phlebotomy (at the beginning of the case) was not done. They concluded that avoidance of plasma transfusion; starting Hb value and maintenance of a low CVP prior to the anhepatic phase were associated with a significant decrease in blood and blood products during this study[35].

On the other hand maintenance of a low CVP during liver resections is associated with a increased risk of complications including air embolism, systemic tissue hypoperfusion and renal failure[7,35,37]. In their study Schroeder and colleagues observed an increase in 30 d mortality and dialysis requirements with higher post operative peak creatinine levels in patients with low intra operative CVP[37].

Use of antifibrinolytics

Hyperfibrinolysis plays a significant role in nonsurgical blood loss in patients undergoing OLT requiring massive transfusion of blood products. Hyperfibrinolysis always occurs late in the anhepatic phase and immediately after the reperfusion of the graft. An increased level of t-PA because of an increased release from the damaged ischaemic endothelium of the graft and lack of its hepatic clearance in the anhepatic phase is the principal causative factor. Also there is associated consumption of alpha-2 antiplasmin and plasminogen activator inhibitor type-1 (PAI-1)[5,40]. The beneficial effects of antifibrinolytics to reduce the bleeding and transfusion requirements in patients undergoing cardiac surgery initiated the assessment of antifibrinolytics in liver transplant.

Dalamu *et al*[41] documented a significant reduction in PRBC transfusion in a prospective double blind randomized study conducted to compare the efficacy of prophylactic infusion of tranexamic acid (TA) or epsilon aminocaproic acid (EACA) with placebo in reducing blood loss and transfusion requirement during LT. In this study, TA and EACA were given prophylactically at a rate of 10 and 16 mg/kg per hour respectively. Thirty-one percent of patients in the TA group did not receive any PRBC transfusion. Also the TEG profiles of the patients given TA in the reperfusion phase were better in TA group. There was no difference in transfusion requirements after OLT, or thromboembolic events, reoperations or mortality between the groups. Boylan *et al*[42] found that a larger dose, *i.e.*, 40 mg/kg per hour of TA reduced not just the intraoperative blood loss but also the transfusion of plasma, platelet and cryoprecipitate. However a Cochrane Hepato-Biliary Group metaanalysis, did not show a significant reduction in blood and blood product requirements in patients receiving tranexamic acid *vs* controls[43].

Nehaus *et al*[44] first reported Aprotinin use in a study in 1989. They reported decreased blood loss, transfusion requirements and duration of surgery with the use of aprotinin in the dose of 2 million KIU (Kallikrien inhibitory units). Studies by Porte *et al*[45], Findlay *et al*[46] have also shown that there is a decrease in transfusion requirement with use of aprotinin. In a review of the use of aprotinin in OLT, Lentschener and colleagues concluded that prophylactic use of large dose aprotinin decreases blood loss and transfusion requirements only when OLT is associated with significant blood loss and does not alter postoperative outcomes[47]. The efficacy of TA *vs* Aprotinin in reducing blood loss and transfusion requirements during OLTx was studied by Massicotte *et al*[48]. Administration of TA and Aprotinin was found to be comparable in terms of intraoperative blood loss and transfusion requirements. Molenaar *et al*[49] in their study concluded that although both Aprotinin and TA significantly reduced RBC transfusion requirements; significant reduction in intraoperative FFP transfusions was achieved with Aprotinin only. Post operative thromboembolic events and mortality was not increased in patients receiving antifibrinolytics.

However, other studies failed to show a significant difference in the transfusion of red blood cells, fresh frozen plasma (FFP), cryoprecipitate, and platelets between the aprotinin-treated group and the placebo group[50].

Use of newer procoagulants

Recombinant factor VIIa (rFVIIa) till date is approved by the United States Food and Drug Administration (FDA) for hemophilia only, but a large number of case reports and studies have reported the use of rFVIIa in uncontrolled hemorrhage due to trauma or surgery including OLT.

Hendriks *et al*[51] first reported that prophylactic administration of 80 μg/kg of rFVIIa in adult cirrhotic patients undergoing OLT led to significant reductions in median total PRBC requirements, although one of the treated patients developed hepatic artery thrombosis. Lodge *et al*[52] were not able to demonstrate any reduction in RBC requirement in rFVIIa-treated patients compared to placebo. The efficacy of rFVIIa in reducing intraoperative blood loss is only modest at the cost of an increased incidence of thromboembolic episodes specially in patients with intracerebral hemorrhage and those undergoing cardiac surgery[53]. Thus, rFVIIa cannot be recommended as a universal prophylaxis to reduce transfusion requirements during OLT particularly considering the high cost of rFVIIa.

Use of point of care monitors of coagulation

New point of care tests are now available which allow monitoring of the haemostasis in the operation theatre which is essential in patients with pre-existing haemostatic abnormalities or in profusely bleeding patients with complex and rapidly changing coagulation profile. Devices assessing viscoelastic properties of whole blood are available include thromboelastography (TEG), rotation thromboelastometry and Sonoclot analysis.

TEG can assist in treatment of intraoperative bleeding by identifying the cause. In combination with clinical assessment of bleeding, it also facilitates selective replenishment of deficient blood components and use of specific drug treatments (antifibrinolytics). Various studies have demonstrated a significant reduction in intraoperative blood and component therapy with coagulation monitoring through TEG when compared with traditional "clinician-directed" transfusion management. Wang *et al*[54] reported that the FFP requirement during OLT in patients being monitored with TEG was lower than patients corrected for deranged PT/INR values using accepted transfusion thresholds.

Transfusion trigger

Still no consensus exists on transfusion practices in liver surgeries especially OLT. There is high variability in the use of blood products in liver resection surgeries with most of the use not being evidence based. Most centers follow the ASA practice guidelines for the transfusion of blood products during OLT. The threshold for RBC, plasma and platelet transfusion is a Hb of 60 to 100 g/L; INR value > 1.5 and platelet < 50000/mL, respectively. Despite following these guidelines a wide range of transfusion rates exist between centers and even among anesthesiologists in the same center.

Massicotte *et al*[8] in their prospective study on 206 patients used aprotinin, a low CVP and a transfusion trigger of 60 gm for administering PRBC transfusion. They did not use PGB, VVB or prophylactic correction of coagulopathy. The investigators concluded that coagulation defects were not linked to PRBC transfusion and there is no benefit of prophylactic correction of coagulation disorders in the absence of uncontrollable bleeding. The use of FFP was the strongest predictor for PRBC transfusion and associated with decrease in one-year survival rate[8].

Intraoperative blood salvage techniques

Autologous blood transfusion and intra operative blood salvage has shown to reduce allogeneic blood transfusion in patients undergoing surgery with high risk of intraoperative blood loss and transfusion. These techniques play an important role in management of special patient populations (Jehovah's Witnesses and patients with rare blood groups) undergoing major surgeries including transplantation.

In adult patients undergoing elective surgery cell salvage was concluded to be an efficacious technique in reducing the need for allogeneic blood transfusion by a Cochrane Collaboration meta-analysis[55]. The cost effectiveness of this technique as compared to allogenic blood transfusion was also corroborated by Waters *et al*[56] in their review. It has also been reported to improve conservation of erythrocytes and reduce exposure of patients to blood and blood components[57,58].

Despite above-mentioned evidence the role of cell salvage techniques in OLT remains controversial with studies reporting higher blood loss with its use due to fibrinolysis and increased costs. A increase in transfusion requirements in liver transplant recipients was reported by Hendriks *et al*[33] with the use of cell salvaged blood with salvaged blood hypothesized as a cause of excessive blood loss. Increased requirements of RBCs, FFP, cryoprecipitate, and platelets in patients given cell salvaged blood have been shown by other studies[59,60]. Degradation products of Fibrinolysis in the salvaged blood either from blood cells or from the transplanted liver, that are not cleared by washing of RBC's in the cell saver are postulated to be the cause of increased blood loss in these patients[59].

However with the decrease in intra operative blood loss in patients undergoing OLT; the cost effectiveness of the technique (requiring intraoperative salvage and use of two or more blood units) in comparison to allogenic blood transfusion is questionable. Thus, the use of cell salvage is helpful in OLT case with anticipated high blood loss.

CONCLUSION

Improvements of the surgical techniques, anesthetic management and graft preservation have resulted in development of OLT as the preferred treatment choices in patients with decompensated liver disease. Predictive risk factors for intraoperative blood transfusion have been reviewed. All the predictive models and associations do not have good specificity in predicting patients requiring excessive blood transfusion requirements. Preoperative factors like disease severity, previous surgery, low hematocrit, surgical factors and intraoperative management including use of antifibrinolytics, CVP, FFP transfusion all influence the blood loss and transfusion requirements during OLT.

Changing trends in blood product use intraoperatively and better anaesthetic and surgical management of these patients are perhaps the most important factors that have lead to decreased blood loss and transfusion in patients undergoing OLT.

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CASE REPORT

Adenocarcinoma arising at ileostomy sites: Two cases and a review of the literature

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Author contributions: Procaccino L made the initial research and reviewed the manuscript; Rehman S and Abdurakhmanov A contributed to researching, reviewing the manuscript, the manuscript composition and patient care; Abdurakhmanov A collected the data; McWhorter P contributed to reviewing the manuscript and the photography credit; La Gamma N, Bhaskaran MC, Rilo H, Nicastro J and Coppa G reviewed, edited and researched the manuscript; Maurer J contributed to reviewing and editing the manuscript and patient care; Grimaldi GM contributed to the radiology interpretation and image credit, and reviewing and editing the manuscript; Molmenti EP reviewed, edited, designed, researched the manuscript; Procaccino J made the initial idea to do literature search and surgery, and contributed to reviewing and editing the manuscript and patient care.

Ethics approval: These case reports and literature review did not require IRB approval. Patient confidentiality was maintained.

Informed consent: Patients provided informed consent.

Conflict-of-interest: We report no conflicts of interest.

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Abstract

Total colectomy with ileostomy placement is a treatment for patients with inflammatory bowel disease or familial adenomatous polyposis (FAP). A rare and late complication of this treatment is carcinoma arising at the ileostomy site. We describe two such cases: a 78-year-old male 30 years after subtotal colectomy and ileostomy for FAP, and an 85-year-old male 50 years after colectomy and ileostomy for ulcerative colitis. The long latency period between creation of the ileostomies and development of carcinoma suggests a chronic metaplasia due to an irritating/inflammatory causative factor. Surgical excision of the mass and relocation of the stoma is the mainstay of therapy, with possible benefits from adjuvant chemotherapy. Newly developed lesions at stoma sites should be biopsied to rule out the possibility of this rare ileostomy complication.

Key words: Ileostomy; Carcinoma; Adenocarcinoma; Familial adenomatous polyposis; Inflammatory bowel disease; Complication of ileostomy

Core tip: A rare and late complication of ileostomy creation is carcinoma arising from the ileostomy site. Physicians and patients should be aware of this phenomenon and require regular physical exams. Any and all parastomal lesions should be biopsied to rule out adenocarcinoma at the ileostomy site.

Procaccino L, Rehman S, Abdurakhmanov A, McWhorter P, La Gamma N, Bhaskaran MC, Maurer J, Grimaldi GM, Rilo H, Nicastro J, Coppa G, Molmenti EP, Procaccino J. Adenocarcinoma arising at ileostomy sites: Two cases and a review of the literature. *World J Gastrointest Surg* 2015; 7(6): 94-97 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i6/94.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i6.94

INTRODUCTION

Total colectomy with ileostomy is the definitive treatment for patients with ulcerative colitis and familial adenomatous polyposis (FAP). Although rare, a late complication of this treatment is carcinoma at the ileostomy. We report two cases of ileostomy carcinoma and review the literature regarding this rare phenomenon.

There has been much speculation regarding the etiology of such cancers. The prevailing theory suggests that chronic inflammation and cell proliferation at the convergence of mucosa and skin are the likely causative factors[1].

CASE REPORT

Case 1

This patient is a 78-year-old male with a history of FAP treated with subtotal colectomy in 1969 and ileostomy in 1984, who presented with a mass at his ileostomy site. He denied having abdominal pain, cramps, or weight loss. His medical history was also relevant for anemia, atrial flutter, essential hypertension, gastroesophageal reflux, gout, hyperlipidemia, myocardial infarction, non-insulin-requiring diabetes mellitus, a perforated gastroduodenal ulcer requiring open repair, and renal calculi. His surgical history includes extracorporeal shockwave lithotripsy for renal calculi, bilateral cataract extraction, trans-urethral excision of bladder stones, prostate vaporization, open cholecystectomy, appendectomy, and tonsillectomy.

On physical exam, a fungating tumor could be detected involving the mucosa of the ileostomy (Figure 1). Ileoscopy revealed multiple polyps up to 30 cm from the ileostomy site.

Biopsy of the lesion showed adenocarcinoma. A work-up for metastatic disease was performed, including a chest X-ray and computed tomography (CT) scans. Laboratory tests, including a carcinoembryonic antigen level, were all within normal range.

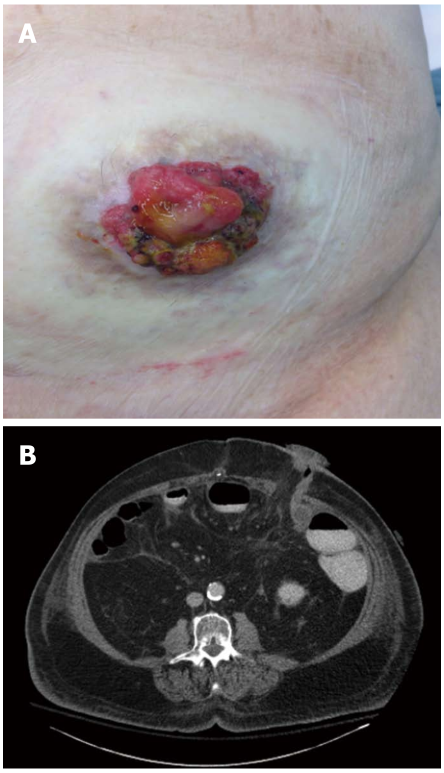

Figure 1 Ileostomy site on physical exam (A) and computed tomography scan (B).

The patient underwent a laparotomy, resection of the terminal ileum, ileostomy, and abdominal wall skin, and creation of a new ileostomy. Pathological evaluation showed invasive intestinal type, moderately differentiated adenocarcinoma of the small bowel arising at the ileostomy site with a background of high-grade dysplasia and intramucosal carcinoma in tubular adenoma. Multiple (at least 50) tubular adenomas were present throughout the length of the specimen. All resection margins were negative for invasive tumor. No adjuvant therapy was recommended. He is currently alive and well one month post-operatively.

Case 2

This patient is an 85-year-old male who had a colectomy and ileostomy created 50 years ago for ulcerative colitis, who presented with lethargy, dehydration, a small bowel obstruction, and a parastomal mass. He had been diagnosed with Crohn's disease three years ago when he had bleeding from the ileostomy. Since that time, he has had significant weight loss, anorexia, and numerous hospitalizations for dehydration. His medical and surgical history is also significant for atrial fibrillation, sick sinus syndrome requiring a permanent pacemaker, and benign prostatic hypertrophy.

Physical exam revealed an ulcerated mass at the ostomy site (Figure 2). Biopsy of the parastomal mass revealed a well-differentiated adenocarcinoma with ulceration involving the stoma. A CT scan of the

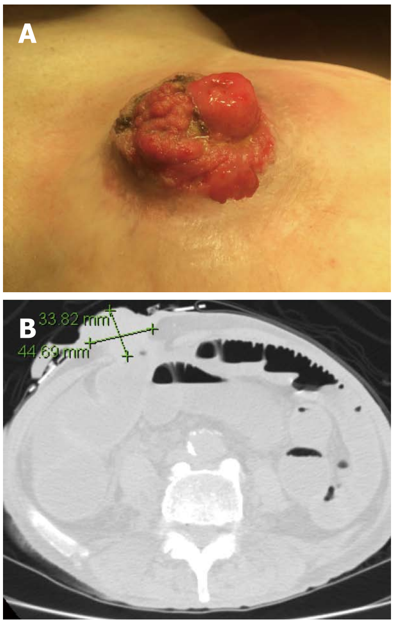

Figure 2 Physical exam (A) and computed tomography scan with measurements (B) of the parastomal mass.

abdomen/pelvis showed diffuse dilation of small bowel loops with air-fluid levels to the level of the mass, consistent with small bowel obstruction. Ileoscopy showed large amounts of friable tissue compressing the ileostomy opening.

The patient underwent resection of the ileostomy and surrounding abdominal wall, followed by creation of a new ileostomy and abdominal wall reconstruction with Strattice mesh. Although he recovered from the surgical intervention, this patient succumbed one month later as a result of urosepsis.

DISCUSSION

The first case of carcinoma arising from an ileostomy site was reported in 1969 in a patient who was treated for ulcerative colitis[2]. The first report associated with FAP was in 1982[3]. There have been 40 adenocarcinomas and 4 squamous cell carcinomas reported as of 2005[1]. This increase in incidence can be attributed to the latency period between creation of ileostomies and the development of carcinoma (estimated to average 30 years) and the introduction of the eversion ileostomy in 1952[4].

Adenocarcinomas at the mucocutaneous junction of an ileostomy were reported in four patients in 1988[5]. All four patients developed cancer approximately 30 years after stoma creation. Another primary mucinous adenocarcinoma was reported at that time in a 60-year-old woman 28 years after subtotal colectomy and ileostomy creation[6]. Histopathology revealed a tubulovillous adenoma origin. The same authors also reviewed five cases of primary adenocarcinomas arising at ileostomy sites. While three of the patients were described as having fungating, exophytic, polypoid growths (similar to our cases), the other two patients presented with skin induration and irritation, providing more of a diagnostic challenge.

A review of 36 primary adenocarcinomas at ileostomy sites by Metzger *et al*[7] affirmed the mechanism to be likely associated with colonic metaplasia from chronic inflammation. The authors found lymph node involvement in 19% of cases, and an 85% survival rate. This study showed an average of 27 years between placement of ileostomy and development of a parastomal lesion, and emphasized the importance of patient education in early detection. Our two cases presented 30 and 50 years post ileostomy placement. Surgical excision and relocation of the stoma is the mainstay of therapy, with possible benefits from adjuvant therapy.

Another report described a 37-year-old man misdiagnosed with a pyogenic granuloma at an ostomy site after presenting with an asymptomatic polypoid lesion 18 years after subtotal colectomy for ulcerative colitis[8]. Only after failed treatment with topical silver nitrate was a biopsy taken, which revealed a primary adenocarcinoma. Although peristomal dermatoses such as contact dermatitis, psoriasis, and pyoderma gangrenosum are far more common than carcinoma at an ileostomy site, a high index of suspicion is warranted for any parastomal lesion. Dermatologists or primary care physicians who often follow up with these patients are urged to be aware of this rare complication of ileostomies.

Other investigators found a total of 14 patients with FAP[9] and metaplasia of pre-existing adenomas discovered on pathology, suggesting still a different mechanism from the previously mentioned chronic irritation and inflammation of the mucosa and skin junction. The median interval between ileostomy creation and adenocarcinoma was 25 years in this small sample. None of the patients had lymph node involvement, while two had local recurrence. The difference in proposed mechanisms of ileostomy adenocarcinomas is attributed to the initial reason for colectomy. If due to FAP, the theory is a pre-existing adenoma that undergoes metaplasia. In ulcerative colitis or Crohn's, chronic inflammation is regarded to be the metaplasia culprit.

Patient and physician education and regular physician physical exams are of paramount importance in early detection. Newly developed lesions at stomas should be biopsied to rule out this rare ileostomy complication.

COMMENTS

Case characteristics

The main symptoms were a fungating mass at the ileostomy site, additionally accompanied by lethargy, dehydration, and a small bowel obstruction in one case.

Clinical diagnosis

The main clinical findings were a parastomal mass.

Differential diagnosis

Common differential diagnoses for parastomal lesions include contact dermatitis, psoriasis, and pyoderma gangrenosum due to the constant contact of surrounding skin with feces. This chronic irritation more commonly causes a dermatological condition rather than a malignancy.

Laboratory diagnosis

Biopsy of the mass is absolutely essential to distinguish it from the previously mentioned more common differentials, and found adenocarcinoma.

Imaging diagnosis

Computed tomography scan was used to visualize the extent of the mass.

Pathological diagnosis

Pathological examination of the biopsies found well-differentiated adenocarcinoma.

Treatment

Treatment consists of surgical excision and relocation of the stoma.

Experiences and lessons

A rare and late complication of ileostomy creation is carcinoma arising from the ileostomy site and physicians and patients should be aware of this phenomenon and require regular physical exams.

Peer-review

The strengths of this article include it's simple core tip and lesson, and it's well written form and language.

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CASE REPORT

Gastrointestinal stromal tumour presenting as palpable abdominal mass: A rare entity

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Abstract

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumour of gastro-intestinal tract. Annual incidence of GIST in United States is approximately 3000-4000. Clinical presentation of GIST varies with location and size of tumour but GIST presenting with palpable abdominal mass is rare. We report a case of 38 years old male who presented with large abdominal lump. Computed tomography (CT) scan showed a large solid-cystic lesion encasing second part of duodenum and distal common bile duct. On CT differential diagnosis of Leiomyoma, Leiomyosarcoma and GIST were made. The diagnosis of GIST was confirmed by immune-histochemical study of the biopsy material. Patient underwent pancreaticodudenectomy. Post-operative course was uneventful. Patient was started on Imatinib therapy post-operatively. No recurrence noted at six months follow up.

Key words: Gastrointestinal stromal tumours; Abdominal mass; Pancreaticoduodenectomy; Imatinib

Core tip: Gastrointestinal stromal tumours presenting with palpable abdominal mass are rare. Diagnosis is based upon histopathology and immunehistochemistry. Pre operatively patient should be evaluated with different modalities for diagnosis and resectability of tumour. Surgical resection with postoperative Imatinib chemotherapy helps to provide long term survival.

Bhambare MR, Pandya JS, Waghmare SB, Shetty TS. Gastrointestinal stromal tumour presenting as palpable abdominal mass: A rare entity. *World J Gastrointest Surg* 2015; 7(6): 98-101 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i6/98.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i6.98

INTRODUCTION

Gastro-intestinal stromal tumour (GIST) is the most common primary mesenchymal tumour of gastro-intestinal tract arising from interstitial cell of Cajal or their stem cell precursor[1,2]. The incidence of GIST in United States is approximately 3000-4000 annually[1,2]. GISTs generally arise in stomach (60%-70%), small intestine (25%-35%), rectum and colon (5%-10%), duodenum (4%) mesentry or omentum (7%) and oesophagus (5%)[2]. They commonly affect men with median age of presentation being 55-60 years[3]. Pre-operative diagnosis is difficult due to its non-specific signs and symptoms. GISTs presents commonly as abdominal pain and bleeding. GISTs presenting with palpable abdominal mass is rare[4]. Only 25 such cases have been published in world literature from 2001 to 2011[4]. We report a case of GIST presenting as a large abdominal mass. Computed tomography (CT) abdomen showed a large solid cystic lesion encasing second part of duodenum, and distal common bile duct (CBD) causing its dilatation. Ultrasonography guided biopsy was taken to aid the diagnosis which was confirmed by Histo-pathological and immune-histochemical study. Patient underwent pancreaticodudenectomy. Post-operative course was uneventful. Patient was started on Imatinib post-operatively. No clinical and radiological recurrence noted at six month follow up.

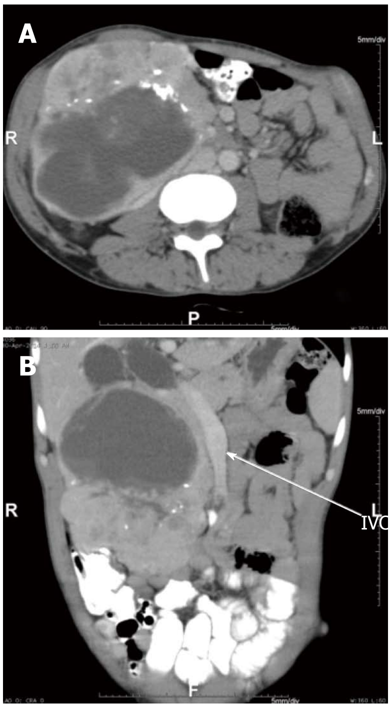

Figure 1 Computed tomography abdomen showing tumour encasing second part of duodenum and dilated common bile duct.

CASE REPORT

A 38-year-old male presented with lump in abdomen of seven years duration,gradually increasing in size associated with intermittent, non-radiating dull aching pain. On abdominal examination a 14 cm × 12 cm firm to hard lump was palpable in epigastric, right hypochondriac, right lumbar region. Systemic examination showed no distant or lymph node metastasis. CT scan of abdomen showed a large solid cystic mass with lobulated margin measuring 14.8 cm × 11.4 cm × 11.2 cm in right hypochondriac and right lumbar region. It showed amorphous calcification with heterogenous enhancing solid component and septae within cystic areas. Mass appeared to be encasing duodenum and distal bile duct causing dilatation of proximal CBD and IHBRD (Figure 1). The diffential diagnosis based on CT Abdomen was leiomyoma, leiomyosarcoma and GIST. The patient underwent USG-guided biopsy of the tumour (Figure 2). Microscopically, the tumour section showed proliferation of non-specific monomorphic spindle cells and small mesenchymal cells. Mitotic figures and atypical cells were occasionally observed (< 5/50 high-power fields).

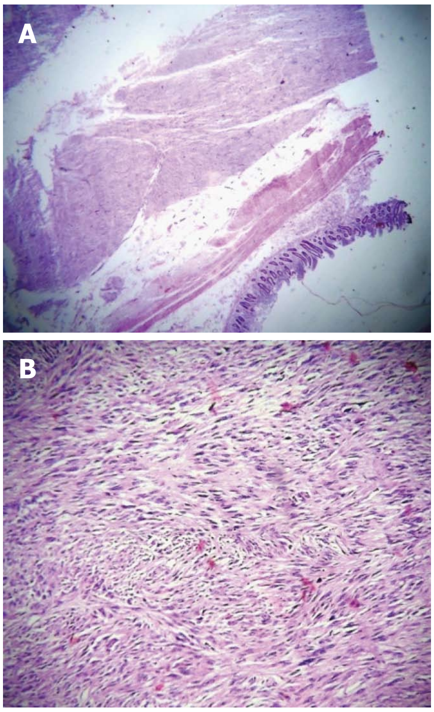

Figure 2 Microscopic findings (hematoxilin-eosin).

On Immunohistochemistry the tumour was positive for Ckit, DOG 1 and SMA whereas it was negative for Desmin and S100.

On exploratory laparotomy through roof top incision a huge mass of 14 cm × 15 cm × 11 cm was found encasing second part of duodenum and adherent to head of pancreas. There was dilatation of CBD. Pancreatico-duodenectomy with en-block resection of mass done (Figure 3). The tumour capsule was intact. Intra-operative and post-operative course was uneventful. Histopathological study revealed GIST of duodenal origin with < 5 mitosis/50 high power field and low to moderate malignant potential. All resection margins were free of tumour (R0). Tablet Imatinib 400 mg was started post-operatively. No clinical and

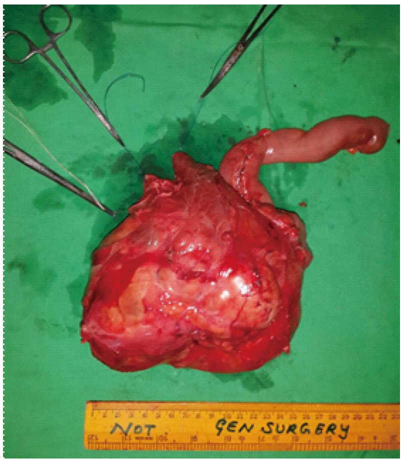

Figure 3 Gross specimen showing tumour.

radiological recurrence noted at six month follow up.

DISCUSSION

GISTs are the most common mesenchymal tumours of gastrointestinal tract, first described by Clarke and Mazur[1,2] in 1983. GISTs are derived from the interstitial cells of Cajal which serves as pace maker of gastrointestinal tract triggering smooth muscle contraction[1,2]. There is male preponderance and peak age is fifth and sixth decade[3].

GISTs are commonly seen in stomach (60%-70%) and rarely in duodenum (4%)[2]. GISTs are characterised by genetic expression of c-kit (a trans-membrane tyrosine kinase receptor) and immune-histo-chemical staining of CD 117, CD34 (70%), SMA (40%) and a novel gene DOG1[2,5].

GISTs are spread by heterogenous route to liver and peritoneum[6] and rarely to lung, bone, lymph nodes.

Pre-operative diagnosis of GIST is difficult as the patient presents with non-specific signs and symptoms[4]. Pain in abdomen and GI bleed being the most common presentation mentioned in the literature[4]. However, patient presenting with palpable abdominal mass is very rare and only 25 cases have been reported[4]. Pre-operative CT Scan and MRI although of not much aid to locate the origin of the tumour, helps in deciding the resectability of the tumour and metastasis[4]. The basic modality of tumour treatment for GIST is surgery with complete removal of the tumour and microscopic negative margins (Ro resection)[4,6].

Recurrence rate of about 40% is reported in patients undergoing complete resection. Most common site of recurrence being local and liver mets[6]. Imatinib has played an important role in neo-adjuvant therapy as well as recurrent disease[2]. In case of advanced disease or resistance/tolerance to imatinib,a newer drug Sunitinib is used as a second line therapy[2].

Prognosis of tumour depends mainly upon size, location and mitotic index[2]. Other important factors are age of presentation, histopathological and immunohistochemistry features and molecular genetics. Poor prognosis is associated with tumours > 5 cm in size and > 5 mitosis per HPF[2].

PET CT is particularly useful auxillary diagnostic modality as baseline for verification of the early response to therapy with Imatinib, aTKI[7]. Literature mentions five year survival rate as 30% and it increases to 54% after complete surgical resection with microscopic negative margins[8].

COMMENTS

Case characteristics

A 38-year-old male presented with lump in abdomen of seven years duration, gradually increasing in size associated with intermittent, non-radiating dull aching pain.

Clinical diagnosis

Physical examination showed firm to hard lump in epigastric, right hypochondriac and lumbar region with no evidence of metastasis.

Differential diagnosis

Hepatoma, malignancy of stomach, lymphoma, gastrointestinal stromal tumours (GIST).

Laboratory diagnosis

Haemoglobin, haematocrit, liver function test, renal function test were within normal range.

Imaging diagnosis

Computed tomography scan of abdomen showed a large solid cystic mass with lobulated margin measuring 14.8 cm × 11.4 cm × 11.2 cm in right hypochondriac and right lumbar region with amorphous calcification, heterogenous enhancing solid component and encasing duodenum and distal bile duct causing dilatation of proximal common bile duct and IHBRD.

Pathological diagnosis

USG-guided biopsy of the tumour showed proliferation of non-specific monomorphic spindle cells and small mesenchymal cells. Mitotic figures (< 5/50 high-power fields). Immunohistochemistry of the tumour was positive for C-kit, DOG 1 and SMA whereas it was negative for Desmin and S100.

Treatment

Pancreatico-duodenectomy with adjuvant imatinib chemotherapy.

Related reports

Only 25 such cases have been published in world literature from 2001 to 2011.

Term explanation

GISTs are the most common mesenchymal tumour of gastrointestinal tract.

Experiences and lessons

The diffential diagnosis of GIST should be kept in mind while dealing with palpable abdominal mass.

Peer-review

The manuscript presents a case report of a very large GIST of duodenal origin.

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EDITORIAL

Perspective of laparoscopic liver resection for hepatocellular carcinoma

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Abstract

Liver resection (LR) for hepatocellular carcinoma (HCC) in patients with chronic liver disease (CLD) is associated with high risks of developing significant postoperative complications and multicentric metachronous lesions, which can result in the need for repeated treatments. Studies comparing laparoscopic procedures to open LR consistently report reduced blood loss and transfusions requirements, lower postoperative morbidity, and shorter hospital stays, with no differences in oncologic outcomes. In addition, laparoscopic LR is associated with reduced postoperative ascites and a lower incidence of liver failure for HCC patients with CLD, due to the reduced surgery-induced parenchymal injury to the residual liver and limited destruction of the collateral blood/lymphatic flow around the liver. Finally, this procedure facilitates subsequent repeat LR due to minimal adhesion formation and improved vision/manipulation between adhesions. These characteristics of laparoscopic LR may lead to an expansion of the indications for LR. This editorial is based on the review and meta-analysis presented at the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan, in October 2014 (Chairperson of the congress is Professor Go Wakabayashi from the Department of Surgery, Iwate Medical University School of Medicine), which is published in the *Journal of Hepato-Biliary-Pancreatic Sciences*.

Key words: Laparoscopic; Liver resection; Hepatocellular carcinoma; Chronic liver disease; Liver failure; Ascites; Indication; Repeat hepatectomy

Core tip: Liver resection (LR) for hepatocellular carcinoma patients with chronic liver disease has high risks for developing significant postoperative complications and multicentric metachronous lesions with need of repeated treatments. Laparoscopic LR has advantages of reduced surgery-induced parenchymal injury and destruction of the collateral blood/lymphatic flow, which leads to reduced production of postoperative ascites, and facilitates repeat LR because of reduced adhesion formation and improved vision/manipulation between adhesions. These characteristics of laparoscopic LR may lead to expansion of the indications for LR.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common primary cancers and causes of cancer-related deaths[1,2]. The options for HCC treatment include transarterial chemoembolization and local ablation therapy[3], but the best chance for cure is with liver resection (LR)[4] or liver transplantation[5]. Liver transplantation should be considered in patients with deteriorating liver function who are within the Milan criteria[6], whereas LR should be considered for those with preserved liver function[7,8]. However, most HCC patients are at high risk for developing significant postoperative complications and multicentric metachronous lesions with underlying chronic liver disease (CLD). For these patients, the oncologic therapeutic effects and degree of invasive surgical stress, especially to the impaired liver, should be considered during the treatments. The variety of symptoms in patients with CLD[9] raises the risks associated with anesthesia and surgery[10], which increase according to the preoperative Child-Pugh class[11]. For severe CLD patients, refractory ascites often develop even with limited LR, which then leads to fatal liver failure[12,13].

Currently, the treatment choice for an HCC patient with CLD depends on the combination of tumor and liver conditions[14]. Nevertheless, there are still a considerable number of these patients who are unable to undergo one of the treatment modalities listed above. Such patients may benefit from less-invasive laparoscopic LR (LLR)[15] compared to open LR (OLR)[16]. Indeed, this procedure has recently been evaluated in a review and meta-analysis[17], which was presented at the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan, in October 2014 (the Chairperson of the Congress is Professor Go Wakabayashi from the Department of Surgery, Iwate Medical University School of Medicine).

OVERVIEW OF LLR

For the review and meta-analysis[17], 2183 and 466 articles were identified under a PubMed search of "laparoscopic liver resection" and "laparoscopic liver resection + hepatocellular carcinoma," respectively. No randomized trials were available. All data were reported as case series, case-control studies, reviews, and meta-analyses. Of these, there was one Cochrane review and 81 comparative studies for LLR, as well as 12 meta-analyses for all types of indications[18-22], colorectal metastases[23,24], left lateral sectionectomy[25], and HCC[26].

In the absence of randomized studies, the Cochrane study could not draw any conclusions. The meta-analyses generally showed that LLR reduced blood loss, transfusion requirements and complication rates, shortened the hospital stay, and resulted in identical or better surgical margins than OLR. Several analyses examined long-term results and showed no differences in oncologic outcomes between LLR and OLR.

The indications for LLR are essentially the same as those for OLR. However, the centers reported in these studies identified technical feasibilities related to tumor conditions (such as size, and location) and extent of resection as the limiting factors. Typically, giant tumors (> 10-15 cm in diameter) are excluded from the indications for LLR due to the lack of appropriate view of operative field in the small abdominal cavity. Also, LR combined with major vessel resection and reconstruction and living-donor LR for transplantation are performed at only a few experienced centers. A previous international survey[27] reported a relatively small percentage (approximately 40%) of LLR procedures with some groups of higher rates over 80%. Although the low rate and disparity of LLR application could lead to selection bias in the reported results, the studies showed that LLR generally produced better perioperative outcomes without compromising long-term oncologic outcome for the patients selected to undergo these procedures.

LLR FOR HCC WITH CLD

Patients who undergo LR are exposed to three different types of stresses that are of particular importance in patients with CLD: (1) general, whole-body surgical stress; (2) reduced liver function due to resected liver volume; and (3) surgery-induced injury to the area around the liver (caused by destruction of the collateral blood and lymphatic flow with laparotomy and mobilization of the liver) and residual liver parenchyma (caused by mesenchymal injury from the compression of the liver). With LLR, the reduced surgery-induced injury can lower the risk of refractory ascites, leading to less successive complications and a smooth recovery without liver failure.

Among the studies in the review, HCC cases were included in four meta-analyses[26,28-30] (with 494 to 1238 patients) and 23 comparative studies[31-53], 13 of which[31-36,41,43,44,49-51,53] examined the rates of postoperative ascites and liver failure. We conducted a meta-analysis for postoperative ascites and liver failure in nine and six of these studies that were of a high quality[17]. The analysis showed reduced incidences of postoperative ascites (odds ratio 0.26, 95%CI: 0.14-0.49; P < 0.001) and liver failure (odds ratio 0.24, 95%CI: 0.10-0.56; P = 0.001), which are associated with LLR.

The impact of LLR on ascites production and liver failure depends on the severity of the background CLD, extent of the resection, and the operative technique (extent of dissection of the peritoneal attachments

Table 1 Possible conditions for the expansion of liver resection indication with laparoscopic liver resection

Patient group	Indications
Patients with severe liver dysfunction (Child-Pugh B/C)	LLR for subcapsular HCCs, particularly for the tumors on suspended ruptures LLR as the bridging therapy to liver transplantation, with the advantage of examination and evaluation of tumor pathology before transplantation LLR for HCCs in the patients with hepatitis B virus-related severe liver dysfunction without previous antiviral treatments who could acquire the recovery of liver function after antiviral treatments[62]
Patients with repeat lesions	Repeat LLR for the patients with deteriorated liver function and multicentric metachronous HCCs who have undergone multiple treatments and are usually treated with local ablation therapy, transarterial chemoembolization, or sorafenib

HCC: Hepatocellular carcinoma; LLR: Laparoscopic liver resection.

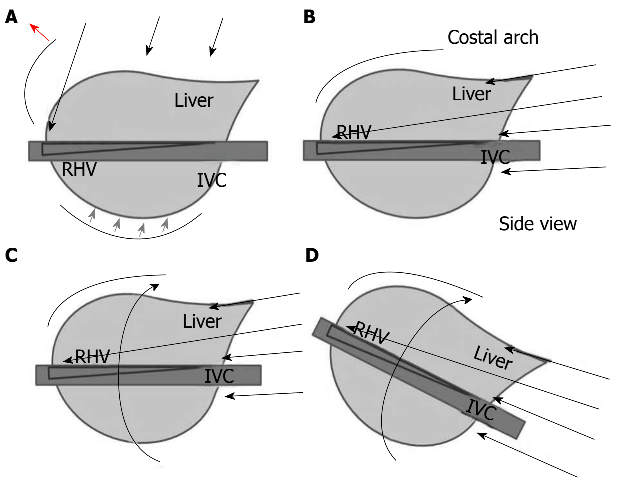

Figure 1 Specific view and approach/manipulation of laparoscopic liver surgery. A: The long arrow shows the direction of view and approach for open liver surgery. The subphrenic space is opened with a large subcostal incision plus lifting of the costal arch (red arrow) and the liver is picked up with the dissection of retroperitoneal attachments (gray arrows); B: Arrows show the direction of approach of the laparoscope and forceps; C,D: In laparoscopic liver resection, adjustments of laparoscopic view allow for fine operative fields and handling of large-volume liver/tumors by postural changes/rotation, which reduce compression of the liver parenchyma. IVC: Inferior vena cava; RHV: Right hepatic vein.

and adhesions). There are six comparative studies from five institutions in which all patients with HCC had liver cirrhosis[31,33,36,42,45,53]. Among them, all three studies[31,33,53] that examined postoperative ascites production showed a significant reduction with LLR. Another study compared the perioperative results after LLR between patients with severe cirrhosis (Child-Pugh B/C and ICG R15 $\geqslant$ 40%) and with mild-moderate cirrhosis[54]. Although it was a retrospective small-sized non-matched study, it showed comparable short-term outcomes, including postoperative ascites production, in these patients. The positive results from these well-designed studies examining the outcome of LLR for severe cirrhotic patients could lead to expansion of the indications for LLR.

Additional benefits of LLR in other aspects were found in other studies. The development of fewer adhesions with laparoscopic surgery was found to facilitate subsequent surgeries[55]. With the initial LR performed in laparoscopic approach, the subsequent salvage transplantation requires a shorter operative time, with reduced blood loss and fewer transfusions[56]. Furthermore, recurrence with potential multicentric metachronous lesions is an important issue for HCC patients with CLD. Repeat LR increases the difficulty of LR as a result of modifications to the anatomy and the formation of adhesions. Two studies[57,58] compared laparoscopic and open procedures with regard to repeat LR. The operating time of repeat LLR was significantly shorter with previous LLR compared to OLR. In addition, repeat LLR was associated with reduced blood loss and postoperative morbidity, and a shorter hospital stay compared with repeat OLR regardless of the approach used in the previous LR. The benefit of LLR for repeat procedures may be due to a reduced need for adhesiolysis because of the specific view and approach/manipulation of LLR (Figure 1)[59-61]. This may also cause the reduction of surgery-induced injury on the liver and the area surrounding it.

CONCLUSION

The advantages of LLR for HCC patients with CLD include reductions of surgery-induced parenchymal injury and destruction of the collateral blood/lymphatic flow around the liver. LLR also minimizes the production of postoperative ascites and results in fewer subsequent fatal complications. The formation of fewer adhesions and improved vision and manipulation between adhesions facilitates subsequent repeat LR procedures. These characteristics of LLR may lead to expansion of the indications for LR for these patients (Table 1). However, further investigations are required to document the benefits of LLR in specific conditions.

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EDITORIAL

Is gall bladder cancer a bad cancer *per se*?

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Abstract

Gall bladder cancer (GBC) has one of the poorest outcomes of all cancers. Early GBC is difficult to diagnose on even computed tomography. GB has no submucosa and the cancer infiltrates directly into the muscularis propria. GB wall is thin and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. Tumor in the GB neck often needs extended right hepatectomy. Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy or even hepato-pancreato-duodenectomy. Mortality of surgical procedures, when performed for GBC, is higher than when performed for other cancers. Survival in GBC, even after R0 resection, is poor. There is no proven role of neo-adjuvant or adjuvant therapy for loco-regionally advanced GBC. There is no role of palliative surgery in metastatic GBC. Early GBC is diagnosed incidentally after cholecystectomy for stones and requires reoperation for completion extended cholecystectomy but unfortunately, most surgeons are not aware of this. GBC has a peculiar epidemiology and is uncommon in the West and has, therefore, not received much attention. Preventive cholecystectomy for asymptomatic stones is not recommended and there is no serum marker for screening. With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

Key words: Gall bladder neoplasms; Cholangiocarcinoma; Cholecystectomy; Hepatectomy; Hepato-pancreato-duodenectomy

Core tip: Gall bladder (GB) wall is thin and important adjacent organs get easily infiltrated. Tumor in GB neck needs hepatectomy and infiltration of duodenum/pancreas necessitates pancreato-duodenectomy; mortality of these procedures is high. Survival in gall bladder cancer (GBC), even after R0 resection, is poor. There is no role of neo-adjuvant or adjuvant therapy. Early GBC, diagnosed incidentally after cholecystectomy for stones, requires reoperation but most surgeons are not aware of this. GBC, uncommon in the West, has not received much attention. Preventive cholecystectomy is not recommended and there is no marker for screening. GBC is a bad cancer *per se*!

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Gall bladder cancer (GBC), the commonest malignancy of the biliary tract, has one of the poorest outcomes of all cancers.

Early GBC has symptoms indistinguishable from gall stone disease (GSD). Diagnosis of early GBC is almost impossible on ultrasonography (US) and difficult on even computed tomography (CT) cf. hepatocellular carcinoma (HCC) and peri-ampullary cancers; endoscopic ultrasonography (EUS) is better but is not available easily and everywhere. Magnetic resonance imaging (MRI) too has no role in the diagnosis of GBC (cf. cholangio-carcinoma). GBC is PET avid but its use is restricted mainly to detect spread than for diagnosis. Laparoscopy again is to look for peritoneal dissemination than for diagnosis.

Even the anatomy of the gall bladder (GB) is against it. Unlike the intestines, GB wall has no submucosa so that a mucosal cancer infiltrates directly into the muscularis propria. Normal GB wall is thin (< 3 mm) and important adjacent organs viz. liver, duodenum and pancreas get easily infiltrated. The hepatic surface of the GB has no peritoneal cover (serosa) so a GB tumor easily infiltrates the liver parenchyma. Surgical resection for GBC involves lymphadenectomy and one (liver) or more organs. A 2 cm liver margin is required for GBC (cf. colo-rectal cancer liver metastases CRLM where even 1 mm margin is acceptable). Liver resection is usually in the form of a wedge but a major liver resection may be required if there is significant liver infiltration. For tumors in the GB neck, CBD has to be resected to achieve a negative margin; right portal pedicle lies at a distance of just a few mm from the GB bed and has to be sacrificed to achieve a 2 cm liver margin thus needing extended right hepatectomy (ERH). Infiltration of duodenum/pancreas may necessitate pancreato-duodenectomy (PD) and some patients with loco-regionally advanced disease may even require hepato-pancreato-duodenectomy (HPD). Involvement of main portal vein and proper hepatic artery contraindicates resection. While minimally invasive surgery has been shown to be technically safe and oncologically adequate for several cancers, *e.g.*, esophagus, stomach and CRC, its role and place in GBC is yet to be established.

Mortality of surgical procedures for GBC is high; mortality of the same surgical procedures when performed for GBC is higher than when performed for other cancers, *e.g.*, mortality of major hepatectomy for GBC is 16% *vs* 4% for cholangio-carcinoma CC[1]. Mortality of HPD for GBC is much higher than that for CC[2]. In a recent review, the Nagoya group observed that HPD, which can be performed for CC remains controversial for GBC[3].

Survival in GBC, even after R0 resection, is poor. In many reports, no T3/T4 or node positive patient survived for 5 years. Even actuarial survival of GBC is much poorer, probably the poorest of all, than every other cancer - 5 year survival of stage Ⅲ GBC is 7%-8% cf. 72% for breast, 38%-74% for CRC and 9%-20% for stomach cancer in stage Ⅲ[4]. In many cancers, the survival curve plateaus after the first two years and very few late recurrences occur, *e.g.*, 5 year survival in CRC is 65% and drops to only 58% at 10 years[4]. In GBC, disease recurs and patients die even after five years; in a report of 165 patients with T3/T4 GBC, 25 patients survived for 5 years but only 11 survived for 10 years[5]. A critical review of major resections, *e.g.*, ERH, PD and HPD for GBC, reported mostly from Japanese centers, reveals that more patients died of these procedures than actually lived for 5 or 10 years because of them.

A large majority of GBCs are metastatic or loco-regionally advanced. In some cancers, *e.g.*, genito-urinary, breast and CRC, cure is possible even in presence of metastases; even repeat resections are indicated. In GBC, there is no role for resection in presence of metastases. Unlike some other cancers, *e.g.*, CRC and stomach, where the primary tumor should be resected for palliation even if metastases are unresectable, there is no role of palliative surgery in metastatic GBC. Total hepatectomy and transplant are options for unresectable HCC and CC and for neuro-endocrine tumors (NETs) with liver metastases but not for GBC. For loco-regionally advanced GBC, there is no proven neo-adjuvant treatment (cf. unresectable pancreatic, esophageal and rectal cancers). As opposed to breast cancer and CRC, where personalized chemotherapy is being increasingly used, the role of even adjuvant therapy is not well established in GBC. No molecular targets have so far been identified for GBC hence no biologicals are suitable for use.

GBC is resectable for cure only when it is confined to the GB and has spread to a few regional lymph nodes. Such early stage disease is invariably an incidental finding on histopathology of the GB removed for GSD. Most such patients need a reoperation for completion extended cholecystectomy (CEC)[6]; unfortunately, most surgeons are not aware of this and the patient is denied a possible attempt at cure. This is reflected in poor (50% for stage Ⅰ and 28% for stage Ⅱ) 5 year survival in more than 10000 patients treated between 1989 and 1996[4].

Injustice has been done to GBC as it was clubbed with liver in the 6th International Classification of Diseases ICD (1950), with other biliary cancers in the 7th ICD (1957) and with extra-hepatic bile duct and ampulla in the 8th ICD (1967); it was only in the 9th ICD (1977) that GBC received an identity of its own as 156 and recently as C 23.9 in the 10th ICD (2007).

The peculiar epidemiology of GBC is also its own enemy. GBC is a "non-western disease" - rare in United States/Canada, United Kingdom/Western Europe and Australia/New Zealand but common in Central/South America, Central/Eastern Europe, South Asia (India) and East Asia (Japan and South Korea)[7]. Not much funding is available and very little investigative work has, therefore, been done for GBC. Even rarer tumors, *e.g.*, cystic pancreatic neoplasms (CPN) and gastro-intestinal stromal tumors (GIST) have received more attention because of the populations they afflict. GBC is one of the few non-gender related cancers which are more common in women than in men; in many under developed and developing economies, women tend to receive less optimal health care as compared to men.

Prevention, therefore, becomes important. Primary prevention remains a dream as the etiology of GBC is not yet known (cf. tobacco for lung and oral cavity, hepatitis for HCC). Secondary prevention, cholecystectomy for asymptomatic GSD, is invasive, expensive and risky and is not recommended. There is no serum marker (cf. PSA for prostate) for screening; surveillance of high risk groups viz. those with asymptomatic GS using US (cf. alfa-feto protein AFP for HCC in patients with cirrhosis or endoscopic, *e.g.*, for esophageal cancer in Barrett's and for CRC in inflammatory bowel disease IBD) is not an option as US detects the disease in advanced stage (Ⅱ or more) only.

With all factors pitched against it, it does appear that GBC is a bad cancer *per se*!

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ORIGINAL ARTICLE

Retrospective Cohort Study

Capillary refill time as a guide for operational decision-making process of autoimmune pancreatitis: Preliminary results

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Author contributions: Yazici P and Aydin U contributed to the conception and design, acquisition of data, or analysis and interpretation of data; Yazici P and Ozsan I drafted the article or revising it critically for important intellectual content; Yazici P and Aydin U made the final approval of the version to be published.

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Abstract

AIM: To investigate the efficacy of a novel intraoperative diagnostic technique for patients with preliminary diagnosis of autoimmune pancreatitis (AIP).

METHODS: Patients with pancreatic surgery were reviewed to identify those who received a preliminary diagnosis of AIP between January 2010 and January 2014. The following data were collected prospectively for patients with a pathological diagnosis of AIP: clinical and demographic features, radiological and operative findings, treatment procedure, and intraoperative capillary refill time (CRT) in the pancreatic bed.

RESULTS: Eight patients (six males, two females; mean age: 51.4 years) met the eligibility criteria of pathologically confirmed diagnosis. The most frequent presenting symptoms were epigastric pain and weight loss. The most commonly conducted preoperative imaging studies were computed tomography and endoscopic retrograde pancreaticodoudenography. The most common intraoperative macroscopic observations were mass formation in the pancreatic head and diffuse hypervascularization in the pancreatic bed. All patients showed decreased CRT (median value: 0.76 s, range: 0.58-1.35). One-half of the patients underwent surgical resection and the other half received medical treatment without any further surgical intervention.

CONCLUSION: This preliminary study demonstrates a novel experience with measurement of CRT in the pancreatic bed during the intraoperative evaluation of patients with AIP.

Key words: Autoimmune pancreatitis; Pancreatic mass;

Inflammation; Hypervascularity; Capillary refill time

Core tip: Autoimmune pancreatitis is still a diagnostic dilemma, and there is a way to go, especially differentiating from pancreatic malignancy. Hence the debate: to cut or to observe. We hypothesized that this infrequent inflammatory event causes increased vascularity on pancreatic tissue. Thus, we aimed to display whether there was a remarkable vascularity on the pancreatic surface or not by using capillary refill time. Preliminary results showed decreased capillary refill time demonstrating hypervascularity on the pancreatic surface and this inspired that capillary refill time could be an additional tool to guide the operational decision-making process of autoimmune pancreatitis.

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INTRODUCTION

Autoimmune pancreatitis (AIP) is clinically defined as chronic inflammatory pancreatitis with irregular narrowing of the main pancreatic duct, presenting with hyperglobulinaemia (especially IgG4)[1,2]. Since its first description[3], this infrequently recognized pathology has posed a diagnostic dilemma; its initial clinical symptoms are generally non-specific (abdominal pain, weight loss and obstructive jaundice) and commonly lead to a misdiagnosis of pancreatic cancer.

Differentiating AIP from malignant pathology in the pancreas requires some clinical judgment in assessing the findings of the diagnostic workup and can be dependent upon the treating physician's surgical experience with both conditions. Although imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI) and endosonography could provide differential findings, the accuracy is not consistent among all patients. Furthermore, there are many pitfalls in the frozen section diagnosis of pancreatic lesions and AIP patients may remain undiagnosed, so that sometimes, experience of the surgeon can play a remarkable role in determination of which management strategy will be performed.

Intraoperative observations may be useful for diagnosing AIP and determining the approach best suited for clinical management of a particular case; for example, surgeons may use macroscopic observations, such as that of a tumoral mass, to differentiate pancreatic cancer from AIP, and consider a pancreatoduodenectomy as treatment. However, it is important to remember that at least 5% of patients undergoing surgery for a preliminary diagnosis of pancreatic cancer are found to have benign inflammatory disease according to their histopathological findings[4]. Although a few policies have been published to help guide the surgeon's decision for managing such borderline cases, this entity remains a diagnostic challenge in general.

For the current study, we were inspired by the inflammatory nature of AIP pathology to investigate whether there is an association between changes in the pancreatic vascular pattern in patients with AIP, and whether such an association would be related to a measurable increase in blood flow in the pancreatic bed due to ongoing inflammation. We hypothesized that such an increase (reflective of the circulatory status) may be measurable as capillary refill time (CRT). Thus, this preliminary report presents our initial experience with measurement of CRT in the pancreatic bed during the intraoperative evaluation of patients with AIP.

MATERIALS AND METHODS

For this study, the medical records of patients undergoing pancreatic surgery were searched to identify patients who received a preliminary diagnosis of AIP between January 2010 and January 2014. All patients provided informed written consent prior to study enrollment and were consented for surgical procedure, as well. Those patients with a pathologically confirmed diagnosis of AIP were selected for study inclusion. All data recorded prospectively were retrieved from an IRB approved database. Clinical and demographic features of the patients, diagnostic methods and radiological findings, intraoperative observations, surgical procedures and outcomes were analyzed. Although systemic disease was investigated in three cases, increased IgG4 levels was detected in only one patient.

A single clinician using the following procedure made all measurements of CRT: First, the patient's core temperature was evaluated (nasopharynx, normal range: 36.5 ℃-37.5 ℃) and proper thermoregulation was ensured. Then, the CRT was determined by pressing a gloved finger against the pancreatic surface, particularly on the most vascularized portion, until the region turned white (pressing time ranged between 4 and 7 s). The finger pressure was then fully released and the time it took for the pancreatic surface to return to its previous color was measured to the nearest second using a chronometer (generally carried out by the anesthesia care team). None of the patients received inotropic agents at the time of the CRT measurement. Each patient's vital signs were recorded during the CRT measurement; in the case of abnormal vital signs, treatment was immediately initiated to restore the hemodynamic profile, after which a repeat measurement was taken. The normal values for CRT are well established and defined as < 2 s, with prolonged refill defined as $\geqslant 2$ s. A digital video camera was used

Table 1 Demographic features of the patients with autoimmune pancreatitis

Sex	Age (yr)	Presentation	Diagnostic tests	Findings	CRT (s)	Surgery
Patient 1, F	69	Jaundice, epigastric pain	Doppler US, CT	4 cm × 4 cm solid mass, Pancreatic head, LAPs	0.80	PPPD
Patient 2, M	61	Epigastric pain, weight loss, jaundice	ERCP, CT	Pancreatic head mass (4 cm × 3 cm), obstruction of the CBD, invasion of SMV	1.35	PPPD
Patient 3, M	34	Jaundice, pruritis, fatigue	ERCP, CT	Periampullary solid mass 2 cm × 3 cm in size	0.68	Biopsy
Patient 4, M	56	Fatty stool, epigastric pain, weight loss	Doppler US, PET-CT	Diffuse swelling of the pancreas	0.58	Biopsy
Patient 5, M	42	Epigastric pain, weight loss, fatty stool	Doppler US, CT, EU	Periampullary solid mass (2 cm × 2 cm)	0.75	Biopsy
Patient 6, F	58	Mild epigastric pain, weight loss	CT, MRI,	Diffuse swelling and 2 cm × 2.5 cm solid mass in pancreatic head	0.77	PPPD
Patient 7, M	45	epigastric and back pain, weight loss	CT, MRI, EU	Diffuse swelling and mass formation 2 cm × 3 cm in size	0.69	Biopsy
Patient 8, M	53	Epigastric pain, weight loss, jaundice	ERCP, MRI	Pancreatic head mass (3 cm × 3 cm), obstruction of the CBD	1.26	PPPD

F: Female; M: Male; CRT: Capillary-refill time; US: Ultrasound; CT: Computed tomography; ERCP: Endoscopic retrograde cholangio-pancreatography; MRI: Magnetic resonance imaging; EU: Endoscopic ultrasound; LAP: Lymphadenopathy; SMV: Superior mesenteric vein; CBD: Common bile duct; PPPD: Pylorus-preserving pancreaticoduodenectomy.

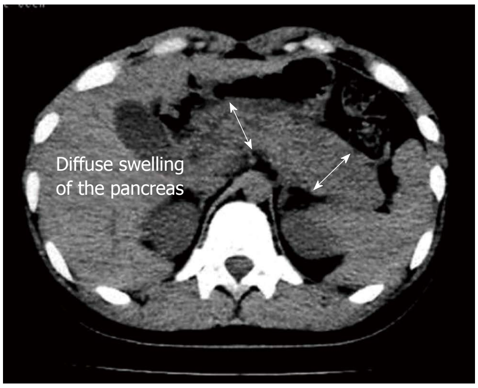

Figure 1 Diffuse swelling and enlargement of the pancreas (double-head arrow).

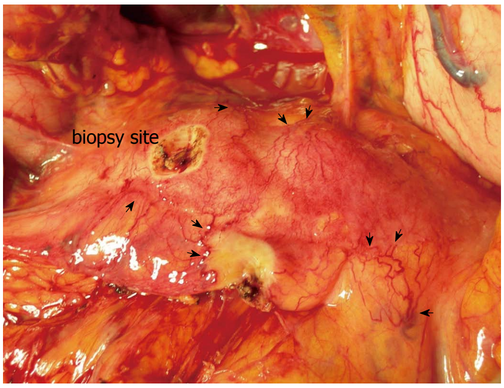

Figure 2 Intraoperative findings of diffusely increased vascularity on the pancreatic surface (black arrows), picture was taken after.

to record the CRT during the operation, and the study investigators reviewed the recorded tape, along with use of a chronometer, to confirm the recorded CRT measurement.

The criteria used by the surgical team to determine whether resection should be performed were standardized and included suspicious findings from endoscopic ultrasound (EU)-guided biopsy, malignant cells detected by frozen section assessment, older age (which increases the possibility of malignancy), and severe obstruction of the common bile duct (CBD) that could not be managed by endoscopic retrograde pancreaticoduodenography (ERCP).

RESULTS

Eight patients with pathologically diagnosed AIP were included in the study; this group was composed of two females and six males, with a mean age of 51.4 years (range: 34-69 years). The duration of symptoms ranged from 2 wk to 3 mo, and the most frequent presenting symptoms were epigastric pain and weight loss. All patients showed mildly elevated levels of liver function enzymes. Among the three patients examined for IgG level, only one (patient 4) showed an elevated level. The methods of and findings from preoperative imaging studies are shown in Table 1. For patient 2, the CBD cannulation failed during ERCP and the pancreatic mass was observed to have invaded the superior mesenteric vein. Patients 3 and 8 also underwent ERCP, to address the CBD dilatation and relieve the obstruction. For some patients, the CT scan revealed diffuse swelling of the pancreatic tissue (Figure 1). The tumor masses were most frequently located in the pancreatic head (6/7 cases). EU-guided fine needle aspiration biopsy (FNAB) was performed in two patients, with both cases showing non-specific inflammatory changes.

For all patients, the intraoperative macroscopic pancreas assessment revealed diffuse hypervascularization (Figure 2). The median CRT was 0.76 s (range: 0.58-1.35 s). Six patients had a CRT of < 1 s, with four of those patients undergoing only a biopsy before the surgical procedure was suspended. Five patients had inconclusive findings of malignancy from the histological analysis of the frozen section biopsy specimens, while four of these patients had findings compatible with inflammatory changes. When the surgical team considered the accumulated findings from each patient's preoperative work-up along with their intraoperative findings, surgical resection (pylorus-preserving pancreaticoduodenectomy) was carried out for one-half of the patients (4/8 cases; Table 1).

All patients experienced an uneventful postoperative recovery. Patients who underwent biopsy only (without further surgery) were administered corticosteroids on a 3-wk 1 mg/kg course followed by a life-long 5 mg maintenance course. In all patients but one, the medical treatment led to symptom improvement. Any patient required pain management was referred to an algologist. The mean follow-up period was 26.4 mo, during which none of the cases showed signs of malignancy. In addition, none of the patients who underwent pylorus-preserving pancreaticoduodenectomy showed symptomology or abnormal findings related to other organ systems, leading to their classification as type 2 AIP cases.

DISCUSSION

We investigated the clinical importance of CRT measurement for patients with a prediagnosis of AIP. In these patients, a decreased CRT was found as an operative observation when the cut-off value of 2 s was used. Half of the patients underwent surgical resection (in accordance with the criteria explained in Methods section). It is well-known that not all pathologically diagnosed AIP cases have preoperative findings consistent with the set of specifications and criteria in the literature, highlighting the clinical dilemma facing physicians treating this disease[5]. In particular, AIP patients present with remarkable variation and no single diagnostic test has been established as the gold standard[6,7].

In the present study, preoperative diagnostic work-up, including imaging methods such as CT, MRI and EU, were not adequate to establish a definitive diagnosis. It is possible that the technical limitations of EU related to tissue sampling, particularly when the head of the pancreas is involved[8], may explain the inadequacy of this method in diagnosing our AIP cases. Moreover, the negative predictive value of EU-guided FNAB for pancreatic cancer has been reported as about 75%[9,10]. However, the focal type of AIP that the majority of our patients were ultimately diagnosed with also presented a diagnostic challenge for ERCP, emphasizing the technical difficulty in diagnosing this condition prior to surgery.

Dominance of elderly patients among AIP cases and presentation with severe jaundice contribute to the diagnostic difficulty or misdiagnosis of AIP[11,12]. Although the clinical manifestation of AIP may vary from patient to patient, most cases mimic the symptoms of pancreatic cancer. Hence, the high suspicion of malignancy leads treating physicians to prefer surgical removal as the treatment, particularly for patients with focal AIP. It is important to note that the case series reported herein included only AIP cases for whom the decision to perform surgery had already been made due to suspicion of malignancy or obstructive pathology which were deemed inappropriate for conservative management. Surgeons frequently need more information, apart from laboratory and radiological findings, demonstrating diffuse enlargement or focal masses in the pancreas, to diagnose AIP[11,13,14]. Therefore, we suggest that some intraoperative findings may help to guide the operational decision-making process.

The "inflammatory hypervascularization" character of the pancreas in AIP was the basis of our hypothesis and CRT was used in our study to evaluate this entity. Findings from this study demonstrated increased blood flow in response to the existing inflammation and subsequent decrease in CRT. It is well known that both malignant and benign pancreatic tissues may be reflected by changes in the vascularization patterns. Central hypervascularization caused by increased flow in the main artery of the organ or local neovascularization is more likely to be present in malignant lesions. However, a carcinoma may also present hypovascularization as desmoplastic changes and vascular encasement leading arterial stenosis or obstruction[15]. On the contrary, benign lesions, especially in inflammatory conditions, increase the propensity to develop diffuse hypervascularization and the capillary flow rate increases due to the associated increase in metabolic activity. Likewise, Hocke *et al*[16] reported that contrast-enhanced EU shows hypervascularization of AIP lesions, whereas pancreatic cancer lesions appear to be more hypovascular masses. In this study, diffuse hypervascularization was observed along the anterior surface of the pancreatic body and confirmed by the CRT measurements. With regard to the CRT results, all cases in our series were diagnosed with a value lower than the normal range reported in the literature. The normal value for CRT should be 2 s[17,18] and, on average, CRT increases 3.3% per decade increase in age. The median CRT for pediatric patients is 0.8 s, while that of adults is 1.0 to 1.5 s[19]. In our case series, the average CRT was 0.76 s.

Most of the focal AIP cases reported in the literature have been diagnosed only when swelling has become diffuse or after surgical observation[20]. In our case series, the definitive diagnosis was achieved according to accumulated findings from histological analyses of frozen section specimens, CRT, the intraoperative observations of pancreatic vascular pattern (particularly diffuse peripheral hypervascularization), and pathological findings (periphlebitis, dense lymphoplasmocytic infiltration, and/or fibrotic changes). For four of our cases, the surgery was halted due to pathological confirmation of notable inflammatory changes and markedly decreased CRT; consequently, each case was referred for non-surgical medical treatment.

Several limitations to our study design exist and must be considered when interpreting our findings. First, the small sample size (eight cases) prevented us from establishing a significant causal relation between decreased CRT and AIP; a comparative study between suspected AIP patients and those with definitive pancreatic cancer might allow strong conclusions to be drawn. Second, the CRT measurement was made using a chronometer and based on visual inspection; this measurement may be more accurate using a standardized method, such as digitalized CRT techniques. Intraoperative ultrasonography-based elastography is an emerging concept and may be also useful in addressing this clinical dilemma. However, this study aimed to describe CRT as an additional tool to lead surgeon to examine the patient for possibility to have AIP in the light of the surgeon's experience and intraoperative observations.

This paper demonstrates preliminary results of a novel experience with measurement of CRT in the pancreatic bed during intraoperative evaluation of patients with AIP. The main finding of this prospective analysis of patients with a prediagnosis of AIP is that changes in macroscopic vascular pattern and decreased CRT, in conjunction with frozen section analysis, can help to guide the treatment approach. Large-scale clinical trials are needed to determine its role in clinical decisions making for this very complicated entity.

COMMENTS

Background

Autoimmune pancreatitis (AIP) remains a diagnostic challenge for both clinicians and surgeons. Differentiating AIP from malignant pathology in the pancreas requires some clinical judgment in assessing the findings of the diagnostic workup and can be dependent upon the treating physician's surgical experience with both conditions.

Research frontiers

The authors aimed to introduce a novel intraoperative diagnostic technique for patients with preliminary diagnosis of AIP.

Innovations and breakthroughs

This preliminary study demonstrating a novel experience with measurement of capillary refill time in the pancreatic bed during the intraoperative evaluation of patients with AIP provided a decreased capillary refill time which can be attributable to hypervascularity.

Applications

Hypervascularization of AIP lesions radiologically inspired us to investigate the efficacy of this feature. It was evaluated by measurement of capillary refill time in the operating theatre. Preliminary results showed that it can be an additional tool in the surgical decision-making process.

Terminology

Pancreatic hypervascularity: increased vascular web secondary to pancreatic inflammation; Capillary refill time: the time taken for color to return to an external capillary bed after finger pressure is applied to cause blanching on pancreatic tissue.

Peer-review

An interesting novel method of assessing of this difficult pancreatic condition. The paper will be of interest to our readers interested in pancreatic problems.

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ORIGINAL ARTICLE

Retrospective Study

Accuracy of computed tomography in nodal staging of colon cancer patients

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Author contributions: Choi AH and Nelson RA contributed equally to this work; Garcia-Aguilar J and Kim J designed the research; Choi AH, Schoelhammer HF, Cho W, Ko M, Arrington A, Oxner CR, Wong J and Garcia-Aguilar J acquired the data; Choi AH, Nelson RA, Schoelhammer HF, Cho W and Oxner CR analyzed the data; Choi AH, Nelson RA, Schoelhammer HF, Cho W and Ko M wrote the manuscript; Arrington A, Oxner CR, Fakih M, Wong J, Sentovich SM, Garcia-Aguilar J and Kim J provided critical revisions for intellectual content; all authors provided final approval of the manuscript.

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Data sharing statement: Dataset available from the corresponding author at jokim@coh.org.

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Abstract

AIM: To predict node-positive disease in colon cancer using computed tomography (CT).

METHODS: American Joint Committee on Cancer stage Ⅰ-Ⅲ colon cancer patients who underwent curavtive-intent colectomy between 2007-2010 were identified at a single comprehensive cancer center. All patients had preoperative CT scans with original radiology reports from referring institutions. CT images underwent blinded secondary review by a surgeon and a dedicated abdominal radiologist at our institution to identify pericolonic lymph nodes (LNs). Comparison of outside CT reports to our independent imaging review was performed in order to highlight differences in detection in actual clinical practice. CT reviews were compared with final pathology. Results of the outside radiologist review, secondary radiologist review, and surgeon review were compared with the final pathologic exam to determine sensitivity, specificity, positive and negative predictive values, false positive and negative rates, and accuracy of each review. Exclusion criteria included evidence of metastatic disease on CT, rectal or appendiceal involvement, or absence of accompanying imaging from referring institutions.

RESULTS: From 2007 to 2010, 64 stage Ⅰ-Ⅲ colon cancer patients met the eligibility criteria of our study. The mean age of the cohort was 68 years, and 26 (41%) patients were male and 38 (59%) patients were female. On final pathology, 26 of 64 (40.6%) patients had node-positive (LN+) disease and 38 of 64 (59.4%) patients had node-negative (LN-) disease. Outside radiologic review demonstrated sensitivity of 54% (14 of 26 patients) and specificity of 66% (25 of 38 patients) in predicting LN+ disease, whereas secondary radiologist review demonstrated 88% (23 of 26) sensitivity and 58% (22 of 38) specificity. On surgeon review, sensitivity was 69% (18 of 26) with 66% specificity (25 of 38). Secondary radiology review demonstrated the highest accuracy (70%) and the lowest false negative rate (12%), compared to the surgeon review at 67% accuracy and 31% false negative rate and the outside radiology review at 61% accuracy and 46% false negative rate.

CONCLUSION: CT LN staging of colon cancer has moderate accuracy, with administration of NCT based on CT potentially resulting in overtreatment. Active search for LN+ may improve sensitivity at the cost of specificity.

Key words: Colon cancer; Lymph nodes; Clinical staging; Computed tomography; Neoadjuvant therapy

Core tip: Clinical staging to determine eligibility for neoadjuvant trials requires accurate imaging. This study compares lymph node identification on preoperative computed tomography (CT) scans by outside radiologists, a tertiary cancer center radiologist and a surgeon, mirroring referral patterns to tertiary care facilities. While re-review of CT scans by a tertiary center radiologist improved sensitivity of lymph node detection, CT staging of colon cancer demonstrated moderate accuracy overall. Our findings suggest that the administration of neoadjuvant chemotherapy based on preoperative CT staging would potentially result in overtreatment of colon cancer patients.

Choi AH, Nelson RA, Schoelhammer HF, Cho W, Ko M, Arrington A, Oxner CR, Fakih M, Wong J, Sentovich SM, Garcia-Aguilar J, Kim J. Accuracy of computed tomography in nodal staging of colon cancer patients. *World J Gastrointest Surg* 2015; 7(7): 116-122 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i7/116.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i7.116

INTRODUCTION

Adjuvant chemotherapy is well-established for treating colon cancer patients with American Joint Committee on Cancer (AJCC) stage Ⅲ disease[1]. More recently, there has been growing interest in administering neoadjuvant chemotherapy (NCT) prior to planned surgical resection to reduce disease recurrence in high-risk tumors. Preliminary results from the Fluoropyrimidine, Oxaliplatin and Targeted-Receptor preOperative Therapy (FOxTROT) trial for patients with high-risk operable colon cancer, an ongoing phase Ⅲ randomized controlled trial in the United Kingdom, have demonstrated that NCT for operable, locally-advanced colon cancer can downstage tumors[2]. Patients for the study were selected on the basis of having either T3 tumors with $\geqslant$ 5 mm extramural tumor depth or T4 tumors by computed tomographic (CT) imaging. Nodal stage was not specifically used as inclusion criteria for the study and only 52% of patients randomized to the adjuvant chemotherapy group demonstrated nodal involvement on final pathologic exam.

Unlike rectal cancer, where neoadjuvant chemoradiation is frequently utilized based on staging with endorectal ultrasound (ERUS) or magnetic resonance imaging (MRI)[3,4], the administration of NCT for patients with resectable colon cancer is controversial. In order to appropriately select colon cancer patients for NCT, an accurate and reliable imaging modality for detecting involved lymph nodes (LN) is mandatory. Due to low sensitivity, MRI and positron emission tomography (PET) are not favorable imaging studies for preoperative pathologic LN detection[5-8]. In contrast, CT is currently the most commonly used imaging study used to stage colon cancer patients preoperatively, particularly to identify liver, lung, and other sites of distant metastases that may exclude patients from NCT trials[9-11]. Our objective was to determine the utility and accuracy of preoperative CT scan in detecting regional colon cancer LN metastases by comparing outside CT reports to independent imaging review at a referral center in order to highlight differences in detection in actual clinical practice.

MATERIALS AND METHODS

Patient selection

After obtaining approval from the Institutional Review Board, we identified and analyzed the medical records of 64 colon cancer patients with AJCC stage Ⅰ-Ⅲ disease who underwent curative resection between 2007 and 2010 at City of Hope Comprehensive Cancer Center. Exclusion criteria included evidence of metastatic disease on CT, rectal or appendiceal involvement, or absence of accompanying imaging from referring institutions. Medical records were reviewed for demographic and treatment-related variables.

Data collection

Prior to treatment at our institution, patients had CT imaging performed at outside community hospitals or imaging centers. Outside CT images and radiology reports were obtained on all patients. Secondary

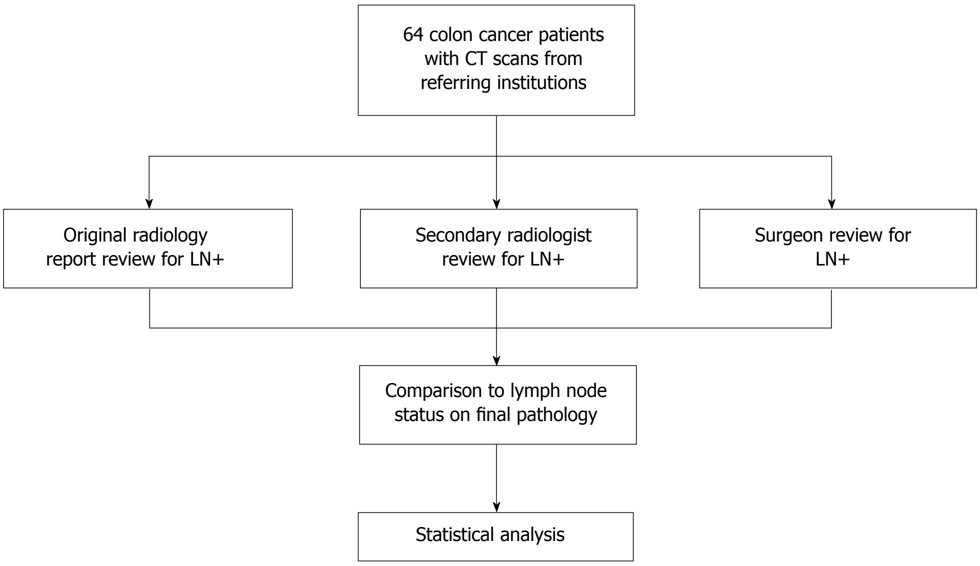

Figure 1 Study design. CT: Computed tomography; LN+: Lymph node positive.

imaging review of the original outside CT scans was conducted by a surgeon and an abdominal imaging radiologist at our institution. They were blinded to the original radiologic report final pathology exam and reviewed the images with the specific goal to identify mesenteric LNs (Figure 1). Once reviewed, each observer's results were compared with the final pathology.

Imaging review

Patients were staged according to the AJCC 7th edition TNM classification system. Variables examined in our study included age, sex, location of primary tumor, T stage, and N stage. Radiographic LN involvement was defined when the longest LN diameter was > 1.0 cm or was 0.7-1.0 cm in size with round shape, heterogeneity, eccentricity, hilar thinning, calcification, central necrosis, or perinodal infiltration. Based on the radiographic review, each patient was designated either lymph node positive (LN+) or lymph node negative (LN-). The reports from outside radiologists were reviewed and the absence of pathologic LN identification was recorded as LN-.

Statistical analysis

Results of the outside radiologist review, secondary radiologist review, and surgeon review were compared with the final pathologic exam to determine sensitivity, specificity, positive (PPV) and negative predictive values (NPV), false positive and negative rates, and accuracy of each review. Both binomial 95%CI and asymptotic *P*-values were calculated to determine the statistical significance of each observer's results compared to a null hypothesis of 50% (*i.e.*, results expected due to random chance). The association between clinical factors and the accuracy of LN detection was also examined.

RESULTS

Study population

From 2007 to 2010, 64 stage Ⅰ-Ⅲ colon cancer patients met the eligibility criteria of our study (Table 1). The mean age of the cohort was 68 years, and 26 (41%) patients were male and 38 (59%) patients were female. Tumors were located in the sigmoid colon (n = 18, 28%), the ascending colon (n = 16, 25%), or the cecum (n = 14, 22%). On final pathology, 19 (30%) patients were stage Ⅰ, 19 (30%) were stage Ⅱ, and 26 (40.6%) patients were stage Ⅲ. LN- disease was diagnosed in 38 patients and LN+ disease in 26 patients. In the LN+ cohort, 17 patients had N1 disease and 9 patients had N2 disease. All patients in our study had ≥ 12 LNs removed with a median of 22 LNs.

Nodal identification by different reviewers

Outside radiology review only identified 14 of 26 LN+ patients and 25 of 38 LN- patients (Table 2). The sensitivity, specificity, and accuracy for the original radiology review for predicting LN disease were calculated, as were PPV, NPV, false positive rate, and the false negative rate (Table 3). The original radiology review had the lowest sensitivity and highest false negative rate compared with the secondary radiologist and surgeon review. Figure 2 shows an example of a LN- CT by the original radiologist; however, this case was LN+ on final pathology, secondary radiology, and secondary surgical reads.

The secondary radiologist correctly identified 23 of 26 LN+ cases and 22 of 38 LN- cases (Table 2). Of the three observers, the secondary radiologist demonstrated the highest sensitivity and accuracy for LN+ detection, 88% (95%CI: 76%-100%, P < 0.01) and 70% (95%CI: 59%-82%, P < 0.01), respectively. The accuracy of the secondary radiologist

Table 1 Patient demographic and final pathologic characteristics

Characteristics	n = 64 (%)
Age (yr)[1]	67.6 ± 12.8
Sex	
Male	26 (40.6)
Female	38 (59.4)
Tumor location	
Cecum	14 (21.9)
Ascending colon	16 (25.0)
Transverse colon	6 (9.4)
Splenic flexure	1 (1.6)
Descending colon	6 (9.4)
Sigmoid colon	18 (28.1)
Rectosigmoid	3 (4.7)
Pathologic stage	
Stage Ⅰ	19 (29.7)
Stage Ⅱ	19 (29.7)
Stage Ⅲ	26 (40.6)
N stage	
N0	38 (59.4)
N1	17 (26.5)
N2	9 (14.1)

[1]Mean ± SD.

Table 2 Comparison of lymph node status prediction by computed tomography against final pathologic examination for three observers

	Final pathology (n = 64)	
	LN+ (n = 26)	LN- (n = 38)
Original radiologist		
LN+	14	13
LN-	12	25
Secondary radiologist		
LN+	23	16
LN-	3	22
Surgeon		
LN+	18	13
LN-	8	25

LN+: Lymph node positive; LN-: Lymph node negative.

was approximately 10% higher than that of outside radiologist review (Table 3).

Surgeon review correctly predicted 18 of 26 LN+ patients and 25 of 38 LN- patients (Table 2). Of the three observers, sensitivity and accuracy of the surgeon review were better than the original radiology review, but not as high as the secondary radiology review (Table 3). The surgeon review had comparable specificity to original radiology review.

Clinical predictors of lymph node identification accuracy

Location of the tumor, sex, body mass index (BMI), and number of LN examined on final pathology were analyzed to determine whether these variables correlated with improved accuracy of LN detection on preoperative CT scan reviewed by the secondary radiologist. LN detection in female patients tended to be more accurate than male patients (76% *vs* 63%, P = 0.27) and BMI < 25 also tended to improve accuracy of LN detection (84% *vs* 67%, respectively; P = 0.16). Total number of LNs examined and location of the tumor did not predict LN detection accuracy (P = 0.91 and P = 0.87, respectively).

DISCUSSION

Given the promising outcomes of preoperative and perioperative therapies in other gastrointestinal malignancies[4,12,13], NCT for node-positive colon cancer remains of great interest. The theoretical benefits of NCT include the reduction of micrometastatic disease and tumor shedding during surgery, and use of tumor response to neoadjuvant chemotherapy to guide further adjuvant therapies if needed after surgery. In addition, patients may be better able to tolerate full-dose chemotherapy regimens in the preoperative rather than postoperative setting. To determine which patients may benefit most from NCT, accurate preoperative imaging to assess nodal disease is essential.

Our study compared CT reviews by the original radiologist and two secondary reviewers (a radiologist and a surgeon) with the final pathology. While the original radiology reviews had low sensitivity, the results from the secondary radiologist and surgeon reviews were comparable to contemporary studies on LN staging by CT. For example, in a meta-analysis of 19 studies that included 907 patients, the overall sensitivity of CT for LN+ detection was 70% and the specificity was 78%[14]. While the majority of prior reports used results obtained only by dedicated abdominal radiologists[10,11,15,16], our study sought to investigate CT reviews performed by three different clinical perspectives in order to compare and contrast the reading results. This approach was designed to mirror actual clinical practice, particularly in tertiary care and referral centers, as patients frequently arrive for initial consultation with outside imaging and reports of variable quality. The sensitivity rates from the original radiology reviews were lower than those from the secondary reviewers, and it is possible that these higher rates of false negatives exist because LN+ detection and staging were not the primary focus of the original review. Compared with the outside radiology review, sensitivity and accuracy for lymph node detection improved with active search for lymphadenopathy on secondary review, while specificity tended to decrease. These findings highlight the importance of independently reviewing outside imaging studies prior to clinical decision making. Of note, in order to avoid multiple insurance charges for preoperative imaging, the majority of patients did not undergo repeat CT scans at our institution. Thus, we were unable to make comparisons in LN detection between outside CT scans and our institutional CT scans.

While CT is the most commonly utilized imaging modality for preoperative staging in colon cancer, the use of PET and MRI for metastatic lymph node detection has been studied by other investigators. PET/CT generally

Table 3 Statistical analysis of lymph node status prediction by computed tomography against final pathologic examination for three observers (n = 64)

	Sensitivity (95%CI, P-value)	Specificity (95%CI, P-value)	PPV (95%CI, P-value)	NPV (95%CI, P-value)	FPR (95%CI, P-value)	FNR (95%CI, P-value)	Accuracy (95%CI, P-value)
Original radiologist	54% (35%-73%, P = 0.69)	66% (51%-81%, P = 0.05)	52% (33%-71%, P = 0.85)	68% (52%-83%, P = 0.03)	34% (19%-49%, P = 0.05)	46% (27%-65%, P = 0.69)	61% (49%-73%, P = 0.08)
Secondary radiologist	88% (76%-100%, P < 0.01)	58% (42%-74%, P = 0.33)	59% (44%-74%, P = 0.26)	88% (75%-100%, P < 0.01)	42% (26%-58%, P = 0.33)	12% (0%-24%, P < 0.01)	70% (59%-82%, P < 0.01)
Surgeon	69% (51%-87%, P = 0.05)	66% (51%-81%, P = 0.05)	58% (41%-75%, P = 0.37)	76% (61%-90%, P < 0.01)	34% (19%-49%, P = 0.05)	31% (13%-49%, P = 0.05)	67% (56%-79%, P = 0.01)

P-value indicates significance of the observer's statistic compared null hypothesis of 0.5. PPV: Positive predictive value; NPV: Negative predictive value; FPR: False positive rate; FNR: False negative rate.

Figure 2 Computed tomography image showing positive nodal disease. This computed tomography image read by outside radiologist as lymph node (LN) negative disease was confirmed to be LN positive by final pathology (arrow head). Contiguous with the base of the appendix, an irregular cecal soft tissue mass (4.5 cm × 2.2 cm × 3.2 cm) can be seen (arrow).

demonstrates lower sensitivity than CT alone[5-7]. Because PET lacks the spatial resolution of CT, even when combined with CT, increased fluorodeoxyglucose (FDG) uptake in lymph nodes can be difficult to interpret, particularly when nodes are in close proximity to a primary tumor with high standardized uptake value (SUV). Similarly, MRI is associated with lower sensitivity, but increased specificity for LN involvement when compared to CT[8], and this may in part due to the fact that MRI criteria for lymph node positivity other than size, such as border criteria or signal criteria, can be subjective and have less reliable inter-observer differences[17].

CT appears to have comparable sensitivity and specificity to ERUS for LN+ detection, although preoperative ERUS staging for rectal cancer depends on the combination of the T and N stage[18]. The ability of ERUS to accurately determine the T stage in rectal cancer is likely better than the ability of CT to determine the T stage for colon cancer. CT can differentiate tumor invasion through the muscularis propria (T1/T2 *vs* T3/T4) in colon cancer with high accuracy[19], but depending on the operator, ERUS better distinguishes invasion of rectal tumors through the layers of the rectal wall with very high accuracy[20]. For these reasons, CT staging for lymph node involvement in colon cancer has not been utilized to select patients for neoadjuvant chemotherapy administration, in contrast to the use of ERUS in rectal cancer staging.

Other groups have also examined the role of preoperative staging with CT in colon cancer patients. Currently, the FOxTROT trial is randomizing patients on the basis of preoperative T staging by CT to determine whether administration of neoadjuvant oxaliplatin, folinic acid and fluorouracil prior to surgical resection impacts long-term outcomes when compared with the current standard of surgical resection followed by adjuvant chemotherapy[2]. Preliminary results showed 91% of patients who were classified as high risk by CT had T3 tumors or above confirmed by final pathology. Of the 99 patients randomized to the preoperative chemotherapy group, 39.4% (39/99) were LN+ on final pathology[2]. Stratification by T stage on CT scan may result in the administration of neoadjuvant chemotherapy to LN- patients, particularly because CT tends to overstage nodal disease compared with the final pathologic diagnosis. In the preliminary results of the FOxTROT trial, 48% of patients were LN- in the postoperative chemotherapy group, but would have received neoadjuvant chemotherapy according to the trial's CT T staging criteria.

The current clinical staging of colon cancer by CT has moderate sensitivity and specificity for detecting lymph node involvement. By implementing a study design that mirrors actual clinical practice, our study demonstrated that although sensitivity increases by actively re-reviewing CT imaging from referral centers for metastatic nodal disease, specificity may be negatively impacted. The patient derived benefit of accurate preoperative CT identification of LNs would be the reliable diagnosis of stage Ⅲ disease prior to surgery with the potential eligibility for neoadjuvant treatment strategies. However, at the current level of CT technology, administration of neoadjuvant chemotherapy based on preoperative CT LN involvement would potentially result in overtreatment of these selected colon cancer patients. Currently, CT scanning is used to determine T stage as entry criteria for clinical trials of neoadjuvant chemotherapy for colon cancer, but the results of these trials are needed before CT becomes the standard imaging modality for detecting presumed LN+ colon cancer and guiding neoadjuvant therapy.

COMMENTS

Background

Adjuvant chemotherapy is well-established for treating colon cancer patients with American Joint Committee on Cancer stage Ⅲ disease. More recently, there has been growing interest in administering neoadjuvant chemotherapy (NCT) prior to planned surgical resection to reduce disease recurrence in high-risk tumors. In order to appropriately select colon cancer patients for NCT, an accurate and reliable imaging modality for detecting involved lymph nodes (LN) is mandatory. The authors' objective was to determine the utility and accuracy of preoperative computed tomography (CT) scan in detecting regional colon cancer LN metastases by comparing outside CT reports to independent imaging review at a referral center in order to highlight differences in detection in actual clinical practice.

Research frontiers

Currently, there is growing interest in preoperatively identifying colon cancer patients who would benefit from neoadjuvant therapy. One such study (Fluoropyrimidine, Oxaliplatin and Targeted-Receptor preOperative Therapy trial) is randomizing patients on the basis of preoperative T staging by CT to determine whether administration of neoadjuvant oxaliplatin, folinic acid and fluorouracil prior to surgical resection impacts long-term outcomes when compared with the current standard of surgical resection followed by adjuvant chemotherapy.

Innovations and breakthroughs

Although previous studies have also demonstrated that CT has modest accuracy for preoperative identification of LNs, this study utilizes comparison of three different clinical perspectives to highlight differences in LN detection in actual clinical practice.

Applications

From a practical standpoint, this results highlight the importance of independently reviewing outside imaging studies prior to surgical resection. The authors have demonstrated that sensitivity for LN detection increases with active search on re-review by the authors' surgeon and dedicated abdominal radiologist compared to the original outside radiology assessments.

Terminology

Node-positive disease in colon cancer involves the metastatic spread of cells from the primary tumor to the regional mesenteric LNs.

Peer-review

This is a timely presentation of important results in clinical oncology.

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CASE REPORT

Delayed esophageal perforation occurring with endoscopic submucosal dissection: A report of two cases

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Abstract

We report two cases of delayed esophageal perforation occurring with endoscopic submucosal dissection. Our cases involved delayed perforation after 10 d in case 1 and after 6 d in case 2. Both cases were related to solid food. We performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall without conservative treatment because both cases involved chest pain and major leakage of food into the mediastinum. Postoperative complications were a local factor (including suture failure and esophageal stricture) in case 1, and we performed endoscopic balloon dilatation five times for esophageal stricture. There was no intrathoracic and mediastinal infection in either case. Surgical treatment for delayed esophageal perforation can be performed safely and surely if diagnosis and assessment are not delayed.

Key words: Esophageal cancer; Endoscopic submucosal dissection; Delayed perforation

Core tip: Patients with early esophageal cancer often experience endoscopic submucosal dissection with complications, including bleeding, perforation, and stenosis. Although most cases are successfully treated conservatively, perforation is a life-threatening complication and can require surgical intervention. In our cases, we performed surgery approximately three hours after the patients' complaints. Postoperative

complications were a local factor (including wound infection and esophageal stricture) and did not include intrathoracic and mediastinal infection. Surgical treatment for delayed esophageal perforation can be performed safely and surely if diagnosis and assessment are not delayed.

Matsuda Y, Kataoka N, Yamaguchi T, Tomita M, Sakamoto K, Makimoto S. Delayed esophageal perforation occurring with endoscopic submucosal dissection: A report of two cases. *World J Gastrointest Surg* 2015; 7(7): 123-127 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i7/123.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i7.123

INTRODUCTION

Patients with early esophageal cancer often undergo endoscopic submucosal dissection (ESD) as a standard treatment. ESD for the esophagus has a high rate of complete resection and a low complication rate[1]. However, performing this procedure on the esophagus is technically difficult because the wall of the esophagus is thin. The risk is particularly high for superficially spreading esophageal cancer. The complications of ESD include bleeding, perforation, and stenosis. The most frequent ESD complication is stenosis (11.6%). Another complication, perforation, is not uncommon (5.0%), and is life threatening. These complications can be successfully treated without surgery in most cases[2]. However, delayed perforation is rare and can require surgical intervention. In this report, we describe our experience with the surgical treatment of delayed esophageal perforation after ESD, and we discuss management strategies.

CASE REPORT

Case 1 was an 83-year-old man with diabetes mellitus who complained of heartburn. Esophagogastroduodenoscopy (EGD) was performed, and middle thoracic esophageal cancer was found (Type 0-Ⅱc). The location was 25-28 cm from the incisor teeth, and the lesion covered three-quarters of the circumference (Figure 1). The depth of tumor invasion indicated that the tumor was in contact with or invaded the muscularis mucosa (M3), as revealed by endoscopic diagnosis. Enhanced computed tomography (CT) did not show a main lesion or lymph node metastases (cT1aN0M0 cStage Ⅰ). We chose to perform ESD, and after resection of the lesion, we injected a steroid (triamcinolone acetonide; Kenacort®-A, Bristol-Myers Squibb, New York, NY, United States) into an artificial ulcer (Figure 1). The histopathological findings were 45 cm × 34 mm, SCC, pT1a-LPM, pHM (2 mm), pVM0, INFa, ly0, v0, and CurA. On day 6 after ESD, the patient began to eat a meal, and esophageal obstruction was suspected due to a complaint of a feeling of blockage while swallowing solid food. Although we performed EGD, stenosis was not found, and the resected area was cured. On day 10, the patient had sudden chest pain during dinner. Enhanced CT showed food residue in his mediastinum, and we diagnosed perforation of the esophagus (Figure 2). After approximately 3 h, we performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall without lymph node dissection. The operative duration was 385 min. The blood loss was 1040 cc (including pleural effusion), and 4 units of red cell concentrate were administered. The perforation extended from the right side to the posterior wall of the esophagus at the inferior mediastinum. The postoperative complications were wound infection and esophageal stricture. The patient did not have an intrathoracic and mediastinal infection. We performed endoscopic balloon dilatation (EBD) for esophageal stricture five times, and the patient was discharged 88 d after surgery.

Case 2 was a 75-year-old man who had experienced ESD three times for upper and middle thoracic esophageal cancer over three years. Ten months after the last ESD, postoperative follow-up found middle thoracic esophageal cancer (Type 0-Ⅱb). The location was 25-28 cm from the incisor teeth, and the extent of the lesion ranged over half of its circumference. The depth of tumor invasion was intraepithelial (M1) as revealed by endoscopic diagnosis. Enhanced CT did not show a main lesion or lymph node metastases (cT1aN0M0 cStage Ⅰ). Although we performed ESD, we could not completely resect the lesion due to marked fibrosis (Figure 3). On postoperative day 3, the patient ate a meal and had no symptoms. On day 6, the patient had sudden chest pain during breakfast. Enhanced CT showed food residue in his mediastinum, and we diagnosed perforation of the esophagus (Figure 4). After approximately 3 h, we performed subtotal esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall with lymph node dissection. The operative duration was 390 min. The blood loss was 270 cc, and no transfusion was administered. The perforation involved the right side of the esophagus below the tracheal bifurcation. Histological examination revealed Ⅱc, 4 mm × 4 mm, SCC, pT1a-EP, ly0, v0, pPM0 (100 mm), and pDM0 (150 mm). There were no postoperative complications in the hospital. The patient did not have an intrathoracic and mediastinal infection and was discharged 47 d after surgery.

DISCUSSION

ESD is a popular endoscopic procedure for the stomach and colon. ESD in the esophagus is accompanied by technical difficulties. Recently, the application of ESD for esophageal lesions has been reported. In the 2007

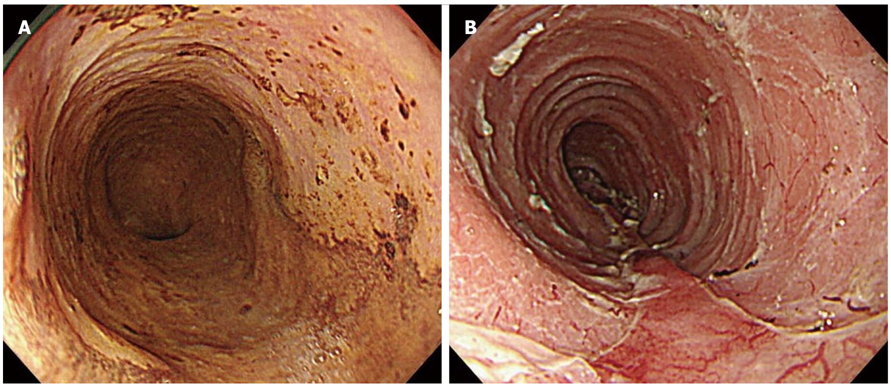

Figure 1 Endoscopic findings in case 1. A: Before endoscopic submucosal dissection (ESD). The lesion covered three-quarters of the circumference; B: After ESD. We injected a steroid into an artificial ulcer.

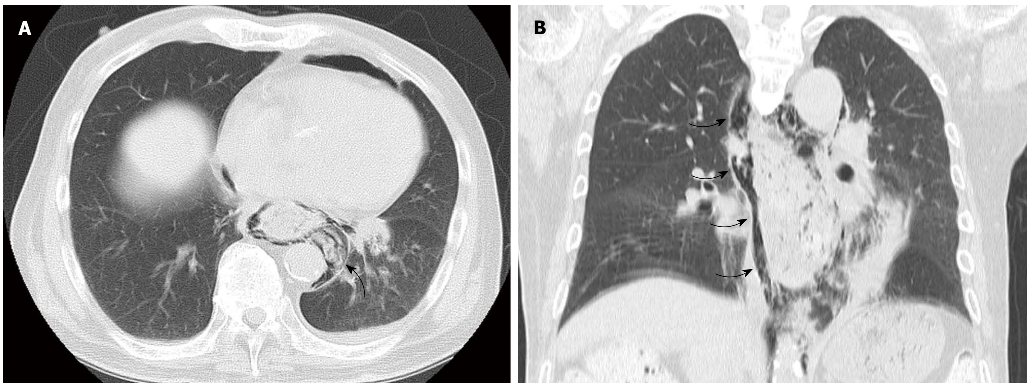

Figure 2 Enhanced computed tomography showed food residue in his mediastinum (arrow) (A) and mediastinal emphysema (arrow) (B).

guidelines of the Japanese Esophageal Society, the absolute indications for this procedure were M1 and tumors invading the lamina propria (M2) that spread to less than two-thirds of their circumference. The relative indication for this procedure was M3 without clinical lymph node involvement[3]. In case 1, the depth of tumor invasion was M3, and the lymph nodes had no metastases. We selected ESD because the patient was elderly. In case 2, we performed ESD because the depth of tumor invasion was M1, and the lymph nodes had no metastases.

The complications of ESD in the esophagus are bleeding, perforation, and stenosis. The most common complication is stenosis, which is reported in 11.6% of cases[2]. Near-circumferential lesions are a risk factor for stenosis, which has been reported in 45% of such cases[4]. Takeuchi *et al*[5] reported that a steroid injected into the remaining submucosal layer of the post-ESD ulcer base was very effective at preventing postoperative stricture after esophageal ESD.

The rate of perforation is low (5.0%) and is caused by perioperative perforation of the ESD and dilation of esophageal strictures[2,6]. Delayed perforation has been reported following the injection of steroids into the deeper layer of the ulcer base and food bolus obstruction[5,7]. Tumor size was not shown to influence the incidence of perforation[1]. In our cases, both perforations were related to solid food. Additionally, a steroid might have been involved in case 1, and fibrosis from a past ESD might have been involved in case 2.

Most perforation cases are treated conservatively, and surgery is rare[2]. Conservative treatment can be selected in cases of effective endoscopic clipping, non-severe mediastinitis related to minor leaks, and stable vital signs. When conservative treatment (such as fasting, intravenous administrations of antibiotics, and drainage) has been ineffective for several days, surgical treatment should be selected[8,9]. Otherwise, the patient is at a risk. Lee *et al*[10] reported that their patient with a perforation developed unstable vital signs during endoscopic clipping, which resulted in an urgent operation. We selected surgery from the outset because the reported chest pain was strong, and enhanced CT showed major leakage of food into the mediastinum. There was no delay in diagnosis or in treatment in either case. Although the surgery was an invasive treatment, postoperative complications were the only local factor (wound infection and esophageal stricture), and the patients' general conditions were stable after surgery. Conservative treatment should not be performed without safety and surety because of the attendant risks[8-10].

In conclusion, surgical treatment for delayed esophageal perforation occurring with ESD can be performed safely when diagnosis and assessment are not delayed.

COMMENTS

Case characteristics

Case 1 was an 83-year-old man with diabetes mellitus who complained of

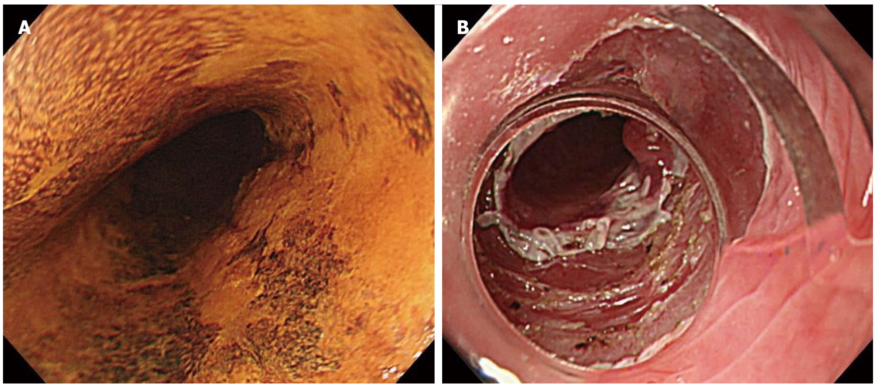

Figure 3 Endoscopic findings in case 2. A: Before endoscopic submucosal dissection (ESD). The extent of the lesion ranged over half of its circumference; B: After ESD. We could not completely resect the lesion due to marked fibrosis.

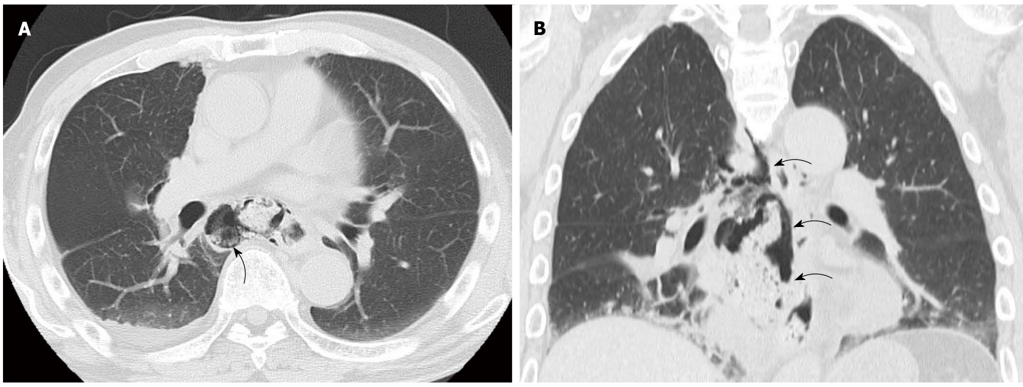

Figure 4 Enhanced computed tomography showed food residue in his mediastinum (arrow) (A) and mediastinal emphysema (arrow) (B).

heartburn. Case 2 was a 75-year-old man who had experienced endoscopic submucosal dissection (ESD) three times for upper and middle thoracic esophageal cancer over three years.

Clinical diagnosis
Delayed esophageal perforation occurring with endoscopic submucosal dissection.

Differential diagnosis
Mediastinitis, empyema, pneumonia.

Laboratory diagnosis
Tumor makers were within normal limits.

Imaging diagnosis
Computed tomography scan did not show a main lesion or lymph node metastases (cT1aN0M0 cStage Ⅰ).

Pathological diagnosis
In case 1, the histopathological findings were 45 mm × 34 mm, SCC, pT1a-LPM, pHM (2 mm), pVM0, INFa, ly0, v0, and CurA. In case 2, histological examination revealed IIc, 4 mm × 4 mm, SCC, pT1a-EP, ly0, v0, pPM0 (100 mm), and pDM0 (150 mm).

Treatment
The authors performed sub total esophagectomy with gastric tube reconstruction of the esophagus *via* the subcutaneous route anterior to the thoracic wall.

Related reports
Delayed esophageal perforation occurring with endoscopic submucosal dissection is rare.

Term explanation
In the 2007 guidelines of the Japanese Esophageal Society, the absolute indications for this procedure were M1 and tumors invading the lamina propria (M2) that spread to less than two-thirds of their circumference.

Experiences and lessons
Food bolus obstruction may be related to delayed esophageal perforation occurring with ESD.

Peer-review
This is a nice case report on the subject of esophageal perforation after endoscopic submucosal dissection.

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EDITORIAL

Laparoscopic pancreatoduodenectomy: How far have we come and where are we headed?

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Abstract

Minimally invasive pancreatoduodenectomy is currently a feasible option in selected patients at high volume centers with available expertise. Although the procedure has been described two decades ago, laparoscopic surgeons have been reluctant to perform it since it is technically demanding. Currently there is no standardized training process for minimally invasive pancreatoduodenectomy and this is required to ensure the safety of the procedure. Even the open pancreatoduodenectomy can be a challenging procedure where the outcome depends much upon the patient volume and surgeon's experience. In the minimally invasive setting, all the current evidence comes from retrospective data with inherent selection bias. Although the proposed benefits have been reported in many series, a randomized trial comparing with the open approach is highly unlikely to happen, given the complexity of pancreatic cancer and patient selection for complex surgery. Rather, in a disease for which cure is an utopian statement, perhaps the ultimate aim of minimally invasive pancreatoduodenectomy can be the improvement in the quality of life. Also further studies are needed to assess the immunologic role affecting the oncologic outcomes in patients undergoing minimally invasive pancreatoduodenectomy. The robotic platforms have got easily accepted since they can overcome some of the limitations of the laparoscopic platforms such as limited range of motion, two dimensional visualization and poor ergonomics. The main limitations of robotic procedures are related to the high costs associated with the system and disposable equipment. Currently evidence is lacking regarding the cost effectiveness of the procedure and also the push from the industry is on rise. All these minimally invasive techniques have a long learning curve and prior extensive experience in hepatopancreatobiliary surgery is mandatory for surgeons embarking on these endeavours.

Key words:Laparoscopic pancreatoduodenectomy; Roboticpancreatoduodenectomy; Minimally invasive pancreatoduodenectomy

Core tip: This editorial while discussing the evidence and controversies surrounding minimally invasive pancreatoduodenectomy, aims to update the reader about the highest level of evidence accumulated over the past few years. Pancreatoduodenectomy remains a demanding procedure even in the open approach and only few surgeons in high volume centres have published the outcomes following minimally invasive pancreatoduodenectomy. All these reports are retrospective data with inherent problems related to bias. To settle this issue, any randomized trial is unlikely to happen given the complexity of the cancer and patient selection for surgery in a resectable cancer. All these issues have been addressed in this editorial so that the pros and cons of minimally invasive pancreatoduodenectomy have been well conveyed and the reader takes home a balanced message.

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HISTORY OF LAPAROSCOPIC PANCREATODUODENECTOMY

Ever since the first description of laparoscopic pancreatoduodenectomy (LPD) in 1994 by Gagner and Pomp[1], the procedure has remained a technically challenging one due to many reasons such as difficult access in laparoscopy, daunting task of controlling hemorrhage laparoscopically due to major vascular injury, demanding skills for biliary and pancreatic reconstruction and also the need to maintain oncologic principles. All these aspects require a high level of surgical expertise. While the safety and feasibility of the technique has been established somewhat, only few published series comprise more than 50 patients[2]. This procedure has been proposed to decrease blood loss, shorten hospital stay, expedite recovery and also shorten time to initiate adjuvant treatment. The ultimate aim of performing minimally invasive pancreatoduodenectomy (PD) should be to perform a better PD with lesser complications and with proven oncologic advantages[3]. Till date, majority of the reports which have shown comparable outcomes with laparoscopic approach are retrospective and they are inherently prone to selection and publication bias.

LPD: FEASIBILITY TO REFINEMENT

In an early experience, Palanivelu *et al*[4]reported the safety of this procedure in a series comprising of 42 patients and safe tumour free margins could be obtained in all patients (Table 1). In another series from Mayo clinic[5], 65 patients underwent LPD with comparable median operative time, blood loss and morbidity. They have shown that LPD has the same advantages which are seen with other minimally invasive procedures. In another review by Gumbs *et al*[6] comprising 285 cases of LPD, the rate of conversion to the open approach was 9% with a morbidity and mortality rate of 48% and 2%, respectively. They concluded that laparoscopic pancreatic head resections were feasible with low mortality rates and acceptable morbidity rates. During these early experiences, there was lack of long term follow-up data and also most were small series retrospectively comparing minimally invasive techniques with open techniques. As more and more experience has been gained in these complex procedures, there are reports where even major venous resections have been performed during LPD. In a cohort of 129 patients undergoing LPD, Kendrick *et al*[7] reported 11 major venous resections with a median operative time of 413 min and 500 mL blood loss without any perioperative mortality.

LPD *VS* OPEN PD: IS IT COMPARABLE OBJECTIVELY?

With increasing number of surgeons rapidly gaining experience in complex laparoscopic pancreatic techniques, a number of comparative studies have been recently published. In a retrospective series involving 51 consecutive patients who underwent either an open or LPD, Kuroki *et al*[8] found decreased blood loss in the laparoscopic assisted PD group compared with the open PD group without any significant difference in the postoperative complications. In another series by Asbun *et al*[3], 215 and 53 patients underwent open PD and LPD respectively. There were significant differences favouring LPD with respect to intraoperative blood loss, length of ICU stay and length of hospital stay (12.4 d *vs* 8 d). They also observed that the operative time was significantly longer in LPD group (608 min *vs* 401 min). However no significant differences were observed with respect to pancreatic fistula rate and delayed gastric emptying. Even though the complication rates were similar, the discrepancy in the length of hospital stay could not be explained and this raises the possibility of bias in outcome measurement commonly observed in retrospective studies. With respect to oncologic clearance, there was no difference in resection margin status. Lymph nodal clearance has been shown to be better with the LPD group (23.4 *vs* 16.8) as well as lower lymph node ratio (0.159 *vs* 0.241). In a retrospective series involving 905 patients undergoing PD, long term survival was better in patients with decreased lymph node ratio[9]. The better vision and magnification offered by the laparoscopy might aid in the better nodal clearance and aggressive lymphadenectomy. However further studies are needed to reach firm conclusions. The time to initiation of adjuvant chemotherapy was not affected by the minimally invasive technique and also

Table 1 Retrospective series showing outcomes following Laparoscopic Pancreatoduodenectomy

Ref.	No. of cases	R0 rate (%)	Mean operative time (min)	Mean node retrieval	Mean blood loss (mL)	Pancreatic fistula rate (%)	Overall morbidity (%)	Mortality (%)	Mean length of stay (d)
Asbun *et al*[3]	53	95	541	23	195	16.7	24	5.7	8
Kendrick *et al*[5]	62	89	368	15	240	18	42	1.6	7
Palanivelu *et al*[4]	42	100	370	13	65	7	NR	2	10
Croome *et al*[10]	108	78	379	21	492	11	5.6	1	6

NR: Near.

there were no reports of port site metastases. The main contraindications for minimally invasive PD included either major vascular involvement or patients with previous abdominal surgeries. The minimal blood loss associated with LPD could be explained by the precise dissection that could be possible due to the better clarity and magnification offered by the state of the art minimally invasive technology. In addition, human instinct is such that laparoscopic surgeons tend to be inherently extra careful with bleeding since any bleeding can greatly obscure telescopic vision. The conversion to open procedure was usually due to failure to progress or difficulty to control a hemorrhage[2].

ONCOLOGIC OUTCOMES: ANY BETTER?

In a retrospective series comprising 108 patients undergoing LPD and 214 patients undergoing open PD, Croome *et al*[10] reported the oncologic advantages over the open approaches. There was no significant difference in the incidence of pancreatic fistula in the LPD *vs* open group (11% *vs* 12%). The median time to initiate adjuvant therapy was 48 d in the laparoscopic group and 59 d in the open group. The authors also observed that a significant proportion (12%) of patients in the open PD group had a significant delay in the initiation of adjuvant chemotherapy when compared to the LPD group (5%). Again this observation is surprising given the fact that tumor size and pancreatic fistula rates between both groups were comparable. The overall survival among the two groups was not significantly different. However the progression free survival was in favour of the LPD group. On univariate analysis, significant predictors of survival included tumour size, positive margins, positive nodal status and those patients having delayed initiation of chemotherapy or no chemotherapy at all. Pertinently, with respect to chemotherapy, the recent ESPAC-3 study has shown that overall survival was better determined by the completion of all cycles of chemotherapy rather than the time of initiation as long as it was started within 12 wk[11].

EVOLUTION OF ROBOTIC PD–HAVE THINGS TRULY PROGRESSED FURTHER?

The well known and accepted advantages of robotic systems with improved 3-dimentional imaging, enhanced dexterity, better visualization with magnification and improved ergonomics fare better than the conventional laparoscopic platform in minimal access approaches[12]. There are a lot of interesting observations from the initial experience of using robotics for PD. Giulianotti *et al*[13] reported in 2010 the first series of 50 patients who underwent robotic assisted PD and showed the operative feasibility of this approach. Few investigators have compared robotic assisted PD with open PD. In the retrospective series reported by Chalikonda *et al*[14] comparing robotic assisted PD with open PD, the duration of surgery was significantly longer in the robotic group but the overall blood loss and the duration of hospital stay (9.79 d *vs* 13.26 d) were lower. Similar results were reported by Zhou *et al*[15] on a cohort of 16 patients, though the number was smaller. Based on these data, the robotic approach has been shown to be associated with faster recovery times but longer operative times. With regards to the oncologic outcomes, Zeh *et al*[16] have reported on 50 consecutive patients who underwent robotic assisted PD where the mean lymph node retrieval was 17 and the overall margin negative resection rate was 89%. Another Italian study has reported on 34 patients who underwent robotic PD without any conversion despite three patients requiring vascular reconstruction[17]. There were no reports of bile leaks and this has been attributed to the precision of robotic suturing in this retrospective study. Although the earlier series of robot assisted PD had documented conversion rates of upto 37%, this rate has decreased with increasing experience[18]. The associated decreased blood loss can have an impact in terms of cancer recurrence[19]. In a recent report by Wada *et al*[20], the use of surgical microscope during reconstruction has shown to decrease the incidence of pancreatic fistula. The precise fine movement in multiple axes as offered by the robotic technology along with its magnified 3-D visual has been claimed to reduce the incidence of fistulas following pancreatic reconstruction in robotic PD. In the Italian cohort[17], there were no clinically significant pancreatic fistulas even though the majority had soft pancreas and small ducts. Quite a significant amount of extra time gets utilized in instrument traffic (upto 1 h in the Italian series) and this necessitates the need for further technical improvisation in order to improve the effective utilization of operative room time. In another major series of 132 patients undergoing robotic PD, Zureikat *et al*[21] have found the median operative time to be 527 ± 103 min and mortality rate of 1.5%. The conversion rate is equivalent or lower than the conversion rates observed in early series of LPD. They concluded that safety and feasibility metrics including the low incidence of conversion support the robustness of this platform with no extra risks apart from inherent risks of this new technology.

CHALLENGES FACING MINIMALLY INVASIVE PD

The minimally invasive approach has been propagated mainly for the advantage of lesser morbidity and reduced hospital stay thereby decreasing cost of treatment. Due to certain inherent disadvantages with LPD such as prolonged operating times, high cost and technical complexity as well as the low quality of evidences for its advantages, currently it may not be possible to recommend it as the standard of care[3]. While well conducted randomized trials have proven the advantages of laparoscopic resections in colonic cancer, the low prevalence of resectable pancreatic cancer, coupled with the complexity of the procedure and the challenges it faces, is likely to ensure that a adequately powered randomized trial is unlikely to happen in the near future[10]. Further, laparoscopic major venous resections can be endeavoured only with extensive laparoscopic experience in pancreatic resections and this demands a long learning curve in a high volume centre. The excess mean operative cost of robotic PD was up to 6193 Euros which is likely to be questioned in the current era[17]. In addition to various challenges mentioned above, cost is also expected to remain a major challenge for minimally invasive PD.

CONCLUSION

Minimally invasive PD is currently a feasible option in selected patients at high volume centers with available expertise. Although the procedure has been described two decades ago, laparoscopic surgeons have been reluctant to perform it since it is technically demanding. Currently there is no standardized training process for minimally invasive PD and this is needed to ensure the safety of the procedure. Even the open PD can be a challenging procedure where the outcome depends much upon the patient volume and surgeon's experience. Even for the open approach, the learning curve extends till the first 60 cases for improvement in measured outcomes[22]. Standardization and service reconfiguration has been shown to improve outcomes following open PD[23]. In the minimally invasive setting, all the current evidence unfortunately comes from retrospective data with obvious selection bias. Rather, in a disease for which cure is an utopian statement, perhaps the ultimate aim of minimally invasive PD can be the improvement in the quality of life. Further studies are needed to define its role concerning quality of life. The robotic platforms have got easily accepted since they can overcome some of the limitations of the laparoscopic platforms such as limited range of motion, two dimensional visualization and poor ergonomics. The main limitations of robotic procedures are related to the high costs associated with the system and disposable equipment. Currently evidence is lacking regarding the cost effectiveness of the procedure and also the push from the industry is on rise. Clearly, with increasing data in this era of information explosion, the surgical fraternity needs to evolve a consensus about minimally invasive PD.

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MINIREVIEWS

Operative considerations for rectovaginal fistulas

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Abstract

To describe the etiology, anatomy and pathophysiology of rectovaginal fistulas (RVFs); and to describe a systematic surgical approach to help achieve optimal outcomes. A current review of the literature was performed to identify the most up-to-date techniques and outcomes for repair of RVFs. RVFs present a difficult problem that is frustrating for patients and surgeons alike. Multiple trips to the operating room are generally needed to resolve the fistula, and the recurrence rate approaches 40% when considering all of the surgical options. At present, surgical options range from collagen plugs and endorectal advancement flaps to sphincter repairs or resection with colo-anal reconstruction. There are general principles that will allow the best chance for resolution of the fistula with the least morbidity to the patient. These principles include: resolving the sepsis, identifying the anatomy, starting with least invasive surgical options, and interposing healthy tissue for complex or recurrent fistulas.

Key words: Rectovaginal fistulas; Anovaginal fistulas

Core tip: There are general principles that will allow the best chance for resolution of a rectovaginal fistula with the least morbidity to the patient. Identifying and addressing the disease process that caused the fistula is critical, including medical management for Crohn's, and resolving inflammation or sepsis with a seton. Then the exact anatomy of the fistula should be defined to determine operative approaches. The operative algorithm should begin with fistula plugs and local advancement flaps, if these fail more invasive options such as diversion, and interposition of healthy tissue should be pursued for complex and recurrent fistulas.

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INTRODUCTION

Rectovaginal fistula (RVF) is an epithelial lined tract between the rectum and vagina, and generally presents with passage of air, stool or even purulent discharge from

Figure 1 Clamp passing through the rectovaginal fistula. Note that the skin bridge courses across the vaginal introitus.

the vagina (Figure 1). This can result in recurrent urinary tract or vaginal infections, but also creates a serious psychosocial burden for the patient[1]. They are well known to dramatically lower a female's self-esteem and prevent successful intimate relationships. Unfortunately, they are also notoriously difficult to manage, despite the numerous surgical options presently described, and may even require fecal diversion to aid closure. When choosing the optimal method to surgically manage these fistulas, the available literature is limited and there currently are no large prospective trials comparing the numerous surgical options. While the paucity of data is driven in part by the relatively low incidence of RVFs and the complex anatomical differences between individual patients, it remains one of the more challenging conditions that surgeons caring for colorectal disease encounter. In this manuscript we will describe the scope and pathophysiology of RVFs, as well as a systematic approach to treating these patients and determining the most suitable operative approach.

RVF ETIOLOGY

RVFs account for approximately 5% of all perirectal fistulas, most commonly occurring as a result of obstetric trauma (85%) and pelvic surgery (5%-7%); while inflammatory bowel disease, malignancy, and radiation therapy encompass the majority of the remaining etiologies[1]. Although obstetric trauma causes the vast majority of RVFs, they are still relatively uncommon in this population, occurring in only approximately 0.1% of vaginal deliveries in Western countries[2]. In contrast, RVFs are considered almost endemic in sub-Saharan Africa and South Asia secondary to obstetrical trauma, with an estimated incidence of 50000 to 100000 new cases annually[2]. With a prevalence of two million, RVFs in developing nations are related to prolonged labors that cause necrosis of the rectovaginal septum. Overall, the past quarter century has seen the rates of episiotomy and operative vaginal delivery decrease dramatically, and with it the number of RVFs. Yet, vaginal deliveries associated with severe perineal lacerations, shoulder dystocia, operative vaginal delivery and prolonged and obstructed labor still occur and remain the highest risk for causing a RVF[3].

Outside of delivery complications, hysterectomy and rectal surgery are the highest risk procedures for causing RVFs. Use of stapling devices (specifically the double-stapled technique) and placement of perineal or vaginal mesh also have been shown to be associated with an increase in the likelihood of RVF formation[3]. The incidence of RVF after a resection for low rectal cancer is widely variable (0.9% to 10%), likely reflecting the heterogeneity in both the individual tumor and operating surgeon. Another possibility is that an anastomotic leak and the resulting pelvic sepsis may lead to the development of a RVF. To avoid the inciting event (*i.e.*, leak), fecal diversion is commonly utilized following a proctectomy and low-lying anastomosis to "protect" it and minimize the clinical consequence of a leak. Although proximal diversion may play a role in improving outcomes (and is itself used in the management of RVFs), fecal diversion does not completely eliminate the risks of RVF, with up to 11% of patients after a proctocolectomy developing RVFs despite complete enteric diversion[2].

Another setting where RVFs can occur is in the setting of malignancy. Anal cancer, rectal cancer and pelvic cancer can all cause RVFs by various mechanisms. First, the lesion itself can be locally destructive, resulting in direct erosion between the two luminal surfaces. Another potential source of the RVF is from the adjuvant radiation therapy that is commonly used to help treat these pelvic malignancies. In this situation, the radiation is cytotoxic, leading to obliterative endarteritis, chronic inflammation and ischemia, and eventually resulting in a fistula between the two anatomical structures[2]. With regards to inflammatory bowel disease, RVFs are most commonly seen in Crohn's disease and rarely in ulcerative colitis. While still relatively infrequent, women with Crohn's disease have a reported cumulative 10% lifetime risk of developing a RVF. Of these, Crohn's patients who have a significant disease burden in their colon are the most likely to be affected by RVFs[2]. While ulcerative colitis patients, especially following total proctocolectomy and ileal-anal pouch procedures, may still develop a RVF, this should be a "red flag" to providers to re-evaluate the patient for the possibility of a misdiagnosis of Crohn's disease.

CLASSIFYING RVFS

Although several classifications of RVFs exist, most RVF are generally broken down into low *vs* high fistulas and simple *vs* complex fistulas. These basic categorizations are extremely helpful in selecting the optimal surgical procedure for the patient. Low fistulas are generally located through or distal to the sphincter complex, but proximal to the dentate line. Due primarily to their location, they may be approached *via* anal, perineal or

Table 1 Reported outcomes with various rectovaginal fistula repairs

	Published number of cases	Success rate	Complications	Fistula anatomy
Advancement flaps	515[10,11]	68%	Incontinence, Recurrence, Larger Fistula	Low
Transperineal/sphincteroplasty	72[12,13]	64%-100%	Incontinence, Sexual dysfunction, Wound Dehiscence	Low
Gracilis muscle flap	99[14,15]	43%-100%	Sexual dysfunction, Cosmesis, Wound dehiscence	Low + High
Plugs	49	45.9%	Recurrence, Cost	Low
Transabdominal ligation[1]	49[16,17]	95%-100%	Bleeding, Intraperitoneal Rectal injuries	High
Mesh repair	48[10,18]	71%-81%	Recurrence, Larger fistula, Cost	Low + High
Martius flap	104[7,19]	65%-100%	Sexual Function, Cosemsis	Low

[1]For high fistula only.

vaginal routes. Anovaginal fistulas have a rectal opening distal to the dentate line and are generally approached the same as a low fistula. High fistulas are proximal to the sphincteric complex, with a vaginal opening near the cervix, and generally require an abdominal approach for repair.

The other classification (simple *vs* complex) primarily differentiates the RVF on whether it will be amenable to a local repair *vs* a more complicated underlying pathogenesis that will require resection, interposition grafts, and/or diversion. A simple fistula is one that is smaller in size (< approximately 2.5 cm), more distally located along rectovaginal septum, and generally occurred a result of trauma or a cryptograndular infection. Complex fistulas are typically a result of inflammatory bowel disease, radiation or invasive cancer. Fistulas that have failed prior attempts at repair are also included in the category. Complex fistulas are commonly more proximal on the rectovaginal septum and are not amenable to primary repair, though may occur anywhere due to the underlying etiology.

PREOPERATIVE CONSIDERATIONS

To optimize outcomes, it is important to ensure that any associated perineal sepsis has resolved completely before attempting an operative repair. This should be achieved primarily by addressing the underlying cause of the fistula (*e.g.*, medical therapy for Crohn's disease, removal of a foreign body such as a staple, or drainage of an abscess). Once this has been addressed, adjunctive measures such as fecal diversion or a draining seton will help resolve the active inflammation and allow the tissues to soften and be more amenable to operative repair.

SURGICAL OPTIONS

The anatomy of the individual patient and the fistula itself are the foremost factors in determining which procedure to perform. In general, our approach has been to recommend an attempt at less invasive procedures first, and if those fail, to then try more complex and potentially morbid procedures. However, depending on the underlying disease state of the patient, individual co-morbidities and the anatomy of the fistula, a more "complex" repair that includes diversion may be recommended at the initial operation (Table 1).

LOW FISTULAS

Plugs

The plugs currently available are composed of synthetic material or made from porcine small intestine submucosa. Regardless of the composition, the tract is debrided, and the plug is brought through the RVF fistula in an attempt to form a biologic seal. In some cases, surgeons will perform a concomitant endorectal advancement flap with plug placement to improve outcomes. Fistula plugs have shown some benefit in perianal fistulas of cryptoglandular origin; yet, the limited data for RVFs has shown only a 20%-50% closure rate. The length of the tract, which is almost always very short, likely plays a role in the high failure rate of this procedure, as has been seen with anal fistulas having short tracts[4].

Advancement flaps

Advancement flaps may be performed by raising either rectal or vaginal mucosa and using it to cover the fistulous tract. This is performed in conjunction with debridement/excision of the fistula tract and primary closure. Healthy surrounding tissue is mobilized along a wide pedicle to ensure adequate blood supply and brought distally to cover the RVF. Different opinions exist as to the best approach. Those that favor an endorectal flap feel it is easier to mobilize and approximate the rectal mucosa when compared with vaginal mucosa, and that the repair is performed from the high-pressure side. Proponents of the vaginal side feel it is better vascularized, less likely to result in a larger fistula, and an easier recovery. In either instance, the reported success rates of this repair are reported between 60%-90%. In general, this is the procedure of choice for low-lying/simple traumatic RVFs without a history of incontinence[4].

Transperineal

A transperineal repair is accomplished by approaching the fistula tract through the perineum, making an incision at the perineal body and dissecting in the rectovaginal septum above the level of the fistula. The tract is then excised, and closure is performed in multiple layers on both the sides. The benefit of this approach is that an overlapping sphincteroplasty can be performed simultaneously for those patients that have associated defects or in those patients in which the fistula can be incorporated into the sphincter repair. This is best used in women with preexisting incontinence, or those a history of failed transanal or transvaginal approach[2]. Success rates are reported to be 64.7%-100%; however, this procedure is often more technically challenging, results in higher morbidity rates, and normally is not a first-line procedure[4].

Martius flap

In 1928 Dr. Heinrich Martius, a professor of gynecology in Gottingen, described using the bulbocavernosus muscle and labial fat pad for vaginal wall defects due to its proximity which allows for a single operative field[5]. The Martius flap was first used in cysto- and urethral-vaginal fistulas. Only later was it adapted to its present use in RVFs. In sum, it is ideally suited for RVF repair, providing a local well-vascularized pedicle of adipose/muscular tissue that is mobile and results in low morbidity. It is most suited for complex, recurrent, or recalcitrant RVFs[6]. The Martius flap is best able to treat low and mid-level fistulas up to approximately 5 cm proximal to the vaginal introitus, but in reality is only limited by the reach of the bulbocavernosus pedicle.

There are approximately 104 cases reported in the retrospective literature with a success rate ranging from 65%-100%[4]. Dyspareunia has been reported in as many as 30% of females at six weeks post operatively when they are allowed to resume vaginal intercourse, but it appears to improve with time. The only other more common complication reported in the literature are labial wound issues (< 10%), which largely resolve with local wound care[7].

Gracilis muscle transposition

In this procedure, the gracilis muscle is harvested from the leg, mobilized on a proximal pedicle, and used as an interposition graft between the rectum and vagina. Success rates are reported from 60%-100%, but there is increased morbidity associated with the harvest site and there appears to be a prolonged decrease in sexual function[4]. Dyspareunia is reported in up to 57% of patients undergoing this operation and the decreased sexual desire has been felt to be, in part, related to the relatively large burden of perineal scarring[8]. Furthermore, when the gracilis is harvested for use in other procedures (*e.g.*, plastic surgery free flaps), a short-term decrease in functionality of that leg has been reported for approximately 6 mo in 26% of the patients, and 6% of patients have long-term difficulties[9].

HIGH FISTULAS

Transabdominal ligation

Transabdominal ligation procedures are typically performed when the RVF is high (*i.e*., vaginal cuff), and may be performed *via* a minimally invasive or open approach. The common bond to these fistulas is often the presence of a prior hysterectomy and an inflammatory condition that resulted in pelvic sepsis that eroded through the vaginal cuff (*e.g.*, Crohn's diverticulitis, anastomotic leak). In this procedure, the offending bowel is resected along with division of the fistula tract. It is often helpful to place a piece of omentum in between the rectum and vagina to avoid recurrence. Some gynecologists prefer to debride and re-close the vaginal cuff, although this is widely variable. Success rates are 95%-100%, and normally this is the preferred treatment for the patient has a high fistula tract[4].

Mesh repair

A mesh repair is essentially the same as transabdominal ligation. However, rather than placing omentum between the rectum and vagina, various biologic meshes have been utilized as an interposition graft between the two structures to prevent re-fistulization. The largest study used porcine small intestine submucosa and showed a success rate of 71%-81% in 48 patients. Other biologic meshes such as acellular porcine dermal graft and acellular human dermal matrix have also been successful in small studies and case reports[4]. Biological mesh placement has also been described following perineal approaches, although this is less well described.

CONCLUSION

RVFs are a disease process that is a significant burden on women that are afflicted, and a difficult problem for surgeons from whom they seek help. The diverse disease pathology has prevented prospective trials, and consensus guidelines on the management of these patients. With a clear understanding of the anatomy, ensuring resolution of the sepsis, and large armentarium of surgical approaches these patients can be treated successfully.

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MINIREVIEWS

Irreversible electroporation and the pancreas: What we know and where we are going?

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Abstract

Pancreatic adenocarcinoma continues to have a poor prognosis with 1 and 5 years survival rates of 27% and 6% respectively. The gold standard of treatment is resection, however, only approximately 10% of patients present with resectable disease. Approximately 40% of patients present with disease that is too locally advanced to resect. There is great interest in improving outcomes in this patient population and ablation techniques have been investigated as a potential solution. Unfortunately early investigations into thermal ablation techniques, particularly radiofrequency ablation, resulted in unacceptably high morbidity rates. Irreversible electroporation (IRE) has been introduced and is promising as it does not rely on thermal energy and has shown an ability to leave structural cells such as blood vessels and bile ducts intact during animal studies. IRE also does not suffer from heat sink effect, a concern given the large number of blood vessels surrounding the pancreas. IRE showed significant promise during preclinical animal trials and as such has moved on to clinical testing. There are as of yet only a few studies which look at the applications of IRE within humans in the setting of pancreatic adenocarcinoma. This paper reviews the basic principles, techniques, and current clinical data available on IRE.

Key words: Irreversible pancreatic adenocarcinoma; electroporation; Apoptosis; Percutaneous; Laparotomy; Overall survival

Core tip: Pancreatic adenocarcinoma continues to have a poor prognosis and as such there is considerable interest in pioneering new techniques. Ablation holds promise in this area, however, the earliest studies looked at thermal ablation techniques which resulted in high morbidity rates. Irreversible electroporation, a relatively new technique, produces apoptosis instead of liquefactive necrosis and preclinical data shows it does not destroy scaffolding cells such as bile ducts and blood vessels. These characteristics have made it of interest in the setting of pancreatic adenocarcinoma. The available clinical data as well as the basic principles of this new technique are reviewed here.

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INTRODUCTION

Pancreatic cancer, despite extensive research, remains one of the most aggressive cancers, having a poor prognosis with 1 and 5 years survival rates of 27% and 6% respectively[1]. According to the American Cancer Society and World Health Organization 46420 patients were diagnosed with pancreatic cancer in the United States in 2014 and 338000 in the world in 2012[1,2]. In the United States 39590 of those patients died in 2014, making it the fourth leading cause of death in both women and men with the prevalence increasing by 1.3% per year as well[1].

Only approximately 10% of these patients present with local disease, which is considered surgically resectable, however even in these patients the 5 year survival rate remains low at 24%[1]. Of the remaining 90% of patients approximately 50% present with metastatic disease, leaving about 40% presenting with localized disease, which is considered surgically unresectable, generally secondary to encasement of adjacent vessels such as the portal vein, celiac artery, and superior mesenteric artery[1]. Patients without metastatic disease, but deemed unresectable due to locally advanced disease are now classified as locally advanced pancreatic cancer (LAPC).

While surgical resection, when a viable option, remains the gold standard the majority of patients will receive chemotherapy and/or radiation therapy. The mainstay of chemotherapy in pancreatic adenocarcinoma for close to fifty years was 5-florouracil (5-FU) monotherapy, despite a mean survival of less than 6 mo[3]. In the late 1990s gemcitabine was introduced and demonstrated a survival benefit as compared 5-FU and thus replaced it as first line therapy[3,4]. As gemcitabine became firmly established as the first line chemotherapeutic agent multiple trials looked at combining gemcitabine with a variety of other chemotherapeutic agents, however, only a few demonstrated a survival benefit[3,5]. The combination of gemcitabine with capecitabine showed a trend toward improved survival with *post hoc* analysis of two randomized controlled trials showing statistically significant improvement in overall survival in patients with a good performance status[6-8]. In 2011 a new trial found that FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) demonstrated a significant overall survival benefit in chemotherapy naive patients as compared to gemcitabine alone[9]. Lastly, a study in 2013 revealed a survival benefit when nab-paclitaxel was combined with gemcitabine as compared to gemcitabine alone[10]. Improving chemotherapeutic options for pancreatic adenocarcinoma remains an active area of research with multiple ongoing studies.

Radiation therapy has been used in the setting of pancreatic adenocarcinoma both in the neoadjuvant setting and in an attempt to reduce local recurrence rates after resection. Attempting to prevent local recurrence after resection seemed like a natural role for radiation therapy, however, to date studies have shown a mixed response[11-13]. This controversial area is the focus of the APACT trial which will hopefully provide a clearer answer[14]. The role of radiation therapy in the neoadjuvant setting is also as of yet unclear with a few studies showing some promise[14,15]. This is also an area of active study, with the recent clear definition of borderline resectable disease assisting in making future studies comparable[14,15].

After the introduction of ablation, interest surrounded it as a possible way of improving patient outcomes in this difficult disease process. Initial investigations into ablation as a possible therapy centered on thermal techniques, with radiofrequency ablation (RFA) being the most studied modality. The reported morbidity rates were regrettably unacceptably high in the majority of these published studies[16-19]. Anatomy at least partially accounts for this elevated morbidity as the pancreas is surrounded by multiple delicate structures such as the common bile and pancreatic ducts. Several vessels, including the celiac artery, superior mesenteric artery, portal vein, and splenic vein also surround the pancreas further complicating and restricting efficacy of thermal ablation techniques primarily as a result of heat sink effect[20,21]. When heat sink effect, defined as tissue cooling during ablation by adjacent blood vessels, occurs the temperature surrounding major vessels does not attain high enough levels to manifest cell death. Although microwave ablation (MWA) has been shown to be less susceptible to heat sink affect it remains vulnerable to the phenomenon[22]. The above difficulties associated with the pancreas anatomically also provide a significant obstacle to other thermal ablation techniques including cryoablation, high intensity focal ultrasonography, and MWA which to date have not been as well studied as RFA.

Irreversible electroporation (IRE) provides a unique alternative, allowing tissue ablation without being reliant on thermal effects. It also has the added ability of maintaining the scaffolding of surrounding tissues, making it of great interest in this anatomically complex area.

IRE TECHNIQUE

Reversible electroporation has been used for many years in the basic science setting to implant foreign molecules into cells[23,24]. Reversible electroporation works by applying an electrical field across the membrane causing the membrane to become porous, through a yet incompletely understood process[23,25]. This lets the investigator introduce a desired molecule, such as RNA or DNA, into the cell[25,26]. IRE uses this theory but applies a higher voltage leading to cell death by apoptosis. Although the exact mechanism by which IRE induces apoptosis is not clear, it appears to be *via* permanent nanopore formation and resultant ion disruption[27].

As previously noted, thermally based techniques struggle with high morbidity when treating pancreatic adenocarcinoma due to the delicate structures in close proximity[28]. IRE on the other hand has been shown, in animal studies, to produce apoptosis of cancer cells while sparing the delicate surrounding scaffolding, including bile ducts and blood vessels[29-31]. This distinctive property makes IRE a desirable modality, particularly given the structurally rich pancreatic region. IRE also provides the benefit of yielding apoptosis, rather than liquefactive necrosis as in thermal techniques, pardoning it from the burdens of heat sink phenomenon[29]. While initially IRE was thought to not induce any thermal effects recent studies have shown that a small area of thermal effect is likely present immediately adjacent to the probe[32].

The unique mechanism of IRE results in a few necessary precautions during its utilization. High voltages created are by IRE and produce significant muscular contractions[33]. It is for this reason the patient must be placed under general anesthesia with full neuromuscular blockade[33]. The blockade is tested with a twitch technique prior to starting. ECG monitoring is also required to monitor for arrhythmias, which are rare and typically transient. The concern of arrhythmia leads some authors to promote the placement and use of arterial lines.

Currently there is one commercially available IRE machine, the NanoKnife (Angio Dynamics, Queensburry, New York). This device supports either unipolar or bipolar probes. The more commonly used unipolar probes require placement in pairs, which is technically challenging as they must be placed in parallel orientation and spaced no further than 1.5-2.0 cm apart. The probes create a relatively small ablation field (approximately 2-3 cm)[34-36] and therefore it is common for multiple probe pairs to be placed, and/or the probes to be repositioned several times during the procedure. Probes can be placed percutaneously, laproscopically, or using an open surgical approach. When placed intraoperatively, intraoperative ultrasound is used[37-39]. When placed percutaneously both ultrasound and CT placement have been described[40,41].

After probe placement the ablation device is set to produce high voltages, usually between 1500-3000 V in pulses of 70-100 microseconds. Typically 90 such pulses are delivered which only takes a few minutes, after which the ablation is complete. Once the intended ablations have been performed the patient will typically undergo imaging, either by intraoperative ultrasound, contrast enhanced ultrasound, or CT to ensure that the lesion has been satisfactorily covered.

After finishing the IRE procedure the patient is observed with the average length of admission varying significantly in the available studies from a same day discharge to admission for two weeks or more[29,37,39-41].

AVAILABLE DATA

A search of the Pubmed database with the terms "IRE AND pancreatic cancer" yielded 34 results, of which 6 studies were found to be case reports, case series, or prospective trials related to IRE and pancreatic cancer without significant patient overlap. Those studies are reviewed here. The remainder represented review articles (n = 16), animal studies (n = 5), or prior publications on a patient set that was reused as discussed below (n = 4). Two studies were excluded as they were case reports only discussing a complication, and therefore not felt to be relevant to this discussion. A single study was eliminated as it was a review of anesthetic requirements during IRE.

Martin and his group have published multiple studies on pancreatic cancer and IRE[37,38,42,43], because of significant patient overlap only two of these studies are included and discussed here. Table 1 provides some of the most pertinent data for the 6 below described studies.

In 2013 Martin *et al*[38] compared a group of fifty-four prospectively gathered IRE patients with pancreatic cancer, retrospectively to a group of eighty-five patients who received only chemotherapy and/or radiation. All of the patients had LAPC disease with none being considered borderline resectable or having metastatic disease. The two groups were matched using propensity scores based on age, size of tumor, performance status, cardiac comorbidities, and pulmonary comorbidities. Of the fifty-four IRE patients fifty-two (96%) patients underwent open surgical ablation and two (4%) underwent laparoscopic ablation. Nineteen patients underwent IRE followed by en bloc resection, after surgical restaging. Forty seven of the fifty-four (87%) IRE patients underwent post procedural chemotherapy while ten (19%) of them underwent post procedural radiation therapy. In a ninety day follow up period thirty two of the fifty-four (59%) IRE patients had adverse events. The average time from diagnosis to treatment was 5.1 mo with a range of 1 to 32 mo. The average length of hospital stay was 7 d. When the IRE and chemoradiation only groups were compared the IRE group had a better overall survival (20.2 mo *vs* 11 mo, P = 0.03), progression-free survival (14 mo *vs* 6 mo, P = 0.01), and distant progression-free survival (15 mo *vs* 9 mo, P = 0.02). However, the survival curves of the two groups appeared to converge back together at twenty months, which was postulated to be secondary to rapid progression of distant metastatic disease by the authors.

Martin *et al*[37] also recently published a series of forty eight patients who had borderline resectable or LAPC disease in which they used IRE in an attempt to obtain a margin free, or R0, resection. Twenty three (48%) of the patients had LAPC while twenty five (52%) had borderline resectable disease. Of note, nineteen of these

Table 1 Comparison of the studies

Ref.	IRE placement technique	No. of patients	Age in years	Sex in male/ female	Time from diagnosis to treatment in months	Survival time in months	Complications	No. of patients with metastasis	No. of patients who received pre IRE chemo and or radiation	No. of patient who received post IRE chemo and or radiation
Martin *et al*[38]	Open 52 (96%) lap 2 (4%)	54	Median 61 range 45-80	23 male/21 female	Median 5.1 range 1-32	Local PFS 14, distant PFS 15, and OS 20	32 (59%)	0 (0%)	49 (90%)	40 (73%)
Martin *et al*[43]	Open 48 (100%)	48	Median 61 range 27-81	26 male/22 female	6 range 4-13	OS 22 and PFS 11	18 (38%)	0 (0%)	33 (69%)	31 (65%)
Paiella *et al*[39]	Open 10 (100%)	10	Median 66	5 male/5 female	Mean 9.2	OS 7.5	2 (20%)	0 (0%)	10 (100%)	3 (30%)
Narayanan *et al*[40]	Perc CT guided 14 (100%)	14	Median 57 range 51-72	7 male/7 female	Mean 16.6 range 2.4-49.5	70% OS at 6 mo	2 (14%)	3 (21%)	14 (100%)	NP
Månsson *et al*[41]	Perc US guided 5 (100%)	5	Median 65 range 46-89	3 male/2 female	NP	40% OS at 6 mo	0 (0%)	0 (0%)	5 (100%)	NP
Bagla *et al*[44]	Perc US with CT confirm	1	78	Male	CT	Alive at 6 mo	None	None	No	No

IRE: Irreversible electroporation; US: Ultrasound; CT: Computed tomography; NP: Nondeterministic polynomial.

patients seem to be included in the previously discussed study by Martin *et al*[38]. Thirty three of the forty eight (69%) had undergone preoperative chemotherapy and thirty one (65%) underwent preoperative radiation therapy[12]. Thirty one of the forty eight (65%) patients underwent R0 resections with the remaining undergoing R1 resections (35%). Adverse events were recorded for 90 d and developed in eighteen of the forty eight (38%) patients. At twenty four months twenty eight patients (58%) had developed recurrence, the majority of which involved the liver or peritoneum.

Paiella *et al*[39] published a prospective study of ten patients who underwent IRE for LAPC utilizing a laparoscopic approach with intraoperative ultrasound (US) guidance. All patients who underwent IRE had previously undergone chemotherapy or chemoradiation therapy. The average length of hospital stay was 9.5 d with 1 patient (10%) developing a postoperative abscess. One other patient (10%) died of septic shock, which was attributed to complications of ulcerative colitis rather than the procedure. The average time of diagnosis to treatment was 9.2 mo. The average overall survival was 7.5 mo following the procedure, with diagnosis to death time averaging 16.8 mo. Three of the ten (30%) patients received post procedural chemotherapy. After treatment, four (40%) patients showed partial response, three (30%) had stable disease burden, and three (30%) demonstrated progressive disease per RECIST criteria.

Narayanan *et al*[40] published a series of fourteen patients who underwent percutaneous IRE in 2012. Eleven (79%) of the patients had disease localized to the pancreas, one (7%) had a sub centimeter lung metastasis, one (7%) had a sub centimeter liver metastasis, and one (7%) had a solitary peritoneal metastasis. All of the procedures were performed using CT guidance and patients were discharged either the same or next day. No grade three toxicities occurred per SIR reporting guidelines. One patient (7%) developed a pneumothorax, while two (14%) others had subclinical complications (small hematoma seen on follow up imaging and subclinical pancreatitis). Two of the fourteen (14%) patients were able to undergo subsequent resection. The median event free survival (EFS) was 6.7 mo, and at 6 mo 70% of the patient cohort remained alive. Additionally the projected overall survival was statistically longer for patients with localized disease as compared to those with metastatic disease ($P = 0.02$). No difference was seen in the overall survival between the patients who did and did not undergo resection, possibly as a result of the few deaths in the resection group.

Månsson *et al*[41] published a case series of five patients treated with US guided percutaneous IRE ablation. The patients all presented with jaundice and were deemed non-surgical candidates, presumably from LAPC although this was not specified. The patients underwent contrast enhanced US to ensure complete ablation. No grade three or higher complications occurred within the first 30 d. One (20%) patient did develop subclinical pancreatitis. Limited follow up data was presented, but 60% of patients were alive at six months, with two (40%) demonstrating no evidence of recurrence.

In 2012 Bagla *et al*[44] published a case report of a single patient with LAPC who was treated with US guided IRE, followed by a CT to confirm probe placement. This patient underwent two separate ablations two weeks apart due to tumor size. The patient developed liver metastasis at the 3 mo follow up exam, which were subsequently treated with RFA. The patient had no evidence of recurrent disease at the 6 mo follow up exam and no significant complications were noted.

DISCUSSION

Pancreatic cancer is the fourth leading cause of cancer related death in the US[1]. Despite considerable and meaningful research into surgical techniques and chemoradiation therapy, survival rates remain poor at 27% and 6% at 1 and 5 years respectively[1]. The majority of patients with pancreatic cancer present with unresectable disease, either due to LAPC (approximately 40%) or metastases (approximately 50%)[1]. Only approximately 10% of patients are considered surgically resectable at presentation, and unfortunately even in this group survival at 5 years is only 24%[1].

IRE appears to hold great promise for improving survival in nonresectable patients, most clearly in the LAPC group. Animal studies have shown IRE has the ability to destroy cancer cells while leaving crucial underlying anatomic scaffolding such as blood vessels and bile ducts intact[29]. This is of paramount importance given the location of the pancreas and resultant high morbidity seen when thermal ablation techniques have been employed[19].

Human data is limited, with only 6 relatively small case series published to date. The most promising data comes from the largest series by Martin *et al*[38] which revealed improved overall survival, progression-free survival, and distant progression-free survival when comparing patients who underwent IRE with those who underwent chemotherapy and/or radiation therapy alone. In this study the overall survival showed significant improvement, rising from 11 to 20.2 mo. This improvement of 9 mo is particularly encouraging given the notably poor prognosis of pancreatic cancer and continued difficulty in attaining improved survival with various other novel treatment methodologies such as new chemotherapeutic agents.

With early data demonstrating the possibility of prolonging overall survival of longer than 6 mo it appears that adding IRE may be of great value for patients without hope for cure. In this particular setting quiescing morbidity is the primary objective however, as clearly demonstrated by several authors, on occasion IRE can be used to downstage patients giving them a chance at curative therapy. The use of IRE to provide definitive therapy has also being investigated by Martin *et al*[38] in their attempts to expand the population of patients able to undergo R0 resections. These advances are vastly promising in regards to the treatment of pancreatic adenocarcinoma, yet they also raise several poignant questions.

Currently IRE is being delivered in a range from maximally invasive (open surgical placement) to minimally invasive (percutaneous placement), with laparoscopic placement falling somewhere in between. It appears likely that both the open surgical placement and percutaneous placement techniques are of benefit. Open surgical placement has the best data to support its use thus far and also allows the surgeon to surgically stage the patient and consider proceeding to resection. Percutaneous placement appears to reduce morbidity and potentially hospital stay, although this point would need further clarification given the long average hospital admission seen in the Mansson *et al*[43] paper of 14 d. Reducing morbidity and hospital stay could be of great importance in maintaining quality of life when the disease is likely to remain unresectable and the goal is palliation. Further investigation into patient selection criteria will be essential in order to differentiate those patients best treated by open, from those best treated with percutaneous, placement. In their paper Narayanan *et al*[39] discussed this in brief, pointing out that certain patients, such as those with large varices, would likely not be best treated *via* the percutaneous approach.

Recent studies have demonstrated that stroma plays a larger than previously recognized role in regards to cancer characteristics, indicating this may be a critical area of future investigation[45-48]. Epithelial cancers such as pancreatic cancer are believed to be maximally affected by stromal cells[49]. The stromal activity prevents drug concentration and may at least partially account for the relatively poor response to chemotherapy seen in pancreatic cancer[50,51]. Disruption of the stromal cells and the cancer cells may help improve outcomes, and to some extent explain the encouraging outcomes which have been seen in early IRE studies. This also raises the question as to whether or not IRE's potential to disrupt the stromal effect could produce better outcomes in patients presenting with limited metastatic disease as well. It also highlights the importance of investigating the possible synergistic effects IRE and chemotherapy could obtain.

More data evaluating outcomes in patients with LAPC is also needed in the form of large case cohorts, and more importantly in the form of randomized controlled trials comparing this technique to radiation and chemotherapy alone. During these investigations the delineation of patient selection will be paramount, as there is likely a group of patients that will confer a good survival benefit, while others will likely not benefit from this invasive procedure. The Martin *et al*[37] paper describing the use of IRE to obtain R0 resections is of marked interest, however, again more data is needed in this newly introduced novel realm.

In conclusion IRE remains a new, exciting area of research in pancreatic cancer with multiple promising possible applications that will require investigation in the future.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Single-port laparoscopic cholecystectomy *vs* standard laparoscopic cholecystectomy: A non-randomized, age-matched single center trial

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Abstract

AIM: To compare the safety of single-port laparoscopic cholecystectomies with standard four-port cholecystectomies.

METHODS: Between January 2011 and December 2012 datas were gathered from 100 consecutive patients who received a single-port cholecystectomy. Patient baseline characteristics of all 100 single-port cholecystectomies were collected (body mass index, age, *etc.*) in a database. This group was compared with 100 age-matched patients who underwent a conventional laparoscopic cholecystectomy in the same period. Retrospectively, per- and postoperative data were added. The two groups were compared to each other using independent *t*-tests and χ^2-tests, P values below 0.05 were considered significantly different.

RESULTS: No differences were found between both groups regarding baseline characteristics. Operating time was significantly shorter in the total single-port group (42 min *vs* 62 min, $P < 0.05$); in procedures performed by surgeons the same trend was seen (45 min *vs* 59 min, $P < 0.05$). Peroperative complications between both groups were equal (3 in the single-port group *vs* 5 in the multiport group; $P = 0.42$). Although not significant less postoperative complications were seen in the single-port group compared with the multiport group (3 *vs* 9; $P = 0.07$). No statistically significant differences were found between both groups with regard to length of hospital stay, readmissions and mortality.

CONCLUSION: Single-port laparoscopic cholecystectomy has the potential to be a safe technique with a low complication rate, short in-hospital stay and comparable operating time. Single-port cholecystectomy provides the patient an almost non-visible scar while preserving optimal quality of surgery. Further prospective studies are needed to prove the safety of the single-port technique.

Key words: Single-port; Minimal invasive; Laparoscopy; Safety; Feasibility; Cholecystectomy

Core tip: Single-port cholecystectomies can be performed safe when performed by experienced surgeons. Low complication and conversion rates are seen, similar to standard multiport laparoscopic cholecystectomies. Single-port cholecystectomies can be performed in similar or even shorter operating times compared to the standard procedure. Single-port cholecystectomies can provide the patient an almost non-visible scar while preserving optimal quality of surgery.

van der Linden YTK, Bosscha K, Prins HA, Lips DJ. Single-port laparoscopic cholecystectomy *vs* standard laparoscopic cholecystectomy: A non-randomized, age-matched single center trial. *World J Gastrointest Surg* 2015; 7(8): 145-151 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i8/145.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i8.145

INTRODUCTION

Laparoscopic cholecystectomy is the standard operative procedure for patients with symptomatic cholelithiasis[1]. Introduced in 1985, laparoscopic cholecystectomy, has been an important development in general surgery[2,3]. Its introduction resulted in surgical procedures with reduced blood loss, enhanced recovery and less major wound complications. Single incision laparoscopic surgery techniques were introduced in the 1990s[4]. When performing this particular type of laparoscopic surgery only one incision is made, usually through the umbilicus. In general, smaller and fewer incisions result in less pain, accelerate postoperative recovery and improve cosmetic result[3,5,6].

After its introduction, standard multiport cholecystectomy was for a long time under debate and frequently contradicted, a situation in which nowadays single-port cholecystectomy finds it-self in. Some studies report higher percentages of bile duct injuries, more blood loss and longer operating time when performing single-port cholecystectomy[7,8]. In contrast, although other studies suggest that single site laparoscopic surgery is a safe and adequate procedure, single site surgery for cholecystectomy for uncomplicated cholecystolithiasis is still subject of debate[9-11].

In 2011, single-port laparoscopic (SPL) also known as laparo-endoscopic single site surgery was introduced at the Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands. Since its introduction more than 100 patients received a laparoscopic cholecystectomy with only one umbilical incision. The aim of this study is to compare short as well as long term surgical outcome parameters, such as safety and patient-outcome, between SPL cholecystectomy and standard four port laparoscopic cholecystectomy (SLC).

MATERIALS AND METHODS

Patients

Between January 2011 and December 2012 all patients who received a SPL cholecystectomy at the Jeroen Bosch Teaching Hospital ('s-Hertogenbosch, The Netherlands) were included in a prospective database in which relevant patient data and surgical outcome parameters were recorded. Also, all patients who received a SLC in the same study period were identified. After an introduction period (n = 36) of the SPL technique, 100 consecutive patients who were operated upon using the SPL technique were matched by age with a group of 100 patients which received a SLC in the same period.

Preoperative data included: age, gender, body mass index (BMI), indication of surgery, previous abdominal surgery, comorbidity and American Society of Anesthesiologists classification. Peroperative data included: operating time (defined as time from first skin incision to completion of closure), need for extra trocar, conversion to open cholecystectomy, first operator (surgeon or resident supervised by surgeon) and peroperative complications. Peroperative bloodloss of more than 200 mL was registered as a complication. Postoperative data included: duration of stay in hospital (including the day of operation), complications (during hospitalisation), reoperation, readministration to the hospital (within 30 d after discharge) and mortality.

Above normal postoperative pain was defined as pain resulting in prolongation of hospital admission with at least one day, without finding a cause of pain.

Hernia cicatricalis was defined as complaints around the umbilical incision caused by herniation of the abdominal wall. Patients were routinely seen 2-6 wk after surgery at the outpatient department and checked on complaints of the incision. All patients were checked in the medical files if they returned to the hospital with complaints of the umbilical incision.

SPL

SPL cholecystectomy is performed under general anaesthesia. Patients are positioned in a supine position with both legs in holders. The surgeon is positioned

Table 1 Patient characteristics

	SPL	SLC	*P* value
Gender (% female)	80	75	0.397
Age (mean, SD)	45 (15)	46 (15)	0.787
BMI (median, range)	25 (17-40)	28 (19-46)	< 0.001[b]
ASA (%)			0.239
Ⅰ+Ⅱ	98	96	
Ⅲ	1	2	
Indication (%)			0.557
Symptomatic cholelithiasis	80	77	
Cholecystitis	13	18	
Biliary pancreatitis	3	1	
Gallbladder polyp	3	4	
Cyst gallbladder	1	0	

[b]Statistical significant. SPL: Single-port laparoscopic cholecystectomy; SLC: Standard laparoscopic cholecystectomy; BMI: Body mass index; ASA: American Society of Anesthesiologists classification.

between the legs of the patient ("French" position) and the first assistant is at the left side of the patient. Through an umbilical incision a 4-access multiport trocar (TriPort+, Olympus surgical) is introduced. Patients are placed in an anti-Trendelenburg position and left lateral tilt. Additional support holders are preoperative placed. The gallbladder is lifted cranially to the liver using a straight laparoscopic clamp. The procedure is the same as the multiport procedure. Before ligation of the cystic duct and artery a critical view of safety is achieved. Ligation is performed using a 5 mm clip applier. If no critical view of safety can be achieved an extra trocar will be placed or the procedure is converted to an open procedure. Conversion means that the single-port or standard procedure was converted to an open cholecystectomy. Total number of placement of extra trocar(s) was registered.

SLC

The standard four-port technique is performed under general anaesthesia. Patients are positioned in a supine position. The surgeon and assistant are positioned at the left side of the patient. A 10 mm trocar is placed periumbilically by open approach and three 5 mm ports are placed in the upper right abdomen under laparoscopic vision. A critical view of safety is achieved before ligation of the cystic duct and artery. When it is not possible to achieve the critical view of safety, the procedure is converted to an open procedure.

Statistical analysis

Data was collected and statistically analyzed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

Continuous variables (means) were analyzed using independent *t*-test. Categorical (ordinal and nominal) variables were analyzed using χ^2-test. *P* values were two tailed. Statistical significance was accepted for *P* values of < 0.05.

RESULTS

In the period January 2011 to December 2012, a total of 795 cholecystectomies were performed of whom 136 patients were treated with the SPL technique. In total 27 of the 795 procedures were converted to an open procedure. All patients' characteristics of the included 100 consecutive patients who underwent a SPL technique and who, matched by age, underwent a four-port technique are noted in Table 1. A significant difference in mean BMI between both groups is observed (25.6 for the SPL group *vs* 28.9 for the SLC group; $P < 0.05$). BMI ranged in the SPL group from 17 to 40 and in the SLC group from 19 to 46.

In the SPL group three operations were performed by residents *vs* 29 in the SLC group. The operating time in the whole SPL group (n = 100) was significant shorter compared with the total SLC group (n =100) (mean operating time was 46 min *vs* 62 min, $P <$ 0.001). The mean operating time together performed by surgeons was 51 min (SD 24; n = 168) whereas the mean operating time for residents for both techniques was 69 min (SD 22; n = 32). Operating times in procedures performed by surgeons were significantly shorter in the SPL group, *i.e.*, mean operating time in SPL procedures performed by surgeons (n = 97) was 45 min compared to a mean operating time of 59 min in the SLC group (n = 71, $P < 0.05$).

A significant correlation (r = 0.22; P = 0.002) between BMI and operating time was found using the Spearman's rho test (n = 200); subgroup analysis showed a significant correlation in the SPL group (r = 0.21; P = 0.037), but the SLC group did not show a significant correlation (r = 0.03; P = 0.787). This suggests more influence of BMI on operating times in SPL cholecystectomies. To exclude the effect of the learning curve in analysing the effect of BMI on the operating time, the procedures performed by surgeons were analysed as a subgroup. Regarding all procedures performed by surgeons a significant correlation was found (r = 0.24; P = 0.003; n = 168). Subgroup analysis of procedures performed by surgeons show significant correlation between BMI and operating time in the SPL group (r = 0.23; P = 0.029; n = 97) and no correlation in the SLC group (r = 0.108; P = 0.385; n = 71). No correlation was seen between BMI and placement of extra trocars.

One conversion was observed in the SPL group because of inadequate critical view of safety (*vs* zero in the SLC group, P = 0.331). Additional ports were placed in seven patients (one extra trocar in six patients and two extra trocars in one patient) in the SPL group *vs* two patients in the SLC group (both one extra trocar, P = 0.122). In this group (extra trocar; n = 9) the median BMI was 28 (range 18-31) *vs* 26 (range 17-46) in patients (n = 191) without the need of placing an extra trocar (P = 0.862). Peroperative complications were seen in three patients in the SPL group (one

Table 2 Operation characteristics

	SPL	SLC	*P* value
Operating time in min (mean, SD)	46 (20)	62 (26)	< 0.001[b]
Peroperative complications (%)	3	5	0.417
Conversions (%)	1	0	0.331
Adding extra ports (%)	7	2	0.122

[b]Statistical significant. SPL: Single-port laparoscopic cholecystectomy; SLC: Standard laparoscopic cholecystectomy.

Table 3 Number of postoperative complications

	SPL	SLC
Bile leakage	1	1
Surgical	0	1
Cardial	0	0
Pulmonairy	2	2
Urogenital	0	0
Pain	0	3
Other	0	2

SPL: Single-port laparoscopic cholecystectomy; SLC: Standard laparoscopic cholecystectomy.

peroperative bleeding, two pneumothoraces) *vs* five patients in the SLC group (all five had a peroperative bleeding; *P* = 0.417). All peroperative characteristics are listed in Table 2.

No patients were admitted to the intensive care and no mortality was seen. A slight difference in postoperative complications in favour of the SPL group in comparison with the SLC group was seen. Three patients of the SPL group suffered from postoperative complications *vs* nine in the SLC group (*P* = 0.071). Postoperative complications are listed in Table 3 (the two complications noted as "other" are biliary colics and neurological dysfunction of one leg; the surgical complication was a superficial wound infection). No significant difference between both groups was found in length of stay in the hospital including the day of operation. Three patients of the SPL group were readmitted *vs* four patients in the SLC group (*P* = 0.700). After a median follow up period of 4 wk (range 1-91 wk) one patient was presented with a hernia cicatricalis in the SPL group *vs* three in the SLC group (*P* = 0.312). For all postoperative data see Table 4.

DISCUSSION

Nowadays, multiport laparoscopic cholecystectomy is worldwide the standard operative procedure for symptomatic cholelithiasis and chronic cholecystitis. This study shows that the single-port procedure (SPL) could be a safe and feasible procedure, performed in a comparable or even shorter operating time. In this age matched control study a similar or even lower percentage of SPL-operated patients suffered from per- and/or postoperative complications compared with data

Table 4 Postoperative characteristics

	SPL	SLC	*P* value
Complications (%)	3	9	0.071
IC admission (%)	0	0	
Length of stay (in days, mean)	1	2	0.239
Readmission (%)	3	4	0.70
Mortality (%)	0	0	

SPL: Single-port laparoscopic cholecystectomy; SLC: Standard laparoscopic cholecystectomy.

found in literature[12-15].

This study was not designed for or aimed to identify superiority for either one of the techniques. This study shows SPL to be non-inferior to SLC.

In 92% of the patients a SPL cholecystectomy could be performed safely without placement of extra trocarts or conversions, whereas only eight patients had a conversion (*n* = 1) or additional port placed (*n* = 7). It is noteworthy to mention that patients in the group who received an additional port still had fewer incisions compared with the multiport procedure.

Furthermore, no increase of biliary or other surgical complications in the single-port group compared with the multiport group was observed. In the beginning of the SPL cholecystectomies surgeons placed a transcutaneous suture for retraction of the gallbladder, causing a pneumothorax in some patients. For this reason after around 45 procedures (including the first 36 procedures performed before this analysis) this suture was not used anymore. This explains the two pneumothoraces seen in the SPL group.

In a meta-analysis published by Trastulli *et al*[7] a significant higher procedural failure was found for the SPL technique compared with the SLC technique, ranging from 0% to 67%. It was also mentioned that the SPL technique led to a significantly higher blood loss. This was possibly due to loss of triangulation that makes the use of instruments for suction and diathermy difficult, resulting in less accurate haemostasis. A possible explanation for the findings of Trastulli *et al*[7] could be the fact that in the included studies the SPL procedures were performed during the surgeon's learning curve.

In contrast to the conclusion of the study of Ma *et al*[16] this study shows a shorter operating time in the SPL group and comparable complication rates. Culp *et al*[17] performed a retrospective study and found slightly longer operating times in the SPL group but also a shorter length of stay in the SPL group with comparable complication rates. We did not find a significant shorter length of stay, but we did see shorter operating times in the SPL group. The learning curve could be an explanation of the longer operating times seen in the study of Culp *et al*[17].

No differences were found in postoperative pain, but no validated tests were taken to score postoperative pain. Single-port laparoscopy is developed to minimize surgical trauma and thereby reduce postoperative pain. Our results suggest less postoperative pain in the SPL group. A study performed by Justo-Janeiro *et al*[18] showed no advantages in postoperative pain for SPL cholecystectomies, however they conclude that more clinical trials are needed. Another shows better postoperative pain scores for a technique comparable to single-port laparoscopy[19]. A study of Sodergren *et al*[20] showed better postoperative pain results and better body image and cosmesis in SPL cholecystectomies.

Despite the fact that the SPL procedure is more challenging to learn for surgeons, no difference in peri-operative complications were found when compared with the multi-port procedure. In literature a learning curve of around 10-15 patients is described for single site laparoscopic cholecystectomy for surgeons with laparoscopic skills. Operating time for SPL procedures became comparable to the SLC operating time when a surgeon performed 10-15 procedures[11]. Another study mentioned a learning curve of 25 patients for surgeons proficient with SLC[21]. In this study the first 36 patients who received a SPL cholecystectomy were excluded, preventing effects of the learning curve.

Last year a Cochrane review concerning fewer than four ports cholecystectomies was published[22]. This review concluded a lack evidence of the benefits of fewer than four ports cholecystectomies. Last years several studies are published regarding the benefits of single-port surgery, to prove its safety and usefulness. One of the benefits of SPL cholecystectomies is better body image[20,23]. As shown by Fransen *et al*[24] the public opinion is in favour for single-port laparoscopy, *i.e.*, when complications risks remain similar, 80% of patients prefers SPL to SLC. Another benefit of the SPL technique is the possible decrease in postoperative pain, however no large clinical trials have proved this advantage yet[20]. Liang *et al*[25] showed some advantages of single-port appendectomies compared to standard laparoscopic appendectomies, like less postoperative complications and returning sooner to oral feeding.

Unfortunately, the study described in this article is limited due to selection bias (higher mean BMI in the SLC group) and bias-by-surgeon. Experienced laparoscopic surgeons performed the majority of the SPL cholecystectomies. Supervised residents performed only three procedures, whereas residents performed 29 SLC procedures. Both sources of bias probably influenced the study outcomes, however the study was designed to investigate safety and feasibility. This reality-based study showed no increase of perioperative complications as result of SPL surgery.

Longer operating time is most frequently mentioned as a disadvantage of performing the single-port technique[16,17,26,27]. A significant shorter operating time was seen in the total SPL group in this study, operating times are is most likely influenced by the experience of the surgeon and possibly the BMI of the patient. Residents performed only three SPL procedures. SLC procedures performed by surgeons showed longer operating times (median operating time for surgeons in the SPL group was 40 min, in the SLC group 51 min). Longer operating times seen in the SLC group could be explained by the higher BMI seen in this group. When analysing all 200 patients included a significant correlation between BMI and operating time is seen (higher BMI results in longer operating time). The same effect is seen in subgroup analysis for the SPL group, however no significant correlation is seen between BMI and operating time in the SLC group. A possible explanation could be that the experience of the surgeon has more influence on the operating time than BMI, more SLC procedures were performed by residents, this could be the cause of no correlation seen between BMI and operating time in the SLC group. However analysis of procedures performed by surgeons show a correlation between operating times and BMI for SPL procedures and not for SLC procedures. This suggests longer operating times in patients with a higher BMI in SPL procedures. Baseline characteristics were significantly different regarding the BMI of the patients comparing the two groups; no conclusions should be made based on this study regarding the effect of BMI on operating times. Nevertheless, in our clinic no limitations regarding BMI are of issue for SPL procedures.

Median follow-up for all patients was four weeks. After cholecystectomy patients regularly are seen only once. Patients suffering from complication or due to other reasons (*i.e.,* malignant disease or trauma) were followed for a longer period. This short follow-up period of four weeks could influence the amount of hernias measured.

Nowadays the single-port technique is not only used for cholecystectomies or other procedures in benign diseases but in malignant resections as well[28-30]. In our hospital more procedures are performed using the single-port technique in the last years, for example hemicolectomies, sigmoidresections and abdomino-perineal resections. In procedures in which the patient will receive a stoma, the single-port device can be placed at the location of the stoma for the best cosmetic result. Surgeons and patients are satisfied with the results. In future these results will be analysed as well.

SPL has the potential to be a safe technique with a low complication rate, short hospital stay and comparable operating time to multiport laparoscopic cholecystectomies. A major advance of SPL cholecystectomy in contrast with other techniques is that it can provide the patient a non-visible scar with preserving optimal quality of surgery. Randomized controlled trials are needed to confirm these advantages of SPL cholecystectomies.

COMMENTS

Background

Single-port procedures are developed to further minimize trauma and provide faster postoperative recovery with a better cosmetic result.

Research frontiers

With this study the safety and feasibility of single-port cholecystectomies is studied. Results of single-port cholecystectomies are compared to standard multiport laparoscopic cholecystectomies, regarding per- and postoperative data.

Innovations and breakthroughs

Previous studies showed single-port laparoscopic (SPL) cholecystectomy to be a safe and feasible technique, but also showed longer operating times and higher conversion rates. The results show faster operating time for the single-port technique with comparable conversions rates and comparable complications. No significant difference was found for the length of stay, but the length of stay was slightly shorter in the single-port group.

Applications

This study shows that SPL cholecystectomies can be performed safe in hands of experienced surgeons. Probably single-port laparoscopy can be performed safe in other laparoscopic procedures as well. Providing patients an almost non-visible scar while preserving high surgical quality.

Terminology

Single-port laparoscopy is a laparoscopic technique in which through one transumbilical incision the laparoscopic instruments are introduced in the intra-abdominal cavity. Using the single-port technique minimalizes surgical trauma and fastens postoperative recovery.

Peer-review

This is a good study.

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SYSTEMATIC REVIEWS

Management and outcome of recurrent gallstone ileus: A systematic review

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Abstract

AIM: To help the surgeon in decision making when treating a patient with recurrent gallstone ileus (RGSI).

METHODS: A systematic review related to RGSI was performed using the databases CINAHL, EMBASE, MEDLINE *via* PubMed from May 1912 to April 2015. All languages were included and the grey literature was also searched. The abstracts were explored for relevance to the topic and full texts obtained as appropriate. A manual search was carried out by scrutinising the reference lists of all the full text articles and further articles were identified and obtained. Total of 903 articles were identified, 656 were excluded after abstract review, 247 full text articles were reviewed and 91 articles selected for final analysis. There were 113 cases of RGSI.

RESULTS: There were 113 cases of RGSI reported in 91 articles. The majority of the recurrences, 62.6%, occurred within 6 wk of the index event. The male to female ratio was 1:7. The mean age was 69.6 years (SD 11.2) with a range of 38-95 years. The small bowel was the commonest site of impaction (92.2%). Treatment data was available for 104 patients. The two main operations performed were: (1) Enterolithotomy without repair of biliary fistula in 70.1% of all patients with a procedural mortality rate of 16.4% (12/73) and (2) a single stage surgery approach involving enterolithotomy with cholecystectomy and repair of the biliary enteric fistula in 16.3% with a procedural mortality of 11.7% (2/17). A subset analysis over last 25 years showed mortality from eneterolithotomy was 4.8% while single stage mortality was 22.2%. Enterolithotomy alone was the commonest operation performed for RGSI with four patients (5.4%) having a further recurrence of gallstone ileus.

CONCLUSION: Enterolithotomy alone or followed by a delayed two-stage treatment approach is the preferred choice offering low mortality and reduced risk of recurrence.

Key words: Recurrent gallstone ileus; Gallstone ileus;

Biliary-enteric fistula; Intestinal obstruction

Core tip: Recurrent gallstone ileus, is an acute but rare surgical condition and there is no clear evidence at present as to the appropriate management of this surgical condition. This review will provide a framework to help decision making for this condition when confronted as an emergency by the general surgeon.

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INTRODUCTION

Gallstone ileus (GSI) is a rare entity first described in 1654 by Bartholini[1,2]. GSI is a result of an inflamed gallbladder becoming adherent to an adjacent part of the enteric system and discharging its stones into the enteric lumen through formation of a biliary-enteric fistula[3-5]. It is estimated that 80% of intraluminal stones will pass spontaneously[6], Gallstones measuring more than 2.5 cm in diameter are a risk factor for impaction and causing bowel obstruction[7]; the latter is referred to as GSI. The mainstay of management is surgical treatment involving enterolithotomy alone or combined with a cholecystectomy and repair of biliary-enteric fistula as a single stage procedure.

Recurrent gallstone ileus (RGSI) is usually a consequence of an untreated biliary-enteric fistula with cholelithiasis[8]. An alternative hypothesis is the presence of a non obstructive biliary calculus more proximal in the small intestine which escaped detection at the first operation despite the need to palpate the entire small bowel looking for a second stone[9]. Predicting the risk of RGSI at the time of first operation is difficult. The literature reports an estimated risk of RGSI of 5%-8%[10-12].

When a patient presents with RGSI the surgeon will not only have to consider how to deal with the emergency obstruction but also how best to manage the cause of the recurrence. There are advocates for enterolithotomy alone without dealing with the biliary-enteric fistula, as low morbidity and mortality are perceived to be associated with this approach. However the advantages of repairing the fistula include preventing recurrence, ascending cholangitis and gallstone related complications[13-15]. These issues are similar to the ones at primary presentation of Gall Stone ileus but increase in significance now as at the primary presentation the risk of recurrence is only 5%-8%.

Although there have been several reviews of GSI, there has been no review focusing on RGSI since 1998[11]. Following a case in our hospital where a patient presented with two recurrences of GSI[16], we performed an up to date systematic review to gain a better understanding of its presentation, management and outcomes. This review will assist clinicians with the management of this rare but important condition.

Aim

To perform a systematic review of the literature from May 1912 to April 2015 to accumulate a body of evidence to help clinicians in the management of patients with RGSI.

MATERIALS AND METHODS

An electronic search was performed using CINAHL, EMBASE, MEDLINE *via* PubMed, from inception of each database to April 2015. A web-based search was also carried out using the Boolean Internet search engine "Google". The search terms used were; "recurrent" or "recurrence" and "intestinal obstruction", "gallstone" or "GSI". The search included articles written in any language.

The abstracts were explored for relevance to the topic and full texts obtained as appropriate. A manual search was carried out by scrutinising the reference lists of all the full text articles and further articles were identified and obtained.

A search of the grey literature was undertaken by searching the Royal College of Surgeon's website and a search of the grey literature database Open Grey http://www.opengrey.eu/. No further articles were identified.

Thirty-six articles of potential relevance in languages other than English were identified. All the articles were translated by native speakers in health related professions. The translations were independently reviewed by the authors before a decision was made about whether the papers were relevant for this review. Of the 36 articles identified, 20 were subsequently included.

Inclusion and exclusion criteria

The definition of a RGSI event was based on a confirmed recurrence of intestinal obstruction by a gallstone demonstrated radiologically or intra-operatively. No article with a case of recurrence of GSI was excluded; papers with incomplete data were included.

Data extraction

Two authors (MS and ZH) independently extracted the data. Data extracted included the names of the authors, date of publication and language. Other data included demographic information about each patient and clinical data such as surgical history, stone characteristics, time interval from the first operation to onset of symptoms, search for second stone at the time of first operation, site of obstruction and its relation to previous enterolithotomy, and details of the surgery performed.

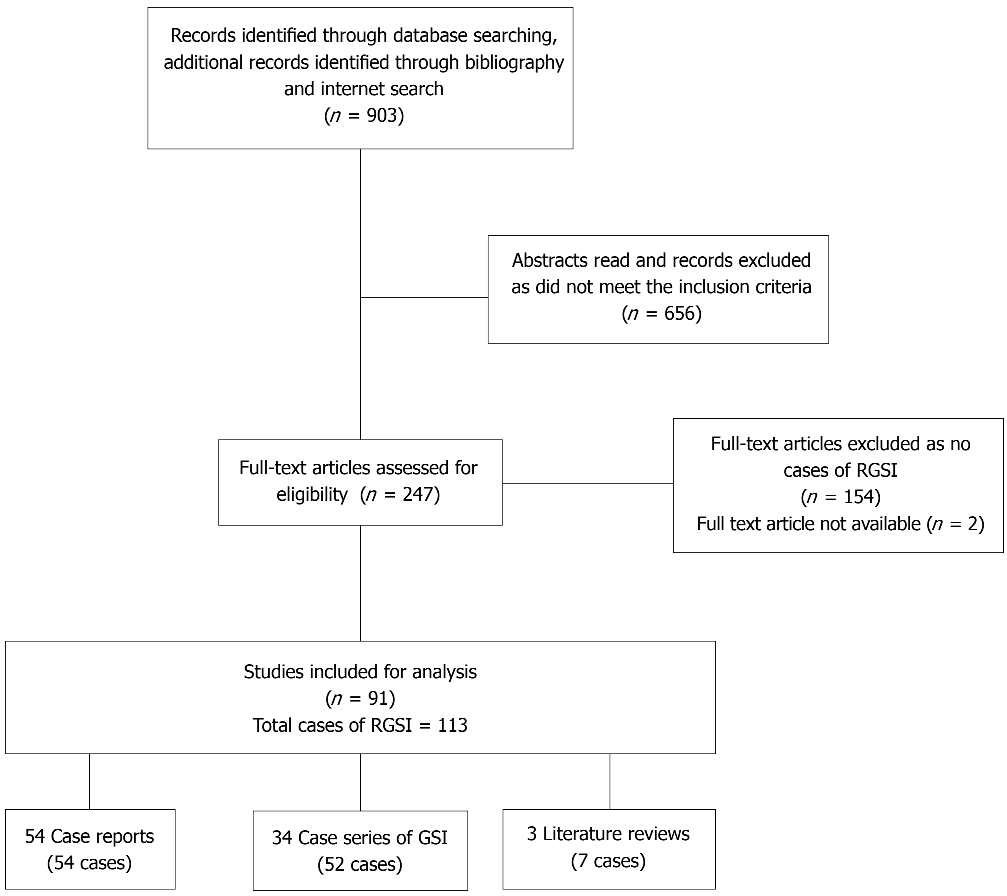

Figure 1 PRISMA flow diagram. RGSI: Recurrent gallstone ileus.

Mortality and morbidity were also noted.

Data analysis

The data analysis was limited to descriptive statistics. No meta–analysis was performed.

RESULTS

The search identified 903 articles from multiple sources as described. Ninety one articles were eventually included (Figure 1). These included 54 individual case reports, 34 case series and 3 review articles[10,17,18]. There were 113 cases of RGSI documented in the 91 articles. Full data were not available on all the categories of interest. Consequently the denominator for each category varies. This is made explicit in the text.

Demographic information

Data on age was available for 89 people. The mean age of these patients was 69.6 years (SD 11.2) with an age range of 38-95 years. The average age in males was 64.5 years (SD 15.1) with an age range of 38-94 years. The average age in females was 70.4 years (SD 10.4) with an age range of 44-95 years.

Data on gender was available for 99 cases. There were 12 males and 87 females (M: F ratio of 1:7). It was not possible to extract the data for age and gender in some case series where data was provided as an aggregate.

The treatment strategies were divided into two broad categories: (1) treatment to relieve intestinal obstruction alone; and (2) treatment to prevent recurrence, *i.e.*, enterolithotomy + cholecystectomy + repair of biliary enteric fistula.

Treatment for primary GSI (n = 106)

We looked at the treatment given for the first episode of GSI that resulted in subsequent recurrence. Data for treatment of this primary gall stone ileus was available for 106 of the 113 patients. The first episode of GSI was treated with enterolithotomy in 92 patients, 86.7%. Five people (4.9%) were treated conservatively and offending stone removed *via* rectum. A single stage surgical approach in two patients (1.9%) still resulted in RGSI. The two patients treated by a single stage procedure by Rodriguez[5] developed recurrence of symptoms two weeks postoperatively. Rodriguez does not mention whether a second stone was missed at the time of the first operation. Other operations included small bowel resection, colostomy, pyloroplasty, gastrostomy accounting for 11.7%.

Cooperman[19] performed transverse colotomy for GSI in a patient who had cholecystostomy three months prior to the first episode of GSI.

Table 1 Surgery for relief of intestinal obstruction alone and mortality (*n* = 87)

Treatment	*n*	%	Mortality	%
Enterolithotomy[1]	73	83.9	12	16.4
Small bowel resection	4	4.5	1	25
Conservative +/manual evacuation	8	9.1	2	25
OGD YAG laser lithotripsy	1	1.1	0	0
Loop colostomy	1	1.1	0	0

[1]Seven patients from this group went on to have an elective cholecystectomy with biliary-enteric fistula repair with no mortality.

Time interval to recurrence (n = 107)

The majority of the recurrences were experienced in the early postoperative period.

In our review, 67 of 107 patients (62.6%) experienced recurrence within six weeks of being treated for GSI. Within six months 91 of the patients out of 107 (85%) had experienced recurrent symptoms. The range varied from 1 d to 3287 d. The median time was 26 d with an interquartile range of 10-90 d.

Of the 16 patients who presented with RGSI after six months, nine had a recurrence of symptoms between six months and a year and seven patients a year or more after the index procedure. We could not elicit data on whether the entire small bowel was palpated for a second gallstone at the primary operation, *i.e.*, whether the reason for RGSI was a missed second gallstone at primary presentation.

Site of recurrent obstruction (n = 103)

The ileum was the commonest site of the stone impaction. Small bowel was the site of obstruction in 92.2% of the patients with RGSI. The recurrent stone was impacted in ileum in 49.5% of the patients. Colon and rectum impaction was seen in 3.8% of the cases respectively.

Size of the stone (n = 56)

The mean size of the obstructing stone was 3.6 cm with a range of 1.5-6 cm. The smallest stone that caused obstruction in the small bowel was 1.5 cm[20] and in the large bowel was 3 cm[21].

The size of the stone appeared to have no correlation with the site of obstruction. The largest impacted stone, measuring 6 cm, was found in the duodenum. The largest stone in the small bowel was 5.5 cm and in the large bowel, 5 cm.

Number of stones (n = 84)

At the time of second laparotomy for RGSI, intestinal obstruction occurred as a consequence of a single stone in 75 cases (89.2%). Two or more stones were found in 9 cases (10.7%), information was not available for 29 cases.

Goldstein[22] published a case in which multiple stones were found at both the laparotomies for GSI.

Table 2 Types of single stage surgery and mortality (*n* = 17)

Treatment	*n*	%	Mortality	%
Enterolithotomy/resection plus cholecystectomy with biliary-enteric fistula repair	14	82.3	2	
Cholecystostomy and repair of biliary enteric fistula	2	11.7	0	11.7
Right hemi-colectomy and cholecystectomy	1	5.8	0	

Shape of the gallstone (n = 36)

The vast majority of the gallstones were faceted in shape. Where the information was found 83.3% of the patients (30 of 36) were faceted in shape. In case of a faceted stone being found at the first surgery the likelihood of finding a second stone is very high and multiple authors have advocated a through search of the residual GI tract to omit recurrence of GSI.

Previous enterolithotomy site and stone impaction (n = 75)

The information comparing the site of obstruction at the first and the second episode was available for 75 patients. In 32 patients (42.5%) the site of impaction was distal to the previous enterolithotomy. In 17 patients (22.6%) the stone impacted at the site of the previous repair, while in 26 patients (34.6%) the site of impaction was proximal to the site of the previous enterolithotomy.

Treatment strategies and mortality in RGSI

Information related to specific treatment for RGSI was available in 104 patients.

In our review the following treatment strategies were adopted.

Surgery on the impacted stone alone[2,3,5,8-10,16-18,20-76]

Enterolithotomy was performed on its own as the main surgical method of relieving the intestinal obstruction in RGSI in 73 patients. When performed on its own it carried a mortality rate of 16.4% (Table 1).

Seven patients treated initially with enterolithotomy alone underwent a staged elective cholecystectomy and repair of the biliary-enteric fistula for the RGSI[9,10,16,17,39,42,51,53,57,61,76,77]. One of these seven patients had a Cholecystostomy with their enterolithotomy[61]. There was no mortality in this group (Table 1).

Other methods to relieve the obstruction were occasionally used. In one patient a stone impacted at the pylorus was dealt with using endoscopic YAG laser lithotripsy accessing the stone by gastroscopylogie[22]. Four patients had small bowel resection with one death, giving a mortality of 25% (Table 1).

Single stage surgery[7,9,77-87]

Only 17 patients had single stage surgery and one of them died giving a mortality rate of 11.7% (Table 2).

Table 3 Morbidity related to recurrent gallstone ileus treatment (n = 36)

Morbidity	Enterolithotomy n = 28	Single stage definitive surgery n = 8
No complications	10	5
Wound related-infection, dehiscence	7	1
Anastomosis related, including leak, fistula, intra-abdominal abscess	2	1
Other medical complications, sepsis, MI, pneumonia, renal failure	9	1

No surgery[18,24,88-91]

Eight patients were treated conservatively with a 25% mortality rate (Table 1). Pybus[88] and Foss[91] each described a person with RGSI not operated on who died and whose RGSI was diagnosed at post-mortem. A conservative approach led to spontaneous passage of the obstructing stone in four cases[18,92]. Rectal impaction of stone necessitated manual evacuation of stone in two patients[89,90].

The mean age of patients in the group who received enterolithotomy alone (data available for 62/73) was 70.5 years (SD 10.5, 47-95 years). The average age of patients in the single stage surgery group (data available for 12/17) was 65 years (SD 13.8, 38-88 years). The youngest patient to have RGSI was 38 years of age, had Crohn's disease, and was treated with right hemi-colectomy and definitive single stage surgery. The oldest patient, 95 years of age, was treated with enterolithotomy and survived.

Morbidity

Data on postoperative morbidity was reported for 36 patients (Table 3). Wound related complication in terms of abscess and wound dehiscence were reported in 8 patients[2,16,24,34,36,40,49,51,64,77,78,83]. Haq[60] reported on a suture line breakdown after a closure of enterolithotomy that was managed conservatively leading to enterocutaneous fistula. McGreevy[38] also reported an enterocutaneous fistula after enterolithotomy for RGSI which was treated with conservative management.

Four case reports also mentioned a recurrent episode of GSI after second enterolithotomy[9,16,73,75].

RGSI treatment in last 25 years

In recent years there has been an improvement in surgical techniques and perioperative care and therefore a subset analysis of treatment outcomes over the last 25 years (1990-2015) was performed.

Thirty published cases of RGSI were found. Twenty one patients (70%) were treated with enterolithotomy with one death (mortality rate 4.8%). This compares with 11 deaths in 52 patients in the previous 77 years for enterolithotomy giving a 21.2% mortality rate (1912-1989).

Nine patients had single stage surgery (30%) between 1990 and 2015, with two postoperative deaths giving a mortality rate of 22.2%. This compares with no deaths in 8 patients having single stage surgery in the previous 77 years (1912-1989) giving a mortality rate of 0%.

With regard to morbidity in the last 25 years, one patient in the single stage group had an intra-abdominal abscess and five patients in the enterolithotomy group had complications related to wound infection (two), evisceration (one), *C.diff* infection (one) and respiratory failure (one).

DISCUSSION

The literature reports an estimated risk of RGSI of 5%-8%[10-12,74]. However reporting of RGSI is probably underestimated because the figures are based on published case reports or series.

The management of RGSI presents a dilemma for the surgeon. Should one only deal with the presenting obstruction once more, in which case an enterolithotomy will suffice, or should one now also deal with the cause of the recurrence in which case additional cholecystectomy and repair of biliary-enteric fistula will be needed. We sought to review existing literature that would help clinicians choose appropriate treatment strategies when faced with RGSI.

In our review RGSI mainly occurred in patients who had their primary GSI treated with enterolithotomy (86.7%). However two patients who had RGSI had single stage surgery including biliary-enteric fistula repair at the initial episode[5]. The latter suggests that recurrence can be due to pre-existing stones in the bowel that have been missed. Identification of multiple stones at the outset is therefore likely to be helpful. While a pre operative CT scan may help, careful per operative manual searching for additional stones is crucial. The authors have personal experience with a patient who had two episodes of recurrent Gall Stone Ileus having been noted to have visible stones within the gall bladder on the CT scan at the time of initial and second presentation[16].

With regard to per operative searching for additional stones, the shape of the index stone may be a useful indicator. The presence of a faceted or a cylindrical stone at the time of first surgery suggests presence of multiple stones[10]. Most of the articles in our review did not comment on the shape of the stone but of the 36 articles that did, 83.3% of the stones were faceted. This suggests that a search for additional stones may be required more often than not, and that the search will be productive.

Treatment of RGSI is usually surgery, though our review found eight cases that had been dealt with conservatively. The mortality in these latter cases was very high (25%) and therefore should be avoided unless severe co-morbidities prohibit surgical intervention.

The surgical options include enterolithotomy alone with removal of the stone thus relieving the obstruction or an enterolithotomy with a definitive operation involving cholecystectomy and repair of the biliary-enteric fistula in order to prevent future RGSI.

Enterolithotomy alone is seen as technically less demanding than single stage surgery. The increased complexity of the latter procedure theoretically carries a higher operative risk. In addition, elderly patients with multiple medical co-morbidities may present a greater physiological risk and this has to be factored into the management of RGSI.

In our review of RGSI cases comparing the recent 25 years to the preceding 77 years, the operative mortality for single stage surgery was 22.2% (1990-2015) compared to 0% (1912-1989). This is despite advanced in surgical techniques and perioperative care. However these results must be interpreted with caution as this is based on published cases only and relatively small numbers of patients.

Of the cases treated with enterolithotomy the mortality rate for 1912-1989 was 21.2% compared to a rate of 4.8% for 1990-2015. The latter concurs with the mortality rate of 5% reported in 2013 by Halabi *et al*[93] from their analysis of the Project Nationwide inpatient sample (NIS) database of just over 2000 cases.

The mortality rate of the whole cohort over the last 100 years was lower for single stage surgery in comparison to enterolithotomy despite the procedure being technically more demanding (11.7% *vs* 16.4%). If age is used as a surrogate marker for physiological fitness then we can perhaps assume that patients undergoing single stage surgery were not only younger but also fitter. However the number of patients having single stage definitive surgery was small and data on age was not available for all patients therefore caution must be taken in the interpretation of these results.

A two-stage strategy with initial enterolithotomy followed by an elective cholecystectomy and biliary-enteric fistula repair had a better outcome with 0% mortality in the seven patients[10,17,39,51,55,59,83], however this represents less than 10% of the cases and probably represents a selection bias in patients fit enough to consider an elective second surgery. However this option should also be considered in the management of RGSI.

The mortality rates from enterolithotomy alone have reduced in the last 25 years and there is a risk, albeit low, of further recurrence. We recommend it as an appropriate choice for the management of RGSI especially for the non hepato-biliary surgeon who has to deal with an emergency obstruction caused by RGSI.

To deal with the problem of possible recurrence Single stage definitive surgery, despite being more technically demanding, may be worth considering but mortality rates remain high. This approach may be appropriate in younger patients who pose a lower risk. This concurs with recommendation from other authors who have reviewed the outcome of primary GSI.

With improvement of surgical techniques and perioperative care a delayed two-stage treatment approach may provide the best results in selected cases.

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COMMENTS

Background

Gallstones can often migrate to the intestinal tract and cause obstruction, called gallstone ileus (GSI). This migration of gallstones is a consequence of an inflamed gallbladder fistulating into the GI tract. The common operation to treat GSI is an enterolithotomy. Enterolithotomy deals with intestinal obstruction alone but risks have recurrence of gallstone ileus (RGSI). Various estimates put the incidence of gallstone ileus to be 5%-8%. A definitive surgery to prevent recurrence compromises of enterolithotomy and repair of the biliary fistula and cholecystectomy, this is a technically more demanding and prolonged operation with significant risks. The mortality from enterolithotomy has been quoted from 11%-18% in various studies. In acute setting the surgeon is faced with the dilemma of trying to balance between the risks of the operation compared to risk of recurrence of symptoms. This review will consolidate current evidence and help in choosing appropriate treatment in acute settings.

Applications

The review collates evidence towards management of RGSI. This condition is not encountered often in clinical practice and can present management dilemma as treatment options vary. This review will assist clinicians in their decision making process.

Terminology

GSI: Gallstone ileus, intestinal obstruction caused by gallstone passing into the intestinal lumen; RGSI: Recurrent gallstone ileus is recurrence of intestinal obstruction due to a second gallstone. This gallstone could have passed from the gallbladder or due to a missed stone at the initial operation; Enterolithotomy: Removal of gallstone from bowel through an incision to the bowel wall; Single stage surgery: In the article, refers to enterolithotomy combined with removal of gallbladder (cholecystectomy) and repair of the biliary enteric fistula; Two stage surgery: Enterolithotomy followed by cholecystectomy and biliary enteric fistula at a later date.

Peer-review

The review content is innovative and concentrates on a rare but hard-to-deal emergence disease. The authors summarized the characteristics and treatment strategies of RGSI by reviewing case reports of this disease, which are valuable and has guiding significance in clinical practice.

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SYSTEMATIC REVIEWS

Laparoscopic management of intra-abdominal infections: Systematic review of the literature

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Abstract

AIM: To investigate the role of laparoscopy in diagnosis and treatment of intra abdominal infections.

METHODS: A systematic review of the literature was performed including studies where intra abdominal infections were treated laparoscopically.

RESULTS: Early laparoscopic approaches have become the standard surgical technique for treating acute cholecystitis. The laparoscopic appendectomy has been demonstrated to be superior to open surgery in acute appendicitis. In the event of diverticulitis, laparoscopic resections have proven to be safe and effective procedures for experienced laparoscopic surgeons and may be performed without adversely affecting morbidity and mortality rates. However laparoscopic resection has not been accepted by the medical community as the primary treatment of choice. In high-risk patients, laparoscopic approach may be used for exploration or peritoneal lavage and drainage. The successful laparoscopic repair of perforated peptic ulcers for experienced surgeons, is demonstrated to be safe and effective. Regarding small bowel perforations, comparative studies contrasting open and laparoscopic surgeries have not yet been conducted. Successful laparoscopic resections addressing iatrogenic colonic perforation have been reported despite a lack of literature-based evidence supporting such procedures. In post-operative infections, laparoscopic approaches may be useful in preventing diagnostic delay and controlling the source.

CONCLUSION: Laparoscopy has a good diagnostic accuracy and enables to better identify the causative pathology; laparoscopy may be recommended for the treatment of many intra-abdominal infections.

Key words: Laparoscopy; Post-operative; Treatment; Perforation; Appendicitis; Cholecystitis; Diverticulitis; Infection; Pregnancy

Core tip: Laparoscopic procedures have become widely accepted as a primary means of diagnosing and treating intra-abdominal infections (IAIs). The diagnostic accuracy of laparoscopy enables surgeons to better identify the causative pathology of acute abdominal pain, and related procedures can be employed to effectively treat a variety of IAIs. Depending on the patient's symptoms, pathological severity, and the attending surgeon's personal experience, laparoscopy may be recommended for the treatment of many IAIs.

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INTRODUCTION

Intra-abdominal infections (IAIs) include a variety of pathological conditions, ranging from uncomplicated appendicitis to fecal peritonitis. IAIs are subcategorized in 2 groups: uncomplicated and complicated IAIs[1]. In the event of an uncomplicated case of IAI, the infection involves a single organ and does not spread to the peritoneum. Patients with such infections can be treated with either surgical intervention or antibiotics.

When the infection is effectively resolved by means of surgery, a 24-h regimen of perioperative antibiotics is typically sufficient. In the event of complicated IAI, the infectious process proceeds beyond a single organ, causing either localized or diffuse peritonitis. The treatment of patients with complicated IAIs involves both surgical and antibiotic therapy[1]. Source control action encompasses all measures taken to eliminate the abdominal source of infection and to control ongoing intra-abdominal contamination. Control of the source of infection can be achieved by either operative or non-operative means. The percutaneous drainage of abscesses is an important non-operative interventional procedure. However, surgery remains the undisputed cornerstone of treatment for IAIs. Surgery may be required depending on the underlying pathology and the type and severity of the intra-abdominal infection. Surgical source control may entail resection or suture of diseased or perforated viscera (*e.g.,* diverticular perforation, gastro-duodenal perforation), removal of the infected organ (*e.g.,* appendix, gall bladder), or drainage of abscesses inaccessible by means of percutaneous drainage. Source control typically involves debridement, which is essential for the removal of infected or necrotic tissue.

Laparoscopic procedures have become widely accepted by the medical community as a primary means of diagnosing and treating IAIs.

For patients with complicated IAIs, the laparoscopic approach is an extremely useful technique, particularly for diagnosing uncertain cases[2].

Depending on the anatomical source of infection and the attending surgeon's experience, laparoscopy may be recommended for the treatment of many IAIs. The aim of the present systematic review is to evaluate the role of laparoscopy in the management of the different causes of complicated IAIs.

MATERIALS AND METHODS

Literature search strategy

Electronic searches were performed using MEDLINE, EMBASE (1988-2014), PubMed (January 1980-December 2014), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and CINAHL from (1966-2014). The search terms were: "appendicitis", "diverticulitis", "perforation", "laparoscopy", "intra-abdominal", "infection", "management" combined with AND/OR. Research included also all the MeSH Terms. No search restrictions were imposed. Progressive filters have been introduced in the research strategy in order to focalize on the highest level of evidence existing articles (*i.e.*, from meta-analysis to case series and case reports). The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Narrative review articles were also obtained to determine other possible studies. Duplicate published trials with accumulating numbers of patients or increased lengths of follow-up, were considered only in the last or at least in the more complete version (Figure 1).

Selection criteria

Studies which have been judged eligible for this systematic review are those in which patients with IAIs from different causes have been treated with laparoscopic approach. Eligibility for study inclusion into the systematic review and study quality assessment were performed independently by two authors (FeCo, FC). Discrepancies between the two investigators were resolved by discussion.

Level of evidence definition was provided according to Oxford Classification (2011).

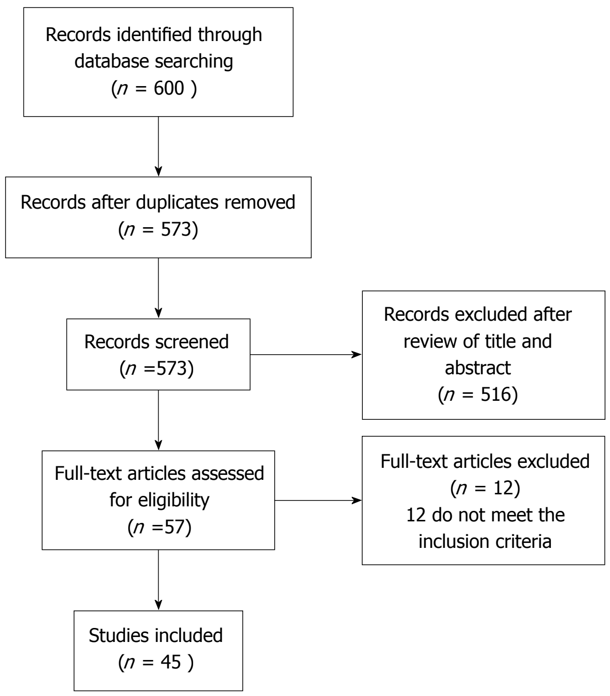

Figure 1 PRISMA flow diagram.

RESULTS

From the research a total of 600 studies were found. Among these papers 45 were selected for the inclusion in the systematic review.

Acute cholecystitis

Laparoscopic cholecystectomy have been widely accepted by the medical community as a safe and effective means of treating acute cholecystitis (AC). About the topic several randomized trials and meta-analysis exist.

The "laparoscopic *vs* open cholecystectomy" debate has been extensively investigated in the past two decades by researchers and clinicians worldwide. In the early 1990s, laparoscopic management techniques for AC were considered highly controversial; however, by today's standards, the laparoscopic cholecystectomy is widely accepted as a safe and effective treatment for AC.

Several randomized trials have demonstrated the safety and efficacy of laparoscopic cholecystectomies in treating AC[3-8].

In 1998, Kiviluoto *et al*[3] published the first randomized trial investigating laparoscopic *vs* open cholecystectomies in the treatment of both acute and gangrenous cholecystitis.

In the Kiviluoto randomized clinical trial, no deaths or bile-duct lesions were reported in both groups, but the post-operative complication rate was significantly higher (*P* = 0.0048) for the open cholecystectomy (OC) group than it was for the laparoscopic cholecystectomy (LC) group. Seven patients (23%) experienced major complications and six patients (19%) experienced minor complications following OC; by contrast, no patients experienced major complications and only one patient (3%) experienced minor complications following LC. The post-operative hospital stay was significantly shorter for the LC group than it was for the OC group [median 4 (IQR 2-5) d *vs* 6 (IQR 5-8) d; *P* = 0.0063].

An additional randomized controlled trial was published in 2005 by Johansson *et al*[4]. This study did not report any statistically significant differences between the laparoscopic and open groups in terms of rate of post-operative complications, pain score at time of discharge, or overall sick leave. For eight patients, laparoscopic interventions were converted mid-procedure to OC. The median operating time was 90 min (range 30-155 min) and 80 min (range 50-170 min) for the laparoscopic and open groups, respectively (*P* = 0.040). The direct medical costs were equivalent for the two groups. Although the median post-operative hospital stay was 2 d in each group, it was significantly shorter for the laparoscopic group (*P* = 0.011).

Common bile injuries occurring during laparoscopic cholecystectomy for AC remain the most serious complication associated with this procedure. At the beginning of the so-called "laparoscopic era", several studies reported alarmingly high rates of common bile duct injuries, but this rate decreased dramatically as the modern surgeon began to hone and fine-tune laparoscopic techniques[6,9-15].

In 2008, Borzellino *et al*[16] published a detailed meta-analysis compiling the results of laparoscopic cholecystectomy in the treatment of severe AC.

Seven studies with a total of 1408 patients who had undergone laparoscopic cholecystectomy were assessed in the meta-analysis. The risks of conversion (RR = 3.2, 95%CI: 2.5-4.2) and overall post-operative complications (RR = 1.6, 95%CI: 1.2-2.2) were significantly higher for cases of severe AC than they were for the non-severe acute forms. However, no differences were reported in terms of local post-operative complications. The authors concluded that laparoscopic cholecystectomies are less effective in treating severe AC (gangrenous or empyematous cholecystitis) than they are in treating less severe forms. A lower threshold of conversion was recommended in order to reduce the likelihood and intensity of local post-operative complications.

In 2014, Catena *et al*[17] published the results from the ACTIVE trial. 144 consecutive patients were randomly assigned to receive either OC or LC for AC. The two groups were homogeneous. Seven patients (9.7%) required conversion to OC. There were no deaths or bile duct lesions in either group, and the postoperative complication rate was similar (*P* = NS). The mean postoperative hospital stay was also comparable. Authors concluded that even though LC for acute and gangrenous cholecystitis is technically demanding, in experienced hands it is safe and effective. It does not increase the mortality and the morbidity rate with a low conversion rate and no difference in hospital stay.

The other question widely debated regarding the surgical treatment of AC concerns the timing.

There is strong evidence to support[18-21] that, compared to delayed laparoscopic cholecystectomies, early laparoscopic cholecystectomies for AC reduce both the duration of hospitalization and the risk of readmission due to recurrent AC.

Gurusamy *et al*[18] recently published a meta-analysis of randomized clinical trials contrasting early laparoscopic cholecystectomies (performed within 1 wk of onset of symptoms) with delayed laparoscopic cholecystectomies (performed at least 6 wk after the first onset of symptoms) in the treatment of AC. Five trials involving 451 patients were included in the study. In the resulting meta-analysis, no statistically significant differences were reported between the two groups regarding either bile duct injury or conversion to OC. The early laparoscopic cholecystectomy group featured a shorter overall hospital stay by 4 d.

The last published randomized controlled trial by Gutt *et al*[22] compared the immediate laparoscopic cholecystectomy (within 24 h from the admission) (ILC) and the initial antibiotic treatment, followed by delayed laparoscopic cholecystectomy at days 7 to 45 (DLC) in 618 patients. All patients were treated with moxifloxacin for at least 48 h. The primary endpoint was the occurrence of relevant morbidity within 75 d. Secondary endpoints were: 75-d morbidity, conversion rate, change of antibiotic therapy, mortality, costs and length of hospital stay. The trial showed as morbidity rate was significantly lower in group ILC (304 patients) than in group DLC (314 patients): 11.8% *vs* 34.4%. The conversion rate to open surgery and mortality did not differ significantly between the two groups. The mean length of hospital stay (5.4 d *vs* 10.0 d; $P < 0.001$) and total hospital costs (€2919 *vs* €4262; $P < 0.001$) were significantly lower in group ILC. Authors concluded that laparoscopic cholecystectomy within 24 h since hospital admission has shown to be superior to the conservative approach concerning morbidity and costs. Moreover authors believe that ILC cholecystectomy should become therapy of choice for AC in operable patients.

A recently published meta-analysis demonstrated that The post-operative morbidity rate was half with LC (OR = 0.46). The post-operative wound infection and pneumonia rates were reduced by LC (OR = 0.54 and 0.51 respectively). The post-operative mortality rate was reduced by LC (OR = 0.2). The mean postoperative hospital stay was significantly shortened in the LC group (MD - 4.74 d). There were no significant differences in the bile leakage rate, intraoperative blood loss and operative times [23].

In order to determine if the treatment delay following the initial onset of symptoms was truly correlated with increased conversion rates in patients with AC, a retrospective case study review of patients undergoing emergency cholecystectomies in a single treatment centre in the 4-year period between January 2002 and December 2005 was conducted[24]. Early intervention for AC (preferably within 2 d of initial onset of symptoms) was the most important criterion for a successful laparoscopic cholecystectomy; treatment delays were associated with a higher likelihood of mid-procedure conversion from laparoscopic to open surgery.

In conclusion, in AC cholecystectomy should be attempted laparoscopically at first (Level of Evidence 1).

Acute appendicitis

Acute appendicitis (AA) is the most common intra-abdominal condition requiring emergency surgery. Although antibiotic treatment has proven to be effective in treating select patients with AA[25-27], appendectomies remain the standard treatment of choice[28].

In recent years, the question of which surgical procedure, laparoscopic or open, is the best way of treating AA has been fiercely debated. Randomized trials and meta-analysis investigating the different surgical means of performing appendectomies have been published in the past 20 years.

In 2010, Li *et al*[29] published an extensive meta-analysis of randomized controlled trials (1990-2009) comparing laparoscopic (LA) and open appendectomies (OA) in both adults and children in the 19-year period from. Forty-four randomized controlled trials involving 5292 patients were included in the meta-analysis. Authors found that operating time was 12.35 min longer for LA (95%CI: 7.99-16.72). Hospital stay after LA was 0.6 d shorter (95%CI: -0.85 to 0.36). Patients returned to their normal activity 4.52 d earlier after LA (95%CI: -5.95 to 3.10), and resumed their diet 0.34 d earlier (95%CI: -0.46 to 0.21). Pain after LA on the first postoperative day was significantly less. The overall conversion rate from LA to OA was 9.51%. With regard to the rate of complications, wound infection after LA was definitely reduced (OR = 0.45, 95%CI: 0.34-0.59), while postoperative ileus was not significantly reduced (OR = 0.91, 95%CI: 0.57-1.47). However, intra-abdominal abscess, intraoperative bleeding and urinary tract infection after LA, occurred slightly more frequently (OR = 1.56, 95%CI: 1.01-2.43; OR = 1.56, 95%CI: 0.54-4.48 and OR = 1.76, 95%CI: 0.58-5.29 respectively). Authors concluded that LA provides considerable benefits over OA.

Wei *et al*[30] in 2011 published another meta-analysis analysing 25 RCTs involving 4694 patients (2220 LA and 2474 OA cases). LA showed fewer postoperative complications (OR = 0.74; 95%CI: 0.55-0.98), less pain [length of analgesia: weighted mean difference (WMD), -0.53; 95%CI: -0.91 to -0.15, earlier start of liquid diet (WMD, -0.51; 95%CI: -0.75 to -0.28)], shorter hospital stay (WMD, -0.68; 95%CI: -1.02 to -0.35), and earlier return to work (WMD, -3.09; 95%CI: -5.22 to -0.97) and normal activity (WMD, -4.73; 95%CI: -6.54-12.92). In term of hospital costs the two techniques seemed comparable. LA demonstrated to need longer operative time (WMD, 10.71; 95%CI: 6.76-14.66). Authors concluded that LA is an effective and safe procedure for AA.

Ohtani *et al*[31] in 2012 published the last meta-analysis reporting results from 39 randomized controlled trials (1990-2012) that compared LA with OA for AA. This meta-analysis included 5896 patients with AA: 2847 had undergone LA, and 3049 had undergone OA. LA was associated with longer operative time (by 13.12 min, 95%CI: 9.72-16.61). As a counterpart, it was associated with earlier resumption of liquid and solid intake, shorter duration of postoperative hospital stay, a reduction in dose numbers of parenteral and oral analgesics, an earlier return to normal activity, work, and normal life, a decreased occurrence of wound infection (OR = 0.44; 95%CI: 0.32-0.60), a better cosmesis and similar hospital charges. Authors concluded that laparoscopic surgery may now be the standard treatment for AA.

From the literature analysis appears that LA has proven to be superior to OA. LA was, however, associated with a slightly increased rate of incidence of intra-abdominal abscesses, intra-operative bleeding, and urinary tract infections. Moreover the use of laparoscopic appendectomy should be used carefully in pregnant women. A systematic review of twenty eight articles (2008) documenting 637 cases of LA in pregnancy were included. The authors concluded that laparoscopic appendectomy in pregnancy is associated with a low rate of intra operative complications in all trimesters. However, LA in pregnancy is associated with a significantly higher rate of fetal loss compared to OA. Rates of preterm delivery appear similar or slightly better following a laparoscopic approach. According to the revised data authors suggested that OA would appear to be the safer option for pregnant women for whom surgical intervention is indicated[32].

A more recent systematic review (2012) with meta-analysis analysing laparoscopic *vs* open appendectomy during pregnancy in eleven studies with a total of 3415 women (599 in laparoscopic and 2816 in open group) showed that fetal loss rate was statistically significantly higher in those women who underwent laparoscopy. The pooled relative risk (RR) was 1.91 (95%CI: 1.31-2.77) with no heterogeneity. The pooled RR for preterm labour was not statistically significant. The mean difference in length of hospital stay was -0.49 (-1.76 to -0.78) d. No significant difference was found for wound infection, birth weight, duration of operation or Apgar score[33]. Authors concluded that laparoscopic appendectomy in pregnant women might be associated with a greater risk of fetal loss.

In conclusion, literature evidences demonstrated that the laparoscopic appendectomy is the treatment of choice in the vast majority of patients (Level of evidence 1).

Diverticulitis

Emergency surgery for colonic diverticular perforations is recommended for patients with large and/or multiloculated diverticular abscesses inaccessible by means of percutaneous drainage, patients with persistent clinical symptoms following CT-guided percutaneous drainage, and patients presenting with diverticulitis associated with free perforation and purulent or fecal diffuse peritonitis.

When a colectomy is performed to address diverticular disease, a laparoscopic procedure appears to be the most viable approach. Even in the event of complicated diverticular disease, laparoscopic resections have proven to be safe and effective; when performed by experienced surgeons, such procedures do not appear to adversely affect the morbidity and mortality rates. However, in most cases the mainstream medical community does not consider laparoscopic procedures to be the optimal treatment of choice, despite the support of the aforementioned clinical evidence.

Although the intra-operative course for perforated diverticulitis patients undergoing laparoscopic resection may appear challenging, many retrospective studies performed by expert laparoscopic surgery groups have demonstrated at least no significant increase in the duration of surgery or the conversion rate among patients with Hinchey stage Ⅰ, Ⅱ, or Ⅲ disease[34-38].

Furthermore, in situations requiring the use of a Hartmann's procedure, laparoscopic resection with subsequent laparoscopic colostomy reversal has often been implemented successfully[39].

In 2009, the results of the only existing randomized multicentre controlled trial, the Sigma trial, were published[40]. One hundred and four patients were randomized: 52 to receive laparoscopic sigmoid resection (LSR) and 52 to open sigmoid resection (OSR). The two groups were homogeneous for gender, age, Body Mass Index, ASA grade, comorbid conditions, previous abdominal surgery, and indication for surgery. LSR took significantly longer but caused significantly less blood loss The conversion rate was 19.2%. The mortality rate was 1%. There were significantly more major complications in OSR patients (9.6% *vs* 25.0%). Minor complication rates were similar (LSR 36.5% *vs* OSR 38.5%). LSR patients had less pain (Visual Analog Scale 1.6), systemic analgesia requirement, and returned home earlier. The short form-36 questionnaire showed significantly better quality of life for LSR.

In 2013, Mbadiwe *et al*[41] published a vast retrospective trial including a total of 11981 patients. Patients undergoing laparoscopy experienced significantly lower rates of complications with both primary anastomosis (14% *vs* 26%) and colostomy (30% *vs* 37%). The laparoscopic approach was associated with decreased mortality rates for patients undergoing primary anastomosis (0.24% *vs* 0.79%). At the multivariate analysis the laparoscopic approach was associated with lower postoperative morbidity for patients undergoing primary anastomosis. The reduced risk of death for patients undergoing laparoscopic primary anastomosis (*vs* open approach) didn't achieve a statistical significance. A small number of patients underwent laparoscopic colostomy (n = 237, 2.4%), and they did not have a significantly different risk of death. Authors concluded that the laparoscopic approach is associated with lower complication rates compared with the open approach for the surgical treatment of diverticulitis with colonic resection and primary anastomosis.

Lastly the laparoscopic approach for exploration, peritoneal lavage, and drainage has recently been developed as a treatment option for patients with acute perforated diverticulitis. However only a small number of studies have been published to date[42-44]. Two prospective cohort studies, nine retrospective case series and two case reports reporting 231 patients have been published. The majority of patients (77%) had purulent peritonitis (Hinchey Ⅲ). The laparoscopic peritoneal lavage approach successfully controlled in 95.7% of cases abdominal and systemic sepsis. Mortality was 1.7%, morbidity 10.4%. Four patients (1.7%) received colostomy[42]. In 2010 the Ladies trial protocol has been published about this topic. This is a nationwide multicentre randomised trial on perforated diverticulitis performed in The Netherlands that aims to provide evidence on the merits of laparoscopic lavage and drainage for purulent generalised peritonitis and on them optimal resectional strategy for both purulent and faecal generalised peritonitis (Trial registration: Netherlands Trial Register NTR2037). No results have still been published.

In conclusion, laproscopy in the treatment of acute diverticulitis demonstrated to be a safe and effective procedure (Level of evidence 3).

Iatrogenic colonic perforation

Colonoscopy or foreign bodies induced iatrogenic perforations are slightly rare and serious complications. Resolution of this condition typically requires segmental colonic resection. In this case, a laparoscopic approach may be ideal in order to minimize the effects of such a complication. Especially if exists the possibility to perform a direct suture of a recent and small perforation[44]. No studies exist about the comparison between the open and laparoscopic repair of iatrogenic foreign bodies colonic perforations. Similarly no prospective studies comparing laparoscopic and open approaches have been conducted, but several retrospective studies have demonstrated that laparoscopic resection is often effective in resolving colonic perforation due to colonoscopy and that it may offer certain clinical advantages over the open procedure[45] (Level of evidence 4).

Gastro-duodenal perforations

Gastroduodenal perforations have decreased significantly in recent years due to the widespread use of stress ulcer prophylaxis and other medical therapies for peptic ulcer disease among critically ill patients. Other causes of gastro-duodenal perforation include trauma, neoplasm, foreign body ingestion, or iatrogenic (endoscopic procedures)[46]. No trials exist about the laparoscopic management of post-traumatic, neoplastic, iatrogenic or foreign body due perforations. Literature however reports many studies about the laparoscopic management of perforated peptic ulcer[47].

Although non-operative management is often attempted, in most cases of perforated peptic ulcer the surgery is considered the standard method of source control[48-51].

Several prospective case-control studies have documented the successful laparoscopic repair of perforated gastric and duodenal ulcers. Recently published literature includes a few systematic reviews[52,53], three controlled, randomized trials published in a 10-year period from 1996 to 2009[53-55] compare open and laparoscopic approaches in the treatment of gastroduodenal perforations and one meta-analysis published in 2004[56].

In 2010, Bertleff *et al*[52] published a literature systematic review investigating laparoscopic corrections of perforated peptic ulcers. Data from 56 papers were extracted and systematically analyzed. The overall conversion rate for laparoscopic procedures addressing perforated peptic ulcers was 12.4%. The perforation diameter appeared to be the most significant factor affecting the rate of conversion. The operating time was significantly longer and the incidence of recurrent leakage at the site of repair significantly higher for the laparoscopic groups. However, laparoscopic patients reported significantly less post-operative pain and exhibited reduced morbidity, less mortality, and shorter hospital stays. The authors concluded that there are solid evidence to support the use of laparoscopic procedures as the primary treatment of choice when addressing perforated peptic ulcers. However, patients 70 years or older with a Boey score of 3 and symptoms persisting longer than 24 h were associated with higher morbidity and mortality rates, and as such, they are typically not viable candidates for laparoscopic procedures.

Lau *et al*[53] in 1996 published the first randomized trial where 103 patients were randomly assigned to receive either laparoscopic suture repair or laparoscopic suturless repair or open repair or open sutureless repair of perforated peptic ulcers. Laparoscopic repair of perforated peptic ulcer (either sutureless either not) took significantly longer than open repairs (94.3 ± 40.3 min *vs* 53.7 ± 42.6 min), but the amount of analgesic required after laparoscopic repair was significantly less than in open surgery (median 1 dose *vs* 3 doses). There was no significant difference in the four groups of patients in terms of duration of nasogastric aspiration, duration of intravenous drip, total hospital stay, time to resume normal diet, visual analogue scale score for pain in the first 24 h after surgery, morbidity, reoperation, and mortality rates[53].

In 2002, Siu *et al*[54] published the results from another randomized trial where 130 patients with a clinical diagnosis of perforated peptic ulcer were randomly assigned to undergo either open or laparoscopic omental patch repair. Nine patients with a surgical diagnosis other than perforated peptic ulcer were excluded; 121 patients entered the final analysis. The two groups were homogeneous in respect to age, sex, site and size of perforations, and American Society of Anesthesiology classification. Nine patients needed conversion to open technique. The laparoscopic repair group patients required significantly less parenteral analgesics and showed a visual analog pain scores in days 1 and 3 after surgery were significantly lower. Laparoscopic repair required significantly less time than open repair. The median postoperative stay was 6 d in the laparoscopic group *vs* 7 d in the open group. The laparoscopic group showed a lower chest infections rate. There were two intra-abdominal collections in the laparoscopic group. One patient in the laparoscopic group and three patients in the open group died after surgery[54].

In 2009, Bertleff *et al*[55] published the results from the last randomized trial where 109 patients with symptoms of perforated peptic ulcer and evidence of air under the diaphragm were scheduled to receive either laparoscopic (52 patients) or open (49 patients) repair. The operating time in the laparoscopy group resulted significantly longer than in the open group (75 min *vs* 50 min). Differences regarding postoperative dosage of opiates and the visual analog scale (VAS) for pain scoring system were in favor of the laparoscopic procedure. The VAS score on postoperative days 1, 3, and 7 was significant lower in the laparoscopic group. Complications were equally distributed. Hospital stay was also comparable (6.5 d in the laparoscopic *vs* 8.0 d in the open group)[55].

The only existing meta-analysis published in 2004 by Lau *et al*[56] in 2004, included 13 studies (658 patients) among which 2 were randomized trials, comparing open and laparoscopic repair in perforated gastro-duodenal peptic ulcers. The overall success rate for laparoscopic repair of perforated peptic ulcer was 84%. Reported rates of conversion to open repair ranged from 0% to 29.1%. Five studies demonstrated a significantly longer operative time for laparoscopic repair, whereas another five trials showed no significant difference. The postoperative assessment of pain score was reported by three studies which showed a lower pain score after laparoscopic repair than after open repair. A significant reduction in the dosage of opiate analgesic required in the laparoscopic group was observed in eight studies. Chest infection was the most common postoperative morbidity. The meta-analyses showed a lower overall chest infection rate after laparoscopic repair (OR = 0.79; 95%CI: 0.38-1.62; P = 0.51). Wound infection was the second most common morbidity after open repair. The meta-analyses showed that laparoscopic repair reduces the wound infection rate (OR = 0.39; 95%CI: 0.16-0.94; P = 0.036). The leakage was more common after laparoscopic repair. The meta-analyses demonstrated a lower leakage rate after open repair (OR = 1.49; 95%CI: 0.53-4.24; P = 0.45). There were no significant difference between open and laparoscopic repair in intra-abdominal collection rate. Prolonged ileus was less common after laparoscopic repair (OR = 0.62; 95%CI: 0.20-1.92; P = 0.41). The reoperation rate after was significantly lower after open repair (OR = 2.52; 95%CI: 1.02-6.20; P = 0.045). The overall mortality rate favored laparoscopic repair (OR = 0.63; 95%CI: 0.34-1.15; P = 0.13)[56].

In conclusion, laparoscopy showed to be safe and effective in treating gastro-duodenal perforations (Level of evidence 1).

Small bowel perforation

Small bowel perforations are more uncommon sources of peritonitis in industrialized nations than they are in less-developed countries. Most small intestinal perforations are a result of undetected intestinal ischemia. Treatment most commonly involves resection of the affected bowel segment. In less-developed countries, small bowel perforations usually accompany enteric fever or intestinal tuberculosis[57].

The laparoscopic management of small bowel perforations has been well documented in retrospective series[58], but studies that systematically compare and contrast this procedure with open surgery especially in intestinal infections are needed (Level of evidence 4).

Post-operative infections

Post-operative peritonitis is a life-threatening manifestation of IAIs that is characterized by high rates of both subsequent complications and mortality.

The inability to effectively control the septic source is one of the most important factors associated with the high mortality rates[59,60].

Delaying a re-laparotomy for more than 24 h in the event of organ failure results in high mortality rates for patients exhibiting post-operative IAIs.

The value of physical tests and laboratory parameters in diagnosing abdominal sepsis is extremely limited. CT scans are believed to yield the most accurate diagnosis. Early (non-delayed) follow-up surgery appears to be the most viable means of treating post-operative infections[59,60].

The laparoscopic control and treatment of post-operative infections have been well documented in recent literature. The diagnostic accuracy of laparoscopy allows for the successful diagnosis of post-operative complications. A few retrospective studies have demonstrated that the laparoscopic approach may prevent delayed diagnoses for post-operative infections and enable experienced surgeons to better control the post-operative source of infection[61,62] (Level of evidence 4).

DISCUSSION

Laparoscopic procedures have become widely accepted by the medical community as a primary means of diagnosing and treating IAIs.

The diagnostic accuracy of laparoscopy enables surgeons to better identify the causative pathology of acute abdominal disease, and subsequent procedures can be employed to effectively treat a variety of IAIs. Depending on the patients' symptoms and clinical conditions, on pathological severity, and on the attending surgeon's personal experience, laparoscopy may be recommended for the treatment of many IAIs.

COMMENTS

Background

Laparoscopy is gaining interest in the field of emergency surgery with several diagnostic and therapeutic possibilities.

Research frontiers

Laparoscopic procedures are becoming widely accepted as a primary means of diagnosing and treating intra-abdominal infections (IAIs) but good quality evidences are lacking.

Innovations and breakthroughs

This systematic review provides the best level of evidence available on this topic.

Applications

This review provides clearly the status of the art of laparoscopy in intra abdominal infections, suggesting the need of further studies in some specific area.

Peer-review

This is a highly valuable study. It provides the first assessment of laparoscopic therapy for IAIs, and clearly provides a data set for moving the operative management of these infections forward.

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CASE REPORT

Large gangliocytic paraganglioma of the duodenum: A rare entity

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Abstract

Gangliocytic paragangliomas are rare tumors that almost exclusively occur within the second portion of the duodenum. Although these tumors generally have a benign clinical course, they have the potential to recur or metastasize to regional lymph nodes. The case report presented here describes a 57-year-old female patient with melena, progressive asthenia, anemia, and a mass in the second-third portion of the duodenum that was treated by local excision. The patient was diagnosed with a friable bleeding tumor. The histologic analysis showed that the tumor was a 4 cm gangliocytic paraganglioma without a malignant cell pattern. In the absence of local invasion or distant metastasis, endoscopic resection represents a feasible, curative therapy. Although endoscopic polypectomy is currently considered the treatment of choice, it is not recommended if the size of the tumor is > 3 cm and/or there is active or recent bleeding. Patients diagnosed with a gangliocytic paraganglioma should be closely followed-up for possible local recurrence.

Key words: Duodenum; Gangliocytic paraganglioma; Ganglion cells

Core tip: We present the case of a patient with a rare duodenal gangliocytic paraganglioma that was treated by tumorectomy. Although there is currently no consensus for treatment, this report demonstrates that local conservative tumorectomy is a feasible, curative therapy. Patients diagnosed with a gangliocytic paraganglioma should be closely followed-up for possible local recurrence.

Gordillo Hernández A, Dominguez-Adame Lanuza E, Cano Matias A, Perez Huertas R, Gallardo Rodriguez KM, Gallinato Perez P, Oliva Mompean F. Large gangliocytic paraganglioma of the duodenum: A rare entity. *World J Gastrointest Surg* 2015; 7(8): 170-173 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i8/170.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i8.170

INTRODUCTION

Gangliocytic paragangliomas (GPs) are rare neuroendocrine tumors that predominantly arise within the second part of the duodenum. GPs seldom recur or metastasize to regional lymph nodes[1], and are considered epithelial tumors according to the classification of tumors of the digestive tract by the World Health Organization[2]. Diagnosis of GP can be achieved based on histopathology showing epithelioid, spindle and ganglion cells, which are similarly observed for paragangliomas[3]. This report describes the case of a 57-year-old woman with melena, progressive asthenia, anemia, and a mass in the second-third portion of the duodenum that was finally diagnosed as a GP.

CASE REPORT

A 57-year-old female presented with upper abdominal pain associated with melena, asthenia, and anemia. She had a history of gluten intolerance but no fever or weight loss. A physical examination revealed pale conjunctiva and no cervical lymphadenopathy. An abdominal examination revealed tenderness in the upper abdomen with no rebound tenderness, hepatosplenomegaly, or palpable masses. Laboratory analyses showed anemia as the only pathologic finding (hemoglobin level of 9 g/dL), with normal renal and liver function. Ultrasound examination was also normal. A polypoid tumor on the third portion of the duodenum was revealed upon endoscopic examination (Figure 1). The tumor was not amenable to endoscopic resection, however, multiple biopsies were performed showing a cellular pattern of intraepithelial lymphocytes ($CD8^+$) with Marsh grade I. The presence of the polypoid formation in the proximal duodenum was confirmed by a capsule endoscopy.

Resection of the neoplasm using a laparoscopic transduodenal approach and a concomitant intraoperative duodenoscopy were planned. However, technical difficulties prevented clear identification of the lesion, and the procedure was converted to an open surgery. The tumor was then completely resected through a longitudinal duodenotomy.

Histopathologic examination of the tumor indicated a 4 cm GP without a malignant cell pattern. The surgical margin was free of neoplastic infiltration and there were no histologic findings indicative of aggressive behavior, such as mitosis and/or pleomorphism. Immunohistochemical analysis showed that the tumor was positive for synaptophysin and enolase. Additionally, epithelioid cells were immunopositive for chromogranin and cytokeratin, and fusocellular cells were S-100-positive[4] (Figure 2).

The patient had an uneventful postoperative period and was discharged after 4 d. At the 3 mo follow-up, the patient was free of symptoms and the endoscopy was normal.

DISCUSSION

GPs are rare tumors that tend to occur in the 5th decade, and more often affect men (1.8:1)[5]. These tumors typically present with gastrointestinal bleeding, whereas obstructive jaundice is very uncommon. Endoscopic ultrasonography is useful for preoperative differential diagnosis from gastrointestinal stromal tumors, carcinoids, and periampullary adenomas. GPs generally follow a benign course, rarely showing invasive growth patterns or lymph node metastasis.

GPs can be curatively treated by endoscopic resection in the absence of local invasion or distant metastasis. Sathyamurthy *et al*[6] described a case successfully treated with endoscopic retrograde cholangiography with biliary sphincterotomy to relieve jaundice. In their patient, a periampullary nodule was detected that partially obstructed the orifice of the major papilla, which was treated with en bloc endoscopic mucosal resection with an electrocautery snare. Several recent reports indicate that endoscopic polypectomy is the treatment of choice, except in cases where the tumor is > 3 cm and/or there is active or recent bleeding[7-9]. A polypectomy was not performed in the current case due to recent bleeding and the diameter of the neoplasm (4-5 cm).

Evans *et al*[10] reported a case of duodenal GP mimicking an ampullary tumor. In their case, marked secondary obstructive chronic pancreatitis was intraoperatively observed in the remaining pancreas necessitating a pylorus-preserving total pancreatectomy. Two years after surgery, the patient remained alive and well on medical treatment with no evidence of tumor recurrence. Although the recurrence index is quite low after local resection[11], Witkiewicz *et al*[12] concluded that the possibility of recurrence, lymph node involvement, and distant metastasis indicates that more extensive surgical therapy may be warranted. Indeed, surgical treatment is indicated for all GPs that are unresectable by upper gastrointestinal endoscopy and for all malignant forms. However, laparoscopic resection may be adequate for

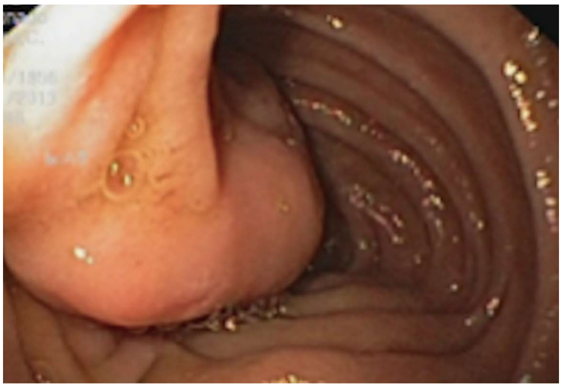

Figure 1 Endoscopic image of the tumor.

benign forms, due to the advantages of the minimally invasive approach, as demonstrated by Parini *et al*[13].

Patients who have undergone successful excision of a large polyp should receive a follow-up endoscopy after 3-6 mo, depending on the histologic findings, to verify that the resection was complete. This process should then be repeated if a residual polyp is detected. If complete resection is not possible after two or three examinations, the patient should then be referred for another surgical therapy.

COMMENTS

Case characteristics

A 57-year-old woman presented with upper abdominal pain associated with melena, asthenia, and anemia.

Clinical diagnosis

A polypoid tumor was observed in the duodenum.

Differential diagnosis

Gastrointestinal stromal tumor; carcinoid; periampullary adenoma.

Laboratory diagnosis

Hemoglobin at 9 g/dL, with normal liver and renal function.

Imaging diagnosis

Computed tomography scans were normal.

Pathological diagnosis

Gangliocytic paraganglioma was diagnosed by microscopic examination and immunohistochemical study.

Treatment

Simple excision of the tumor was performed.

Related reports

Gangliocytic paragangliomas are rare tumors, with very few reports published in the literature.

Term explanation

Gangliocytic paraganglioma is a rare neuroendocrine tumor predominantly arising in the second part of the duodenum, with rare local recurrence or metastasis to regional lymph nodes.

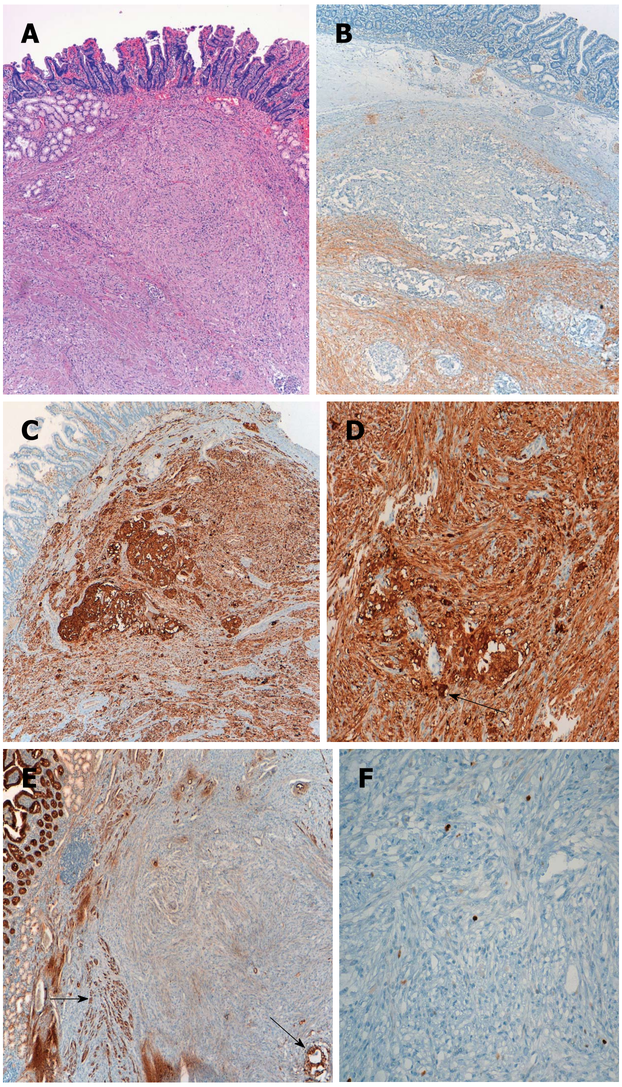

Figure 2 Histologic characteristics of the gangliocytic paraganglioma. A: Submucosal location of the tumor (× 40); B: Immunohistochemistry showing S-100 positivity of the spindle cell component (× 40); C: Immunohistochemistry showing positive staining for neuron-specific enolase in three cellular components (× 40); D: Epithelioid cells showing cytokeratin expression. Black arrow indicates ganglion-like cells (× 40); E, F: Nuclear staining with Ki-67 showing a proliferative index of < 2% (but ranged from 5% to up to 20% in other fields). Black arrows indicate epithelioid (paraganglioma-like) cells (E: × 40; F: × 100).

Experiences and lessons

Complete surgical resection remains the only curative treatment, and long-term careful follow-up is necessary for these patients.

Peer-review

This manuscript is well designed with visual materials and will contribute to the literature. It is a nice case report with good description of symptoms and treatment of this tumor entity.

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CASE REPORT

Congenital peritoneal encapsulation

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Abstract

Peritoneal encapsulation (PE) is a rare congenital malformation, characterized by a thin accessory peritoneal membrane which covers all or part of the small bowel, forming an accessory peritoneal sac. Most cases are asymptomatic and diagnosed incidentally during surgery and/or autopsy. Clinical presentation with intestinal obstruction is extremely rare and we report a case. A 25-year-old male, referred to emergency department with diffuse abdominal pain, crampy, with 8 h evolution, associated with nausea, vomiting and constipation in the last 48 h. The abdominal examination revealed an asymmetric and fixed distension, with hard consistency on palpation of lower abdominal quadrants. The abdominal radiography reveals a small bowel distension and fluid levels. Submitted to laparoscopic surgery that recourse to conversion because there is a total peritoneal encapsulation of the small bowel. After opening the peritoneal sac, we find a rotation of mesentery, at its root, conditioning twisting of small bowel and consequently occlusion. Uneventful postoperative with discharged at the 6th day. The PE is a very rare congenital anomaly characterized by abnormal bowel back into the abdominal cavity in the early stages of development. Your knowledge becomes important because, although rare, it might be diagnosis in patients with intestinal obstruction, in the absence of other etiologic factors.

Key words: Peritoneal encapsulation; Surgery; Intestinal obstruction

Core tip: Peritoneal encapsulation is a rare congenital malformation, characterized by a thin accessory peritoneal membrane which covers all or part of the small bowel, forming an accessory peritoneal sac. Most cases are asymptomatic and diagnosed incidentally during surgery and/or autopsy. Clinical presentation with intestinal obstruction is extremely rare and we report a case.

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INTRODUCTION

Peritoneal encapsulation (PE) is a rare congenital malformation, characterized by an accessory peritoneal membrane covering partially or totally the small bowel. Most cases are asymptomatic and diagnosed incidentally during surgery and/or autopsy[1-4].

PE, abdominal cocoon (AC) and sclerosing encapsulated peritonitis (SEP) are rare entities causing small bowel encapsulation. PE is an embryological malformation, while AC is idiopathic and SEP is predominantly associated with peritoneal dialysis[3]. However, on current literature these entities are predominantly represented by clinical cases.

Clinical presentation with intestinal obstruction is extremely rare[1-4].

CASE REPORT

A 25-year-old male with past history of gastritis, that has no medication or surgical history, referred to Emergency Department presenting diffuse and crampy abdominal pain, within 8 h, associated with nausea, vomiting and constipation for the last 48 h.

At admission, he was hemodynamically stable, apyretic and slightly dehydrated. The abdominal examination reveals a fixed and asymmetrical distension, with superficial and deep pain on palpation, especially in lower quadrants, with hard consistency and signs of peritoneal irritation.

The analytical study hasn't significant changes and the simple abdominal radiograph documented distention of small bowel loops with air-fluid levels. Submitted to laparoscopic surgery that recourse to conversion after establishing pneumoperitoneum.

When abdominal wall was opened, there was a thin membrane covering the small bowel with hypoplasia of the great omental (Figure 1A). The obstruction was caused by the posterior aspect of right edge's sac. The band, which obstructed the small bowel, was traced to the superior mesenteric artery, near its origin, and passed downwards until a few inches proximal to the ileocaecal valve, where it lays just above the sacral promontory (Figure 1B-D). At this point, it trapped the ileum against the sacral promontory causing obstruction. The band was divided to release the obstruction. The band contained a vessel which splits into two branches above the terminal ileum (Figure 1E). One passed downwards and backwards, deep into the pelvis, towards the upper part of the rectum. The other passed across the ileum, to end up in the sigmoid colon. The accessory peritoneal sac was excised.

Histological examination of specimen demonstrated fibrovascular tissue covered by mesothelium of peritoneal origin (Figure 1F).

Postoperative period held without complications and patient has been discharged at the 6th postoperative day.

DISCUSSION

PE is a rare congenital malformation, characterized by an accessory peritoneal membrane covering partially or totally the small bowel. It was first described in 1868 by Cleland. There're less than 20 reports described in literature, the most diagnosed accidentally[1]. However, the actual incidence of PE becomes a challenge due to difficulty in distinguishing between this entity and the AC/SEP.

The boundaries of the peritoneal sac are laterally the ascending and descending colon, superiorly the transverse colon and inferiorly the near surface of parietal peritoneum. The membrane covers entire small bowel, since Treitz angle to ileocolic junction. The great omental, if present, covers the bag but is separated from it in full[1-4].

Embryologically, PE appears to be explained by abnormal return of small bowel to the abdominal cavity during the 12th week of pregnancy. Concomitantly the yolk sac's coat migrates together with intestine, rather than remaining in umbilical pedicle[1].

Most cases are asymptomatic and diagnosed incidentally during surgery and/or autopsy. The case we described exemplifies clinical presentation with intestinal obstruction, which is extremely rare[1-4].

With respect to the physical examination, a patient with intestinal obstruction caused by peritoneal encapsulation presents some clinical signs: asymmetrical and fixed abdominal distension, peristalsis without variation and differences in consistency on abdominal palpation[1,5].

The preoperative diagnosis may be impossible because abdominal radiography is often normal or only reveal distended loops of small bowel, as presented in our case, such as computed tomography scan[1]. During abdominal contrast injection, the AC is characterized as a serpentiniform layout of small bowel, with a set of U-shaped loops, and slowed transit. Abdominal CT scan may reveal a central cluster of small bowel loops, with a dense coat, and signs of obstruction; intestinal wall thickening; ascites and fluid collections[1,3,5]. Differential diagnoses of PE are SEP and AC.

SEP was first described in 1907[6] being an acquired entity, in which the small bowel is covered by a whitish-gray dense collagen membrane. Is usually associated with chronic peritoneal dialysis therapy with beta-blockers, recurrent peritonitis, peritoneum or venous ventricular-peritoneal shunts, sarcoidosis, tuberculosis, Mediterranean fever, protein S deficiency, after liver transplantation, Lupus Erythematosus and fibrogenic foreign material.

The AC was first described by Foo *et al*[7] in 1978. It typically occurs in adolescent females in tropical or subtro

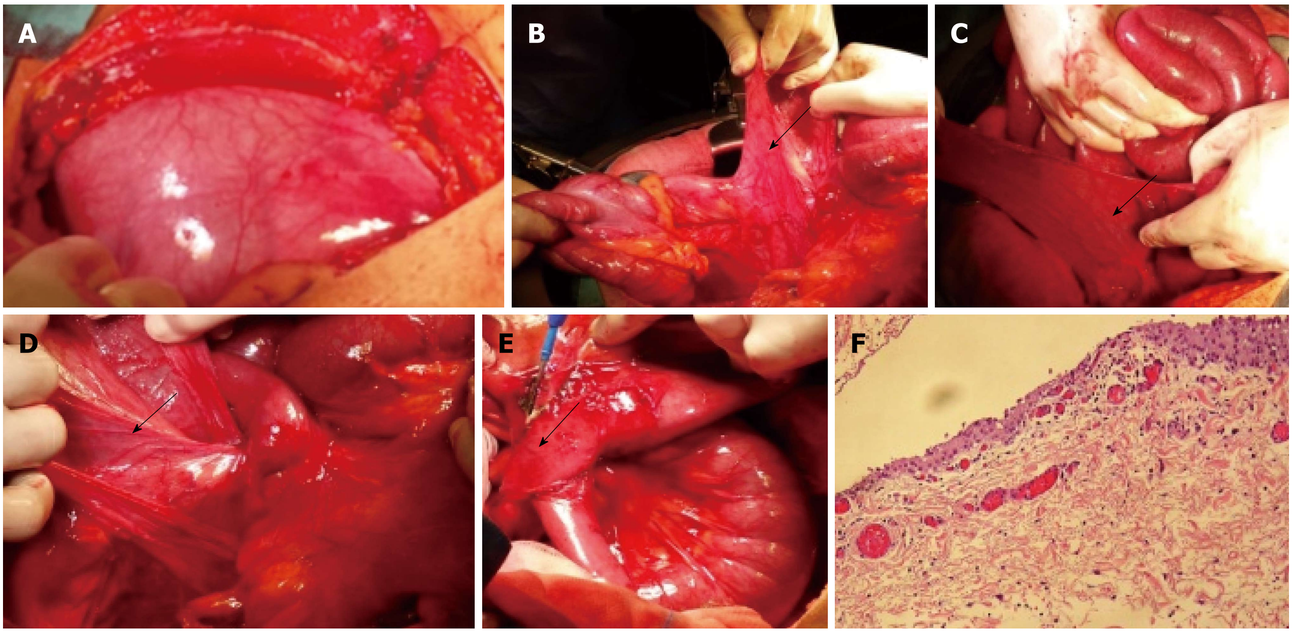

Figure 1 Intraoperative aspect. Total peritoneal encapsulation of small bowel and great omental hypoplasia (A). Opening the peritoneal sac and excision of almost all of anchor points up (B-D). The obstruction was found to be caused by the posterior aspect of the right edge's sac. At this point, it trapped the ileum against sacral promontory causing obstruction. The band was divided to release the obstruction.The band contained a vessel which splits into two branches above the terminal ileum (E). Histological examination of specimen demonstrated fibrovascular tissue covered by mesothelium of peritoneal origin (F).

pical countries. The etiology is unknown, although several theories have been presented, such as the retrograde menstruation with over-viral infection peritonitis and retrograde cell-mediated immune response promoted by gynaecological infection. It is likely that AC may be result of subclinical peritonitis. The small bowel is encapsulated by a fibrocollagenous membrane similar to SEP.

It may be associated with other anomalies such as embryological hypoplasia of great omental, as exemplified by our case, as well as malformations of mesenteric vessels[5].

The therapeutic approach in cases of intestinal obstruction, caused by PE, consists on urgent surgery, with excision of the membrane and lysis of adhesions between loops. Normally, enterectomy is not necessary, except in cases of non-reversible ischemia[3,4].

In our case, there was a twisting of peritoneal membrane, on its emergency root, conditioned by an adherence that, after lysis, provided reversibility on the caliber of small bowel loops, without ischemia. Unlike cases of SEP related to peritoneal dialysis, which earns surgical mortality beyond 60%-80%, the PE has a high survival rate, with low recurrence[5]. Histologically the membrane is composed of fibrovascular tissue covered by mesothelium from peritoneal origin. The postoperative course usually runs uneventfully, with no reported cases of recurrence[2-4].

The PE is an extremely rare congenital anomaly characterized by abnormal bowel back into the abdominal cavity in the early stages of development. Your knowledge becomes important because although rare, it might be diagnosis in patients with intestinal obstruction, in absence of other etiologic factors, such as the authors describe in this clinical case.

COMMENTS

Case characteristics

Peritoneal encapsulation (PE) is a rare congenital malformation, characterized by an accessory peritoneal membrane covering partially or totally the small bowel.

Clinical diagnosis

Most cases are asymptomatic and diagnosed incidentally during surgery and/or autopsy. Asymmetrical and fixed abdominal distension, peristalsis without variation and differences in consistency on abdominal palpation are the main clinical signs.

Differential diagnosis

Differential diagnoses of PE are sclerosing encapsulated peritonitis and abdominal cocoon.

Laboratory diagnosis

The preoperative diagnosis may be impossible because abdominal radiography is often normal or only reveal distended loops of small bowel, as presented in our case, such as computed tomography scan.

Pathological diagnosis

The small bowel is encapsulated by a fibrocollagenous membrane from peritoneal origin.

Treatment

The therapeutic approach in cases of intestinal obstruction, caused by the PE, consists on urgent surgery with excision of the membrane and lysis of adhesions between loops. Normally, enterectomy is not necessary, except in cases of non-reversible ischemia.

Related reports

The postoperative course usually runs uneventfully, with no reported cases of recurrence.

Peer-review

This paper is reporting an interesting congenital anomaly.

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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Melissa Teo, MBBS, FRCS, FAMS, Department of Surgical Oncology, National Cancer Centre of Singapore 11 Hospital, Singapore 169610, Singapore

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EDITORIAL

Detection methods and clinical significance of free peritoneal tumor cells found during colorectal cancer surgery

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Author contributions: Sibio S and Sica GS wrote the paper; Fiorani C, Stolfi C, Divizia A, Pezzuto R, Bagaglini G and Sammartino P performed the literature review; Montagnese F and Sica GS critically reviewed the paper.

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Abstract

Peritoneal washing is now part of the standard clinical practice in several abdominal and pelvic neoplasias. However, in colorectal cancer surgery, intra-peritoneal free cancer cells (IFCC) presence is not routinely investigated and their prognostic meaning is still unclear. When peritoneal washing results are positive for the presence of IFCC a worse outcome is usually expected in these colorectal cancer operated patients, but it what is not clear is whether it is associated with an increased risk of local recurrence. It is authors' belief that one of the main reasons why IFCC are not researched as integral part of the routine staging system for colon cancer is that there still isn't a diagnostic or detection method with enough sensibility and specificity. However, the potential clinical implications of a routine research for the presence IFCC in colon neoplasias are enormous: not only to obtain a more accurate clinical staging but also to offer different therapy protocols, based on the presence of IFCC. Based on this, adjuvant chemotherapy could be offered to those patients found to be positive for IFCC; also, protocols of proactive intraperitoneal chemotherapy could be applied. Although presence of IFCC appears to have a valid prognostic significance, further studies are needed to standardize detection and examination procedures, to determine if there are and which are the stages more likely to benefit from routine search for IFCC.

Key words: Colorectal cancer; Cytology; Free cancer cells; Peritoneal recurrence; Proactive treatment

Core tip: This invited editorial looks for the role of

intra-peritoneal free cancer cells (IFCC) in the surgical practice for colorectal cancer. Prognostic significance of IFCC in colorectal cancer patients is still not clear. Several studies have been published but detection systems are still highly heterogeneous and results remain misleading. Peritoneal cytology could be useful in early-stage cancers to identify subsets of patients with potential worse prognosis, who may be good candidates for adjuvant treatment or even prophylactic intraperitoneal chemotherapy. Current available data need stronger validation to include IFCC in the routine staging protocols of colorectal cancer patients. However, it is the authors' belief that cancer cells found free in the peritoneum of patients with colon cancer, must have a biological and a clinical role. The means of detection based on real time polymerase chain reaction, will surely add power to conventional cytology and with the improvement in sensibility of the methods the clinical role of IFCC could eventually become clear. New therapy protocols might be applied.

Sibio S, Fiorani C, Stolfi C, Divizia A, Pezzuto R, Montagnese F, Bagaglini G, Sammartino P, Sica GS. Detection methods and clinical significance of free peritoneal tumor cells found during colorectal cancer surgery. *World J Gastrointest Surg* 2015; 7(9): 178-184 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/178.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.178

INTRODUCTION

Worldwide, colorectal cancer is the third most prevalent malignancy accounting for over 1 million new cases per year with more than 500000 deaths[1]. Incidence in Europe exceeds 400000 per year[2].

More than 25%-35% of patients with either early or advanced colorectal cancer will develop peritoneal recurrence alone after a first line treatment; peritoneal carcinomatosis is present in up to 44% of patients with recurrent colorectal cancer; the presence of synchronous or metachronous peritoneal metastasis is associated with poor prognosis[3,4] accounting for more than one third of all deaths.

Despite recent advances in gaining a thorough knowledge of clinical, biological and pathological behavior of colorectal cancer, the most commonly used staging systems for colorectal cancer are the Tumor-Node-Metastasis (TNM) and the modified Duke's staging systems[5-7]. Expected prognosis, treatment choice and adjuvant chemotherapy are based on results provided by these staging systems which consider the local extension of the disease, the lymph nodes involvement and the eventual presence of distant metastases[8].

Both these staging systems are highly heterogeneous within each stage, sometimes resulting in very different prognosis for patients that share the same stage. This is particularly true in patients in stage Ⅱ and Ⅲ[9-11] and it may explain why also patients with early stage cancers could develop local or distant recurrence. Furthermore, according to this staging procedure, early stage patients are not appropriate candidates for adjuvant chemotherapy even though the probability of peritoneal recurrence in these patients seems to be equal to those with more advanced cancers.

Recent studies identified only a limited subset of patients suitable for the extensive surgical treatment and the intraperitoneal heated chemotherapy (HIPEC) with promising results in terms of both recovery from disease and overall survival[12-16]. Nevertheless, ten years survival in this limited cohort of patients appears to be a disappointing accomplishment in most qualified studies, in 10% of patients[17]. More recently extensive surgery and HIPEC has been proposed to prevent peritoneal recurrence in selected cases found to have advanced mucinous cancers with positive peritoneal lavage: although the first results seem promising, such an approach is still merely investigational[18-20].

Peritoneal cytology from peritoneal lavage is routinely performed in in staging esophageal - gastric and pancreatic malignancies and it has a definitive prognostic role in ovarian cancer[21-26]. Free intra-peritoneal cancer cells (IFCC) dissemination can occur either spontaneously or because of surgical manipulation, and follows a complex mechanism of circulation, adhesion and invasion of peritoneal surfaces.

MECHANISM OF PERITONEAL SHEDDING, CIRCULATION AND SEEDING OF CANCER CELLS

IFCC are found in peritoneal washing of as much as 25% of colorectal cancer patients[27]. Mechanisms of seeding and the cascade of events, which may lead to their adhesion to peritoneal surface and subsequent peritoneal metastasis development, consist in several well-defined steps. Detachment of cells from primary tumor is the first and it can occur spontaneously. Down regulation of cell adhesion molecules CAMs, such as E-cadherin, associated with high interstitial pressure due to the lack of a well organized lymphatic drainage inside the tumor explains this mechanism, which is effective just when the tumor involves the colon serosal surface (T3) or when spontaneous bowel perforation occurs[28,29].

Surgery itself represents a highly effective mechanism to (that favors) peritoneal cancer spread. Theoretically, even when tumor's manipulation is limited, tumor spill is possible from blood or lymphatic vessels section[30]. This cells show proliferation and invasive potentials and are capable of developing metastasis. Once detached, cells follow well known peritoneal routes which are the same of peritoneal fluid drainage and reabsorption, driven by gravity force, diaphragmatic excursion and mesenteric reflections, towards and from the pelvis, along the right para-colic gutter and the sub-diaphragmatic space. Moreover, tumor cells showed inherent motility[31]. Another possible iatrogenic mechanism of free cancer cells spilling and diffusion could be associated with the laparoscopic technique[32]. However, large clinical trials found no differences in peritoneal recurrence risk between open and laparoscopic surgery for colorectal cancer, possibly because the carbon dioxide potential effect is minimized by the reduced peritoneal trauma of the laparoscopic access[33]. A preferred location for free tumor cells seeding is represented by the omentum because of its discontinuous mesothelial lining and the presence of milky spots.

Surgery contributes to tumor cells spilling and adhesion even by other post surgical physiological effects: Post-operative tissue inflammation and wound healing is mediated by macrophages which produce an array of mediators able to enhance tumor growth, while pro-inflammatory cytokines enhance mesothelial adhesion molecules expression. Even fibrin can entrap tumor cells during the wound healing process. After mesothelial adhesion, tumor cells become able to pass through the peritoneal discontinuity areas or even to promote mesothelial cells apoptosis as well[34]. Matrix metalloproteinases inhibition seems also to be associated with extracellular matrix degradation, thus allowing tumor cells invasion of layers.

IFCC DETECTION METHODS

Several studies tried to detect IFCC immediately before and after curative surgery for colorectal cancer[35-37], using different methods and arrays with different sensitivity. A recent large review on this issue by Mohan *et al*[38] revised 18 studies out of 3805 found, on 3197 colorectal cancer patients; large heterogenicity was found in peritoneal washing methods in terms of volume and solutions, timing of washing, and laboratory techniques. Most used techniques include conventional cytology, immunological or radio-immunoassays methods, molecular techniques as real time or endpoint polymerase chain reaction (PCR). Heterogeneity of peritoneal washing techniques, timing and samples analysis accounts for the main issue in clarifying the impact of intraperitoneal free cancer cells on prognosis and risk to develop peritoneal recurrence in colorectal cancer patients[39].

Disseminated intraperitoneal cancer cells in colorectal cancer patients may be detected using a range of techniques including examination of peritoneal fluid using conventional cytology, cytology following immune-marker staining, PCR or immunocytochemistry.

The timing of the detection may vary and can occur either pre or post-tumor resection[40].

CONVENTIONAL CYTOLOGY AND CYTOLOGY FOLLOWING IMMUNE-MARKERS STAINING

Peritoneal cytology can be performed without lavage when free peritoneal fluid is present. In the absence of peritoneal fluid, a lavage with saline serum (NaCl 0.9%) is needed. The volume of fluid used is extremely variable, ranging from 50 to 1000 mL, but most authors use a small amount of liquid (100-200 mL) delivered around the tumor, where most cells are usually found. Wet fixed direct smears are prepared from the aspirated material after centrifugation and discarding the supernatant. Two or three slides are fixed immediately to prevent cell degeneration. Papanicolaou is a highly suitable staining method also to sediment preparations from fluids. It offers a great advantage with regard to comparative cell studies in histological sections. However Hematoxylin-Eosin, May-Grünwald-Giemsa, Diff-Quik, and other staining methods are also used.

Cyto-centrifuge preparation is recommended for small amounts of fluid with sparse cellular content. Thin layer preparation (cytospin, ThinPrep, and others) is becoming more and more popular. The method may be preferred for adjacent analyses. The remaining cellular material should be retained and stored at 4 ℃, mixed up with a certain amount of the supernatant.

Adenocarcinoma of the large bowel may be suggested by those cases that display small and large compact irregular papillary clusters. The epithelial glandular cells are large and cylindrical, and show a palisade arrangement.

Immuno-stains for CK7 and CK20 expression yield a negative and a positive staining result, respectively[41,42].

IMMUNO-CYTOCHEMISTRY

Immuno-cytochemical methods are based on the staining of tumor cells using specific antibodies against tissue (tumor) specific antigens. Target antigens include EpCAM members of the cytokeratin family or other antigens, which are overexpressed on tumor cells (HER2-neu or MUC-1) but not on other normal cells. These antibodies are either directly labeled with horseradish peroxidase, alkaline phosphatase or fluorescent proteins, or otherwise the antigen-antibody complex is visualized by a labeled second antibody, as in the alkaline phosphatase anti-alkaline phosphatase method. To discriminate between malignant cells and non-specifically stained non-malignant cells, an additional evaluation step that includes morphological criteria and/or an additional counterstaining is necessary. This step employs a second tumor cell-specific antigen or an antibody against a CD marker as CD45. During the last years several computeraided search systems have been developed which are used for scanning of microscope slide analysis. Enriched fractions are commonly centrifuged onto microscope slides (cytospins) for immune-cytochemical detections.

PCR-BASED METHODS

PCR-based methods are widely used for the detection of IFCC, targeting both DNA and RNA markers. DNA is generally stable and independent of the transcription

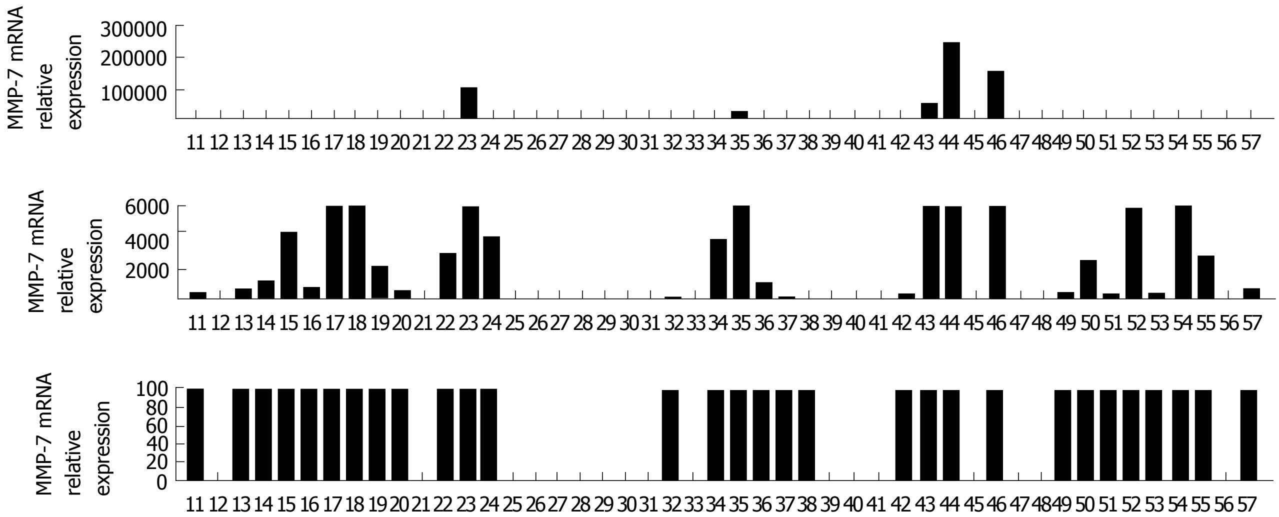

Figure 1 Patterns of expression of matrix metallo-proteinase-7 RNA transcripts in 47 peritoneal washing samples taken from 47 patients who had undergone surgery for colorectal cancer[45]. MMP: Matrix metallo-proteinase.

mechanism of the cell. DNA markers are used based on specific genetic abnormalities that occur in certain types of cancers, although it has been reported that, at least in some cases, disseminated tumor cells are not necessarily clonal to the primary tumor. In general, few chromosomal alterations specifically characterize certain types of cancer, or even are frequent enough to serve as molecular markers. The most frequently encountered genomic alterations in colorectal cancer, commonly used for the detection of free peritoneal cancer cells, include mutations in *k-Ras* and *p53* genes, sometimes investigated together with mRNA markers. More specifically, the detection of occult tumor cells engages targeting of tumor specific mRNA, meaning mRNA that encodes for antigens that are specific either for the malignant phenotype or for the normal tissue. The use of mRNA markers is based on the notion that tumor cells continue to display the same pattern of antigen expression as their normal tissue of origin. Once released from malignant cells, mRNA is relatively unstable; therefore, once detected, mRNA markers are indicative of the presence of viable tumor cells in the examined sample[43].

In a recent meta-analysis, positive peritoneal washing was seen as an independent prognostic factor for poor survival and was associated with a greater risk of both local and systemic recurrence in colorectal cancer patients[44]. Yield rates of intraperitoneal neoplastic cells ranged from 5% to 40% depending on the methods and on the time of detection. In general, immunocytochemistry appears to result in a far greater yield of intraperitoneal neoplastic cells than either PCR or cytopathology. Furthermore it must be considered that immunocytochemistry (along with other histological staining techniques) is subjective and depends on the strength of cellular staining, while PCR-based methods have inherent problems as they detect DNA, not viable cells, and cannot delineate cancerous cells from nonmalignant cells or cellular debris.

However, several cancer cell proteins may be identified by mean of PCR based methods, such as the matrix metallo-proteinase (MMP) class and specifically the MMP-7 (Figure 1) which has been recently proved a highly sensible predictive factor involved in colorectal cancer recurrence after curative treatment. In a recent article by Sica *et al*[45] expression of MMP-7 on IFCC correlated with higher recurrence rate after curative surgery for colorectal cancer and worse prognosis[45]. Patterns of expression of MMP-7 RNA transcripts in a sample of 47 patients who underwent surgery for colorectal cancer are shown in Figure 1.

CLINICAL AND PROGNOSTIC SIGNIFICANCE

In the last ten years, several studies attempted to state the prognostic and clinical meaning of free peritoneal cancer cells found during colorectal cancer surgery, investigating either their presence and prognostic impact[26,38-40,42,43,46].

If their clinical importance in gastric cancer has been clearly identified[47-51], results from this large series of studies on colorectal cancer are misleading. The first concern has to be moved to the large heterogeneity of detection techniques used: If conventional cytology appears to be very sensitive, easily applicable and low costing, its specificity is low, yielding positive results in 4% to 35.5% of series, also providing for a 2% of inconclusive examinations[42]. Immunoassays and PCR seem to be more specific as well as more expensive and subject to laboratory availability[37].

This variability partially explains the differences in results from the studies. A recently closed large trial by French authors, based on 1364 patients, found no relationship between positive cytology and incidence of recurrence and no predictive value regarding the development of peritoneal carcinomatosis. In this study positive cytology correlated with depth of invasion of colorectal wall, synchronous presence of minimal peritoneal carcinomatosis, lymph nodes metastasis, presence of ascites or not radical surgery; this reflected on survival analysis which led to worse survival in patients with positive cytology (P < 0.001) in univariate analysis although it didn't reach statistical significance as independent prognostic factor[40]. Otherwise, other studies found higher risk of overall and loco-regional recurrence when peritoneal free cancer cells are found[39] as well as predictive of poorer outcome[38].

Two studies showed that poorer outcomes are associated with positive post resection washing compared to positive pre-resection one, in terms of recurrence[52] and survival[36].

In most studies, increasing disease staging correspond to higher rates of positive cytology[53] although they can be detected also in early stage patients[54], mostly in stage 2, where Lloyd *et al*[36] found worse survival among stage 2 patients with positive cytology rather than negative ones.

Some authors found correlation between positive cytology and poorly differentiated cancers[55] while the correlation with mucinous or signet ring cells histology remains unclear, even because these histological types are mostly found in advanced stage diseases.

When positive cytology is found, a prophylactic intraperitoneal chemotherapy may be considered in selected cases within clinical trials.

This proactive treatment is proposed in order to prevent peritoneal diffusion in colorectal cancer patients at high risk of peritoneal metastasis. The risk factors which were identified are as follow: Mucinous or signet ring cell hystologies, T3/T4 or perforated tumors and positive peritoneal cytology.

Two recent comparative studies by Sammartino *et al*[18,19] showed that on a sample of 25 patients affected by colorectal cancer at high risk of peritoneal metastasis, a more aggressive surgical treatment including omentectomy, appendectomy, hepatic round ligament resection and oophorectomy in non-fertile women, associated with prophylactic intraperitoneal hyperthermic chemotherapy led to better disease free survival and lower peritoneal recurrence rates[18-20]. It is clear, at this point, that peritoneal washing should become a standardized procedure and that the clinical implications of IFCC are potentially enormous. Effort should be spent on obtaining reliable results in terms of sensibility and specificity of the methods of analysis.

CONCLUSION

Positive peritoneal washing for IFCC is associated with worse outcome in colorectal cancer patients, however it is not clear whether it is associated with an increased risk of local recurrence or not. IFCC can be found in advanced stage or in the acute setting (occlusion or perforation). However, positive cytology can occur also in colorectal cancer at an earlier stage (especially TNM stage Ⅱ patients) and it could affect the strategic plan of treatment. Nevertheless, available data still do not allow to include peritoneal washing and cytology as routine procedures procedures in staging colorectal cancer.

Potentially, peritoneal washing could improve the outcome of those selected patients with apparent early stage colorectal cancer, to receive adjuvant chemotherapy.

Patients with positive cytology may also become candidates to receive proactive intraperitoneal chemotherapy.

Peritoneal washing examination techniques must be improved in order to achieve a better sensitivity. It is the authors' belief that until a proper reliable tumor marker for RT-PCR will be identified, probably the most suitable procedure remains conventional cytology. However, giving the recent studies in this direction it is desirable that highly sensible proteins such as the MMP class and specifically the MMP-7 are employed to increase the specificity of conventional cytology[45].

Further studies are needed to standardize detection and examination procedures, to determine if there are and which are the stages more likely to benefit from routine search for IFCC in the view of offering a proactive management, keeping in mind what Benjamin Franklin once stated: "an ounce of prevention is worth a pound of cure".

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MINIREVIEWS

Need for simulation in laparoscopic colorectal surgery training

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Abstract

The dissemination of laparoscopic colorectal surgery (LCS) has been slow despite increasing evidence for the clinical benefits, with a prolonged learning curve being one of the main restrictions for a prompt uptake. Performing advanced laparoscopic procedures requires dedicated surgical skills and new simulation methods designed precisely for LCS have been established: These include virtual reality simulators, box trainers, animal and human tissue and synthetic materials. Studies have even demonstrated an improvement in trainees' laparoscopic skills in the actual operating room and a staged approach to surgical simulation with a combination of various training methods should be mandatory in every colorectal training program. The learning curve for LCS could be reduced through practice and skills development in a riskfree setting.

Key words: Surgical simulation; Laparoscopic surgery; Surgical training; Colorectal surgery

Core tip: Performing advanced laparoscopic procedures requires dedicated surgical skills and new simulation methods tailored precisely for laparoscopic colorectal surgery (LCS) have been established. This review focuses on a very actual topic in gastrointestinal surgery: The learning curve in minimally invasive surgery and the need for mechanisms to shorten the time needed for a trainee surgeon to safely move towards independent practice. This review article critically analyses the current role of simulation for LCS training.

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INTRODUCTION

Laparoscopic colorectal surgery (LCS) has been increasingly applied because of its many advantages over conventional surgery, including reduced postoperative pain, earlier recovery of bowel function and shorter hospital stay[1].

Despite the evidence for the clinical benefits of LCS and its oncologic safety[2,3], the dissemination of this technique has been hesitant, one of the main constraints for a swift uptake being an extended learning curve[4].

The high level of technical complexity associated with laparoscopic colectomies was held partially responsible for its relatively low adoption rate when compared with other laparoscopic operations[5,6] and learning curves have been estimated as being between 30 and 60 cases[7,8] with the need to acquire specific skills dissimilar to those used during conventional surgery[9].

LCS is a technically challenging procedure, frequently being self-taught by senior surgeons[10], despite there is available evidence that the absence of appropriate training may lead to patient safety compromise[11].

Nowadays, trainee surgeons are required to gather more technical skills in less time[12]: Research has demonstrated a deficiency of successful performance of enough critical laparoscopic colorectal cases by trainees[13,14].

The proportion of operations undertaken by surgical trainees has reduced in the past decade[15] as they spend less time in theatre and more time covering nights and acute admissions[16,17].

This gap between expected level and actual practice[18] has promoted the use of advanced training in laparoscopic colorectal surgery, with the evident need to improve the training opportunities available to trainees out-of-hours. Aim of this review is to summarize the different simulation strategies currently available for LCS training and the evidence demonstrating their advantages for colorectal trainees.

NEW CHALLENGE FOR SURGICAL TRAINING

Surgical training has traditionally been one of apprenticeship, based on a Halsted's "see one, do one, teach one" classic scheme[19] where the surgical trainee learns to perform surgery under the supervision of an experienced surgeon.

Performing laparoscopic procedures requires special surgical skills to overcome the technical difficulties that it presents (Table 1), which include two-dimensional vision with loss of depth perception, less range of motion of the instruments when compared with open surgery, impaired tactile sensation, and the disparity between visual and proprioceptive feedback known as the fulcrum effect[21,22]. Laparoscopic surgery is difficult to learn by observation and practice alone[23] and competency requires dedicated training and mentoring[24].

Moreover, augmented rates of adverse clinical outcomes at the beginning of the learning curve introduce ethical questions and emphasize the demand for mechanisms to decrease complications and unnecessary conversions to open surgery during the early stage of independent practice. As it is no longer accepted that surgeons acquire experience at the expense of patient safety, patients should not be exposed to the opportunity of harm when other training approaches are available for skill acquisition.

Table 1 Distinctive features and challenges of laparoscopic surgery[20]

Features	Challenges
Two dimensional vision	Reduced perception of depth
A disturbed eye-hand-target axis	Decreases ergonomy and dexterity
Long and inflexible instruments	Natural hand tremor magnified
Rigid instruments with five degrees of freedom	Decreased dexterity and range of motion
Fixed abdominal entry points	Limited freedom of motion and movement of the instrument: The fulcrum effect
Camera instability	Increased fatigue
Limited tactile feedback	Decreases dexterity

It has also been demonstrated that the surgical theatre can be a suboptimal place for beginner learning as high stress leads to deleterious effects on performance[25] and surgical training in the operating room implicates additional cost, estimated in approximately United States $47979 per year per trainee[26].

Concerns regarding cost, time, schedule restriction and safety have arisen and this forced surgeons to innovate and develop new methods of surgical training[27,28] and it became obvious that the learning curve must be abbreviated by learning outside of the surgical theatre[29].

Committed practice on simulators corresponds with improved operative times and efficiency of movement for minimally invasive cholecystectomy. These results indicate that the learning curve for LCS may be reduced with this approach[30]. However, colonic and rectal resections performed laparoscopically are retained to be more difficult than a cholecystectomy as they involve added challenges like the need to operate within multiple quadrants in the abdominal cavity, the dissection of inflamed or obliterated tissue planes, and the safe mobilization of the bowel from confined spaces. LCS training is obviously less adapt to simple box trainers because of the necessity to work in multiple quadrants, transect and extract often large bulky specimens, and perform bowel anastomosis: Advanced surgery needs advanced simulation training.

Laparoscopic training not only has changed the traditional perspective challenging the Haldsted's one century old apprenticeship model[31], but has also induced a prompt development of simulation techniques given the versatility of the video environment and the capability to monitor the motions of the trainees. Adequate training clearly is the desirable way to prevent and diminish potential laparoscopic surgical errors[32].

SIMULATION PRACTICE IN LCS

New simulation methods designed peculiarly for LCS have been established (Table 2). These embrace a combination of virtual reality simulators and box trainers, animal and human tissue, and synthetic materials[33-36].

Traditionally, animal and human cadaver training models have been utilized to improve spatial perception

Table 2 Characteristics of the different types of simulators

Type of simulator	Main features
Box trainers	Low-cost, portable, can be used repeatedly by multiple users. Used to teach basic laparoscopic skills: hand-eye coordination, cutting, suturing, bimanual dexterity. Provide sensory feedback Requires direct observation and supervision by a trainer
Virtual reality simulators	Record several procedure metrics providing feedback to trainees. Recording of training performance for objective evidence of skill performance. Minor degree of sensory feedback and higher initial are the main disadvantages
Hybrid models	Reduced costs compared to cadaveric models. Questionable value of a training model with an alternative structure
Animal and human cadaveric models	Best anatomic and clinical-like model. Avaibility is limited and their use is expensive. Require operative facilities and a funeral service

of surgical anatomy[37,38]: This method of simulation is outstanding to demonstrate dissection, tissue handling and complex surgical techniques, but unfortunately, both these models require very specialized training environments, are very expensive with limited availability, and each trainee probably only gets to perform part of the procedure once.

Box-simulators use laparoscopic instruments set within a physical box. They provide tactile feedback and are relatively inexpensive, however require ongoing maintenance and materials, and require feedback from an observing trainer for maximum efficacy. Lack of availability of trainers and dedicated time for feedback may therefore limit this system.

Virtual reality simulators enable trainees to interface with a computer-generated environment that reproduces individual skills or entire procedures. Modern virtual reality simulators utilize increasingly advanced hardware and software for complex and realistic simulation: They have an higher initial cost but are valuable not only as a training device but also as a tool to assess surgical skills. In fact they provide pre-task tutorials and feedbacks at the completion of the procedure on a range of outputs such as time taken, efficiency of motion and knot integrity. Virtual reality simulator systems are convenient for the trainer as performance of the trainee can be monitored easily and remotely, meaning this system can be well utilized out-of-hours.

FUTURE PERSPECTIVES

Several studies have demonstrated that training in laparoscopic techniques in a simulated setting, including on virtual-reality simulators, has enhanced the capabilities of the surgical trainees during and beyond the course of their training[39,40]. Some studies have even shown an amelioration in trainees' laparoscopic skills in the actual surgical theatre[41,42] and it is now largely accepted that laparoscopic simulation training should be mandatory[43] to facilitate trainees acquire basic laparoscopic skills, and a growing consensus by regulation training bodies is desirable.

Proficiency-based simulator curricula have proven effective in improving the performance of trainees. An assessment of baseline skills level on laparoscopic colectomy for trainee surgeons may be used to fashion a tailored program dedicated to improve specific competences and to meet the needs of novice surgeons according to their specific pre-training skills.

Skills of different complexity can be achieved using a phased approach and a mixture of distinct simulation training techniques. Basic surgical competences such instrument handling and suturing should be developed in box trainers and virtual reality simulators, while advanced key steps in complex procedure mastered using torso-shapped mannequin with synthetic materials. Finally, as LCS requires cooperation among the surgeon, the assistants and the operating team personnel, advanced laparoscopy team training should be done in animal/cadaver/hybrid labs with a minimal number of required animals or cadavers.

CONCLUSION

Training in LCS requires specific psychomotor skills that trainee surgeons are required to gather in less time. Simulation may offer a safe, reproducible environment for development of technical skills and procedural knowledge. The learning curve for LCS could be reduced through practice and skills development in a risk-free setting and a staged approach to simulation training should be mandatory in every colorectal training program.

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MINIREVIEWS

Management of afferent loop obstruction: Reoperation or endoscopic and percutaneous interventions?

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Abstract

Afferent loop obstruction is a purely mechanical complication that infrequently occurs following construction of a gastrojejunostomy. The operations most commonly associated with this complication are gastrectomy with Billroth Ⅱ or Roux-en-Y reconstruction, and pancreaticoduodenectomy with conventional loop or Roux-en-Y reconstruction. Etiology of afferent loop obstruction includes: (1) entrapment, compression and kinking by postoperative adhesions; (2) internal herniation, volvulus and intussusception; (3) stenosis due to ulceration at the gastrojejunostomy site and radiation enteritis of the afferent loop; (4) cancer recurrence; and (5) enteroliths, bezoars and foreign bodies. Acute afferent loop obstruction is associated with complete obstruction of the afferent loop and represents a surgical emergency, whereas chronic afferent loop obstruction is associated with partial obstruction. Abdominal multiple detector computed tomography is the diagnostic study of choice. CT appearance of the obstructed afferent loop consists of a C-shaped, fluid-filled tubular mass located in the midline between the abdominal aorta and the superior mesenteric artery with valvulae conniventes projecting into the lumen. The cornerstone of treatment is surgery. Surgery includes: (1) adhesiolysis and reconstruction for benign causes; and (2) by-pass or excision and reconstruction for malignant causes. However, endoscopic enteral stenting, transhepatic percutaneous enteral stenting and direct percutaneous tube enterostomy have the principal role in management of malignant and radiation-induced obstruction. Nevertheless, considerable limitations exist as a former Roux-en-Y reconstruction limits endoscopic access to the afferent loop and percutaneous approaches for enteral stenting and tube enterostomy have only been reported in the literature as isolated cases.

Key words: Afferent loop; Obstruction; Reoperation; Endoscopy; Enterostomy

Core tip: Management strategy of afferent loop obstruction (ALO) depends on: (1) the benign or malignant nature of the obstruction. ALO caused by a benign lesion needs definitive repair of the primary cause by surgery. ALO caused by a malignant lesion needs palliative treatment (percutaneous and endoscopic interventions, by-pass surgery) or excision; and (2) the site of obstruction. An obstruction at the inframesocolic portion of the afferent loop can be easily reconstructed, whereas an obstruction at the supramesocolic portion needs copious mobilization and may require revision of the hepaticojejunostomy or pancreaticojejunostomy and/or a modified Puestow procedure in the setting of a preceded pancreaticoduodenectomy.

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DEFINITIONS

Creation of a gastrojejunostomy leaves a segment of proximal small bowel, most commonly consisting of duodenum and proximal jejunum, lying upstream from the gastrojejunostomy. This limb of intestine conducts bile, pancreatic juices, and other proximal intestinal secretions toward the gastrojejunostomy and is termed the afferent loop[1]. Afferent loop obstruction (ALO) is a purely mechanical complication that infrequently occurs following construction of a gastrojejunostomy. The operations most commonly associated with this complication include total gastrectomy with loop esophagojejunostomy and simple or pouch Roux-en-Y reconstruction, partial gastrectomy with Billroth Ⅱ and Roux-en-Y reconstruction, and pancreaticoduodenectomy with conventional loop and Roux-en-Y reconstruction performed for treatment of benign and malignant causes[2].

ETIOLOGY

Causes of ALO include: (1) Entrapment, compression and kinking of the afferent loop by postoperative adhesions[3]; (2) Internal herniation, volvulus and intussusception of the afferent loop[4]; (3) Scarring due to marginal ulceration of the gastrojejunostomy[5]; (4) Locoregional recurrence (lymph nodes, peritoneum, gastric remnant, anastomotic sites)[6]; (5) Radiation enteritis of the afferent loop[7]; and (6) Enteroliths, bezoars and foreign bodies impacted in the afferent loop[8]. The causes of ALO can be classified according to the benign or malignant nature of the obstructing lesion to emphasize the presentantion, natural history and management of ALO (Table 1). Risk factors for ALO include: (1) Redundant (longer than 30-40 cm) and antecolic afferent loops which are more prone to kinking, volvulus, and entrapment by adhesions; and (2) Improperly closed mesocolic defects which predispose to internal herniation of the retrocolic afferent loop[9].

INCIDENCE

The incidence of ALO after distal gastrectomy with Billroth Ⅱ or Roux-en-Y reconstruction has been reported to be 0.3%-1.0%[10]. Although there are several specific predisposing factors for ALO following laparoscopic gastrectomy such as partial omentectomy and antecolic anastomosis, the incidence of ALO after open and laparoscopic surgery is similar. Kim *et al*[11] in their retrospective cohort study, reported 4 (1.01%) patients who developed ALO among 386 gastric cancer patients submitted to laparoscopic distal gastrectomy with Billroth Ⅱ reconstruction. The interval between the initial gastrectomy and the operation for ALO ranged from 4 to 540 d (median 33 d). The causes of ALO included adhesions in 2 patients and internal herniation in 2 patients. All patients recovered following emergency operations[11]. Aoki *et al*[12] in their retrospective cohort study, reported 4 (0.2%) patients who developed ALO among 1908 gastric cancer patients submitted to distal gastrectomy with Roux-en-Y reconstruction. The causes of the ALO included internal herniation in two patients, adhesions in one patient, and peritoneal recurrence in one patient. The interval between the initial gastrectomy and emergency operations for ALO ranged from 3 wk to 2 years (median 5 mo). All patients recovered following emergency operations.

There are limited data on the incidence of ALO after pancreaticoduodenectomy, especially among long-term pancreatic cancer survivors (> 2 years). In one of the few studies in the literature, Pannala *et al*[13] evaluated the incidence of ALO in pancreatic cancer patients submitted to pancreaticoduodenectomy. Pannala *et al*[13] in their retrospective cohort study, reported 24 (13%) patients who developed ALO among 186 pancreatic cancer patients treated with pancreaticoduodenectomy. Median time to diagnosis was 1.2 years (range 0.03-12.3 years). Obstruction was primarily caused by recurrent pancreatic cancer in 8 patients (33%) and radiation enteritis of the afferent loop in 9 patients (38%)[13].

PATHOPHYSIOLOGY

Symptoms associated with ALO are attributed to the increased intraluminal pressure and distention due to accumulation of enteric, biliary and pancreatic secretions in the partially or completely obstructed afferent loop. The severity of symptoms mainly depends on the degree and duration of obstruction[14]. Acute ALO represents a closed-loop obstruction and can be complicated by: (1) Ischemia and gangrene of the completely obstructed afferent loop with subsequent perforation and peritonitis; and (2) Ascending cholangitis and pancreatitis. Chronic

Table 1 Classification of afferent loop obstruction and management strategy

Causes			Management
Benign	Intraluminal	Foreign bodies Bezoar Enteroliths Intussusception	Surgery[2]
	Intramural	Gastrojejunostomy ulceration	
	Extrinsic	Adhesions Volvulus Internal hernia	
Malignant	Recurrence	Gastric remnant Anastomotic sites Lymph nodes Peritoneum Carcinomatosis	Endoscopy for enteral stenting[32] Transhepatic percutaneous enteral stenting or direct percutaneous tube enterostomy[29] By-pass surgery[2]
Radiation enteritis			Excision of the former afferent loop and reconstruction[31,33]

ALO represents an open-loop obstruction and can be complicated by: (1) Events similar to those seen in closed-loop obstruction despite the fact that the partially obstructed afferent loop can be partially decompressed; (2) Ascending cholangitis and pancreatitis; and (3) Bacterial overgrowth which can lead to steatorrhea, malnutrition, and vitamin B-12 deficiency[15].

PRESENTANTION

The primary symptoms of patients with acute ALO are sudden, severe abdominal pain and vomiting. The pain often occurs before associated findings of localized abdominal tenderness and involuntary guarding develop. When physical findings develop, there is a high level of suspicion that the viability of the bowel is compromised. Consequently, when ALO is the most likely diagnosis, abdominal pain out of proportion to physical findings represents a surgical emergency. The vomitus is not bilious because the biliary and pancreatic secretions remain trapped in the obstructed afferent loop[16].

Chronic ALO is more difficult to diagnose than acute ALO. Chronic ALO may manifest as periumbilical discomfort developing 15-30 min after eating and often lasting 1 to 4 h. These patients develop food fear and modify their pattern of eating so that they only consume small quantity of food. Patients with chronic ALO almost always have a profound weight loss, which raises suspicion of intraabominal malignancy. The progression from open-loop obstruction which is characterized by minor symptoms to closed-loop obstruction which represent a true surgical emergency is unpredictable. Projectile bilious vomiting may occur as the distended afferent loop decompresses forcefully providing rapid relief of symptoms. Chronic ALO with stasis and bacterial overgrowth can be further complicated by steatorrhea, diarrhea, B-12 and iron deficiency anemia[17].

Physical examination can reveal one or more of the following findings: (1) Upper abdominal distention. An ill-defined mass in the upper abdomen may be palpated representing the completely obstructed afferent loop; (2) Localized upper abdominal tenderness and involuntary guarding if perforation and peritonitis have occurred; (3) Jaundice; and (4) Signs of pancreatitis.

IMAGING STUDIES

Prior to the era of CT, conventional upper gastrointestinal barium studies were used to assess ALO. Two classical findings of ALO were described: (1) Non-filling of the afferent loop; and (2) Retention of barium in the dilated afferent loop for at least 60 min. However, several limitations existed as 20% of normal afferent loops were not filled with a barium meal and the underlying cause of obstruction was poorly identified[18].

CT plays a key role in the diagnosis of ALO. Zissin *et al*[19] reported that the characteristic CT appearance of the obstructed afferent loop is a U or C-shaped, fluid-filled, 5.3 cm in average diameter, tubular mass (C-loop sign) located in the midline between the abdominal aorta and the superior mesenteric artery with valvulae conniventes projecting into the lumen (keyboard sign) which can help in the differential diagnosis of pancreatic pseudocysts. Juan *et al*[20] reviewed multiple detector computed tomography scans of 22 patients who developed ALO after partial gastrectomy and pancreaticoduodenectomy. The C-loop appearance was present in 22 patients (100%) and the keyboard sign in 21 patients (95%) (Figure 1). There was only 1 patient without the presence of the keyboard sign due to bowel perforation. The maximal diameter of the afferent loop ranged from 3.3 to 5.8 cm.

CT images should be evaluated for the presence of: (1) the C-loop sign; (2) the keyboard sign; (3) pancreaticobiliary tract dilatation; (4) bowel wall thickening at the anastomotic sites, the afferent and efferent loops; and (5) lymphadenopathy, ascites, peritoneal enhancement, and metastatic lesions. Adhesions are suspected when a point of transition from a dilated to a normal-caliber loop is observed without other apparent cause. An internal hernia is suspected when crowding, stretching, and crossover of mesenteric vessels and the whirl sign are observed. Local recurrence and radiation enteritis are suspected when focal and diffuse bowel wall

Figure 1 C-loop (black arrow) and the keyboard sign (white arrows).

thickening are observed, respectively. Carcinomatosis is suspected when ascites and peritoneal enhancement are present and bowel wall thickening around the level of obstruction is absent[21]. Kim *et al*[22] reviewed helical CT scans of 18 patients who developed ALO after partial gastrectomy. The presumed cause of obstruction on CT was compared with surgical findings and clinical courses. In all 8 patients who underwent a second operation the cause of afferent loop was correctly suggested on CT. In all 10 patients who were not re-explored, the clinical findings or biopsy indicated recurrent tumor as suggested on CT. The authors concluded that CT correctly predicted the causes of ALO[22].

Diagnostic evaluation of ALO in the setting of a preceded pancreaticoduodenectomy should embrace magnetic resonance cholangiopancreatography (MRCP) or secretin-enhanced MRCP. The incidence of biliary and pancreatic stricture after pancreaticoduodenectomy is 2.6% and 2%, respectively. The patency of the primary hepaticojejunostomy and pancreaticojejunostomy should be thoroughly evaluated because the presence of a stricture can alter management strategy of ALO. Anatomic variants (pancreas divisum, dominant dorsal duct, aberrant ductal communications) and ductal pathology including filling defects, stenosis or obstruction should be recorded[23]. A hepaticojejunostomy stricture is characterized by the presence of a fixed filling defect at the anastomotic site, along with postobstructive extra- and intra-hepatic ductal dilation. A pancreaticojejunostomy stricture is characterized by the presence of a fixed filling defect at the anastomotic site, along with post-obstructive ductal dilation, side-branch enhancement and/or decreased functional excretion into the jejunal drainage limb[24].

MANAGEMENT

As ALO is an infrequent complication after gastrectomy and pancreaticoduodenectomy, the literature on management of this complication is limited and much of the current knowledge is derived by the accrual of single-institution series. Management strategy (Table 2) depends on the following three factors: (1) The benign or malignant nature of the obstructing lesion. ALO caused by benign lesions needs definitive treatment by surgery with the exception of anastomotic ulcerations which can be managed by endoscopic balloon dilation. Surgery includes repair of the primary cause along with a form of afferent loop reconstruction including: Addition of a Braun anastomosis in a former Billroth Ⅱ reconstruction, excision of the redundant loop and conversion of Billroth Ⅱ to Roux-en-Y gastrojejunostomy, and excision of the redundant loop and reconstruction of the former Roux-en-Y jejunojejunostomy. ALO caused by malignant lesions needs primarily palliative treatment (percutaneous and endoscopic interventions, by-pass surgery) and secondarily surgery with curative intent (excision and reconstruction); (2) The site of obstruction. An obstruction at the inframesocolic portion of the afferent loop can be easily reconstructed, whereas an obstruction at the supramesocolic portion of the afferent loop needs copious mobilization of the supramesocolic segment of the afferent loop through a field of dense adhesions; and (3) The patency of the primary hepaticojejunostomy and pancreaticojejunostomy. ALO in the setting of a preceded pancreaticoduodenectomy may require revision of the hepaticojejunostomy and pancreaticojejunostomy and/or a modified Puestow procedure during reconstruction of the obstructed afferent loop due to an anastomotic stenosis demonstrated in the preoperative secretin-enhanced MRCP[25].

As mentioned above, surgery has the principal role in the management of benign ALO. On the contrary, palliative approaches are preferred in the setting of malignant ALO as in the literature there are no data showing differences in survival between patients who submitted to palliative and curative treatment for management of malignant ALO. Endoscopic interventions at the afferent loop (balloon dilation, double-pigtail stents traversing the afferent loop strictured area, balloon dilation and double-pigtail stent placement, afferent loop metal stent placement), the bile duct (biliary balloon dilation and plastic or metal stent placement through ERCP), and the pancreatic duct (pancreatic duct balloon dilation and stent placement through ERCP or EUSguided rendezvous drainage after unsuccessful ERCP) have the principal role in the management of malignant ALO[26]. In Pannala *et al*[13] series, fifteen patients (62%) had an endoscopic intervention for management of malignant ALO after pancreaticoduodenectomy with Billroth Ⅱ reconstruction for pancreatic cancer. These patients required a median of 2 endoscopic procedures (range 1-17 endoscopic procedures); eleven patients (73%) had clinical and laboratory improvement, two patients (13%) did not improve, and two patients (13%) were lost to follow-up[13]. However, a Roux-en-Y reconstruction limits endoscopic access to the afferent loop[27]. Enteral stenting and ERCP with double-balloon enteroscope in patients with Roux-en-Y anastomosis have only been reported in small single-institute series[28]. Moreover, transhepatic enteral stent insertion and direct percutaneous tube enterostomy for management of ALO have only been reported in the literature as isolated

Table 2 Management of afferent loop obstruction

Causes		Management	
		Former Billroth Ⅱ	Former Roux-en-Y
Benign	Enteroliths Bezoar Foreign bodies	Endoscopy and balloon dilation of anastomotic stenosis[34] or adhesiolysis, enterotomy, removal and repair of anastomotic stenosis (stricturoplasty, addition of Braun anastomosis, conversion to Roux-en-Y)[8,16]	Endoscopy and balloon dilation of anastomotic stenosis or adhesiolysis, enterotomy, removal and repair of anastomotic stenosis (stricturoplasty, revision of the Roux-en-Y reconstruction)
	Intussusception	Manual reduction or enterectomy and conversion to Roux-en-Y[4]	Manual reduction or enterectomy and revision of Roux-en-Y reconstruction
	Anastomotic ulceration	Balloon dilation[34], stricturoplasty or conversion to Roux-en-Y	Balloon dilation, stricturoplasty or revision of the Roux-en-Y reconstruction
	Adhesions	Adhesiolysis, Braun anastomosis or excision of redundant loop and conversion to Roux-en-Y[35]	Adhesiolysis, excision of redundant loop and revision of the jejunojejunostomy
	Volvulus	Enterectomy and conversion to Roux-en-Y[36]	Enterectomy and revision of the Roux-en-Y reconstruction
	Internal hernia	Reduction and repair of the defect or reduction, repair of the defect, enterectomy and conversion to Roux-en-Y[37]	Reduction and repair of the defect or reduction, repair of the defect, enterectomy and revision of the Roux-en-Y reconstruction
Malignant		Endoscopy for enteral stenting[32]	Double-balloon endoscopy for enteral stenting
Radiation enteritis		Transhepatic percutaneous enteral stenting or direct percutaneous tube enterostomy[38]	Transhepatic percutaneous enteral stenting or direct percutaneous tube enterostomy
		Redo-surgery when other approaches fail: By-pass[2]	Redo-surgery when other approaches fail: By-pass
		Adhesiolysis, mobilization and excision of the afferent loop, Roux-en-Y reconstruction	Adhesiolysis, mobilization and excision of the afferent loop, revision of the Roux-en-Y reconstruction
		In preceded pancreaticoduodenectomy assessment of HJ and PJ patency with MRCP. Revision of the strictured HJ, revision of the strictured PJ and/or modified Puestow[31] or pancreaticojejuno-jejunostomy if primary PJ has normal patency[33]	In preceded pancreaticoduodenectomy assessment of HJ and PJ patency with MRCP. Revision of the strictured HJ, revision of the strictured PJ and/or modified Puestow or pancreaticojejuno-jejunostomy if primary PJ has normal patency

HJ: Hepaticojejunostomy; PJ: Pancreaticojejunostomy; MRCP: Magnetic resonance cholangiopancreatography.

cases[29].

When endoscopic and percutaneous approaches are neither successful nor feasible for management of malignant ALO, redo surgery becomes inevitable. Reoperative surgery is a difficult undertaking and reoperation itself may be the cause of further morbidity and mortality. Reoperation rates vary from 4% to 11% among small-volume series[30]. When redo surgery is indicated, more conservative surgical approaches, such as by-pass surgery, should be performed in this challenging group of patients. When all the above approaches (percutaneous and endoscopic interventions, by-pass surgery) fail, excision of the obstructed afferent loop and reconstruction should be considered as a treatment option[31].

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ORIGINAL ARTICLE

Basic Study

Response to chemoradiotherapy and lymph node involvement in locally advanced rectal cancer

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Abstract

AIM: To establish the association between lymph node involvement and the response to neoadjuvant therapy in locally advanced rectal cancer.

METHODS: Data of 130 patients with mid and low locally advanced rectal adenocarcinoma treated with neoadjuvant chemoradiation followed by radical surgery over a 5-year period were reviewed. Tumor staging was done by endorectal ultrasound and/or magnetic resonance imaging. Tumor response to neoadjuvant therapy was determined by T-downstaging and tumor regression grading (TRG). Pathologic complete response (pCR) is defined as the absence of tumor cells in the surgical specimen (ypT0N0). The varying degrees TRG were classified according to Mandard's scoring system. The evaluation of the response is based on the comparison between previous clinico-radiological staging and the results of pathological evaluation. χ^2 and Spearman's correlation tests were used for the comparison of variables.

RESULTS: Pathologic complete response (pCR, ypT0N0, TRG1) was observed in 19 cases (14.6%), and other 18 (13.8%) had only very few residual malignant cells in the rectal wall (TRG2). T-downstaging was found in 63 (48.5%). Mean lymph node retrieval was 9.4 (range

0-38). In 37 cases (28.5%) more than 12 nodes were identified in the surgical specimen. Preoperative lymph node involvement was seen in 77 patients (59.2%), 71 N1 and 6 N2. Postoperative lymph node involvement was observed in 41 patients (31.5%), 29 N1 and 12 N2, while the remaining 89 were N0 (68.5%). In relation to ypT stage, we found nodal involvement of 9.4% in ypT0-1, 22.2% in ypT2 and 43.7% in ypT3-4. Of the 37 patients considered "responders" to neoadjuvant therapy (TRG1 and 2), there were only 4 N+ (10.8%) and the remainder N0 (89.2%). In the "non responders" group (TRG 3, 4 and 5), 37 cases were N+ (39.8%) and 56 (60.2%) were N0 (P < 0.001).

CONCLUSION: Response to neoadjuvant chemoradiation in rectal cancer is associated with lymph node involvement.

Key words: Response to treatment; Neoadjuvant therapy; Rectal cancer; Chemoradiotherapy; Lymph node involvement

Core tip: The treatment of rectal cancer has evolved significantly in recent decades. The response of the primary tumor to neoadjuvant therapy, measured by tumor regression grading, seems to be a good prognostic factor, although this relationship is controversial. One of the most important prognostic factors is lymph node stage, but its relationship with the response to neoadyuvant therapy has not been studied extensively. In our series the response is correlated with lymph node involvement in the surgical specimens. Tumor regression grading score could therefore have clinical implications in the future in order to provide tailored therapies.

García-Flórez LJ, Gómez-Álvarez G, Frunza AM, Barneo-Serra L, Fresno-Forcelledo MF. Response to chemoradiotherapy and lymph node involvement in locally advanced rectal cancer. *World J Gastrointest Surg* 2015; 7(9): 196-202 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/196.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.196

INTRODUCTION

Colorectal cancer is one of the most common tumors worldwide, both in males and females, with an estimated 600000 deaths per year[1]. About 70% are located in the colon and 30% in the rectum. The treatment of rectal cancer (RC) has evolved significantly in recent decades. Neoadjuvant therapy with chemoradiation (CRT) improves local control and reduces toxicity compared to postoperative therapies. Sauer *et al*[2] showed that neoadjuvant CRT is superior in terms of local recurrence (LR) and acute toxicity. Around 60% of these patients experience some degree of tumor regression, but only a minor percentage will show pathologic complete response (pCR)[3].

According to data from the German Rectal Cancer Study Group[4], pCR is associated to better local control, lower risk of distant metastasis and better diseasefree survival. The response of the primary tumor to neoadjuvant therapy, measured by tumor regression grading (TRG) seems to be a good prognostic factor, however this relationship is controversial. In some studies no association with survival was found[5,6], whilst in others it was[7,8]. One of the most important prognostic factors is lymph node stage[9], but its relationship with the response to neoadyuvant therapy has not been studied extensively.

The aim of this study was to establish the relationship between lymph node involvement and the response to neoadjuvant CRT in locally advanced RC.

MATERIALS AND METHODS

Sample population

Data of patients with mid and low locally advanced rectal adenocarcinoma treated with neoadjuvant CRT followed by radical surgery in the University Central Hospital of Asturias over a 5 year period were reviewed. Rectal location is divided into low (2 to 6 cm from anal verge) and mid rectum (7 to 12 cm) measured by rigid proctoscope or magnetic resonance imaging (MRI). Locally advanced RC is defined as a tumor extending beyond the rectal wall (T3-4) or with lymph node involvement (N+), according to the TNM classification of the UICC[10], based on clinical and radiological criteria. Patients with skin or anal cancer, stage T1-2N0 RC, distal margin in upper rectum, with no completion of CRT or with previous pelvic radiotherapy were excluded of the study. Also excluded were those with no record of diagnostic endoscopic biopsy or those with no radical surgery. All patients received long course radiotherapy (45-50.4 Gy) with 5-FU based chemotherapy followed by radical surgery with total mesorectal excision (TME) after a mean of 7 wk interval.

Pathological evaluation

Morphologic evaluation of the surgical specimens was carried out by two experienced pathologist with no knowledge of other clinical data. The evaluation of the response to neoadjuvant CRT is based on the comparison between previous clinico-radiological staging and the results of pathological evaluation, measuring T-downstaging and TRG. PCR is defined as the absence of tumor cells in the surgical specimen (ypT0N0). T-downstaging was evidenced by TNM staging and is defined as the reduction of at least one T level measured initially by endorectal ultrasound and/or pelvic MRI and finally by pathological evaluation. The varying degrees of TRG were classified according to Mandard *et al*[11] scoring system.

Table 1 Characteristics of the sample population (n = 130)

		n (%)
Age	Mean	67.4 ± 10.6
	Range	42-86
Gender	Male	87 (66.9)
	Female	43 (33.1)
Tumor location	Mid rectum	75 (57.7)
	Low rectum	55 (42.3)
Tumor differentiation	Well	68 (52.3)
	Moderate	53 (40.8)
	Poor	9 (6.9)
Staging method	Endorectal ultrasound	119 (91.5)
	Magnetic resonance imaging	47 (36.2)
Radiotherapy	45 Gy	84 (64.6)
	50.4 Gy	46 (35.4)
Interval to surgery	Mean	7.1 ± 1.1
	Range	5-12
Surgical procedures	Low anterior resection	55 (42.3)
	Abdominoperineal resection	47 (36.2)
	Hartmann procedure	25 (19.2)
	Total proctocolectomy	3 (2.3)

Table 3 Postoperative pathologic evaluation (ypTN stage) (n = 130)

ypTN	*n*	%
T0N0	19	14.6
T1N0	10	7.7
T2N0	21	16.2
T3N0	38	29.2
T4N0	2	1.5
T0N1	3	2.3
T2N1	6	4.6
T3N1	16	12.3
T4N1	3	2.3
T3N2	11	8.5
T4N2	1	0.8

Statistical analysis

For the statistical analysis the software SPSS Statistics v21 was used. Two groups were established: "Responders", including TRG1 and 2, and "non responders", including TRG3, 4 and 5. χ^2 and Spearman's correlation tests were used for the comparison of variables. A P below 0.05 was considered significant. The statistical review of the study was performed by an expert in biomedical statistics.

RESULTS

A sample of 130 patients who met the study criteria was included (Table 1). All patients received full treatment with long cycle radiotherapy (45-50.4 Gy) and 5-FU based chemotherapy (oral capecitabine) followed by radical surgery.

For staging at baseline, endorectal ultrasound was available in 119 cases and pelvic MRI in 47. In early years of the study, the main staging method was ultrasound. Pelvic MRI is commonly used in recent years (Table 2). In case of disagreement between the two methods (10 cases), MRI was preferably considered.

Table 2 Tumor staging

	n	%
Pelvic MRI (*n* = 47)		
T3N1	21	44.6
T3N0	12	25.5
T3N2	4	8.5
T4N0	3	6.4
T4N1	3	6.4
T2N1	2	4.3
T4N2	2	4.3
ERUS (*n* = 119)		
T3N1	53	44.6
T3N0	50	42
T4N1	9	7.6
T4N0	3	2.5
T2N1	3	2.5
T3N2	1	0.8

MRI: Magnetic resonance imaging; ERUS: Endorectal ultrasound.

Table 4 Tumor regression grading according to Mandard *et al*[11] scoring system

TRG	*n*	%
1	19	14.6
2	18	13.9
3	39	30
4	41	31.5
5	13	10

TRG: Tumor regression grading.

The ypTN (postoperative) staging is showed in Table 3.

The result of TRG is included in Table 4. Complete response (pCR, ypT0N0, TRG1) was observed in 19 cases (14.6%), and other 18 (13.8%) had only very few residual malignant cells in the rectal wall (TRG2). These two groups were considered "responders" to neoadjuvant therapy. T-downstaging was seen in 63 patients (48.5%) and progression of tumor stage only in one case.

Mean lymph node retrieval was 9.4 (range 0-38). In 37 cases (28.5%) more than 12 nodes were identified in the surgical specimen. Preoperative lymph node involvement was seen in 77 patients (59.2%), 71 N1 and 6 N2. Postoperative lymph node involvement was observed in 41 patients (31.5%), 29 N1 and 12 N2, while the remaining 89 were N0 (68.5%). In relation to ypT stage, we found nodal involvement of 9.4% in ypT0-1, 22.2% in ypT2 and 43.7% in ypT3-4.

Of the 37 patients considered "responders" to neoadjuvant therapy (TRG1 and 2), there were only 4 N+ (10.8%) and the remainder N0 (89.2%). In the "non responders" group, 37 cases were N+ (39.8%) and 56 (60.2%) were N0 (P < 0.001) (Figure 1).

DISCUSSION

Conventional treatment for locally advanced, clinically resectable (T3-4 and/or N+) tumors is neoadjuvant CRT followed by radical surgery. Our ability to identify the N+

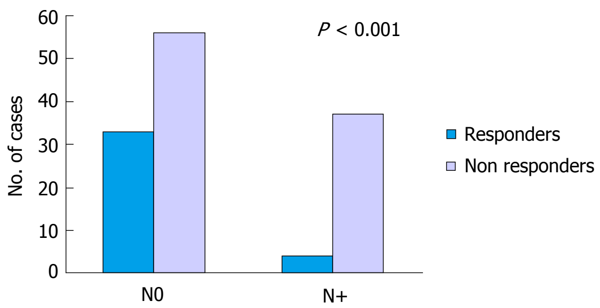

Figure 1 Correlation between ypN stage and tumor regression grading. Tumor regression grading according to Mandard *et al*[11] scoring system.

is limited, which leads to potentially overtreat 15%-20% of patients, as the German Trial shows[2], or undertreat 20%-30%. For N stage, both endorectal ultrasound and MRI have similar low sensitivity and specificity rates. Nonetheless, MRI is preferred for N-stage assessment because it allows the evaluation of the whole mesorectum. With radiological imaging advances we have progressed in the identification of adjuvant and neoadjuvant therapy needs. High resolution pelvic MRI with expert radiologist interpretation would help us to select patients that will be correctly treated with just surgery[12]. We are now using MRI to be selective and only irradiate those with a big volume, threatened mesorectal fascia, significant N+ or those with signs of venous invasion. In this line, the prospect trial is investigating the possibility of selectively eliminating the use of neoadjuvant radiotherapy in patients with upper and mid RC[13].

Response rates to CRT are highly variable. Approximately 15%-40% are resistant, while 5%-35% show a pCR. Our results are in that line. Pathological stage and TRG have a significant prognostic impact. Several studies link the TRG with disease-free survival but only pCR is clearly correlated[7,14]. TRG has been studied extensively. Rödel *et al*[4] analyzed 385 cases and found significant differences when grouped TRG 2 and 3, but not when stratified by pathological stage, giving doubts about the exact significance of this factor. Losi *et al*[15] found differences in 106 patients only when grouped TRG 3 and 4, although there was a trend towards improved disease-free survival when TRG was stratified by pathological stage. Moreno García *et al*[16] found that both disease-free survival and overall survival significantly improved with increased TRG. However, the correlation of the response to neoadjuvant CRT and LR and survival is still controversial[17,18].

In our series, we found a 14.6% of pCR. Patients with pCR have a better prognosis, with excellent local control and disease-free survival, regardless of previous TN stage[4,15,19-22]. Capirci *et al*[23] reviewed a large series of 566 cases with pCR in 61 centers and found better prognosis in this group. A number of groups are currently studying the possibility of treating the RC when a complete clinical response is achieved with local excision or observation (wait and see approach). Because approximately 40%-50% of patients treated with CRT will be ypT0-2 stage and a 10%-20% will be pCR (in our series 45.4% and 14.5% respectively), these preservation strategies of the rectum may have a potential application in many patients. However, there is a weak correlation between clinical and pathological response. Complete pathologic response cannot be accurately identified by clinical, endoscopic or radiological examination and, in most cases, is carried out with subjective exploration data[24-26]. One of the main questions that arise when performing local surgery is the nodal status. The incidence of lymph node involvement after neoadjuvant therapy varies. Some studies indicate differences in response between the tumor and the mesorectal lymph nodes[24,27]. The risk of lymph node involvement in patients treated with CRT and ypT0 tumors is low, but increases significantly with the degree of tumor penetration if any residual neoplastic cells remain in the rectal wall[28]. The risk of nodal metastasis in ypT0-1 is about 7%, compared to 30% for ypT2-4 (range 23%-37%). Read *et al*[29] found 3.5% involvement in T0-1, 23% in T2 and 51.5% in T3-4. Zmora *et al*[30] observed a higher incidence in T0-1, 12.1%. Park *et al*[31] found similar data: ypT0 9.1%, ypT1 17.1%, ypT2 20.8%. In our series we found 9.4% nodal involvement in ypT0-1, 22.2% in ypT2 and 43.7% in ypT3-4. Therefore, the identification of predictive criteria related both the primary tumor and lymph nodes seems to be important to select patients for local surgery, because we must not forget that radical surgical resection with TME, gold standard to compare with other alternatives, is associated with very good oncologic outcomes. In line with our study, Berho *et al*[32] found correlation between postoperative N stage and TRG, suggesting that neoadjuvant therapy should have a positive impact on overall survival. This study shows the low incidence of lymph node metastasis (14.2%) in good responders, findings similar to ours, where the percentage in TRG1 and 2 patients was 10.8%.

Our data confirms the association between the response to neoadjuvant therapy and lymph node involvement in RC[29,32,33]. Some studies have shown a relationship between good response to CRT and survival, suggesting that oncologic outcomes are more related to postoperative TNM stage, so TRG may be emerging as an independent prognostic factor[15,22,34]. The correlation with ypT stage strengthens this hypothesis. Dhadda *et al*[35] (n = 158) concluded that Mandard's scoring system is an independent prognostic factor predicting long-term outcomes. This index has already shown association with prognosis in esophageal cancer patients after CRT[11]. The authors propose its use in assessing the adjuvant therapy. Patients with TRG1-2 would be those with tumors sensitive to 5-FU therapy, while TRG3-5 or with positive nodes have worse prognosis and will require more intensive therapies.

The number of positive nodes is related not only with vascular invasion, but also with the reported number, which varies depending on factors related to the patient (age, sex, body mass index), the tumor (size, stage, grade), and the experience of the surgeon and the pathologist[36]. In our series the average nodes retrieval in the surgical specimen was 9.4. Although the American Joint Committee on Cancer recommends a minimum of 12 nodes for a correct staging, the number of isolated nodes in RC without treatment ranges from 9 to 13 and in patients with neoadjuvant therapy is usually lower[37-39], in part because of the depletion due to treatment and fibrosis, which makes the nodes smaller and more difficult to identify. The significance of this issue is unclear. Some authors consider it a marker of better response and is associated with a higher rate of pCR[26]. Marks *et al*[40] (n = 176) found only 28% of patients treated with CRT followed by TME in which more than 12 lymph nodes were identified in the resected specimen. Similar data were observed in a study by Govindarajan *et al*[41] (n = 429), where the average retrieved nodes was 10% and 63% of cases were under 12. In our series, only in 28.5% of cases more than 12 lymph nodes were identified. The inability to study more than 12 nodes is not associated to a worse prognosis in RC. Habr-Gama *et al*[42] showed that patients with no identifiable lymph nodes in the resected proctectomy specimens after CRT have excellent oncologic outcomes similar to those with ypN0 stage. Sprenger *et al*[43] have managed to increase, by intensive pathological examination, the number of identified lymph nodes and the incidence of N+, often with the presence of micrometastasis, although with no prognostic significance. Newer therapy strategies could have an impact in the near future[44].

In conclusion, in our series the response to neoadjuvant CRT in locally advanced rectal cancer is correlated with lymph node involvement in the surgical specimens. TRG therefore could have clinical implications in the future in order to provide tailored therapies.

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COMMENTS

Background

Neoadjuvant therapy with chemoradiation (CRT) improves local control and reduces toxicity compared to postoperative therapies. CRT is superior in terms of local recurrence and acute toxicity. Around 60% of these patients experience some degree of tumor regression, but only a minor percentage will show pathologic complete response. The response of the primary tumor to neoadjuvant therapy, measured by tumor regression grading seems to be a good prognostic factor, nevertheless this relationship is controversial.

Research frontiers

One of the most important prognostic factors is lymph node stage, but its relationship with the response to neoadyuvant therapy has not been studied extensively.

Innovations and breakthroughs

This is a study to establish the relationship between lymph node involvement and the response to neoadjuvant CRT in locally advanced rectal cancer.

Applications

In the series the response to neoadjuvant CRT in locally advanced rectal cancer is correlated with lymph node involvement in the surgical specimens. TRG therefore could have clinical implications in the future in order to provide tailored therapies.

Terminology

T-downstaging, evidenced by TNM staging, is defined as the reduction of at least one T level measured initially by endorectal ultrasound and/or pelvic magnetic resonance imaging and finally by pathological evaluation. Pathologic complete response is defined as the absence of tumor cells in the surgical specimen.

Peer-review

This work describes the efficacy of chemoradiation therapy in local advanced rectal cancer and concludes that lymph node metastasis is associated with the treatment failure. The writing is good and the conclusion is considerable.

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ORIGINAL ARTICLE

Case Control Study

Validation of a new scoring system: Rapid assessment faecal incontinence score

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Author contributions: de la Portilla F was responsible for the conception and design of the study, he acquired, analyzed and interpreted the data and drafted the manuscript and was responsible for revising the manuscript critically for important intellectual content; Calero-Lillo A, Jiménez-Rodríguez RM, Reyes ML, Segovia-González M and García-Cabrera AM contributed to the establishment of the methods and the development of the study.

Institutional review board statement: This study was approved by the Institutional Review Board of our hospital.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at fportilla@us.es. Participants gave informed consent for data sharing. No additional data are available.

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Abstract

AIM: To implement a quick and simple test - rapid assessment faecal incontinence score (RAFIS) and show its reliability and validity.

METHODS: From March 2008 through March 2010, we evaluated a total of 261 consecutive patients, including 53 patients with faecal incontinence. Demographic and comorbidity information was collected. In a single visit, patients were administered the RAFIS. The results obtained with the new score were compared with those of both Wexner score and faecal incontinence quality of life scale (FIQL) questionnaire. The patient without influence of the surgeon completed the test. The role of surgeon was explaining the meaning of each section and how he had to fill. Reliability of the RAFIS score was measured using intra-observer agreement and Cronbach's alpha (internal consistency) coefficient. Multivariate analysis of the main components within the different scores was performed in order to determine whether all the scores measured the same factor and to conclude whether the information could be encompassed in a single factor. A sample size of 50 patients with faecal incontinence was estimated to be enough to detect a correlation of 0.55 or better at 5% level of significance with 80% power.

RESULTS: We analysed the results obtained by 53 consecutive patients with faecal incontinence (median age 61.55 ± 12.49 years) in the three scoring systems. A total of 208 healthy volunteers (median age 58.41 ± 18.41 years) without faecal incontinence were included in the study as negative controls. Pearson's correlation coefficient between "state" and "leaks" was excellent (r = 0.92, P < 0.005). Internal consistency in the comparison of "state" and "leaks" yielded also excellent correlation (Cronbach's α = 0.93). Results in each score were compared using regression analysis and a correlation value of r = 0.98 was obtained with Wexner score. As regards FIQL questionnaire, the values of "r" for the different subscales of the questionnaire were: "lifestyle" r = -0.87, "coping/behaviour" r = -0.91, "depression" r = -0.36 and "embarrassment" r = -0.90, (P < 0.01). A multivariate analysis showed that all the scoring systems measured the same factor. A single factor may explain 80.84% of the variability of FI, so all the scoring systems measure the same factor. Patient's continence improves when RAFIS and Jorge-Wexner scores show low values and when the values obtained in the FIQL questionnaire are high.

CONCLUSION: RAFIS is a valid and reliable tool to assess Faecal Incontinence.

Key words: Faecal incontinence; Measure; Score; Test; Faecal incontinence quality of life scale questionnaire

Core tip: There are different scales for measuring the severity and impact of faecal incontinence (FI), but no together. The authors recommend the combined use of them to get a complete evaluation of FI. The aim of the present study is to implement a quick and simple test to assess faecal incontinence - the rapid assessment faecal incontinence score - and show its reliability and validity. Its validity and reliability has been proved when compared with other widely used scores.

de la Portilla F, Calero-Lillo A, Jiménez-Rodríguez RM, Reyes ML, Segovia-González M, Maestre MV, García-Cabrera AM. Validation of a new scoring system: Rapid assessment faecal incontinence score. *World J Gastrointest Surg* 2015; 7(9): 203-207 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/203.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.203

INTRODUCTION

Faecal incontinence (FI) refers to the inability to control gas, liquid or solid stool passage[1]. FI has a high prevalence in our environment, affecting 10% of primary care patients and having a significant impact on mental health[2]. The cause of FI can be stool characteristics, rectal or sphincter dysfunctions or neurological disorders[3].

The assessment of FI should be performed in a simple way but it must take into account two different factors which may be associated, that is, FI severity and impact of FI on quality of life of patients. As a result, its assessment may be difficult.

Severity refers to the number and characteristics of leaks and it can be measured using nominal scales, which is less frequent or by means of ordinal scales. The latter assign a numeric value to FI and are nowadays the preferred assessment method[4-7]. One of the most widely used scales is the Jorge-Wexner score (the wexner cleveland clinic florida score)[3].

The impact of FI on patient's quality of life can be measured using generic scales such as the SF36 questionnaire. Visual analogue scales for grading FI have been employed as well[8]. Widely used is the rockwood faecal incontinence quality of life scale (FIQL)[9] which contains a total of 29 different items assessing social, emotional, occupational and functional aspects. This scale has been translated and validated into Spanish[10].

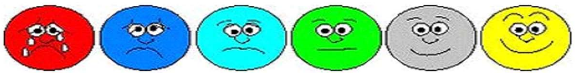
Although severity scales have progressively included items which try to measure "impact", the impact FI has on patients is more thoroughly assessed using its own specific scales. Some authors even recommend the use of a combination of two different scoring systems for severity and impact on quality of life respectively in order to attain a complete evaluation of FI[11].

The objective of this study is to implement a new score that allows the joint measurement of severity and impact in a simple way. Reliability and validity have been analysed comparing the new score with the Jorge-Wexner score and FIQL questionnaire.

MATERIALS AND METHODS

From March 2008 through March 2010, we evaluated a total of 261 consecutive patients (145 females, median age 59.05 ± 17.39 years) from the Proctology clinic. Demographic and comorbidity information was collected. In a single visit, patients were administered the Rapid Assessment Faecal Incontinence Score (RAFIS) (Figure 1), and the Jorge-Wexner score. The patient without influence of the surgeon completed the

According to the number of leaks I feel



You are very bad	You are bad	You are regular	You are well	You are very well	You are excellent
10	8	6	4	2	0

Note down the frequency of leaks (you can only tick one)

Several leaks daily	10	
Several leaks weekly but not daily	8	
Several leaks monthly but there is a week without leaks	6	
Leaks from time to time, but there is a full month without leaks	4	
Leaks occur rarely	2	
No leaks	0	

Figure 1 Rapid assessment faecal incontinence score.

Table 1 Demographic data and results of the different scores

	Incontinent patients	Control patients
Number of patients	53	208
Age (mean ± SD)	61.55 ± 12.49	58.41 ± 18.41
RAFIS state (mean ± SD)	6.91 ± 2.37	0
RAFIS leaks (mean ± SD)	7.25 ± 2.48	0
RAFIS global (mean ± SD)	14.15 ± 4.09	0
Jorge-wexner score (mean ± SD)	13.32 ± 4.95	0
FIQL test lifestyle (mean ± SD)	2.99 ± 0.96	4.99 ± 0.06
FIQL test coping/behaviour (mean ± SD)	2.48 ± 0.95	4.99 ± 0.06
FIQL test depression (mean ± SD)	3.23 ± 1.63	4.20 ± 0.84
FIQL test embarassment (mean ± SD)	2.59 ± 0.95	5 ± 0

RAFIS: Rapid assessment faecal incontinence score; FIQL: Faecal incontinence quality of life scale.

test. The role of surgeon was explaining the meaning of each section and how he had to fill.

The score is composed of two sections: (1) Visual-descriptive ordinal trying to define in concrete terms how it affects the patient fecal incontinence; and (2) the frequency of episodes, which generally describes many episodes of incontinences have the patient in a month.

RAFIS total score was obtained after each patient made a selection in our score according to the frequency and number of leaks.

A sample size of 50 patients with faecal incontinence was estimated to be enough to detect a correlation of 0.55 or better at 5% level of significance with 80% power.

Reliability of the RAFIS score was measured using intra-observer agreement and Cronbach's alpha (internal consistency) coefficient. In both cases, the items "State" and "Leaks" were compared. A value $\geqslant$ 0.7 is acceptable in the case of intra-observer agreement. As for Cronbach's alpha, an internal consistency value of $\alpha \geqslant 0.7$ is acceptable and a value of $\alpha > 0.9$ is excellent.

Validity of RAFIS score was assessed by means of convergent validity. RAFIS was compared with Jorge-Wexner score and with FIQL questionnaire. Also, a multivariate analysis of the main components within the different scores was performed in order to determine whether all the scores measured the same factor and to conclude whether the information could be encompassed in a single factor.

The statistical analysis was performed using SPSS 20.0 software and a value of $P < 0.05$ was considered significant.

Since no intervention was performed on patients, approval by the Ethics Committee was not necessary.

Table 2 External validity of the score compared with Jorge-Wexner score and faecal incontinence quality of life scale questionnaire

	Correlation
RAFIS global - Jorge-Wexner score	0.98[b]
RAFIS global - FIQL test lifestyle	- 0.87[b]
RAFIS global - FIQL test coping/behaviour	- 0.91[b]
RAFIS global - FIQL test depression	-0.36[b]
RAFIS global - FIQL test embarassment	-0.90[b]

[b]Significance at 1% ($P < 0.01$). RAFIS: Rapid assessment faecal incontinence score; FIQL: Faecal incontinence quality of life scale.

RESULTS

We analysed the results obtained by 53 consecutive patients with faecal incontinence (median age 61.55 ± 12.49 years) in the three scoring systems. A total of 208 healthy volunteers (median age 58.41 ± 18.41 years) without faecal incontinence were included in the study as negative controls. Age below 18 was an exclusion criteria. Table 1 shows demographic data and the results obtained in the scores.

RAFIS reliability was measured using intra-observer agreement. Pearson's correlation coefficient between "state" and "leaks" was excellent ($r = 0.92$, $P < 0.005$). Internal consistency in the comparison of "state" and "leaks" yielded also excellent correlation (Cronbach's α = 0.93).

Validity assessment of the new score yielded a high correlation with both Jorge-Wexner score and with the different subscales of FIQL, as shown in Table 2.

In order to complete the study, a multivariate analysis was also carried out of the global results obtained in the different scoring systems (Jorge-Wexner, FIQL lifestyle, coping/behaviour, depression and embarrassment) and RAFIS. A single factor may explain 80.84% of the variability of FI, so all the scoring systems measure the same factor. Patient's continence improves when RAFIS and Jorge-Wexner scores show low values and when the values obtained in the FIQL questionnaire are high (Table 3).

DISCUSSION

RAFIS comprises two items: State and leaks. The former is measured by means of a visual analogue scale and the latter by means of an ordinary scale.

Table 3 Multivariate analysis

RAFIS global	0.96
Jorge-Wexner score	0.96
FIQL test lifestyle	-0.95
FIQL test coping/behaviour	-0.97
FIQL test depression	-0.47
FIQL test embarrassment	-0.97

RAFIS: Rapid assessment faecal incontinence score; FIQL: Faecal incontinence quality of life scale.

Visual analogue scales were chosen as measurement tool because they have a high correlation with reality and are easy to understand by patients. Moreover, the advantages of visual analogue scales of faces are wellestablished[12].

In our study, the measurement of leaks introduces a novel simplification as it does not consider the quality of faecal leaks but only their frequency. We do not take into account such variables as pad usage (evaluated in Jorge-Wexner score or Vaizey test[6]), the necessity to change underwear (included in RFIS test[7]), faecal urgency or anti-diarrheal drugs (measured in Vaizey test).

In our country, Devesa *et al*[8] have used numeric visual analogue scales to assess the severity of FI and its impact on quality of life of patients. They found no correlation between visual analogue scales for FI and Jorge-Wexner score but they observed a significant correlation with the "embarrassment" subscale of FIQL. They also found correlation between visual analogue scales for quality of life and the "coping/behaviour" subscale of FIQL. Our study shows a significant correlation between RAFIS global and Jorge-Wexner score.

The impact of FI on quality of life has long been discussed and several studies have established the importance of such impact. Minguez *et al*[10] validated the FIQL into Spanish and compared it with the Jorge-Wexner score. These authors observed a strong correlation among all the items. Their study also showed that pad usage is an independent factor which worsened quality of life scores. Similar results have been reported by Bols *et al*[11] when they compared Jorge-Wexner score and Vaizey score with FIQL. They found a strong correlation between results, particularly in "embarrassment" and "coping/behaviour" subscales.

However, there are some studies which do not agree with these results. For instance, Bordeianou *et al*[13] in their analysis of the correlation between faecal incontinence severity index and every one of the subscales in FIQL, found moderate correlations with embarrassment and coping/behaviour but no correlation at all with lifestyle and depression.

Another study by Damon *et al*[14], comparing Jorge-Wexner score with gastrointestinal quality of life index questionnaire, found a poor correlation between FI severity and quality of life.

Our study shows significant correlation between RAFIS and every subscale of FIQL with the exception of "depression" although higher depression scores as well as prior hysterectomy have moderate to severe quality of life impairment. Some authors said when evaluating FI, screening for mood disturbances should be undertaken[15]; however depression is multifactorial, in fact biological and environmental factors may be involved. This explains why scales depression associated with FI only have a lower correlation, without implication to determine the complete evaluation of FI.

In our opinion, the election of aggressive therapy for the treatment of FI should consider not only severity of symptoms but also impact on the quality of life of patients.

Our study has some limitations. In order to assess the reliability of our score, we compared two factors: Leaks and state. We obtained a high correlation. However, the best statistical tool is the Test-Retest, as has been proven by similar studies[16]. The same measurement is performed repeatedly at short intervals, which does not allow patients to change their status. Unfortunately, logistical reasons made it impossible to perform the tes-retest. In spite of it, our score shows high reliability. Also, we could not demonstrate the sensitivity of our score to change after faecal incontinence therapy as our objective was to evaluate our new test to assess FI, so the test was not repeated after faecal incontinence therapy.

In our opinion RAFIS could be improved taking into account the factor of faecal urgency and a third section that refers to the type of incontinence (hard, liquid or gas feces). Urgency item was not taken into account due to the chosen gold standard scale for severity was Jorge-Wexner score, which does not include it, instead of Vaizey[6]. Vaizey score determines faecal urgency asking patients the ability to defer defecation for 15 min. We suggest asking about the need to stop the current activity in order to go to the toilet.

Bols *et al*[11] compared Jorge-Wexner, Vaizey and FIQL scores, and Vaizey score showed that items "medication use," "pads," and "flatus incontinence" had poor external responsiveness, whereas "urgency" had adequate external responsiveness. The item "pad use" of the Wexner score also had poor external responsiveness.

Although RAFIS seems a valid and reliable scoring system in our environment, which could even replace Jorge-Wexner score and FIQL questionnaire, we still believe it is highly advisable to use a diary system as it provides an objective measurement of FI if correctly filled out by patients.

In our opinion RAFIS could be improved taking into account the factor of faecal urgency.

Faecal incontinence severity comprises two factors: objective (severity/leaks) and subjective (impact on quality of life/state). A new quick and simple score to assess FI has been tested showing its validity and reliability when compared with other widely used scores.

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COMMENTS

Background

Several questionnaires have been used in different studies to evaluate fecal incontinence and how patient's life is disturbed by the symptoms. There are different scales for measuring the severity and impact of faecal incontinence (FI), but no together and a simple and quick score.

Research frontiers

Creating a faecal incontinence scoring system which is both reproducible and simple to use is complex due to the variable nature of the condition.

Innovations and breakthroughs

There are different scales for measuring the severity and impact of FI, but no together. The authors recommend the combined use of them to get a complete evaluation of FI. The aim of the present study is to implement a quick and simple test to assess FI - the rapid assessment faecal incontinence score - and show its reliability and validity. Its validity and reliability has been proved when compared with other widely used scores. The research fulfills the criteria of novelty and innovative because it proposes and shows a new and reliable way to mesure faecal incontinence.

Applications

Clinical assessment of severity of faecal incontinence varies between clinicians according to their expertise. This causes difficulties when comparing results of published data, often making comparisons of treatment modalities meaningless. Many attempts have been made in the past to develop scoring systems but their clinical applicability has not been validated adequately. This study has established the validity of a quick and simple test to assess FI, and it could also help select patients who could benefit from a affective treatment.

Peer-review

The research is important, because it proposes a method of inquiring that could facilitate the communication between physicians and faecal incontinence patients. This new approach could have a positive impact on these patients treatment. Regarding the significance of the study findings, the authors showed excellent agreement and consistency for both criteria analyzed.

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ORIGINAL ARTICLE

Retrospective Study

Impact of surgical delay on outcomes in elderly patients undergoing emergency surgery: A single center experience

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Author contributions: Ong M designed the study, collected data and wrote the paper; Guang TY collected the data and helped write the paper; Yang TK helped design the study, analyzed the data and helped edit the paper for final submission.

Institutional review board statement: The study was reviewed and approved by the Khoo Teck Puat Hospital Institutional Review Board.

Informed consent statement: Consent was not obtained in view of retrospective nature of study but the presented data are anonymized and risk of identification is low.

Conflict-of-interest statement: There were no conflicts of interest to disclose among the authors.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at tan.kok.yang@alexandrahealth.com.sg.

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Abstract

AIM: To determine predisposing factors leading to surgical delay in elderly patients with acute abdominal conditions and its impact on surgical outcomes.

METHODS: A retrospective review of a total of 144 patients aged 60 years and older who had undergone emergency abdominal surgery between 2010 and 2013 at a regional general hospital was analysed. The operations analysed were limited to perforated or gangrenous viscus and strangulated hernia. Patient demographic features, time taken to obtain a computed tomography scan, time taken to surgery and the impact on postoperative morbidity and mortality were analysed.

RESULTS: The mean age was 70.5 ± 9.1 years and median time taken to surgery was 9 h. The overall mortality and complication rates (Clavien Dindo 3 and above) were 9% and 13.1% respectively. Diabetes mellitus was a significant predisposing factor which had an impact on surgical delays. Delays in surgery more than 24 h led to higher complication rates at 38.9% (P = 0.003), with multivariate analysis confirming it as an independent factor. Delays in obtaining a computed tomography (CT) scan was also shown to result in higher complication rates (Clavien Dindo 3 and above).

CONCLUSION: Delays in performing emergency surgery in elderly lead to higher complication rates. Obtaining CT scans early also may facilitate prompt diagnosis of certain abdominal emergencies where presentation is more equivocal and this may lead to improved surgical outcomes.

Key words: Outcomes; Delay; Emergency; Surgery; Elderly

Core tip: Emergency surgery in elderly is regarded as a subject matter with growing interest as many countries are faced with an ever increasing aging population. The unique and varied characteristics of the elderly make surgical decisions and management an evolving conundrum and challenge. In this paper, we will discuss the outcomes of elderly patients undergoing emergency surgery in our institution, dwell deeper in possible factors that lead to surgical delay and also look into the relationships between surgical delay and surgical outcomes.

Ong M, Guang TY, Yang TK. Impact of surgical delay on outcomes in elderly patients undergoing emergency surgery: A single center experience. *World J Gastrointest Surg* 2015; 7(9): 208-213 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/208.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.208

INTRODUCTION

Like its many Asian counterparts, Singapore is expected to face an ageing population over the next few decades. As of 2012, the elderly (aged > 65) make up 10.5% of the population, and this number is expected to increase threefold by 2030. The management of elderly population has always been a challenging topic and surgical emergencies of the abdomen are more common in the elderly than in other population[1,2]. Yet delays in appropriate surgical treatments are also higher in this population, which translates to poorer morbidity and mortality[3,4]. Wakayama *et al*[5] noted in gastrointestinal perforations, the mortality is doubled after a delay of > 12 h, eight fold after 24 h, and the tolerance to delay is inversely proportional to age.

There are numerous documented reasons for these delays. Firstly, the elderly population tends to have atypical presentation, with symptoms and signs frequently milder and less specific than in younger adults[6]. Some studies also show that elderly patients are generally less likely than younger patients to receive analgesia due to multiple factors including depression, failures in memories and cognitive deficits that may hinder obtaining an accurate pain history[7]. More importantly, elderly patients often have multiple medical conditions that require optimizations prior to surgery, which increases the time delay[8]. The presence of coexisting diseases is also shown to be a stronger negative prognostic indicator on outcomes when compared to age[9].

Given the conundrums in managing elderly patients, the aim of this study is to report our institution's experience in managing elderly patients undergoing emergency surgeries, paying particular attention to the factors that lead to delays in early surgical interventions and also the impact of such delays on post-operative morbidity and mortality. Our hypothesis was that delays in surgery translated to poorer outcomes and by analyzing contributing factors to such delays, we could potentially reduce such delays and improve surgical outcomes in the elderly.

MATERIALS AND METHODS

A retrospective study was performed between 2010 and 2013 on a cohort of 144 elderly patients aged above 65 years old who had undergone emergency abdominal surgery at our institution, Khoo Teck Puat Hospital, Singapore. Since there is no one standard definition of emergency surgery, we defined emergency surgery as those who had undergone surgery within 48 h of admission to the hospital through the Emergency Department for an acute presentation. We limited the study to strangulated hernia, gangrenous or perforated viscus as these were the conditions that required immediate surgery upon diagnosis (unlike some cases of intestinal obstruction).

Pre-operatively, 120 out of 144 patients underwent computed tomography scans of the abdomen and pelvis (CTAP) as part of their diagnostic workup and the other 18 patients had diagnoses confirmed *via* plain radiographs. The remaining 6 patients had clinically irreducible hernias which turned out to have gangrenous bowel.

The primary outcomes measured were mortality and surgical complication rates, based on the Clavien Dindo grading system[10]. Delays to surgeries were stratified into 4 groups: 1-6 h, 7-12 h, 13-24 h, and more than 24 h and compared against the rates of inhospital mortality and complication rates. We defined patients to have major morbidity when they had a complication Clavien-Dindo grade 3 and above either requiring surgical intervention or high dependency/ICU supportive care.

To elucidate possible predisposing factors for surgical delay, we looked at the patients' comorbidities based on the Charlson's weighted comorbidity index. This index is widely used in the geriatric population giving different weights to different cormorbidities[11]. It was first used to predict lifespan but subsequently had been found to be useful to predict risk of surgery in the geriatric population[12]. We also studied other factors including medications, cognition, mobility, nursing home residency, American Society of Anesthesiologists (ASA) physical status classification system and hemodynamic status on admission. We then measured the time interval taken to surgery, defined as time of arrival at the emergency department to the time emergency surgery was performed. In a subgroup of patients, we also measured the time interval taken to complete CTAP upon admission. Multivariate analysis was then performed to compare complication rates and mortality against surgical delays, adjusting for independent effects of predisposing factors on surgical delays.

Table 1 Distribution of cases according to diagnosis (n = 144)

Indications	Patients, n (%)	Mortality[1], n (%)	Morbidity[2] (Clavien Dindo 3 and above)
Strangulated hernia			
Inguinal	3 (2.0)	0 (0)	0 (0)
Obturator	2 (1.4)	0 (0)	0 (0)
Periumbilical	1 (0.7)	0 (0)	0 (0)
Hollow viscus perforation			
Esophagus	1 (0.7)	0 (0)	0 (0)
Gastric ulcer	39 (27.0)	5 (12.8)	7 (17.9)
Duodenal ulcer	13 (9.0)	0 (0)	3 (23)
Gallbladder	2 (1.4)	0 (0)	0 (0)
Small bowel	12 (8.3)	0 (0)	2 (16.7)
Colonic malignancy	8 (5.6)	3 (37.5)	3 (37.5)
Colonic diverticulitis	6 (4.2)	1 (16.7)	1 (16.7)
Appendix	37 (25.7)	0 (0)	0 (0)
Gangrenous viscus			
Small bowel gangrene	10 (6.9)	4 (40)	4 (40)
Large bowel gangrene	3 (2.0)	0 (0)	0 (0)
Empyema gallbladder	7 (4.8)	0 (0)	0 (0)

[1]Overall mortality n = 13 (9%); [2]Overall patients with severe morbidty (Clavien Dindo 3 and above) n = 20 (13.8%).

Table 2 Outcomes after emergency abdominal surgery

Outcome	Patients (n = 144)	(%)
Surgical		
Post op ileus	11	7.6
Wound infection	13	9
Abdominal abscess	4	2.7
Anastomotic leak	4	2.7
Post op bleeding	2	1.4
Medical		
Respiratory complication	32	22.2
Cardiac complication	20	13.8
Renal complication	12	8.3
Cerebrovascular complication	1	0.7
Thromboembolic complication	5	3.5
Others	6	4.2
Return to OR		
Post op bleeding	2	1.4
Anastomotic leak	4	2.7
Anastomotic stenosis	1	0.7
Abdominal collection	1	0.7
Others	1	0.7

All analyses were done using IBM SPSS statistics ver 20.2. Univariate analyses for categorical variables were done with χ^2 test and Fisher exact test and continuous date were analyzed by using Student t test and analysis of variance method. Multivariate analyses were done using multinomial and binary logistic regression methods. A 2 tailed P value of less than 0.05 was taken to be statistically significant in this study.

RESULTS

A total of 144 patients underwent emergency surgery. The mean age was 70.5 (9.1 SD), with 87 males and 57 females. The two leading causes of surgical emergency were perforated gastric ulcer and perforated appendicitis shown in Table 1. The total number of deaths was 13, representing an overall mortality of 9%. We found that the highest rates of mortality occurred in patients presenting with small bowel gangrene (40%) followed by perforated colonic malignancy (37.5%). There were 6 cases of strangulated hernia but none resulting in death. Table 2 highlights the post-operative outcomes in our series. There were 20 patients which had more serious post-operative complication (Clavien Dindo grade 3 and above), indicating a major morbidity rate of 13.8%. Nine patients required repeat surgery (6.2%) mainly for post-operative bleeding, anastomotic leakage and anastomotic stenosis. The mean length of hospital stay was 11 d.

The median time taken from presentation to surgery was 9 h (range 1-48 h). The primary independent variable of delay in surgery was further categorized into 4 groups for risk estimation: 1-6 h, 7-12 h, 13-24 h, and more than 24 h. Table 3 shows the relationship between the stratified times and the mortality and complication rates. There were no statistically significant differences in mortality between the groups. But when comparing complication rates, we found that 7 out of 11 patients (38.9%) had complications when surgery was delayed more than 24 h, which was much higher compared to the other groups (P = 0.003).

Patients undergoing surgery for any viscus other than the appendix also had a higher mortality rate (13 out of 94) than those with appendiceal diseases (P = 0.026). There were no mortalities observed in the latter group. Regardless, after adjusting for ASA, diabetes mellitus, comorbidity index, bedbound patients and nonappendiceal cases, surgeries delayed > 24 h was found to be an independent factor associated with Clavien 3 and above complications; ORs was 12.7 (CI: 1.19-136.5, P = 0.035) as highlighted in Table 4.

Of the predisposing factors analyzed which might potentially delay surgical intervention, only diabetes mellitus was found to be a significant factor in patients with surgical delays > 24 h, shown in Table 5. The other factors including cognitive impairment, pre-admission medications, comorbidity index, bedbound state, presence of hypotension on arrival in the ED were found to have no significance on the time taken to surgery.

In a sub-set analysis of the 120 patients who underwent CTAP, the mean time taken to perform at computed tomography (CT) scan was 7.5 h. Incidentally, we noted that patients which required a longer time to perform CT scans ended up with higher complication rates. Table 6 reveals that the mean time taken to perform CT scan in patients with post-operative complications (Clavien Dindo grade 3 and above) was 13.1 h, compared to those with lesser complications being 6.5 h (P = 0.006). However again, no association was found between time to CT imaging and mortality rates.

DISCUSSION

As the number of persons reaching old age continues

Table 3 Stratified time to surgery against morbidity and mortality

		Stratified by time to surgery				Total	P value
		1-6 h	6-12 h	13-24 h	> 24 h		
Clavien 2 and below		32	56	25	11	124	
Clavien 3 and above		7	5	1	7	20	
% of total		17.9%	8.2%	3.8%	38.9%	13.9%	0.003[a]
Total		39	61	26	18	144	
Mortality	No	34	58	24	15	131	
	Yes	5	3	2	3	13	
% of total		12.8%	4.9%	7.7%	16.7%	9%	0.351
Total		39	61	26	18	144	

[a]$P < 0.05$ statistically significant difference between groups.

Table 4 Multivariate analysis of factors associated with Clavien Dindo grade 3 and above complications

Factors	Odds ratio	95%CI	P value
Surgical delay > 24 h	12.75	1.19-136.57	0.035[a]
Surgical delay > 12 h	0.45	0.05-3.89	0.467
ASA score ⩾ 3	0.53	0.16-1.68	0.278
Diabetes mellitus	1.97	0.56-6.87	0.288
Comorbidity index score ⩾ 4	0.64	0.06-7.27	0.716
Bedbound patients	1.53	0.09-25.43	0.765

[a]$P < 0.05$ statistically significant difference between groups. ASA: American Society of Anesthesiologists.

Table 5 Multivariate analysis of predisposing factors associated with surgical delay > 24 h

Predisposing factors	Odds ratio	95%CI	P value
ASA score ⩾ 3	2.66	0.77-9.26	0.123
Comorbidity index score ⩾ 4	1.29	0.19-8.57	0.787
Diabetes mellitus	4.08	1.32-12.55	0.014[a]
Bedbound patients	0.54	0.02-18.32	0.73
Cognitive impairment	0.45	0.03-6.63	0.566
Chronic analgesia	0.26	0.03-2.33	0.23
Anticoagulants	0.71	0.15-3.36	0.669
Nursing home resident	5.57	0.31-100.25	0.244

[a]$P < 0.05$ statistically significant difference between groups. ASA: American Society of Anesthesiologists.

Table 6 Mean time taken to perform computed tomography against morbidity and mortality

		n	Mean time taken to perform CTAP	Standard error mean	P value
Clavien 2 and below		19	6.5 h	3.436	0.006[a]
Clavien 3 and above		101	13.1 h	0.776	
Mortality	Yes	12	11.667	4.962	0.119
	No	108	7.139	0.797	

[a]$P < 0.05$ statistically significant difference between groups. CTAP: Computed tomography scans of the abdomen and pelvis.

to grow, there is a concomitant and imperative need to provide surgical care to an ever increasing number of older patients. There has also been an increase in operations performed for patients older than 65 years old, which is generally accepted as baseline age for geriatric surgery[13]. Increased age alone should not be the sole reason to deny surgery in the elderly[14]. Van Geloven reported on patients over age 80 who presented to the emergency department with abdominal pain and found 27% required surgery, with an overall mortality of 17% that doubled to 34% among those who required operative intervention[15].

Delays before surgical treatment are often recognized as a contributor to adverse outcomes in emergency surgery and can lead to increased mortality rates[9,16]. Our results appears consistent with these studies and we noticed a higher rate of post-operative complications (Clavien Dindo grade 3 and above) occurring when surgery was delayed especially when delay was greater than 24 h. With respect to predisposing factors associated with delays greater than 24 h, diabetes mellitus (DM) came up as an independent predisposing factor contributing to delay in surgical intervention as shown in Table 3. We propose that DM could have contributed to a blunted physiological response and hence atypical presentations. FT de Dombal previously described how the case mix and disease evolution is very different in the elderly population and emphasizes the importance of having a greater sense of awareness in diagnosis[17]. Similarly, for elderly patients with DM, symptoms may be misleading resulting in diagnostic and possible subsequent surgical delays; hence a high index of suspicion is required.

We believe that the type of surgical emergencies, independent of time, also has a direct impact on the morbidity and mortality. Perforated appendicitis constituted the second most common cause in this study. The incidence of perforation in acute appendicitis is estimated to be 20%-30% but increases to 32%-72% in patients above 60 years of age[18]. However, these patients tend to have better outcomes compared to the rest who presented with acute abdomen. In our study, none of the 37 patients who presented with perforated appendicitis had significant morbidity (Clavien 3 and above) or mortality. In stark contrast, we noted a total of 20 morbidities and 13 mortalities in the remaining population. In particular, 40% and 37.5% of patients with small bowel gangrene and perforated colonic malignancies respectively had significant complications that eventually resulted in death. Guo *et al*[19], in his study of 233 patients with perforated malignant colonic obstructions, recorded a 24.5% 30-d post-operative mortality, regardless of the Dukes cancer staging. Previous studies have also reported hollow viscus perforations, acute biliary diseases and strangulated hernias accounting for the majority of reasons for emergency surgery in elderly[14,20]. These conditions often have similar presentations and early accurate diagnosis is paramount in facilitating appropriate treatment.

Abdominal pain constitutes 10%-15% of all complaints in older persons seen at our Emergency Department and this indolent, nonspecific nature of initial symptom is what makes accurate diagnosis difficult. Radiological imaging is often employed in aiding diagnosis in these conditions, however while advances in diagnostic skills and improvements in diagnostic facilities improve diagnostic accuracy, delay in performing these investigations can impact surgical outcomes[21]. Hence we also sought to determine the potential effect of delay in obtaining radiological diagnosis on eventual outcomes as well.

While the leading cause for acute abdomen in our series was peptic ulcer, perforations of small bowel, colonic diverticulitis, colonic malignancies and gallbladder were other causes in our study population. Because of the atypical manifestation of these acute abdominal conditions in the elderly, a CT scan is often helpful. In our series, we noted that in the 120 patients where a CT scan was performed, a greater complication rate (Clavien 3 and above) was observed when the scan was delayed. The mean time to taken to perform CT scan in patients where more serious complications were observed was found to be significantly higher than those with less severe complications as discussed earlier. Delays in performing CT scans in the former group could be attributed to several reasons namely hemodynamically unstable patients requiring further resuscitation and even transferring to high dependency or ICU first, delayed presentation of illness, lack of physical signs at first presentation, inability to illicit proper history from uncommunicative or cognitively impaired patients, and also patients presenting with acute kidney injury requiring intravenous rehydration before performing a contrasted CT scan. The breakdown of the time attributed to the aforementioned factors were not the focus of this particular study but could be looked into with greater detail in subsequent studies.

According to Table 3, we noticed that the overall morbidity seemed to initially decrease with time when surgery was performed within 24 h. However beyond 24 h, it was noted there was the highest percentage of patients with Clavien 3 and above complications (7 out of 18 patients, 38.9%). This bimodal representation could possibly be explained by there being 2 groups of patients: The first group where patients were more stable and diagnosis was made early with resultant earlier operation performed and the second group where patients were more unstable and required a period of resuscitation first before undergoing an operation. In the latter group, the patients were initially too unstable to perform a CT scan resulting in delayed diagnosis and hence a delay in surgery. The 25 patients who eventually underwent surgery after 24 h were mostly patients already in severe sepsis and this could have explained the majority of them ending up with greater complications post-operatively.

Therefore, we believe that in an elderly population where symptoms of abdominal pain maybe equivocal, the threshold to perform CT scan should be lowered. Once a decision is made to perform a scan, one should expedite its execution to reduce any delays. The earlier a CT scan is performed, the sooner a definitive diagnosis is made and this minimizes total time delay till surgery is performed. Ultimately, we believe this possibly could reduce the severity of post-operative complications especially in patients presenting with the specific conditions in this study. Omari *et al*[22] has also suggested that the early use of CT scan can cut short the way to appropriate treatment for perforated viscus.

There are certain limitations to this study. Firstly, it is a retrospective study and we were unable to take into account the delays which occurred before presentation to the ED. We also did not look into other specific causes which resulted in delays besides those encountered in obtaining CT scans and also the factors that result in a delay in performing a scan. A prospective study can be performed looking at these causes so we can identify other areas to improve and reduce delays in surgery. Lastly, the study also does not include a comprehensive list of all emergency surgeries in the elderly as certain conditions such as cholecysitis and intestinal obstruction are sometimes treated with a trial of conservative management first. The majority of the conditions included in the study were either perforated viscus or gangrenous viscus hence outcome measures should be compared with only this specific group of patients.

Our study demonstrates clearly that delay in performing emergency surgery in elderly lead to higher complication rates. Elderly patients presenting with abdominal pain should be admitted and prudently evaluated with a view to avoid diagnostic and thus surgical delays. Obtaining CT scans early also may potentially facilitate earlier diagnosis of perforated or gangrenous viscus, especially in this group of patients where clinical presentations may be more atypical, and thus possibly lead to improved surgical outcomes.

COMMENTS

Background

With an ever increasing ageing population faced in most countries, there is an expected rise in the number of surgical emergencies encountered. Elderly patients are an entirely different group of patients with their multiple comorbidities, cognitive impairment, altered body physiology and more fragile state contributing to the challenges in their management. Many studies have looked into outcomes of emergency surgery but few have focused on the predisposing factors that lead to delay in surgery and how such delays impact outcomes.

Research frontiers

Delays in surgery are often inherent in any healthcare system and more studies can be performed to look into the breakdown of each contributing factor with the intention to improve workflow processes and system practices to reduce such delays. With a reduction in delays to surgery, there can be anticipated greater improvements in patient outcomes.

Innovations and breakthroughs

By studying at the predisposing factors that lead to delay in surgery, the authors can have a higher index of suspicion in certain groups of patients. The authors have found that patients with diabetes mellitus were at higher risk of having a delay in surgery and this could be due to blunted physiologic response. The authors also have noted a delay in performing a computed tomography scan resulted in higher complication rates and hence the authors intend to look into ways to reduce such delays in future studies.

Applications

The study results suggest that delays in surgery in elderly patients lead to higher complication rates and it is crucial to identify patients with predisposing factors which may lead one to have higher index of suspicion. Such patients should also have any scans (if indicated) expedited to reduce any delays and ultimately improve surgical outcomes as well.

Terminology

Certain acute abdominal emergencies include perforated or gangrenous viscus and strangulated hernia. Any defect in the walls of abdominal viscus result in peritoneal soiling and eventual peritonitis. Gangrene of the viscus occurs when there is inadequate blood supply most often from vascular occlusion and sepsis usually ensues. Such conditions are usually terminal unless surgical intervention is performed. Hence it is crucial to identify such conditions promptly and initiate surgery at the earliest possible chance to improve outcomes.

Peer-review

Dr. Ong *et al* reported clinical outcomes in the elderly patients who came to ER in the single center. They reviewed morbidity and mortality of the 144 patients and tried to identify clinical factors to predict poor clinical outcomes. Overall the article is interesting and manuscript is well written.

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ORIGINAL ARTICLE

Prospective Study

Laying open (deroofing) and curettage under local anesthesia for pilonidal disease: An outpatient procedure

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Author contributions: Garg P thought of the concept; Garg P, Garg M, Gupta V, Mehta SK and Lakhtaria P designed the study, acquired the data, analyzed it, drafted, revised and finally approved the draft; Garg P submitted the manuscript.

Institutional review board statement: The study was reviewed and approved by the Indus Hospital Ethical Committee.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at drgargpankaj@yahoo.com. No consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To test the efficacy of lay open (deroofing, not excision) with curettage under local anesthesia (LOCULA) for pilonidal sinus as an outpatient procedure.

METHODS: LOCULA procedure was done for all types of pilonidal disease. The primary outcome measure was cure rate. The secondary outcome measures were hospital stay, operating time, return to work, healing time and complication rate.

RESULTS: Thirty-three (M/F-30/3, mean age-23.4 ± 5.8 years) consecutive patients were operated and followed for 24 mo (6-46 mo). Eleven were pilonidal abscess and 22 were chronic pilonidal disease. Six had recurrent disease. Operating time and the hospital stay was 22.3 ± 5.6 min and 63.8 ± 22.3 min respectively. The patients could resume normal work in 4.3 ± 3.2 d and the healing time was 42.9 ± 8.1 d. Thirty (93.8%)

patients had complete resolution of the disease and two (6.2%) had a recurrence. Both the recurrences happened in patients who had complete healing but ignored the prescribed recommendations. One out of these got cured after getting operated again with the same procedure. Thus the overall success rate of this procedure was 96.9%.

CONCLUSION: Lay open (deroofing) with curettage procedure under local anesthesia is an effective procedure to treat both simple and complicated pilonidal sinus and abscess. It is a simple procedure, has a high cure rate (up to 97%), doesn't require admission and is associated with minimal morbidity and scarring. Considering the distinct advantages, this procedure has the potential to become the first line procedure for treating pilonidal disease.

Key words: Pilonidal; Lay open; Deroofing; Curettage; Sinus

Core tip: This study demonstrates that lay open with curettage under local anesthesia is a simple procedure to treat simple and complicated pilonidal disease. It is quite effective with high cure rate and can be done as an outpatient procedure. Apart from this, this procedure has distinct advantages - can be learnt easily, less time to operate, almost pain free, back to work faster, minimum incision, simple dressings after operation, small scar, minimal change in body shape, economically better and easy to repeat after a recurrence. This procedure can potentially become the frontline operation for all types of pilonidal disease.

Garg P, Garg M, Gupta V, Mehta SK, Lakhtaria P. Laying open (deroofing) and curettage under local anesthesia for pilonidal disease: An outpatient procedure. *World J Gastrointest Surg* 2015; 7(9): 214-218 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/214.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.214

INTRODUCTION

"Pilonidal sinus" as a term was first used in the year 1880[1]. Though Mayo described this disease in detail in 1833, its optimal treatment is debated even today[2]. Several procedures have been described for pilonidal disease. Acute abscess is treated by incision and drainage[3]. Chronic disease is usually treated by wide excision. After excising, the wound may be left open so that it heals with granulation tissue[4], or the wound may be closed on the operating table. The latter may be a midline closure[5] or usage of a flap - Z-palsty[6], Karydakis flap[7], Bascom flap[8] and Limberg flap[9]. The principle behind these extensive procedures had been to remove all the diseased portion and to close the wound away from the midline[10,11]. However, these excisional procedures lead to extensive incisions, removal of large amount of skin, big wounds and hence increase morbidity. In spite of increased morbidity, the recurrence rate also didn't necessarily come down after these extensive procedures[12-14].

Laying open of pilonidal sinus and curettage of tract under local anesthesia (LOCULA) procedure is a simple procedure to mange pilonidal sinus[15,16]. Though this procedure has been described in the past yet no study has determined the feasibility and efficacy of this procedure done under local anesthesia as an office procedure.

We performed a prospective study between 2011 and 2014 to analyze the benefits and drawbacks of this procedure in all types of pilonidal disease - acute (abscess), chronic simple and complicated (recurrent, multiple tracts, *etc.*).

MATERIALS AND METHODS

Study population

In the period between January 2011 and July 2014, all the consecutive patients of pilonidal sinus (simple as well as complicated) were prospectively included in the study. The inclusion criteria were: Patients with chronic simple pilonidal sinus, patients having recurring disease and pilonidal disease having an associated abscess. All patients gave consent in writing in the language they understood. The hospital ethics committee approved the study protocol. All the operations were performed by a single surgeon (Garg P).

Surgical procedure

No preoperative preparation was done. All the procedures were done on an outpatient basis under local anesthesia and no hospital admission was done. No patient required general or spinal anesthesia. During operation, the patient was placed in a prone position. An adhesive tape was used to separate the buttocks so that proper exposure of the diseased area could be obtained. The solution of Povidine iodine was used to disinfect the operative area.

The sinus opening was probed gently to gauze the direction and length of the tract (Figure 1). The local anesthetic agent (2% Lignocaine with Adrenaline 0.005%) was infiltrated around the opening and along the tract/tracts (Figure 1). The anesthetic agent was kept ready in case the tracts were found to be longer than expected or any side tract was encountered. The tracts were identified with the help of mosquito (small artery) forceps and were laid open (Figure 1). If there were more than one tracts, then all the tracts were opened at the same time. All the hairs and debris were removed from the tracts (Figure 1) and all the granulation tissue was removed by rubbing the sinus cavity with a dry gauze or with a curette. The skin edges were trimmed. The wound was checked thoroughly for any extensions or side/downward branches. The

Figure 1 Lay open plus curettage under local anesthesia procedure for pilonidal disease. A: Preoperative photo without preparation; B: Preoperative photo after preparation; C: Infiltration of local anesthesia; D: Laying open after inserting an artery forceps in the sinus; E: Hairs and debris removed from the sinus; F: Immediate post-operative; G: One week postoperative; H: Three weeks post-operative; I: Completely healed wound - 6 wk postoperative.

lateral wall and the base of the sinus were left intact and no marsupialization was done. The bleeding points were electrocauterized and haemostasis achieved. The wound was packed tightly with a povidone iodine soaked gauze.

The patient walked off to the recovery room and kept under observation for an hour. After this, the dressing was checked for any active bleeding and the patient was sent back home with instructions to resume daily routine. However, he/she was instructed to avoid strenuous work. Oral antibiotic (Cefixime 200 mg twice a day) and analgesic (Aciclofenac 500 mg) were prescribed twice a day for five days.

Follow-up

All the patients were examined in the out-patient office on the next day of operation. The dressing was taken off, the wound gently rubbed with a dry gauze and then lightly packed with a povidine iodine soaked gauze. The process was explained to the relative and the latter was made to do the same under our supervision. After this, the patient's relative was instructed to clean the operated area at home (once or twice a day) and the patient was encouraged to resume his normal work as soon as possible. The patient was followed up on weekly basis till the wound healed completely.

After the wound healed completely, the patient was instructed to keep three centimeters area all around the wound free of hair till he/she reached the age of thirty years. He/she was also advised to put powder in the intergluteal cleft for the same period (India is a hot and humid country and increased sweating and moistness in the intergluteal region was reported by all our patients. We suspected this to be one of the contributing reasons). The patient was told to report back in case of any swelling, pain or pus discharge from the operated

Table 1 Demographic data and characteristics of the patients

Parameter	*n* = 33
Age	23.4 ± 5.8 yr
Sex (M/F)	30/3
Anesthesia	Local anesthesia
Inclusion criteria	Chronic, recurrent, abscess
Exclusion criteria	Refused consent
Recurrent	6 (18.2%)
Abscess	11 (33%)

M/F: Male/female.

Table 2 Results about the recurrences of the patients

Parameter	*n* = 33
Operating time	22.3 ± 5.6 min
Hospital stay	63.8 ± 22.3 min
Resume normal work	4.3 ± 3.2 d
Healing time	42.9 ± 8.1 d
Recurrence	6.2%
Complications	3.1%

area.

RESULTS

The various characteristics of the patients are summarized in Table 1. Thirty three consecutive patients were prospectively recruited over a three and a half years period. The patients had a 24 mo of median (range: 6-46 mo) follow-up. One patient was lost to follow up. The age of the patients ranged from 16 to 39 years (mean: 23.4 ± 5.8) and the sex ratio-M/F - 30/3. Eleven were pilonidal abscess and 22 were chronic pilonidal disease. Six had recurrent disease. The operating time was 22.3 ± 5.6 min and the hospital stay after the operation was 63.8 ± 22.3 min. The patients were able to resume their normal work in 4.3 ± 3.2 d and the healing time was 42.9 ± 8.1 d. Thirty (93.8%) patients had complete resolution of the disease and two (6.2%) had a recurrence (Table 2). Both the recurrences happened in the patients who didn't adhere to the prescribed recommendations after the complete healing. One patient with a recurrence was operated again with the same procedure and he got cured. The second patient was lost to follow up. Thus the overall cure rate was 96.9%. One patient had a bleeding episode six days after the operation. She was managed conservatively in the outpatient clinic and the wound got healed subsequently.

DISCUSSION

In this study, LOCULA was done on an outpatient basis in 33 patients with 96.9% success rate. All types of pilonidal sinus patients, simple and complicated (recurrent, abscess and multiple tracts) were included in the study. This is perhaps the first study in the literature which demonstrated that this simple procedure was highly effective (low recurrence rate) and could be done on outpatient basis without the need for hospital admission. This was possible because LOCULA could be done under local anesthesia. None of the patient required general or regional anesthesia. This makes it quite cost effective as well. The morbidity was minimal as the procedure was done under local anesthesia on an outpatient basis (all the patients left the hospital within one and a half hour after the procedure) and could resume their normal routine within a week (mean: 4.3 d). The recurrence happened in only two (6.2%) patients and one of them underwent the same procedure and got cured. The recurrence also happened in those patients who didn't follow the post-operative instructions (to regularly clean the area of hair). The only drawback seen in this procedure was slightly longer healing time (6 wk). But this delayed healing time did not interfere with the normal routine and resumption of work, hence didn't bother the patient much.

During the operation, no attempt was made to excise the sinus. Only laying open (deroofing) was done and some trimming of the lateral walls was done to prevent adhesions and ensure healing by secondary intention. This made the procedure simple, took less time, led to minimal bleeding and resulted in a small wound. The postoperative pain was very less and the wound care was not demanding.

Though lay open with curettage procedure had shown to be effective in the past[15,16], yet it could not become the preferred procedure for treating pilonidal disease. One of the reasons could be that this procedure was perhaps confused with another procedure - drainage of acute abscess in pilonidal disease after simply incising it (without curetting the tracts and the cavity). The latter procedure was associated with a recurrence rate of up to 24%[3,17-19]. However, when the cavity was curetted along with the drainage, the recurrence rate reduced significantly. In a large study (150 patients) with long follow-up (65 mo), Vahedian *et al*[19] compared the success rate of only drainage procedure vs laying open with curettage and found that the cure rate in these procedures differed significantly (simple drainage group - 46%, curettage group - 90%). This is not difficult to understand because when the wound is thoroughly curetted, all the debris, hairs and granulation tissue are removed and any side braches/extensions are easily identified. The latter can then be laid opened and curetted.

To conclude, LOCULA is a simple procedure to treat simple and complicated pilonidal disease. It is quite effective with high cure rate and can be done as an outpatient procedure. Apart from this, this procedure has distinct advantages - can be learnt easily, less time to operate, almost pain free, back to work faster, minimum incision, simple dressings after operation, small scar, minimal change in body shape, economically better and easy to repeat after a recurrence. This procedure has full potential to become the gold standard operation for all types of pilonidal disease. The only slight drawback is slightly longer healing time but this aspect doesn't much bother patients as they can carry out their normal chores during the dressing period.

COMMENTS

Background

Pilonidal sinus is a dreaded disease in which a tract (sinus) is formed in the lower back inside which there is a collection of hairs. This usually happens in sedentary, sweaty, slightly obese, hairy young males. This disease is characterized by regular pus formation and is notorious for recurrence after the operation.

Research frontiers

As of today, chronic disease is usually treated by wide excision. After excising, the wound may be left open so that it heals with granulation tissue, or the wound may be closed on the operating table. The latter may be a midline closure or usage of a flap - Z-palsty, Karydakis flap, Bascom flap and Limberg flap. However these extensive big operative procedures require administration of spinal or general anesthesia, hospital admission for 2-3 d and bed rest for 5-10 d. The resumption of normal work can take up to 4-6 wk. In spite of all this, the recurrence rate also is also 4%-10% after these extensive procedures.

Innovations and breakthroughs

This is the first study which demonstrates that a simple procedure (lay open with curettage) can treat simple and complicated pilonidal disease in an effective manner. This procedure can be done as an outpatient procedure without needing any hospital admission. Therefore, no hospital admission is required. Apart from this, this procedure has distinct advantages - can be learnt easily, less time to operate, almost pain free, back to work faster, minimum incision, simple dressings after operation, small scar, minimal change in body shape, economically better and easy to repeat after a recurrence.

Applications

As this simple procedure has so many distinct advantages over all other preferred procedures, this procedure can potentially become the frontline operation for all types of pilonidal disease.

Terminology

Pilonidal sinus - a tract or a sinus in the lower back in which a cluster of hairs go in leading to recurrent infection and pus formation. Excisional procedures - operations in which the sinus is removed by operation taking a big margin all around which results in a large wound.

Peer-review

This study presented a novel procedure to treat simple and complicated pilonidal disease. The data was full and accurate. And the authors present a study on a modified approach to the operative treatment of pilonidal sinus disease. It's an interesting and simple surgical procedure with good short-term results.

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CASE REPORT

Acute pancreatitis complicated with splenic rupture: A case report

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Author contributions: Assef JC and De Campos T conceived of and designed the study and critically revised the paper; Hernani BL, Silva PC and Nishio RT acquired the data; Mateus HC analyzed the data; Mateus HC, Assef JC and De Campos T contributed technical procedures; Hernani BL, Silva PC, Nishio RT and Mateus HC interpreted the data; Silva PC and Nishio RT contributed to manuscript preparation; Hernani BL wrote the manuscript.

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Abstract

Atraumatic splenic rupture is an uncommon complication of acute pancreatitis. This report describes the case of a 30-year-old man with acute pancreatitis and splenic vein thrombosis complicated by splenic rupture. The patient was admitted to the emergency department with pain in the upper abdomen that had been present for six hours and was associated with vomiting and sweating. He was diagnosed with acute pancreatitis of alcoholic etiology. Upon computed tomography (CT) of the abdomen, the pancreatitis was scored as Balthazar C grade, and a suspicious area of necrosis affecting 30% of the pancreas with splenic vein thrombosis was revealed. Seventy-two hours after admission, the patient had significant improvement in symptoms. However, he showed clinical worsening on the sixth day of hospitalization, with increasing abdominal distension and reduced hemoglobin levels. A CT angiography showed a large amount of free fluid in the abdominal cavity, along with a large splenic hematoma and contrast extravasation along the spleen artery. The patient subsequently underwent laparotomy, which showed hemoperitoneum due to rupture of the splenic parenchyma. A splenectomy was then performed, followed by ultrasound-guided percutaneous drainage.

Key words: Acute pancreatitis; Pancreatitis; Rupture; Splenic rupture; Spontaneous

Core tip: This report describes a rare case of atraumatic splenic rupture that occurred in a 30-year-old male

patient with acute pancreatitis and splenic vein thrombosis. A computed tomography angiography showed a large amount of free fluid in the abdominal cavity, along with a large splenic hematoma and contrast extravasation along the spleen artery. The patient underwent a splenectomy followed by ultrasound-guided percutaneous drainage.

Hernani BL, Silva PC, Nishio RT, Mateus HC, Assef JC, De Campos T. Acute pancreatitis complicated with splenic rupture: A case report. *World J Gastrointest Surg* 2015; 7(9): 219-222 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i9/219.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i9.219

INTRODUCTION

Atraumatic splenic rupture is a rarely reported complication of acute pancreatitis[1]. Approximately 10% of atraumatic splenic ruptures are related to local inflammatory processes[2]. These ruptures can be accompanied by other complications, such as perisplenic/intrasplenic pseudocysts, splenic infarction, subcapsular hematomas, and intrasplenic hemorrhage[3-6]. Morbidity and mortality rates for pancreatitis with splenic complications vary from 39% to 79% and 3.5% to 0.8%, respectively[7], demonstrating the importance of prompt recognition. This report describes a rare case involving a patient with acute pancreatitis and splenic vein thrombosis complicated by splenic rupture.

CASE REPORT

A 30-year-old man was admitted to the emergency department with pain in the upper abdomen that had been present for six hours accompanied by vomiting and sweating. He reported chronic alcoholic abuse, including recent consumption prior to the onset of symptoms. He had no other comorbidities. An initial examination showed normal blood pressure, a heart rate of 120 bpm, respiratory rate of 40 ipm, and a distended abdomen that was painful to palpation but with no signs of peritonitis. Laboratory exams showed: amylase, 199 IU/L; lipase, 410 U/L; C-reactive protein, 56 mg/L; WBC, 14.8 × 10^6/μL, hemoglobin, 18.1 g/dL hematocrit 52% pH7.30 HCO_3, 12.7 mmol/L; lactate, 5.0 mmol/L. A diagnosis of alcoholic pancreatitis was confirmed. The Apache Ⅱ classification was 2 at admission.

A computed tomography (CT) of the abdomen indicated that the pancreatitis was Balthazar grade C, and a suspicious area of necrosis affecting 30% of the pancreas with splenic vein thrombosis was observed (Figure 1). The patient was given antibiotics because of an increased C-reactive protein level (326 mg/L at 48 h after admission) and necrosis of the pancreas. The patient's symptoms substantially improved after 72 h, with acceptance of an oral diet. However, clinical worsening occurred on the sixth day of hospitalization, with increasing abdominal distension and a reduced hemoglobin level (9.2 g/dL). Diagnostic paracentesis was then conducted on hematic content output. A subsequent CT angiography of the abdomen revealed a large amount of free fluid in the abdominal cavity, a large splenic hematoma, and contrast extravasation along the spleen artery (Figure 2).

The patient underwent a laparotomy, which showed hemoperitoneum due to the rupture of the splenic parenchyma and surrounding hematoma. A splenectomy was thus performed with cavity drainage. The patient was administered norepinephrine and blood components replacement. Six days after the operation, he was hemodynamically stable without vasoactive drugs and extubated; he showed acceptance of enteral nutrition and no signs of pancreatic fistula.

Forty-eight hours after withdrawal of antibiotics, on postoperative day 20, the patient exhibited a fever. Abdominal CT revealed peripancreatic collection of liquefied content and gas. He subsequently underwent ultrasound-guided percutaneous drainage with a Shiley catheter, which provided purulent content. CT performed after the procedure showed a significant decrease in the collection volume. Seven days after drainage, the fever returned and a second percutaneous procedure was performed, which resolved the fluid collection. The patient was subsequently discharged, with no complaints at a 30-d follow-up.

DISCUSSION

Splenic complications are considered rare events during the course of acute and chronic pancreatitis and have varied descriptions, including pseudocyst, subcapsular hematoma, splenic infarction, intrasplenic hemorrhage, and splenic rupture. Subcapsular hematomas, pseudocysts, and splenic rupture are more common in chronic pancreatitis[8], whereas splenic infarctions and intrasplenic hemorrhage tend to be more frequent in acute pancreatitis[9].

The anatomic relationship between the pancreatic tail and the splenic hilum contributes to the pathology of splenic complications[10]. For example, splenic rupture is more often described as a complication of chronic pancreatitis, where it occurs secondary to the enzymatic erosion of pseudocysts or as a result of direct action in the splenic parenchyma. In contrast, it has been reported in acute pancreatitis following splenic vein thrombosis, perisplenic adhesions, and acute inflammation of ectopic intrasplenic pancreatic tissue[3,8]. The cause of the splenic rupture in the present case was likely the splenic vein thrombosis observed in the first CT scan, as the histopathologic finding was sinusoidal hypertension in the spleen.

The diagnosis of splenic complications is challenging due to the absence of specific symptoms and signs.

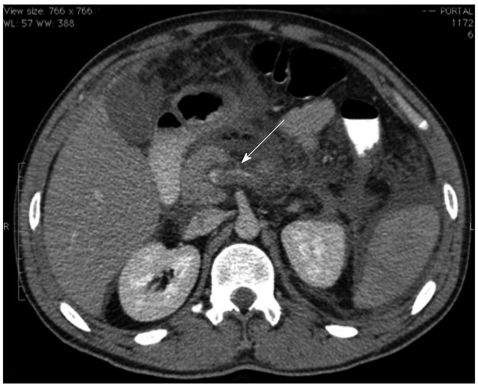

Figure 1 Abdominal computed tomography showing Balthazar C pancreatitis with splenic vein thrombosis (arrow).

Figure 2 Abdominal computed tomography angiography showing a large amount of free fluid and a splenic hematoma (arrows).

However, the presence of pain in the left upper quadrant and referred pain in the left shoulder are indications. Thus, CT is valuable for identifying splenic complications, as well as for patient follow-up, as demonstrated in the case presented here. Magnetic resonance imaging may also be useful, as it allows for better characterization of the various soft tissues and vascular alterations compared to CT[8]. Furthermore, the case presented here suggests that worsening of abdominal pain and distension followed by acute anemia are clinical indicators for diagnosis. A diagnostic paracentesis was also performed on the patient in this case, followed by CT angiography, which was used to locate the hemorrhage.

The treatment of splenic complications depends upon the hemodynamic status of the patient. A variety of treatments can be considered for patients who are hemodynamically stable, including a conservative approach, percutaneous drainage, angiography study, embolization, or even surgery. However, use of a conservative approach requires strict follow-up with serial ultrasound or CT. In contrast, surgical intervention with splenectomy or distal pancreatosplenectomy is convenient for patients who are hemodynamically unstable[8,9]. As the patient in the present case was hemodynamically stable, the first choice was angiography study followed by embolization. However, technical problems and clinical worsening of the patient led to the need for a laparotomy followed by splenectomy and drainage of the abdominal cavity. Importantly, despite signs of pancreatic necrosis, no necrosectomy was performed as the patient was treated for hemorrhagic complications rather than the pancreatitis. Indeed, necrosectomy is not recommended in the early phase of the disease[10], and thus, the maximal procedure recommended for this patient was drainage.

Even though splenic complications are rare conditions in both acute and chronic pancreatitis, clinical suspicion and prompt diagnosis using CT or other imaging methods are important for the patient's prognosis. As this condition can change in a short period of time, early diagnosis followed by appropriate treatment can dramatically alter the morbidity and mortality associated with splenic rupture.

COMMENTS

Case characteristics

Thirty years old man with pain in the upper abdomen that had been present for six hours and associated with vomiting and sweating.

Clinical diagnosis

Acute pancreatitis.

Differential diagnosis

Subcapsular hematoma, intrasplenic haemorrhage, and necrotizing hemorrhagic pancreatitis.

Laboratory diagnosis

Amylase, 199 IU/L; Lipase, 410 U/L; C-reactive protein, 56 mg/L; WBC, 14.8 × $10^6/\mu L$; hemoglobin, 18.1 g/dL hematocrit 52% pH7.30, HCO_3, 12.7 mmol/L; lactate, 5.0 mmol/L.

Imaging diagnosis

Computed tomography (CT) of the abdomen showed Balthazar grade C with pancreatic necrosis and CT angiography revealed a large amount of free fluid in the abdominal cavity, a large splenic hematoma, and contrast extravasation along the spleen artery.

Treatment

Splenectomy was performed with cavity drainage.

Related reports

Atraumatic splenic rupture is a very rare complication of acute pancreatitis, with few reports in the literature.

Experiences and lessons

Even though splenic complications are rare, a clinical suspicion and prompt diagnosis are critically important for a positive patient prognosis; because this condition can change in a short period of time, an early diagnosis followed by appropriate treatment was helpful in this case.

Peer-review

The case report by Hernani *et al* presents a case of a young adult male who developed a splenic rupture associated with an episode acute pancreatitis. The authors briefly discuss the relationship of this complication to pancreatic inflammation, its presenting signs and symptoms, and recommended therapy.

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Way forward: Geriatric frailty assessment as risk predictor in gastric cancer surgery

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Abstract

In gastric cancer patients chronological and biological age might vary greatly between patients. Age as well as American Society of Anaesthesiologists-physical status classifications are very non-specific and do not adequately predict adverse outcome. Improvements have been made such as the introduction of Charlson Comorbidity Index. Geriatric frailty is probably a better measure for patients resistance to stressors and physiological reserves. An increasing amount of evidence shows that geriatric frailty is a better predictor for adverse outcome after surgery, including gastric cancer surgery. Geriatric frailty can be assessed in a number of ways. Questionnaires such as the Groningen Frailty Indicator provide an ease and low cost method for gauging the presence of frailty in gastric cancer patients. This can then be used to provide a better preoperative risk assessment in these patients and improve decision making.

Key words: Gastric cancer; Surgery; Geriatric frailty

Core tip: Geriatric frailty assessment is an important way forward in order to provide a better preoperative risk assessment in gastric cancer surgical patients.

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FRAILTY ASSESSMENT AS RISK PREDICTOR

Gastric cancer constitutes a major health problem and in Western countries is predominantly a disease of the elderly with a mean age of 70 years in Western populations[1]. The ageing problem in gastric cancer is not reserved for Western countries. The proportion people over 65 years old in South Korea was 9.9% in 2007, and the proportion of ageing patients is also expected to increase[2]. Elderly patients are at an increased risk for increased complications and mortality likely due to higher incidence comorbidities[3,4].

The American Society of Anaesthesiologists (ASA) - Physical status has been introduced in the former century and gained widespread acceptance as a scoring system for determining a patient's physical status. It has long been used to assess risks from surgery. But surgical risk assessment is complex and ASA classification is only a component of overall assessment. A major problem with ASA classification is the degree of interobserver variability, *i.e.*, different scores are ascribed to the same patient by different assessors[5]. Moreover, it is also limited as a predictive measure for adverse postoperative events; it performed moderately for prediction of postoperative mortality in a recent meta-analysis[6]. Also, it performed better in populations with lower rather than higher mortality rates[6].

The Charlson Comibidity Index (CCI) is another method for classifying comorbid conditions that determine risk of mortality[7]. This method has a much more clearly defined scoring system than the ASA classification. A study in octo- and nonogenarians who underwent surgery for gastric cancer showed that higher morbidity and mortality rates were associated with higher CCI (CCI $\geqslant$ 5)[8]. In contrast, a German study, which included 139 patients, did not find this association between CCI and adverse postoperative events. Age was an independent predictor for post-operative course[9]. So age and comorbidities are not universally found to be predictors for adverse outcome.

The fact that age is not sufficient to exclude patients from treatment is fairly widely accepted[10-12].

It is almost redundant to say that a patient's chronological age does not necessarily correspond with their biological age. Biological age is mainly determined by frailty, a state of vulnerability to stressors in older individuals, which leads to an increased risk of developing adverse health outcomes[13]. Frailty, as a predictor for adverse outcome after surgery, has gained attention in recent years[14,15]. Frailty, in this case increased scores > 7 on Edmonton frail scale, have been shown to predict increased complications after non-cardiac surgery (OR = 5.1, 95%CI: 1.55-16.25)[16]. In a larger study included patients undergoing various types of elective surgery frailty was predictive for increased postoperative complications and length-of-stay[17].

Geriatric frailty assessment is a very useful tool for preoperative risk assessment in gastric cancer patients, because gastric cancer is a disease predominantly in the elderly in Western countries and in an ageing population worldwide.

A thorough assessment of frailty can be performed with a comprehensive geriatric assessment (CGA). This employs the use of multiple questionnaires and physical tests and is usually conducted by trained professionals in an outpatient setting. In a CGA, all areas of geriatric frailty are assessed, *e.g.,* cognitive functions, mobility, Activities of Daily Living functioning, mood and nutrition. This is performed by clinical history taking as well as use of multiple questionnaires and tests (*e.g.*, timed get up and to test). Performing is a time and resource consuming effort. Therefore, questionnaires have been developed to assess or screen for presence of frailty in elderly individuals. Questionnaires offer a low-cost, low-effort, low-resource consuming way to gauge levels of frailty in patients. Examples of short questionnaires that have been used in this way in surgical populations include Hopkins Frailty score, Edmonton Frail Scale and Groningen Frailty Indicator (GFI)[14,16,18]. In gastric cancer surgery GFI $\geqslant$ 3 has been shown to be associated with increased in-hospital mortality, increased serious complications and increased length of stay[18]. In this study GFI was independently associated with in-hospital mortality.

Improved risk assessment which includes geriatric frailty assessment can be used to provide a better assessment of operative risks. This can aid the physician to better inform individual patients of their risks and improve shared decision making and informed consent. Geriatric frailty assessment does not aim to exclude patients from treatments rather improve decision making.

In conclusion age and physical status (*i.e.,* ASA classification) do not provide adequate risk assessments especially in elderly patients with gastric cancer. Frailty can provide better estimates of perioperative risks. Evidence seems to suggest that frailty questionnaires provide clinically applicable solutions for frailty ass-essment.

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EDITORIAL

Mesh implants: An overview of crucial mesh parameters

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Abstract

Hernia repair is one of the most frequently performed surgical interventions that use mesh implants. This article evaluates crucial mesh parameters to facilitate selection of the most appropriate mesh implant, considering raw materials, mesh composition, structure parameters and mechanical parameters. A literature review was performed using the PubMed database. The most important mesh parameters in the selection of a mesh implant are the raw material, structural parameters and mechanical parameters, which should match the physiological conditions. The structural parameters, especially the porosity, are the most important predictors of the biocompatibility performance of synthetic meshes. Meshes with large pores exhibit less inflammatory infiltrate, connective tissue and scar bridging, which allows increased soft tissue ingrowth. The raw material and combination of raw materials of the used mesh, including potential coatings and textile design, strongly impact the inflammatory reaction to the mesh. Synthetic meshes made from innovative polymers combined with surface coating have been demonstrated to exhibit advantageous behavior in specialized fields. Monofilament, large-pore synthetic meshes exhibit advantages. The value of mesh classification based on mesh weight seems to be overestimated. Mechanical properties of meshes, such as anisotropy/isotropy, elasticity and tensile strength, are crucial parameters for predicting mesh performance after implantation.

Key words: Hernia repair; Hernia mesh; Incontinence mesh implant; Synthetic mesh; Mesh properties; Textile structure; Structure parameters; Mechanical parameters; Mesh weight; Synthetic raw materials

Core tip: Hernia repair is one of the most frequently performed surgical interventions that use mesh implants. This article evaluates crucial mesh parameters to facilitate selection of the most appropriate mesh implant based on raw material, mesh composition, and structural and mechanical parameters. The structural parameters of the mesh, especially the porosity, are the most important predictors of the biocompatibility performance of synthetic meshes. Monofilament large-pore meshes exhibit less inflammatory infiltrate, connective tissue and scar bridging, which allows increased soft tissue ingrowth. The value of mesh classification based on the mesh weight seems to be overestimated. Other properties, such as the isotropy, elasticity and tensile strength, are crucial parameters for predicting the performance of meshes after implantation.

Zhu LM, Schuster P, Klinge U. Mesh implants: An overview of crucial mesh parameters. *World J Gastrointest Surg* 2015; 7(10): 226-236 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i10/226.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i10.226

INTRODUCTION

Synthetic mesh implants are frequently used in many surgical interventions, especially in hernia repair. Mesh implants are composed of polypropylene (PP), polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), polyvinylidenefluoride (PVDF), and absorbable materials, such as polylactide (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and polydioxanone (PDO). Potential mesh-related complications include chronic infections, chronic pain and mesh rupture[1-3]. The reasons for chronic pain and the impact of mesh fixation in this context are controversial[4,5]. Chronic infections are favored by concomitant inflammatory and fibrotic reactions to the foreign body, hindering the local clearance from bacterial which leads to a chronic inflammatory wound with marked scarring, loss of compliance, mesh contraction, migration, physiochemical changes, seroma, infection, and in some cases, eventual mesh removal to resolve the problem[6]. A basic understanding of the physicochemical properties of meshes is essential for rational selection of the most appropriate device. This article evaluates the following crucial mesh parameters to facilitate selection of the most appropriate mesh implant: raw material, mesh composition, and structural and mechanical parameters (Figure 1).

The impact of mesh implants on clinical results is the current subject of much litigation in the field of stress urinary incontinence and pelvic prolapse, and some manufacturers were sued because of allegedly defective implants. However, many other factors besides mesh parameters must be considered in evaluations of the overall outcome of an intervention, including the patient's constitution, the selection of a proper operation technique and the operation performance, which are essential for the success or failure of a therapy.

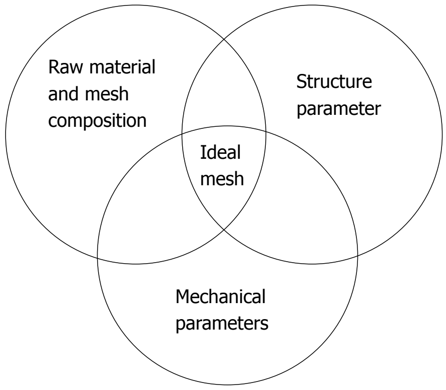

Figure 1 Crucial mesh parameters for selection of an ideal mesh.

BIOCHEMICAL FUNDAMENTALS

Implantation of a mesh triggers a foreign-body reaction, which plays a crucial role in the incorporation of the mesh into the host tissue. Incorporation of mesh into tissues is a complicated biochemical healing process. Implantation initiates an acute inflammatory cellular response that is initiated by protein absorption at the surface and attracts local inflammatory cells, such as macrophages, that converge to foreign body giant cells and eventually create a chronic wound around the mesh fibers. New blood vessels and collagen form around the mesh[7]. A relatively high level of macrophage invasion is detectable 20 min after mesh implantation, and these levels increase slightly and then decrease within 24 mo[8]. More than 80% of the cells in the mesh infiltrate positively express CD68, CD8, CD45R0 and vimentin, which indicates a mixture of cells of various origins and confirms the existence of multiple transition forms that are involved in the inflammatory response[9]. Complement and mast cell activation may also be involved in the mediation of local tissue responses to synthetic hernia meshes[10,11]. Cell migration is followed by collagen deposition, with an increase in the type Ⅰ to type Ⅲ collagen ratio over time[12]. The majority of tissue ingrowth and strength may be completed 2 wk after mesh implantation, but the final remodeling process is a very significant challenge[13]. Mesh-induced foreign body responses must be balanced to result in normal wound healing. Swift and adequate tissue ingrowth into the mesh results in superior biocompatibility and likely improved clinical performance. Intense or prolonged inflammation, bad infiltration, and immature collagen deposition result in scar plate formation, which can be accompanied by increased stiffness of the abdominal wall, shrinkage or deformation of the biomaterial, recurrence, adhesion, fistula or erosion of nearby tissue[14].

TEXTILE FUNDAMENTALS

Textile structures consist of mono- or multifilament fibers. Figure 2 shows the schematic appearance of

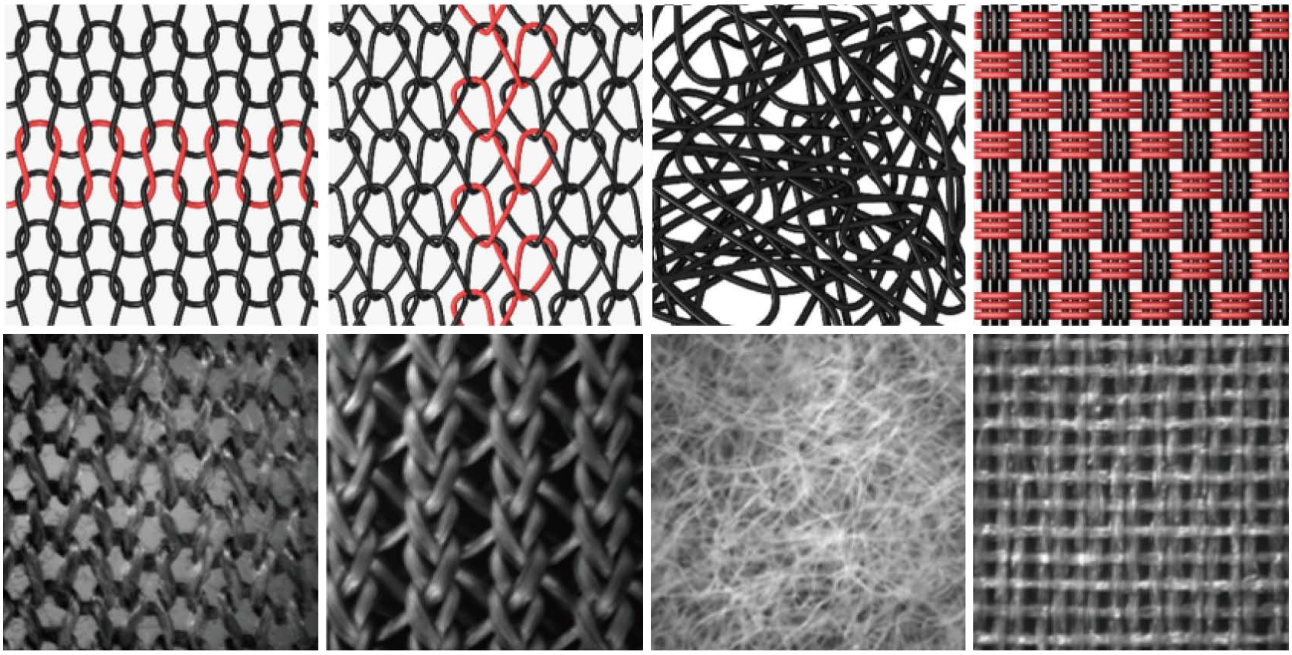

Figure 2 Textile structures from left to right: Knitted structure, warp-knitted structure, nonwoven structure, and woven structure.

Table 1 Definitions of the knit, warp-knit, nonwoven and woven textile structures

Textile structure	Definition
Knitted fabric	Knitted fabric consists of a number of consecutive rows of loops, called stitches. Knitted structures are manufactures from single yarn systems. Thus, knitted structures can be ribbed off. Trimming of knitted structures often leads to a complete falling apart
Warp-knitted fabric	Warp-knitted fabric consists of a number of consecutive courses of loops, called stitches. Warp-knitted structures are manufactures from multi yarn systems whereby the number of separate strands of yarn equals the number of stitches in a row. In contrast to knitted structures warp-knitted structures can be trimmed and sewed
Nonwoven fabric	Nonwoven fabric consists of non orientated or to a certain degree orientated staple or endless fibers. After the nonwoven formation the structure needs to be bonded which either is realised by mechanical, thermal or chemical bonding
Woven fabric	Woven structures consist of two distinct sets of yarns or threads which are interlaced at right angles to form a fabric

Table 2 Essential properties of the knit, warp-knit, nonwoven and woven textile structures

Textile structure	Porosity (macropores)	Elasticity	Mechanical behaviour	Trim-ability
Knitted fabric	++	++	Anisotropic	--
Warp-knitted fabric	++	++	Isotropic, anisotropic	++
Nonwoven fabric	-	-	Isotropic	++
Woven fabric	-	--	Isotropic	++

knitted, warp-knitted, nonwoven and woven structures. Table 1 provides definitions of these different textile structures.

Table 2 presents the general essential properties of these textile structures. These properties are adjustable in a wide range through the selection of production technology and through the specific settings of the production process parameters. Most textile mesh implants are warp-knitted because of the ability of these implants to provide large pores and elasticity under load. Warp-knitted meshes also do not lose material or structural strength at margins when trimmed to the size of the surgical need. Nonwoven meshes are used as mesh implants in exceptional cases.

RAW MATERIAL AND MESH COMPOSITION

Raw material

The polymer and fiber surface affect the inflammatory response within the granuloma. Most synthetic meshes use one of following raw materials: nonabsorbable materials, such as PP, PET, PVDF and ePTFE, or absorbable materials, such as PLA, PGA, PCL, PDO

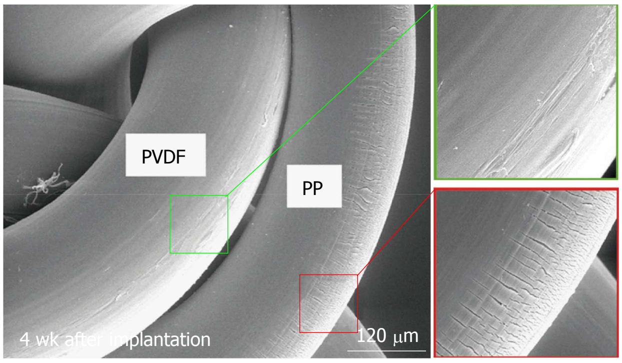

Figure 3 Comparison of the *in vivo* stability of the surface of polypropylene and polyvinylidenefluoride 4 wk after implantation[18]. PP: Polypropylene; PVDF: Polyvinylidenefluoride.

and PHB. These materials may also be used in combination with each other or a range of additional materials, such as titanium and hyaluronate. The foreign body reaction is fairly uniform regardless of the type of mesh implanted, but the different raw materials affect the extent of the reaction. PP meshes result in an intensified inflammatory reaction with deposition of more collagen fibers and significantly higher collagen type Ⅰ/Ⅲ ratios within the resulting scar neotissue compared with ePTFE meshes[15]. PET meshes induce the greatest foreign body reaction and longest-lasting chronic inflammatory response, which may be enhanced by the construction of PET fibers as a multifilament. Marked fibrosis and encapsulation surround ePTFE films[16]. PTFE is a more reactogenic material than PP, and it primarily stimulates the local production of pro-inflammatory cytokines. Therefore, the local anti-inflammatory effect of PP is less pronounced in comparison, but the inflammation persists for a longer time[17]. PVDF meshes produce a significantly reduced foreign body granuloma size compared with PP. PP is less stable than PVDF *in vivo*. Clear cracks in the surface of PP filaments have been detected 4 wk after implantation (Figure 3)[18]. These findings suggest that the raw material strongly influences the inflammatory and fibrotic responses.

Mesh composition

The primary aspects of mesh compositions are the use of different raw materials with or without surface coating in various textile designs.

Coatings may influence the degree of the inflammatory response. Nonabsorbable and absorbable materials are used for coatings. Absorbable materials are preferred if the coating provides a drug-eluting function. However, the degradation products may also influence the inflammatory response. A comparison of PP meshes, PP + polyglactin (PP + PG) meshes and PP + titanium (PP + TI) meshes demonstrated a reduced inflammatory reaction in the PP mesh group and increased reaction in the PP + PG mesh group. The PP mesh induced large early elevations in vascular endothelial growth factor, cyclooxygenase-2 and collagen levels, whereas the PP + PG mesh caused only small elevations in the levels of these factors. PP + TI meshes induced inflammatory response levels in between those of the other 2 meshes[19]. Human fibroblasts colonized on the macroporous PP side of a composite mesh made of two PP layers, but no cell growth occurred on the film PP side[20]. The suppressive effect of the mesh on the transforming growth factor β1 was more pronounced for partially absorbable materials compared with pure PP meshes, which suggests that a change in raw material composition and type affects the early biological reaction of connective tissue cells to the mesh[21]. Woven and nonwoven meshes have received less attention. Raptis *et al*[22] demonstrated that woven PP meshes became fully peritonealized intraperitoneally but generated thicker and more plentiful adhesions than nonwoven PP. PP nonwoven prosthesis are comparable to conventional warp-knitted meshes[23].

The textile design markedly influences the inflammatory reaction to the mesh. Using the best polymer in a poor textile design may lead to pronounced inflammation and scar formation. In contrast, an adequate tissue reaction may be achieved with a suboptimal polymer if the essential parameters of the textile design (*e.g.*, the filament structure and pore size) are considered. The particular type of mesh used in hernia repair may affect the wound healing response and clinical outcome[24].

STRUCTURE PARAMETERS

Pore characteristics

The characteristics of the mesh used - primarily the pore characteristics especially the collapse of pores under strain, amount of mesh material, prosthesis weight, and mechanical properties - crucially influence the dynamic incorporation. In 1997, Amid[25] identified mesh porosity as the decisive factor for risk of infection. Amid defined pores larger than 75 μm as macropores before large-pore meshes (3-5 mm) were developed. Klinge *et al*[26] evaluated a remarkable number of explanted meshes and found that the mesh porosity was the most important determinant of the tissue reaction and risk of scar entrapment. The pore size must be much larger than 75 μm to preserve tissue integration without filling the pores with scar tissue. A pore size > 1 mm is required for PP, and the pore size should be > 3 mm in cases of mechanical strain. Meshes with large pores exhibit less inflammatory infiltrate, connective tissue, fistula formation, calcification, and bridging (*i.e.*, the pores are filled by scar tissue) than meshes with small pores[27,28]. Granulomas normally form around individual mesh fibers as part of the foreign body reaction, but the term "bridging" describes the process whereby individual granulomas become confluent with each

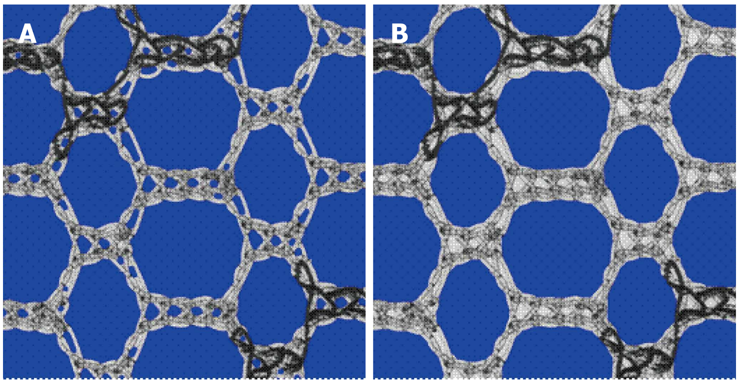

Figure 4 Comparison of the textile porosity (A) and the effective porosity (B).

other and encapsulate the entire mesh, which leads to a stiff scar plate and reduced flexibility[29]. A pore that is not completely filled by scar tissue is considered "effective" according to Mühl *et al*[30]. Therefore, large pore sizes preserve the "effective porosity" and thus avoid formation of scar bridges (Figure 4).

It is difficult to define a best pore size a priori because different raw materials result in different "effective porosities". Bridging of granuloma and encapsulation of the entire mesh is more likely for PP meshes with small pores (< 800 μm)[31]. In contrast, PVDF meshes do not exhibit bridging even for pore sizes of < 650 μm[32,33]. Klinge *et al*[26] characterized large-pore meshes using a textile porosity > 60% or an effective porosity > 0%. Pore shape may also determine integration. Lake *et al*[34] found that hexagonal pores resulted in the strongest tissue ingrowth, followed by square pores and diamond pores.

Mesh weight

Synthetic meshes may be classified as heavyweight or lightweight. The mesh weight depends on the polymer weight (raw material) and the amount of material used.

Coda *et al*[35] proposed a classification system based on the mesh weight that includes simple, composite and combined meshes. Meshes with weight per unit area of greater than 140 g/m² are defined as heavyweight meshes, meshes with weight per unit area in the range 35-70 g/m^2 are defined as lightweight meshes and meshes with weight per unit area in the range of 70-140 g/m^2 are defined as standard-weight meshes. Lightweight meshes generally contain less material and induce a less-pronounced foreign body reaction and decreased inflammatory response, which results in better tissue incorporation, increased prosthesis compliance, and decreased patient discomfort and pain. In an animal study, restriction of the abdominal wall mobility was significantly reduced and the inflammatory reaction and connective tissue formation were markedly diminished with lightweight meshes compared with heavyweight meshes[36]. Randomized prospective trials compared lightweight and heavyweight meshes for ventral hernia repair and found that they had equal outcomes in terms of ventral hernia recurrence[37]. Patients with lightweight mesh hernia repair exhibited better outcomes in terms of pain and seroma and an earlier return to activity[38].

Most current lightweight meshes have larger pores than heavyweight small-pore constructions[39]. However, mesh classification only in terms of weight disregards fiber and pore characteristics. Weyhe *et al*[40] considered the textile mesh construction, which they characterized in terms of the pore size and filament structure, as a more important determinant of foreign body reactions after implantation than absolute material reduction. This result attenuates the importance of mesh weight for the prediction of biocompatibility[41]. The advantages of lightweight meshes may be primarily related to their tendency to utilize a large pore size and/or monofilament.

However, an excessive reduction of mesh weight may also decrease the tensile strength. Lightweight meshes are sufficiently strong to resist abdominal wall pressure, but these meshes lose some burst strength compared with heavyweight meshes[32,42]. Experiments using small animals suggest that heavyweight small-pore meshes may withstand greater forces of scar contraction than large-pore lightweight meshes and may exhibit less shrinkage. Zogbi *et al*[43] found that lightweight PP mesh exhibited greater median shrinkage than heavyweight PP mesh in rats 7, 28 and 90 d after implantation.

MECHANICAL PARAMETERS

Mechanical properties are important parameters to consider when determining the suitability of a particular mesh for a specific clinical situation. However, surgeons typically implant meshes to provide maximum overlap over the defect with little regard for the mechanical properties of the mesh. Each synthetic mesh is composed of a unique combination of the material properties of the polymer and the textile design. The textile properties depend on the manufacturing process and the manufacturing process parameters.

The choice of raw materials determines a material's properties, which in many cases implies a combination of the properties of more than one raw material. These features ultimately determine the mechanical properties

Table 3 Definitions of mechanical mesh properties based on the definitions given by the American Society for Testing and Materials[44]

Property	Definition
Tensile strength	Tensile strength is the maximum force that can be applied to a mesh without tearing or breaking of the mesh. The tensile strength is measured in Newton (N) and is usually given in relation to the clamping width as Newton per centimeter (N/cm)
Burst strength	The burst strength is the maximum uniformly distributed pressure applied at right angle to its surface that a material will withstand under standardized conditions. The burst strength is given in pressure per unit area (Pa/cm²)
Elasticity (elastic elongation)	Elasticity (elastic elongation) is the property of a material whereby it changes its shape and size under the action of opposing forces (%), but recovers its original configuration when the forces are removed. In contrast, to the elastic elongation the plastic elongation indicates the elongation ratio which does not recover after unloading the structure
Stiffness	Stiffness can be expressed as ratio of steadily increasing or decreasing force acting on a deformable elastic material to the resulting displacement or deformation. Stiffness is a crucial aspect that reflects the drapablity of a textile structure, means the ability of a textile structure to be adapted to a 3-dimensional geometry

of the resulting mesh. An important consequence of the manufacturing process is the anisotropy of the tensile strength, elasticity, burst strength and stiffness. The American Society for Testing and Materials (ASTM) specification (D 4850 Terminology of textile structures) provides definitions of these properties (Table 3)[44].

The actual load on the abdominal wall is of major relevance for the selection of the suitability of meshes for use in ventral hernia repair. Different groups often perform simple tensile tests (N/cm), measurements of the inner abdominal pressure (Pa = N/mm²) or calculations of the abdominal wall tension (N/cm) using the Young-Laplace equation to characterize the native abdominal wall properties. The different measuring methods and different units should be considered when comparing these measurement results. Conversion of the inner abdominal wall pressure (Pa = N/mm²) (using the Young-Laplace equation) to the abdominal wall tension (N/cm) is only possible if the circumference of the patient is also provided. Use of the Young-Laplace equation requires a distinction between the sphere-like anatomy of the groin and the cylinder-like anatomy of the abdominal wall.

Hollinsky *et al*[45] measured the tensile load of the linea alba, the anterior and posterior rectus sheath, and scar tissue following median laparotomy in fresh cadavers and found that the tissue in the epigastric region ruptured at a mean horizontal load of 10 N/mm^2 in the linea alba and 6.9 N/mm^2 in scar tissue and at a mean vertical load of 4.5 N/mm^2 in the linea alba and 3.3 N/mm^2 in scar tissue. In earlier research, Williams *et al*[46] estimated the maximum force applied to the abdominal wall after hernia repair surgery as 22 N/cm in the cranial/caudal direction and 32 N/cm in the lateral direction. Cobb *et al*[47] investigated the intra-abdominal pressure using a transurethral bladder (Foley) catheter under different physical situations, including standing, sitting, bending at the waist, bending at the knees, performing abdominal crunches, jumping, climbing stairs, bench-pressing 25 pounds, arm curling 10 pounds, and performing a valsalva and coughing while sitting and standing, and identified a pressure of 22.7 kPa (171 mmHg) as the maximum pressure during coughing. Deeken *et al*[48] argued that stress in the transverse direction can reach levels of 47.8 N/cm in obese males with a large abdominal circumference. The true peak pressure in situations such as expectoration or sternutation in the abdominal wall was not fully addressed, but it is accepted that 22 N/cm in the cranial/caudal and 32 N/cm in the lateral direction are the maximum forces applied to the abdominal wall after hernia repair surgery[49]. A load of 16 N/cm is accepted as the maximum load in the groin because of the more sphere-like anatomy of the groin[50].

The natural elasticity of the abdominal wall at 32 N/cm is approximately 38%, with higher resilience in the horizontal direction than the longitudinal direction[45,46]. DuBay *et al*[51] indicate that the use of meshes in ventral hernia repair increases abdominal wall elasticity, which results in lower recurrence rates. Lightweight meshes exhibit an elasticity of approximately 20%-35% at 16 N/cm, but heavyweight meshes exhibit half of this elasticity (4%-15% at 16 N/cm), which may restrict abdominal distension[39]. An inappropriate mesh tensile strength, which results in an inappropriate ability of the mesh material to stretch, may potentially lead to poor functional results, with pain, hernia recurrence or prolapse. Elongation rates of greater than 30% indicate that these materials may stretch more than the native human abdominal wall. These meshes may not maintain functional repair, which could result in bulging or recurrence[48].

Tensile strengths of greater than 100 N/cm of conventional heavyweight meshes (*e.g.*, Prolene) are disproportionate and not necessary for effective repair[39]. Most synthetic meshes, even the lightest meshes, reach a tensile strength of at least 32 N/cm and are sufficiently strong. The mean burst strength and stiffness of lightweight meshes 5 mo after implantation in a pig was significantly less than those of heavyweight and middleweight meshes, but the burst strength for all meshes tested was much greater than the strengths measured for the abdominal wall fascia alone[32]. Bellón *et al*[52] demonstrated that the tensile strengths of lightweight and heavyweight meshes were comparable 90 d after implantation. However, Petro *et al*[53] recently reported 7 cases of mechanical failure or fracturing of lightweight monofilament polyester meshes after open incisional

Table 4 Essential properties of hernia meshes used for groin and abdominal wall hernia repair

Property	Recommendation
Tensile strength (abdominal wall)	22 N/cm (cranial/caudal) 32 N/cm (lateral)
Tensile strength (groin)	16 N/cm
Elongation	20%-40%
Orientation	No specific orientation for meshes with isotropic properties For meshes with anisotropic properties: orientation in the appropriate direction to match the physiological stretchability
Pore size	Depending on the used raw material and the foreign body reaction, respectively. To achieve a high effective porosity: for PP meshes a pore size ≥ 1000 μm should be used; for PVDF meshes a pore size ≥ 600 μm should be used

PP: Polypropylene; PVDF: Polyvinylidenefluoride.

hernia repair. Zuvela *et al*[3] and Lintin *et al*[54] reported central ruptures of low-weight PP meshes after initial sublay incisional hernia repair. These isolated case reports are insufficient to question the use of lightweight meshes in ventral hernia repair, but one should consider that the maximum initial tensile strength of synthetic meshes did not predict long-term strength after implantation[55]. Eliason *et al*[56] demonstrated that BardMesh, Dualmesh, and Prolene exhibited significantly reduced tensile strength, and BardMesh, Proceed, Prolene, ProLite, ProLite Ultra, and Ultrapro exhibited significantly increased permanent elongation after exposure to 1000 cycles of repetitive loading sequences that simulated changes in the intra-abdominal pressure. Mesh elongation also led to the loss of effective porosity in most meshes, which is an important aspect for scar formation and foreign body reaction[57]. Stiffness and breaking strength also vary widely among available meshes for hernia repair, and most meshes exhibit significant anisotropy in terms of their mechanical behavior. Pott *et al*[49] compared six meshes composed of different raw materials and different textile structures. All six mesh types exhibited differences in maximum tensile strength (11.1 ± 6.4 to 100.9 ± 9.4 N/cm), stiffness (0.3 ± 0.1 to 4.6 ± 0.5 N/mm), and elongation at break (150% ± 6% to 340% ± 20%) based on the load direction: the warp direction, or "longitudinal direction", *vs* the weft direction, or "orthogonal direction". Deeken *et al*[58] recently evaluated 13 mesh types that exhibited a wide range of mechanical properties. Some meshes were nearly isotropic, with nearly similar properties in the vertical and horizontal strain directions [C-QUR™, DUALMESH(®), PHYSIOMESH™, and PROCEED(®)], but other meshes were highly anisotropic (Ventralight™ ST, Bard™ Mesh, and Bard™ Soft Mesh). Some meshes exhibited a nearly linear behavior (Bard™ Mesh), but other meshes were non-linear, with a long toe region followed by a sharp rise in tension.

Meshes with different mechanical properties are treated as uniform and interchangeable, but it is important to understand the characteristics of the meshes to identify an appropriate mesh for each patient and place the mesh in an appropriate position to avoid mechanical mismatch, which may impair graft fixation, and enable optimized integration into the host tissue[59,60]. Therefore, surgeons may use meshes with isotropic properties regardless of the mesh orientation, but surgeons should pay attention to the orientation of meshes with anisotropic properties, which should be placed with their major elasticity in the appropriate direction to match the physiological stretch abilities (Table 4).

NEW DEVELOPMENTS

The evolution of meshes is not complete. New synthetic meshes are continuously developed, and new polymers and innovative coatings are continuously introduced. Ulrich *et al*[61] examined 3 new warp-knitted synthetic meshes composed of different polymers with different tensile properties, polyetheretherketone, polyamide (PA) and a composite, gelatin-coated PA (PA + G), in a rat model. All new materials exhibited better tissue integration, new collagen deposition and sustained neovascularization compared with PP meshes. Therefore, these new materials provide a promising alternative for future mesh developments. Meshes manufactured from native spider dragline revealed rapid cell migration, complete degradation, formation of a stable scar with constant tensile strength values and the highest relative elongation among standard biological and synthetic meshes[62].

Biosynthetic meshes are a possible cost-effective alternative to synthetic and biological meshes. Biodegradable polymers, instead of animal or cadaver tissue, provide a temporary scaffold for deposition of proteins and cells that are necessary for tissue ingrowths, neovascularization, and host integration[63]. Powell *et al*[64] reported good results in the early phase for "synthetic remodeling meshes" made from PGA/trimethylene carbonate in a study of 70 patients who underwent hiatal hernia repair. However, Symeonidis *et al*[65] used the same "synthetic remodeling mesh" in a pilot study of inguinal hernia repair and reported discouraging results, with a 38% recurrence rate after a mean follow-up of 2 years, which questions the general suitability of this mesh. Another fully absorbable mesh composed of knitted poly-4-hydroxybutyrate monofilament fibers, named the Phasix mesh, exhibited a strength that was 80%, 65%, 58%, 37% and 18% greater than the native abdominal wall at 8, 16, 32, and 48 wk post-implantation, respectively. The significant reduction of the polymers' molecular weight over time demonstrated successful transfer of load-bearing from the mesh to the repaired abdominal wall[66].

Configurations that include a metal component may also add new properties to standard synthetic meshes. Mesh shrinkage, migration, and configuration changes in the host tissue cause severe complications and discomfort after mesh implantation. There is no way to revise an implanted mesh postoperatively except for access to samples that have been explanted because of severe infection, chronic pain and recurrence. However, incorporation of small iron particles into the polymer provides an effective option for noninvasive revision using magnetic resonance imaging[67]. Another promising metal to improve mesh performance is nitinol. Nitinol-containing memory frame mesh is a valuable tool to achieve complete deployment in transinguinal preperitoneal repair for inguinal hernias that offers an acceptable morbidity and a low recurrence rate[68].

Coatings are another effective method to modify the properties of synthetic meshes. A titanium-coated PP mesh was associated with less postoperative pain in the short term, lower analgesic consumption and shorter convalescence compared with the Parietex composite mesh[69]. Intraperitoneal implantation of PP meshes is not recommended because of the likeliness of inducing intense adhesion and intestinal fistula. A PP mesh coated with poly(L-lactic acid) exhibited an additional property of anti-adhesion in a rat model[70]. Extracellular matrix-coated PP meshes attenuated the pro-inflammatory response with reduced cell accumulation, fewer foreign body giant cells and decreased collagen density without changes in the mechanical properties of the mesh[71,72]. Chitosan-coated PP meshes elicited preferential attachment of myoblasts over fibroblast attachment *in vitro*, which was associated with the restoration of functional skeletal muscle with histomorphological characteristics that resembled native muscle *in vivo*[73]. Degradable drug delivery coatings with incorporated antibiotics provide a specific approach to reduce post-surgical infections[74]. These promising laboratory and animal trial results may be incorporated in clinical practice in the future.

The use of electro-spun nanofibers of various polymers as tissue scaffolds in hernia repair has been an active research topic in recent years. Electro-spun materials feature three-dimensional nanofibrous structure with high surface-to-volume ratios and high porosity with high pore-interconnectivity that are similar to the native extracellular matrix. Drugs and growth factors for the prevention of incisional hernia formation have also been incorporated into electro-spun nanofibers[75]. Recent research revealed that PET and PET/chitosan electro-spun meshes performed well during incisional hernia surgery. However, the formation of foreign body granuloma in response to electro-spun structures was greater than when conventional meshes were used[76]. Further studies are required to elucidate the mechanisms that underlie the interactions between cells/tissues and nanofibrous materials.

CONCLUSION

Large-pore, monofilament, lightweight synthetic meshes are the current standard of practice. However, the risk of infection and other complications associated with the use of meshes are inevitable. An ideal synthetic mesh should consist of a monofilamentous large-pore structure with anisotropic mechanical properties that are similar to the native properties of the healthy host tissue and composed of a highly biocompatible raw material with long-term stability. An optimal mesh for intraperitoneal use must resist visceral adhesions to limit the risk of bowel obstruction and intestinal fistula. The use of innovative raw materials or coatings of currently available raw materials are promising approaches to realize these ideals. The individual response of the patient influences the local response after mesh implantation. Therefore, a thorough understanding of the biological processes of tissue formation and remodeling in the context of wound-healing processes after hernia repair is needed.

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MINIREVIEWS

Risk factors and implications of anastomotic complications after surgery for Crohn's disease

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Abstract

Anastomotic complications occur more frequently in patients with Crohn's disease leading to postoperative intra-abdominal septic complications (IASC). Patients with IASC often require re-operation or drainage to control the sepsis and have an increased frequency of disease recurrence. The aim of this article was to examine the factors affecting postoperative IASC in Crohn's disease after anastomoses, since some risk factors remain controversial. Studies investigating IASC in Crohn's operations were included, and all risk factors associated with IASC were evaluated: nutritional status, presence of abdominal sepsis, medication use, Crohn's disease type, duration of disease, prior operations for Crohn's, anastomotic technique, extent of resection, operative timing, operative length, and perioperative bleeding. In this review, the factors associated with an increased risk of IASC are preoperative weight loss, abdominal abscess present at time of surgery, prior operation, and steroid use. To prevent IASC in Crohn's patients, preoperative optimization with nutritional supplementation or drainage of abscess should be performed, or a diverting stoma should be considered for patients with multiple risk factors.

Key words: Crohn's disease; Risk factors; Complications; Resection; Postoperative septic complications; Anastomosis

Core tip: Intra-abdominal sepsis is a common complication in intestinal anastomoses in Crohn's disease; therefore, identifying the risk factors prior to surgery can improve outcomes. This review identified preoperative weight loss, abdominal abscess present at surgery, prior surgery, and steroid use as risk factors for postoperative anastomotic complications. Outcomes in Crohn's operations with these risk factors may be improved with preoperative nutritional supplementation and drainage of the intra-abdominal abscess. If multiple risk factors are present and preoperative interventions are not feasible, a diverting stoma should be considered.

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INTRODUCTION

Crohn's disease is a chronic inflammatory disease which will eventually lead to surgical intervention in a majority of patients. Medical therapy can prolonged the time spent in remission and delay the need for surgery, but the rate of surgical intervention has not subsequently decreased as 70%-90% of patients will require an operation during their lifetime[1,2]. Although any portion of the bowel may be affected, Crohn's disease is found most commonly in the terminal ileum thus ileocolectomy is the most common operation[3,4]. Patients with Crohn's have a higher complication rate, especially anastomotic complications leading to intra-abdominal sepsis, than patients without an inflammatory state. Intra-abdominal septic complications (IASC) include anastomotic leak, intra-abdominal abscess, and development of a fistula with in approximately 30 d postoperatively. Multiple observational studies have investigated the risk factors associated with IASC in order to identify patients to optimize preoperatively or include a diverting stoma to decrease the severity of complications, although some risk factors remain controversial. This review will focus on risk factors for IASC in patients undergoing surgery with intestinal anastomoses, mainly with ileocolic anastomoses, with Crohn's disease.

A Medline search was performed using keywords Crohn's disease, complications, anastomosis, post-operative sepsis, and surgery. From the articles reviewed, additional articles from the references were also included. Articles after 1980 were considered. A total of 27 articles were finally used.

RISK FACTORS FOR ANASTOMOTIC COMPLICATIONS IN CROHN'S DISEASE

Nutritional status

The preoperative nutritional status of patients in most studies was assessed by at least one of three parameters: preoperative serum albumin level, weight loss, and body-mass index (BMI). There is no gold standard for nutritional assessment in inflammatory bowel disease (IBD). BMI and unintentional weight loss are agreed upon measures for nutrition in Crohn's patients[5,6]. Albumin is associated with nutritional status in IBD; however, during an acute phase response, such as active Crohn's disease, albumin levels can fall[5]. Thus low albumin could be indicative of the disease state rather than nutritional status alone.

Serum albumin was the most commonly assessed nutritional parameter in studies included in this review. One study found albumin less than 3.0 mg/dL to be associated with an increased risk of IASC in a multivariate analysis[7], while another study found association in a univariate but not multivariate analysis[8]. Other studies using the same cutoff value, albumin < 3.0 mg/dL, did not find a similar association[9-11]. These results are further complicated by a study including preoperative nutritional supplementation in patients with an albumin less than 3.0 mg/dL[9]. Moreover, albumin level less than 3.5 mg/dL[12,13] and less than 4.0 mg/dL[14] were reported to have no association with IASC. One study that did not find albumin to be associated with IASC did not define albumin parameters[15]. A recent meta-analysis using many of these described studies found a correlation with low albumin and increased risk of IASC[16], but the definition of low albumin is quite inconsistent in these studies making even the pooled results difficult to determine.

Unexpected weight loss described as loss of 5%-10% body weight from the pre-morbid condition provides inconsistent data. Weight loss is associated with increased IASC in some studies[17,18]. Another study did not identify weight loss as a risk factor for IASC, although the definition for weight loss included patients requiring the need for preoperative nutrition[15]. Including patients receiving preoperative nutrition may confound the results by improving nutritional status at the time of surgery. Serradori *et al*[19] also found that weight loss before surgery did not impact IASC rate and included patients receiving preoperative nutritional support, although without specification of parenteral or enteral nutrition. In addition, no patients receiving preoperative nutrition developed an IASC. This data could suggest that patients who have weight loss preoperatively may benefit from nutritional supplementation prior to surgery to ameliorate the risk of complications.

Multiple studies reported BMI, although no study found BMI to be a risk factor for ISAC[8,14,17,18]. Despite the lack of association between BMI and abdominal septic complications, it should be noted that in these studies there were multiple variations in reporting BMI, such as, mean BMI[17,19], BMI less than 18.5[8], less than 20[18], or BMI less than 25[14]. Although BMI may be a reliable measure of malnutrition in preoperative Crohn's patients, BMI is not a risk factor for post-operative abdominal sepsis.

Abdominal sepsis

Intra-abdominal sepsis includes intra-abdominal abscess and/or fistula present at the time of surgery. Studies that investigated the presence of intra-abdominal abscess at the time of surgery for Crohn's disease found these patients at an increased risk of IASC[7,15,17,20]. In contrast, abscess was not associated with abdominal complications in other studies[13,14]. The studies that combined presence of preoperative abscess and fistula were inconsistent. Some studies found no effect on the rate of IASC with abscess and fistula[9-11] while other studies reported an association in univariate analysis[8,21], and one found association also in a logistic regression analysis[8]. Some studies included abscesses that were drained preoperatively and found no association with abscess and postoperative IASC[14,18]. In contrast, studies which excluded preoperatively drained abscesses from the analysis, abscess present at time of surgery increased the risk of IASC with an odds ratio (OR = 3.4, 95%CI: 1.2-9.8)[15] and (OR =7.5 , 95%CI: 1.5-37.69)[17]. A meta-analysis which included most studies discussed regarding intra-abdominal abscess, including studies which combined abscess and fistula or included drained abscesses, found an increased risk of IASC with intra-abdominal abscess. Thus, the risk of IASC is higher when an intra-abdominal abscess is present, but the risk is likely ameliorated if the abscess is drained preoperatively.

The presence of an intra-abdominal fistula at the time of surgery has conflicting results as well. Multiple studies found no correlation between presence of fistula and IASC[13-15,18]. One study found fistula to be an independent risk factor for IASC[7], and in addition, one study found an association of fistula and IASC in a univariate analysis but not in a multivariate analysis[17]. These observational studies are the best data currently, as a meta-analysis of fistula alone has not been performed. There is no clear consensus that fistula alone at the time of surgery increases the IASC rate.

Medications

Most patients undergoing surgery for Crohn's disease are on medical therapy, either a single medication or a combination of medications including immunosuppressive medications, biologics, and steroids. Many studies have investigated these medications, and a majority of those studies report overall complications or just septic complications without specifying intra-abdominal sepsis. This review will only discuss those publications reporting IASC.

The use of corticosteroids in managing Crohn's disease has decreased with the advent of immunomodulators and biologics, but corticosteroid use in the perioperative period is still prevalent. Many studies investigated the postoperative complications with perioperative steroid use. Studies prior to 2010 only include corticosteroids in the analyses[7,9,12,13,17,18], while the more recent studies also include other medications[8,10,11,14,19,21,22]. The inclusion criteria for steroids widely varies between studies, as some studies do not define steroid use[9,11,13,18,19,22,23] while others require at least 4 wk[7,8,14,15,21] or 3 mo of steroid use prior to surgery[10,17]. Multiple studies found preoperative steroid use to be an independent risk factor in multivariate analysis[7,9,15,17]. Other studies found that steroid use increased IASC in a univariate analysis but not with a multivariate analysis[10,19]. In contrast, one study found steroid use to be protective of IASC[21], while other studies did not find an association between steroid use and postoperative abdominal sepsis[8,10,11,13,14,18,22]. In a meta-analysis including many of the studies presented here, steroid use was identified as a risk factor for IASC[16]. Thus perioperative steroid use should be considered an independent risk factor for IASC.

Immunosuppressants investigated were most commonly azathioprine, but some studies also included 6-mercaptopurine and methotrexate. Since these medications are not widely used, there are fewer studies reporting the postoperative outcome in conjunction with immunosuppressants. Only two studies reported a length of use criteria for inclusion, greater than 3 mo[8,21], while other studies did not define the inclusion criteria for length of preoperative steroid use. Immunomodulators were an independent risk factor for IASC in two studies[8,11]. Other studies[10,14,19,21,22] did not find an association with IASC and immunosuppressants, nor did a meta-analysis[16]. Immunosuppressants do not definitively affect postoperative outcomes.

Anti-tumor necrosis factor alpha (anti-TNF-α) drugs, or biologics, are increasingly used in Crohn's disease especially since a "top-down" approach for severe Crohn's disease is becoming more common to facilitate remission and delay surgery. A meta-analysis in 2014 suggested increased infectious complications with the use of anti-TNF agents, but all types of infectious complication not only intra-abdominal septic complications were included[24]. Individual studies investigating only IASC with biologics did not have similar findings. These studies included patients with biologic use within 8-12 wk before surgery[19,21,25], and one study also included anti-TNF use up to 4 wk postoperatively[22]. Some studies found biologics to be independent risk factors for IASC[19,22] while others did not find an association[10,21,22]. Moreover, a meta-analysis found no clinical implication of IASC risk with biologic use[16]. Anti-TNF agents do not increase the risk of postoperative intra-abdominal sepsis, although the association with overall postoperative complications is beyond the scope of this review.

Disease characteristics

Crohn's disease can behave as penetrating, stricturing, or nonstricturing/nonpenetrating, in order from least to most common presentation[4]. Most studies do not differentiate disease type, but Kanazawa *et al*[14] found penetrating disease to have an increased risk of IASC. Other studies did not find that disease classification impacted the IASC rate[9,10,22]. Patients with obstructing disease can have progression to perforating behavior, so in studies that included recurrent resections it is unclear if the disease type was readdressed for patients undergoing subsequent operations. Due to the limited number of studies investigating disease type, the presence of an abscess likely is a more important risk factor for postoperative complications than the disease type.

Duration of disease and prior operations

The duration of disease prior to an operation is shown to correlate with IASC, but only one study found an association with disease greater than 10 years and risk of IASC[10]. Another study further classified disease severity into less than 1 year, 1-10 years and greater than 10 years without finding the same correlation[7]. The average duration of disease was found to be associated with IASC in univariate but not multivariate analysis in some studies[17,21], while other studies found no association[9,12]. Moreover, a prior resection or operation for Crohn's disease was not correlated with the risk of postoperative IASC[7-10,14,15]. Regardless of these studies finding no influence of prior operation on IASC, a meta-analysis showed an increased risk with an OR of 1.5[16]. The duration of disease does not appear to be a clinical factor associated with IASC, but prior operation appears to be a risk factor for IASC from the meta-analysis results despite lack of significant finding in each study.

Anastomosis technique

The type of anastomosis, stapled side-to-side and hand-sewn end-to-end anastomoses, have been thoroughly investigated. Some studies found an increased risk of IASC with hand-sewn anastomoses compared to stapled anastomoses[13,14]. Multiple other studies found no difference in postoperative IASC between stapled and hand-sewn anastomoses[7,8,10,21]. Alves *et al*[17] found no difference with only hand-sewn side-to-side and hand-sewn end-to-end configuration of anastomoses. A meta-analysis did not find an association with the method of anastomotic configuration[16], therefore, there is no increased risk of IASC with either stapled or hand-sewn anastomosis. Although a majority of studies included only ileocolic resections or ileal strictureplasties, three of these studies included colocolonic anastomoses and found an independent increase risk for IASC with these anastomoses[8,10,21], but other studies found no association of large *vs* small bowel involvement at the time of operation, although the site of anastomosis was not specified[7,9]. Thus the method of creating an anastomosis does not affect early postoperative complications in ileocolic anastomoses; however, there is not enough data to support the same conclusion for colonic anastomoses.

Extent of resection and margins

The extent of resection was only investigated in one study, in which IASC was not associated with extent of resection[12]. The number of anastomoses was reported in multiple studies to have no association with postoperative intra-abdominal sepsis[8,9,14,21]; furthermore, multiple resections were associated with increased IASC in a univariate but was not associated in a multivariate analysis[18]. The presence of macroscopic disease in the margin was investigated in a randomized controlled trial by Fazio *et al*[26], which reported that recurrence rate is not affected by either the width of macroscopic margin or presence of microscopic Crohn's disease at the margins. Conflicting results were found in two studies which investigated the impact of microscopically positive margins on IASC. One study found histologically positive margins to be an independent risk factor for IASC[10], while another study found no increased risk of IASC with inflammation present at the margins[9]. Although no meta-analysis has been performed on these data, the majority of studies suggest that multiple resections and extent of resection are not associated with increased intra-abdominal sepsis.

Operative timing

Crohn's disease can require urgent or elective surgeries depending on the indication for surgery. Only one study found an association between emergent operation and increased risk for IASC although it was not an independent risk factor in a multivariate analysis[10]. In contrast, emergent surgery was not associated with IASC in other studies[14,17]. Thus the setting of emergent compared to elective operation does not greatly impact postoperative intra-abdominal complications.

Operative time

The length of time in the operating room has previously been identified as a risk factor for anastomotic leak in colorectal surgery[27]. The operative time was independently associated with IASC in two studies[14,21], however it was not associated with IASC in another study[17]. Like other colorectal surgeries, prolonged operations could increase the risk of IASC especially anastomotic leak, but larger studies or a meta-analysis would provide more definitive recommendations.

Perioperative bleeding

Blood loss in the operating room greater than 150 mL is an independent risk factor for IASC[21], and blood loss greater than 300 mL was associated with an increased risk of IASC in univariate but not multivariate analysis[14]. Some studies reported perioperative blood transfusion, suggesting increased blood loss; however, blood loss or transfusion does not clinically impact IASC[8,17].

Smoking

Cigarette smoking can affect the disease course as those who smoke have an increased need for surgery as well as increased risk of recurrence[20]. Smoking has been associated with an increased risk in overall complication rates after surgery for Crohn's disease[23], but intra-abdominal sepsis was not association with an increased rate of postoperative abdominal septic complications. Smoking did not affect the rate of IASC[10,11,15,17] thus smoking is not a risk factor for IASC.

DISCUSSION

Preoperative nutritional status in Crohn's patients, measured by unexpected weight loss, increased the risk for postoperative IASC. When patients with weight loss receive preoperative nutritional supplementation, this effect is no longer seen. Albumin level also seems to be associated with higher IASC rate in meta-analyses, but the albumin ranges varied widely between studies, complicating the combined data interpretation for albumin. Preoperative malnutrition nonetheless is associated with increased IASC. Intra-abdominal sepsis, with presence of an abscess at time of surgery, increased the risk for IASC, and some studies showed preoperative drainage decreased this risk. Steroid use before surgery was associated with an increase in IASC. Prior operation was a risk factor in a meta-analysis, but each study included in that analysis did not find and association with IASC. Further investigations, such as a larger study, are needed to verify the increased IASC risk with prior operation for Crohn's disease. Although prolonged operative time was the final variable associated with a higher rate of IASC, this was based upon limited number of studies thus further investigation is warranted. Factors not associated with IASC are use of immunomodulators or biologics, duration of disease, operative setting: emergent or elective, blood loss, and smoking. Since IASC is associated with an increased risk of early recurrence, preventing IASC can assist in lowering the recurrence rate and subsequently the need for further surgery.

CONCLUSION

Risk factors associated with postoperative anastomotic complications in Crohn's disease include preoperative weight loss, abdominal abscess present at surgery, prior surgery, and steroid use. Preoperative optimization should be attempted to decrease postoperative complications in these patients, particularly nutritional supplementation and abscess drainage. Since IASC is associated with an increased risk of early recurrence, preventing IASC can assist in lowering the recurrence rate and subsequently the need for further surgery. In patients with multiple risk factors that cannot be optimized preoperatively, a diverting stoma should be considered.

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MINIREVIEWS

New minimally invasive approaches for cholecystectomy: Review of literature

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Abstract

Laparoscopic cholecystectomy is the most commonly performed abdominal intervention in Western countries. In an attempt to reduce the invasiveness of the procedure, surgeons have developed single-incision laparoscopic cholecystectomy (SILC), minilaparoscopic cholecystectomy (MLC) and natural orifice transluminal endoscopic surgery (NOTES). The aim of this review was to determine the role of these new minimally invasive approaches for elective laparoscopic cholecystectomy in the treatment of gallstone related disease. Current literature remains insufficient for the correct assessment of emerging techniques for laparoscopic cholecystectomy. None of these procedures has demonstrated clear benefits over conventional laparoscopic cholecystectomy. SILC cannot be currently recommended as it can be associated with an increased risk of bile duct injury and incisional hernia incidence. NOTES cholecystectomy is still experimental, although hybrid transvaginal cholecystectomy is gaining popularity in clinical practice. As it is standardized and almost identical to the standard laparoscopic technique, MLC could lead to limited benefits without exposing patients to increased postoperative complications, being therefore adoptable for routine elective cholecystectomy. Technical challenges of SILC and NOTES cholecystectomy could be addressed with the evolution of new surgical tools that need to catch up with the innovative minds of surgeons. Regardless the place of these approaches in the future, robotization may be necessary to impose them as standard treatment.

Key words: Cholecystectomy; Laparoscopy; Single-incision laparoscopic surgery; Minilaparoscopy; Natural orifice transluminal endoscopic surgery; Review

Core tip: In an attempt to reduce the invasiveness of laparoscopic cholecystectomy, surgeons have developed single-incision laparoscopic cholecystectomy (SILC), minilaparoscopic cholecystectomy (MLC) and natural orifice transluminal endoscopic surgery (NOTES), which are hereby evaluated. SILC cannot be recommended as

it can be associated with an increased risk of bile duct injury. NOTES cholecystectomy is still experimental, although hybrid transvaginal cholecystectomy is gaining popularity. As it is standardized and almost identical to the standard laparoscopic technique, MLC could lead to limited benefits without exposing patients to increased postoperative complications, being therefore adoptable for routine elective cholecystectomy.

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INTRODUCTION

Laparoscopic cholecystectomy has become the procedure of choice for routine gallbladder removal and is currently the most commonly performed abdominal intervention in Western countries[1]. Compared to open cholecystectomy, laparoscopic cholecystectomy decreases postoperative pain and the need for postoperative analgesia, shortens hospital stay and return to full activity, with improved cosmesis and patient satisfaction[2]. The laparoscopic approach has gained acceptance not through organized and carefully conceived clinical trials but through commendation. Prospective randomized trials were late and irrelevant because advantages were already clear at the moment of their conception. Thus, laparoscopic cholecystectomy has received universal acceptance and is now considered the gold standard for the treatment of symptomatic cholecystolithiasis[3]. Moreover, trials have shown that day-case laparoscopic cholecystectomy was safe and successful, indicating that it should be offered to most patients in an outpatient basis[4].

Conventional laparoscopic cholecystectomy (CLC) is traditionally carried out with four ports (two 10-mm and two 5-mm ports). Since its introduction, investigators have attempted to achieve further improvements to the established technique, aiming to reduce the invasiveness of the procedure by decreasing the number and the size of the operating ports. The use of smaller incisions to complete the standard 4-port technique is broadly referred to as minilaparoscopic cholecystectomy[5] (MLC). Needlescopic surgery is a subcategory of minilaparoscopic surgery using ports and instruments that are less than or equal to 3 mm in diameter[6]. In reduced trocar surgery, cholecystectomy is performed with less than 4 incisions, up to single incision laparoscopic cholecystectomy (SILC)[7]. More recently, in an attempt to eliminate all skin incision, surgeons have described cholecystectomy with an endoscope through a natural orifice then through internal incision of a intraperitoneal viscus, so-called natural orifice transluminal endoscopic surgery (NOTES)[8].

The aim of the current review is to determine the role of these new minimally invasive approaches for elective laparoscopic cholecystectomy in the treatment of gallstone related disease.

FOREWORD TO LITERATURE REVIEW

CLC is a well-established technique, with minimal conversion to open surgery and low incidence of complications[9], allowing day-case surgery as a standard procedure[4]. Therefore, it is unlikely that the trials assessing minimally invasive approaches can be powered to measure either reduction in the complication rate or in the length of hospital stay. Use of pain as the primary outcome can also be misleading, as the clinical significance of reduction in pain scores measured by visual analogue scale is unknown for laparoscopic cholecystectomy[9]. Moreover, patient's perception of the cosmetic outcome after CLC is excellent[10,11], and improvements in cosmesis seems difficult to achieve when high rates of satisfaction exist with the established technique.

Another issue on the evaluation of these new minimally invasive approaches is the low quality of the existing studies[12,13], reporting mostly low samples with lack of blinding. There appears to be no standardization of the emerging techniques, limiting the relevance of a meta-analysis for comparison with CLC. In addition, a large majority of studies described follow-up of less than 12 mo, avoiding adequate interpretation of cosmetic outcome or incisional hernia rate[14,15].

It must be mentioned that existing studies comparing CLC to either SILC, MLC or NOTES cholecystectomy describe selected patients, including only uncomplicated cholecystolithiasis without previous upper abdominal laparotomy. At this time, no selection criteria for the optimal choice of minimally-invasive technique have been defined in the literature.

SINGLE-INCISION LAPAROSCOPIC CHOLECYSTECTOMY

The first SILC was described in 1997 by Navarra *et al*[7] in a report on 30 selected patients with favorable outcomes. The technique spread slowly until more recent years, with publication of numerous prospective randomized controlled trials. However, these randomized control trials had several drawbacks[16], most reporting small sample size. Moreover, there is significant heterogeneity amongst surgical procedures defined as single-incision surgery. A wide variation of techniques is described with regard to the use of multiport device or separate trocars in one incision, the instrumentation, the method of gallbladder anchorage and the exposure of Calot's triangle. Thus, there appears to be no standardization of the technique and comparison of SILC with standard multiport laparoscopic cholecystectomy suffers from this heterogeneity and lack a firm evidence base.

Proximity of instruments when used through a single incision results in inadequate retracting abilities and loss of triangulation, which may lead to suboptimal exposure of Calot's triangle. Furthermore, clashing of instruments is common and complicates a smooth and meticulous dissection. In the literature, SILC is associated with a longer operative time than the standard technique. The addition of at least one instrument is necessary in 5% to 8.4% of SILC procedures[12,17].

Potential advantages of SILC were that it could reduce postoperative pain, allow earlier return to work, result in greater patient satisfaction, and especially improve cosmetic results. A total of 16 meta-analysis have compared the outcomes of SILC to conventional 4-ports laparoscopic cholecystectomy[9,12,16-29]. The majority of these studies observed comparable postoperative pain[17,19,21-28] and time to return to normal activities[16,25], although 3 meta-analysis describe better postoperative pain scores within 24 h following SILC[12,16,20]. Likewise, SILC does not seem to provide a better quality of life[9,28]. Ten meta-analyses showed that SILC offered a better cosmetic score than CLC, three reported no difference, but all report short-time evaluation[9,12,16,17,19,20,22-28]. Interestingly, recent studies assessed long-term cosmesis after 4-port laparoscopic cholecystectomy, showing excellent cosmetic outcome with this standardized technique[10,11]. Moreover, these studies suggest that the umbilical port is the most related to wound-related issues such as pain, infection, or cosmesis dissatisfaction, problems that will not be eradicated with the use of a single-port approach.

Complication rates are low after laparoscopic cholecystectomy, thus no meta-analysis found statistical differences between single-incision and CLC. However, Allemann *et al*[18] specifically assessed the risk of bile duct injuries following these two procedures and observed a non statistically significant increase in the rate of bile duct injury (0.4%) and other biliary complications (1.6%) after SILC (0% and 0.5% respectively for CLC). A possible increased risk of port-site hernia after SILC is also difficult to evaluate, firstly because it is underestimated due to the lack of long-term results and secondly because of its low incidence. One meta-analysis[22] showed a higher risk of incisional hernia after SILC, while others observed a trend towards a higher rate of incisional hernia after SILC without reaching statistical significance[16,17,19]. Moreover, although data regarding cost-effectiveness is scarce, a longer average operative time and the need for advanced surgical supplies could lead to potential added costs[30,31].

Finally, it appears that SILC is at present unable to preserve the well-established safe principles of laparoscopic cholecystectomy and could thus be associated with an increased risk of complications. No distinct benefit of SILC over CLC has been identified to date, with the arguable exception of cosmesis. Therefore, until further trials demonstrate the safety of SILC, it cannot currently be recommended as a routine procedure for laparoscopic cholecystectomy. Technical challenges of SILC could be eradicated with the evolution of novel instrumentation. Regardless the role of this approach in the future, robotization may be necessary in order to propose it as standard treatment.

MINILAPAROSCOPIC CHOLECYSTECTOMY

The benefits, safety and feasibility of MLC were established in small series at the late 1990s[5,6,32,33]. Several prospective randomized controlled trials comparing MLC with CLC were published in the past decade, gathered in two systematic reviews[34,35] and three meta-analyses[13,36,37], although the latter include studies reporting less than 3-port laparoscopic cholecystectomy as minilaparoscopic approach.

By definition, MLC is carried out with the use of smaller diameter instruments than the 5-mm instruments used for CLC, a range of 1.7 to 3.5 mm being described. Most surgeons perform dissection of Calot's triangle with a 10-mm laparoscope in the umbilical site, only reverting to a 2- or 3-mm laparoscope for clipping the cystic duct and cystic artery[3,38-40]. Others reported using the 10-mm umbilical port for instrumental introduction and a 2- or 3-mm laparoscope[33]. The only difference between MLC and CLC being the size of the incisions made and the instruments used, the surgical technique remains almost identical, offering satisfactory triangulation and retraction. In our experience, MLC can be easily standardized, with a relatively short learning curve. MLC can be completed successfully in more than 80% of patients, the remaining being mostly converted to CLC[34]. In addition, the rate of conversion to open approach is similar for minilaparoscopic and CLC[13,35]. Operative time can be increased when performing MLC, but various studies did not observe a statistically significant difference[13,34,35].

The available data in the literature suggest that the advantages of MLC over CLC are limited. There appears to be no advantage of MLC over CLC regarding postoperative pain, length of hospital stay and return to professional activities[34-36]. The impact of minilaparoscopic approach on cosmetic outcomes is inconsistent, the evaluation being challenged by the heterogeneity of the studies[13,34,37], the excellent results of the conventional laparoscopic approach[10,11] and the absence of a reliable objective evaluation scale. Postoperative morbidity is not affected by the minilaparoscopic approach[34,35,37], demonstrating that MLC is a safe alternative to CLC. Additional cost related to the acquisition of minilaparoscopic instruments and ports is not assessed in the literature. However, instruments and ports are reusable and can be employed routinely for other laparoscopic procedures, such as hernia repair[41].

Finally, it seems that the use of smaller incisions in selected patients could lead to limited benefits (mainly cosmetic), without exposing them to increased occurrence of adverse events. MLC appears as a standardizable and safe procedure, suitable for routine elective cholecystectomy.

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC CHOLECYSTECTOMY

A new evolution in the history of gallbladder surgery occurred in the past few years with the first cases of cholecystectomy by NOTES. After several reports in animal models[42], Marescaux *et al*[8] performed the first NOTES cholecystectomy in a patient using transvaginal access and a single 2-mm abdominal entry port. Subsequently, several teams joined the development of NOTES cholecystectomy. Pure NOTES techniques have been described, using transvaginal access in humans or transgastric and transcolonic approaches in animal models[43-45]. However, in clinical practice, the hybrid technique is widely used, aiming to further add benefits of decreased invasiveness. Hybrid transgastric cholecystectomy has been reported in small case series[46], but the procedure is still technically challenging with the currently existing instrumentation. To date, due to the established safety of colpotomy, the majority of clinical NOTES cholecystectomy is performed through hybrid transvaginal access (TVC), which is hereby analyzed.

The novelty of the technique and the lack of operative standardization lead to heterogeneity between the studies in the literature. However, a trend towards standardization appeared in the last years, as the majority of studies use a 5-mm umbilical incision for initial laparoscopic visualization and deployment of instrumentation, and a transvaginal incision for insertion of a laparoscope along with a grasping forceps and for extraction of the specimen. This technique is associated with longer operative time than CLC, and the conversion rate of TVC to CLC is estimated at 10%[47].

To date, three randomized control trials have been published, comparing transvaginal hybrid cholecystectomy to conventional[47,48] or needlescopic[49] laparoscopic cholecystectomy, along with one meta-analysis[50]. The proponents of NOTES cite reduced postoperative pain as an advantage of TVC over CLC. However, a recent meta-analysis showed a non-significant reduction in postoperative pain but a significant decrease in time for return to normal activities[50]. Another clear benefit of TVC is improved cosmesis. Importantly, there appears to be no significant difference in postoperative complications or rate of bile duct injury between TVC and CLC in these trials, conducted in centers of excellence and on selected patients[50]. Moreover, several studies reported no dyspareunia or difference in return to sexual activity between TVC and CLC groups after short-term follow-up[47-49].

Therefore, the hybrid transvaginal technique is a promising minimally invasive approach for cholecystectomy, though it demands further standardization. Despite the lack of high-powered studies, TVC seems safe in selected patients when performed by skilled surgeons. Furthermore, it has a similar morbidity to CLC and may be associated with decreased postoperative pain and time for return to normal activities. The major drawback of TVC is its applicability to only half of the patients with symptomatic cholecystolithiasis. In addition, even among women, the use of the transvaginal approach should be evaluated with regards to potential risks on subsequent fertility and discomfort during sexual intercourse.

Impediments for the adoption of other types of NOTES cholecystectomy include skepticism on transgressing and closing mucosal barriers[51], but also the lack of technological evolution of surgical tools and platforms that need to catch up with the innovative minds of surgeons.

CONCLUSION

Technical innovation within surgery is laudable and the progress that results is generally a consequence of the quest to achieve optimum outcomes for patients. To date, current literature remains insufficient for the correct assessment of new minimally invasive approaches for laparoscopic cholecystectomy. None of these emerging techniques has demonstrated clear benefits over CLC. SILC cannot be currently recommended as it appears to be associated with an increased risk of bile duct injuries and a potential for increased incisional hernia incidence. NOTES cholecystectomy is still experimental, although hybrid TVC is gaining popularity in clinical practice. As it is standardized and almost identical to the conventional technique, MLC could provide limited benefits without exposing patients to increased postoperative complications, and is therefore suitable for routine elective cholecystectomy.

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MINIREVIEWS

Bursectomy at radical gastrectomy

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Abstract

Radical gastrectomy with extended lymph node dissection and prophylactic resection of the omentum, peritoneum over the posterior lesser sac, pancreas and/or spleen was advocated at the beginning of the 1960s in Japan. In time, prophylactic routine resections of the pancreas and/or spleen were abandoned because of the high incidence of postoperative complications. However, omentectomy and bursectomy continued to be standard parts of traditional radical gastrectomy. The bursa omentalis was thought to be a natural barrier against invasion of cancer cells into the posterior part of the stomach. The theoretical rationale for bursectomy was to reduce the risk of peritoneal recurrences by eliminating the peritoneum over the lesser sac, which might include free cancer cells or micrometastases. Over time, the indication for bursectomy was gradually reduced to only patients with posterior gastric wall tumors penetrating the serosa. Despite its theoretical advantages, its benefit for recurrence or survival has not been proven yet. The possible reasons for this inconsistency are discussed in this review. In conclusion, the value of bursectomy in the treatment of gastric cancer is still under debate and large-scale randomized studies are necessary. Until clear evidence of patient benefit is obtained, its routine use cannot be recommended.

Key words: Gastric cancer; Gastrectomy; Bursectomy; Omentum; Pancreas

Core tip: Components of radical gastrectomy have decreased over time but bursectomy has been still accepted as an integral part of radical gastrectomy by Far East surgeons but not world-wide. More large-scale comparative studies are necessary to determine its benefits for cancer recurrence and patient survival. Until patient benefits are demonstrated by future studies, its routine application cannot be justified.

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INTRODUCTION

The top three causes of cancer deaths in the world are lung cancers (1.4 million deaths/year), stomach

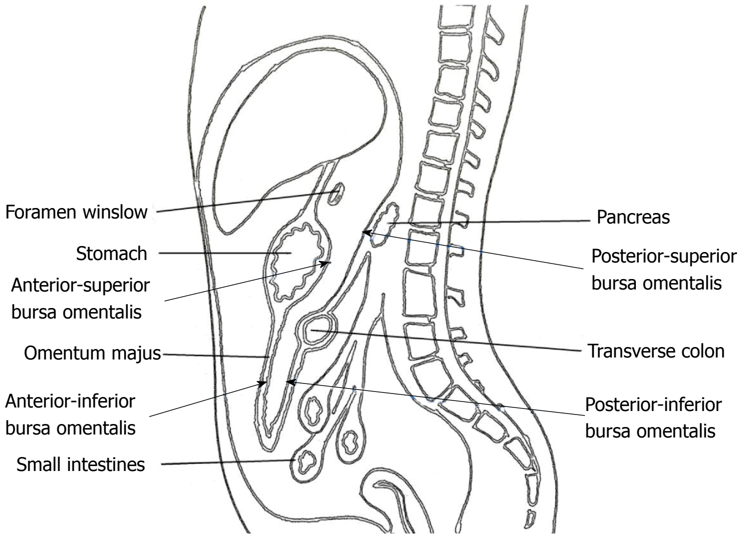

Figure 1 Anatomy of the bursa omentalis.

cancers (738000 deaths/year), and liver cancers (695900 deaths/year), respectively[1]. Stomach cancer refers to several different histological types of stomach tumors (stromal, carcinoid, lymphoma) but more than 90% of stomach cancers arise from the gastric mucosa as adenocarcinoma. The incidence of gastric adenocarcinoma shows a certain geographic distribution and it is highest in the Far East. A gender difference is also present and it is almost twice as common in men as in women. Surgery with curative intent such as radical gastrectomy and regional lymph node dissection produces the best treatment outcomes for advanced (beyond the submucosa) gastric adenocarcinomas. The extent of surgical resection includes gastrectomy (total or subtotal), lymphadenectomy (D1, D2 or D3), and prophylactic or therapeutic resection of the surrounding organs or tissues (*e.g.*, omentum, peritoneum, pancreas, spleen, colon, liver). Prophylactic or therapeutic peritonectomy over the lesser sac during radical gastrectomy is called bursectomy. The value of bursectomy in the treatment of gastric cancer is still under debate. This surgical technique is usually preferred by Far East surgeons[2] but is not accepted in the rest of the world. The aim of this article is to review the current data about the role of bursectomy in the treatment of gastric cancers.

HISTORY AND LOGIC OF BURSECTOMY

Radical gastrectomy with extended lymph node dissection was advocated at the beginning of the 1960s in Japan by Jinnai[3]. At that time, additional prophylactic resection of the omentum, the peritoneum over the posterior lesser sac, the pancreas and/or spleen had been justified as the standard procedure to perform during complete radical gastectomy. In time, prophylactic routine resections of the pancreas and/or spleen were abandoned because of the high incidence of postoperative complications[4]. However, omentectomy and bursectomy continued to be standard parts of traditional radical gastrectomy.

The omental bursa, also known as the lesser sac, is a posterior cavity in the abdomen and is demarcated anteriorly by the liver, stomach, and omentum. Posteriorly it is marked by the pancreas, left surrenal, and kidney (Figure 1). It is connected with the main anterior peritoneal cavity *via* the foramen of Winslow. The bursa omentalis was thought to be a natural barrier against invasive of cancer cells at the posterior part of the stomach and resection of the peritoneum lining over this cavity as bursectomy was accepted as a integral part of radical gastrectomy. The theoretical rationale for this procedure was to reduce the risk of peritoneal recurrences by eliminating the peritoneum over the lesser sac that might have included free cancer cells or micrometastases[5].

Bursectomy includes the removal of the peritoneal lining covering the pancreas (anterior pancreatic capsule) and the anterior plane of the transverse mesocolon along with a total omentectomy. Omentectomy has two objectives in a radical gastrectomy. First, it eliminates the perigastric lymph nodes along the greater curvature of the stomach, and second, it provides for the excision of the gastrocolic ligament that covers the anterior/inferior part of the lesser sac (Figure 1). The anterior/superior part of the lesser sac is removed by the gastrectomy itself. The posterior wall of the bursectomy is completed by removing the peritoneal sheath over the transverse mesocolon and the pancreas.

This Japanese-originated surgical technique has been known for 50 years and is mainly accepted by Far East surgeons but also by some other groups[6-9]. It was routinely recommended in the Japanese Gastric Cancer Treatment Guidelines as a part of radical surgery for gastric cancer without any supporting evidence, but was included due to traditional acceptance (version 1, 2001)[10]. The Japanese Gastric Cancer Association revised the gastric cancer treatment guidelines three years after the first version and recommended bursectomy only for serosa-invading tumors (version 2, 2004)[11]. Recently, they changed the guidelines again and this time they limited the indication of bursectomy only to posterior gastric wall tumors penetrating the serosa (version 3, 2010)[12].

WEAKNESSES OF BURSECTOMY

Gastric cancers can penetrate the serosa at the anterior or posterior gastric walls. Penetrating tumors can cause seeding of the micrometastatic tumor cells to the free peritoneal surfaces. Anterior-wall-located serosal invasions can cause implantation into the entire intraperitoneal abdominopelvic cavity (greater sac) and prophylactic peritonectomy of all of the peritoneum is not justified. In theory, the risk of posteriorly located serosa-invading cancers may be reduced by peritonectomy of the lesser sac (bursectomy) and the posterior location itself can provide an advantage for controlling the tumor cells.

In 2004, Yoshikawa *et al*[13] analyzed the clinical records of patients who underwent radical gastrectomy with bursectomy for gastric cancer invading the serosa, with special reference to the location of tumor invasion. A total of 134 patients were divided into two groups, which included patients with serosa positive tumors that invaded only the posterior or anterior gastric walls. Survival rates at 3 and 5 years were 67.3% and 53.0% for the posterior group and 68.8% and 53.8% for the anterior group, respectively. There was no significant difference in survival between the two groups and multivariate analyses demonstrated that the significant independent factor for survival was the stage of the tumor, not the location as anterior or posterior. They suggested that bursectomy for posterior-located serosa invading tumors did not provide any survival benefit over their anterior counterparts. This was one of the first studies to raise doubts about the bursa omentalis being a natural barrier against implanted cancer cells and the role of bursectomy.

Histopathological confirmation of invisible tumor deposits in the retro-gastric cavity and on the peritoneum of the lesser sac can be good supporting evidence for prophylactic bursectomy. To study this, we sent bursectomy specimens (the anterior layer of the mesocolon and the pancreas) from 40 gastric cancer patients separately from the main gastrectomy specimens for pathological examination[14]. We also examined the cytology of bursa omentalis wash-out of these patients. Only four bursectomy specimens (10%) demonstrated positive cancer cells, and all of these patients already had macroscopic tumors on the peritoneal surfaces of the transverse mesocolon or pancreas. The cytology of bursa omentalis wash-out results was parallel to these pathological reports. Therefore, we failed to demonstrate invisible tumor cells in or on the lesser sac by conventional histopathology.

Anatomically, the cavity of the bursa omentalis is not a closed space and it is connected with the greater sac *via* the foramen of Winslow. Demonstration of the migration of tumor cells from the lesser sac to the greater sac or the contrary demonstration of the restriction of tumor cells to the lesser sac are important issues for the justification of bursectomy.

Yamamura *et al*[15] in 2007 examined the cytology of the peritoneal washes obtained from the Douglas pouch, left subphrenic cavity, and the inside of the omental bursa in 136 patients by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. Cancer-related cells were detected in one or more samples from the three different sites of peritoneal washes in 43 (31.6%) patients. In 14 patients, these tumor cells were detected in the samples obtained from the bursa omentalis and in 12 (85.7%) of these 14 patients, cancer-related cells were also detected in the samples taken from the Douglas pouch or subpherenic cavity. This study demostrated that viable cancer cells disseminated into the bursa omentalis and did not remain restricted to this cavity. The authors suggested that these cells are unlikely to be optimal targets for surgical removal, and the emergence of more effective locoregional therapy is urgently needed to improve the survival of serosa-positive patients.

Lastly, quality control of the complete *en-bloc* bursectomy is not easy. It depends on both the experience of the surgeon and the patient's mesenteric fat content. While bursectomy is technically more comfortable in slim patients, finding the right plane over the transverse mesocolon in fatty patients can be troublesome. In some fatty patients, we tried to inject normal saline between the peritoneum and the mesenteric fat of the transverse colon to provide an easier bursectomy technique; however, this hydrodissection method failed.

TECHNIQUE OF BURSECTOMY

We usually prefer to begin bursectomy with the entrance to the avascular plane between the greater omentum and the transverse mesocolon in the midline. To facilitate finding the correct plane, the first assistant should hang the greater omentum up for retraction and the transverse colon should be retracted to the opposite site by the surgeon (Figure 2). Diathermy can be used for entering the embryonic avascular plane just over the colon and can improve these dissections. Care must be taken not to damage the appendicular arteries of the colon and dissections should be skipped over these arteries. Once entered into the avascular plane, it is easier to extend the dissections to the hepatic and splenic flexure of the mesocolon. During this peritoneal peeling, continuous counter-traction to both sides of the mesocolon and to the omentum is mandatory. We usually prefer sharp dissections but sometimes gentle blunt dissection can provide an easy and fast peritonectomy. *En-bloc* resection without any window on the peritoneum is desired, but it is not always possible. If there is a tear in the peritoneum over the mesocolon, patiently going back a few steps to work on removal from the free edge of the torn peritoneum should be the preferred approach. Care should also be taken to not damage the mesocolic vessels at the bottom. When the procedure reaches

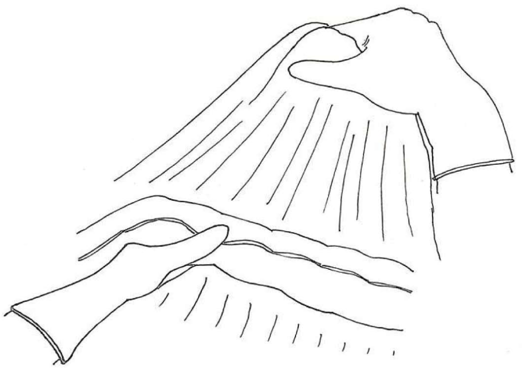

Figure 2 Traction and counter-traction of the omentum, stomach and colon.

the lower border of the pancreas, the dissection should be extended over it lengthwise. The entire posterior leaf of the peritoneum covering the lesser sac over the transverse mesocolon and the pancreas should be excised *en-bloc*.

CLINICAL RESULTS OF BURSECTOMY

There are only a limited number of studies that analyzed the influence of bursectomy on the survival of patients with gastric cancers[5,13,16-20]. Three studies are from Japan, one from South Korea, and one from the Ukraine. One of the early studies by Yoshikawa *et al*[13] compared the outcomes of bursectomy and non-bursectomy groups in a total of 134 serosa-positive gastric cancers. They suggested that there was no survival benefit of bursectomy in patients with gastric cancer[13]. In 2012, Fujita *et al*[5] reported the first results of their randomized study including 210 patients with T2-T3 gastric cancers. They found that bursectomy could improve survival and should not be abandoned as a futile procedure until more definitive data can be obtained[5].

Recently, the same group reported their updated results with the same conclusions[17]. However, their study included only 48 serosa-positive gastric cancers and there were no data about the comparability of the serosa-positive patients between groups. Cox multivariate analysis of the overall survival in that study pointed out that the most important independent factor for survival was the stage of the tumor (T stage, P < 0.001). Although nonbursectomy was found to be an independent risk factor (P = 0.034), male sex was also determined to be an independent risk factor in the same multivariated analysis (P = 0.032). These findings indicate that there were too few patients in that study to allow for clear conclusions.

The third study from Japan by Kochi *et al*[18] had a similar deficit in that only 41 of 254 patients had serosa-positive gastric cancers, and these authors found no survival benefit of bursectomy. In 2013, a congress abstract reported from the Ukraine that included 108 patients (T1-4) with gastric cancers concluded that the bursectomy group had a better 5-year survival, but the details of this study have not yet been published[19]. Eom *et al*[20] from South Korea compared bursectomy and nonbursectomy patients in a total of 381 serosa positive gastric cancers (nonbursectomy = 284 *vs* bursectomy = 97) and found in multivariate analyses that bursectomy was not a significant independent factor for survival.

CONCLUSION

Recently a meta-analysis that included all published studies on prophylactic bursectomy at radical gastrectomy was published[21]. According to the available data, the bursectomy did not show superiority to non-bursectomy in terms of survival in gastric cancer patients. Although the subgroup analyses suggested that bursectomy may improve survival in serosa-positive patients, this was not statistically significant and a definitive conclusion could not be made[21]. Because of the risk of potential morbidities[22], unless the exact benefits are demonstrated by forthcoming studies, its routine application cannot be justified. A large-scale multicentric Phase Ⅲ trial is currently underway for macroscopically subserosa or serosa-positive gastric cancer in Japan (JCOG 1001)[23]. This study included only patients from Japan, and it has already closed patient enrollment[23]. The long-term outcomes of this study will provide important information about the role of bursectomy at radical gastrectomy.

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ORIGINAL ARTICLE

Retrospective Study

Iatrogenic bile duct injury with loss of confluence

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Abstract

AIM: To describe our experience concerning the surgical treatment of Strasberg E-4 (Bismuth Ⅳ) bile duct injuries.

METHODS: In an 18-year period, among 603 patients referred to our hospital for surgical treatment of complex bile duct injuries, 53 presented involvement of the hilar confluence classified as Strasberg E4 injuries. Imagenological studies, mainly magnetic resonance imaging showed a loss of confluence. The files of these patients were analyzed and general data were recorded, including type of operation and postoperative outcome with emphasis on postoperative cholangitis, liver function test and quality of life. The mean time of follow-up was of 55.9 ± 52.9 mo (median = 38.5, minimum = 2, maximum = 181.2). All other patients with Strasberg A, B, C, D, E1, E2, E3, or E5 biliary injuries were excluded from this study.

RESULTS: Patients were divided in three groups: G1 (n = 21): Construction of neoconfluence + Roux-en-Y hepatojejunostomy. G2 (n = 26): Roux-en-Y porto-enterostomy. G3 (n = 6): Double (right and left) Roux-en-Y hepatojejunostomy. Cholangitis was recorded in two patients in group 1, in 14 patients in group 2, and in one patient in group 3. All of them required transhepatic instrumentation of the anastomosis and six patients needed live transplantation.

CONCLUSION: Loss of confluence represents a surgical challenge. There are several treatment options at different stages. Roux-en-Y bilioenteric anastomosis (neoconfluence, double-barrel anastomosis, portoenterostomy) is the treatment of choice, and when it is technically possible, building of a neoconfluence has better outcomes. When liver cirrhosis is shown, liver transplantation is the best choice.

Key words: Bile duct injury; Hepatojejunostomy; Biliary repair; Portoenterostomy; Neoconfluence; Double-barrel anastomosis

Core tip: Strasberg E-4 (Bismuth Ⅳ) bile duct injuries represent a surgical challenge. These injuries which involve two separated right and left ducts are of multifactorial etiology, and may be the result of ischemic or thermal damage, an inflammatory reaction, or anatomical variants that predispose the patient to injury. The treatment options are many, mainly surgical. Best results are obtained with Roux-en-Y hepatojejunostomies, as we describe in this article.

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INTRODUCTION

Bile duct injuries following laparoscopic approach have been extensively studied. Several classifications have been developed to describe both the mechanism by which the injury occurs and the anatomic result. Classification of these injuries is challenging, although possible, since each lesion is not only anatomically unique, but also the final result of several factors, such as duct ischemia, thermal injury and ablation, and transection of the duct. These injuries have been found to have a constant rate, regardless of the surgeon's experience or the hospital (0.3%-0.6%).

One of the most feared types of injury is that which involves the confluence. They are classified as Bismuth IV and Strasberg E4 injuries, and represent a surgical and multidisciplinary challenge (Figure 1). Loss of the confluence, in which one or two right ducts are separated from the left duct, represent a technical challenge with several therapeutic options. These include various types of bilioenteric anastomosis as well as major hepatectomy. Here we describe our experience with this type of injury and the results of our surgical treatment, which in most instances, is the only option available to treat this type of injuries.

MATERIALS AND METHODS

During an 18-year period we studied 603 patient candidates for surgical treatment of iatrogenic bile duct injury. The conditions in which these patients arrived at our center are highly variable; each patient has an individual history and timeline. Several have received previous endoscopical, radiological, or surgical therapy.

Patients were evaluated by a multidisciplinary group that selects patients with ductal continuity for endoscopical and/or radiological treatment. Those with loss of continuity are selected for surgical management. Patient selection and injury classification are carried out based on results of several imaging studies, including magnetic resonance cholangiography, computerized tomography, and ultrasound. Endoscopic retrograde cholangiography is selectively performed on patients in whom there is a suspicion of a lateral injury that can be resolved with a stent. Patients who arrive with acute cholangitis, or in whom injury classification cannot be determined, are studied by percutaneous cholangiography. Surgery is programmed according to the general condition of the patient. When patients present multiple organ failure and/or evident sepsis, the procedure is delayed as long as needed. Until the general condition of the patient improves, percutaneous or surgical placement of a drain is the treatment of choice. Injuries are classified according to the Strasberg and Bismuth classifications.

All cases in which there is loss of duct continuity and thickness, duct transection is treated surgically by means of a Roux-en-Y hepatojejunostomy. The type and characteristics of the anastomosis have been described previously[1,2].

Medical records of all patients in whom loss of confluence was found (injuries classified as Bismuth IV, Strasberg E4) were analyzed and their general data were recorded. Type of surgical procedure, postoperative outcome with emphasis on postoperative cholangitis, liver function tests, and quality of life were also recorded. The mean time of follow-up of these patients was of 55.9 ± 52.9 mo (median = 38.5, minimum = 2, maximum = 181.2). For analysis purposes, patients were divided into three groups according to type of surgical repair. These groups and their characteristics are described on Table 1.

RESULTS

Among the 603 cases of biliary duct injuries, 53 cases with loss of confluence were identified. Most of the cases had a preoperative external biliary fistula (n = 27) with different types of abdominal or percutaneous drains. There was a wide range of time between the index surgery (where the injury was produced) and the attempts to repair in our institution (mean 14 d). In 28 cases the diagnosis of loss of confluence was

Table 1 Patient groups according to surgical procedure followed

Group	Surgical procedure to repair loss of confluence	*n* (%)
G1	Construction of neo-confluence + Roux-en-Y hepatojejunostomy	21 (40%)
G2	Roux-en-Y Portoenterostomy	26 (49%)
G3	Separated (right and left) Roux-en-Y hepatojejunostomy	6 (11%)

Figure 1 Strasberg E-4 injury.

established preoperatively through the imaging methods mentioned, with magnetic resonance cholangiography being the method of choice for injury classification, as it has been for the last 10 years. If bilomas, abscesses, and/or fluid collection were identified, drainage (usually percutaneously) was carried out.

During the surgical procedure, loss of confluence was confirmed after completely dissecting the porta hepatis and lowering the hilar plate to expose the right and left ducts. In all cases, a 40 cm long Roux-en-Y hepatojejunostomy was performed.

Group 1: Loss of confluence, neoconfluence, Roux-en-Y hepatojejunostomy

In 21 cases, after a wedged resection of segments Ⅳ and Ⅴ over the hilar plate, and after identification of the right and left ducts, a neo-confluence was constructed with fine everted stiches with a 6-0 hydrolysable monofilament. Also, the anterior aspect of the left duct (if necessary the right duct as well) was opened in order to obtain a wide, tension-free bilio-intestinal anastomosis that included the neo-confluence (Figure 2A).

Group 2: Loss of confluence, portoenterostomy

Twenty-six patients were treated by means of a Roux-en-Y portoenterostomy: after partial resection of segments Ⅳ and Ⅴ the two ducts were found separated and partially scarred and/or ischemic. In 9 of these cases a transhepatic transanastomotic stent was placed; in the remaining 17 no stent was placed. These were considered as portoenterostomies since in more than 50% of the circumference of the anastomosis a high quality bilioenteric anastomosis was not achieved due that the biliaryepithelium could not be joined with

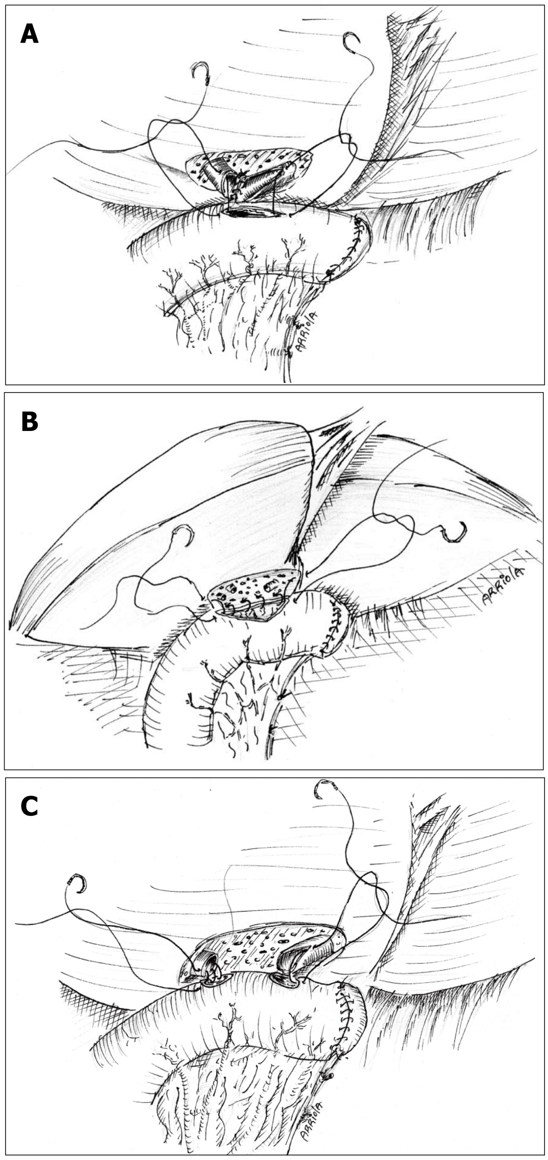

Figure 2 Hepatojejunostomy. A: Neoconfluence; B: Portoenterostomy; C: Double-barrel.

the intestinal mucosa (Figure 2B).

The 9 cases in which stents were placed have had an adequate postoperative evolution without symptoms and cholangitis. Stents were removed between the 6th and the 9th postoperative months. In two cases they were left in place longer, one for 12 mo due to patient non-compliance, and one for 84 mo due to patient's request. After this, the patients were left without a stent. In the other 7 patients whose stent was removed, 4 remained asymptomatic, 1 patient died in the fourth postoperative year because of secondary biliary cirrhosis, 1 patient in whom cirrhosis and liver failure were recorded was lost to follow-up, and 1 has developed cirrhosis and jaundice.

Group 3: Loss of confluence and double-barrel anastomosis

In 6 cases, both ducts were identified, but construction of a neo-confluence was not possible. Therefore, a

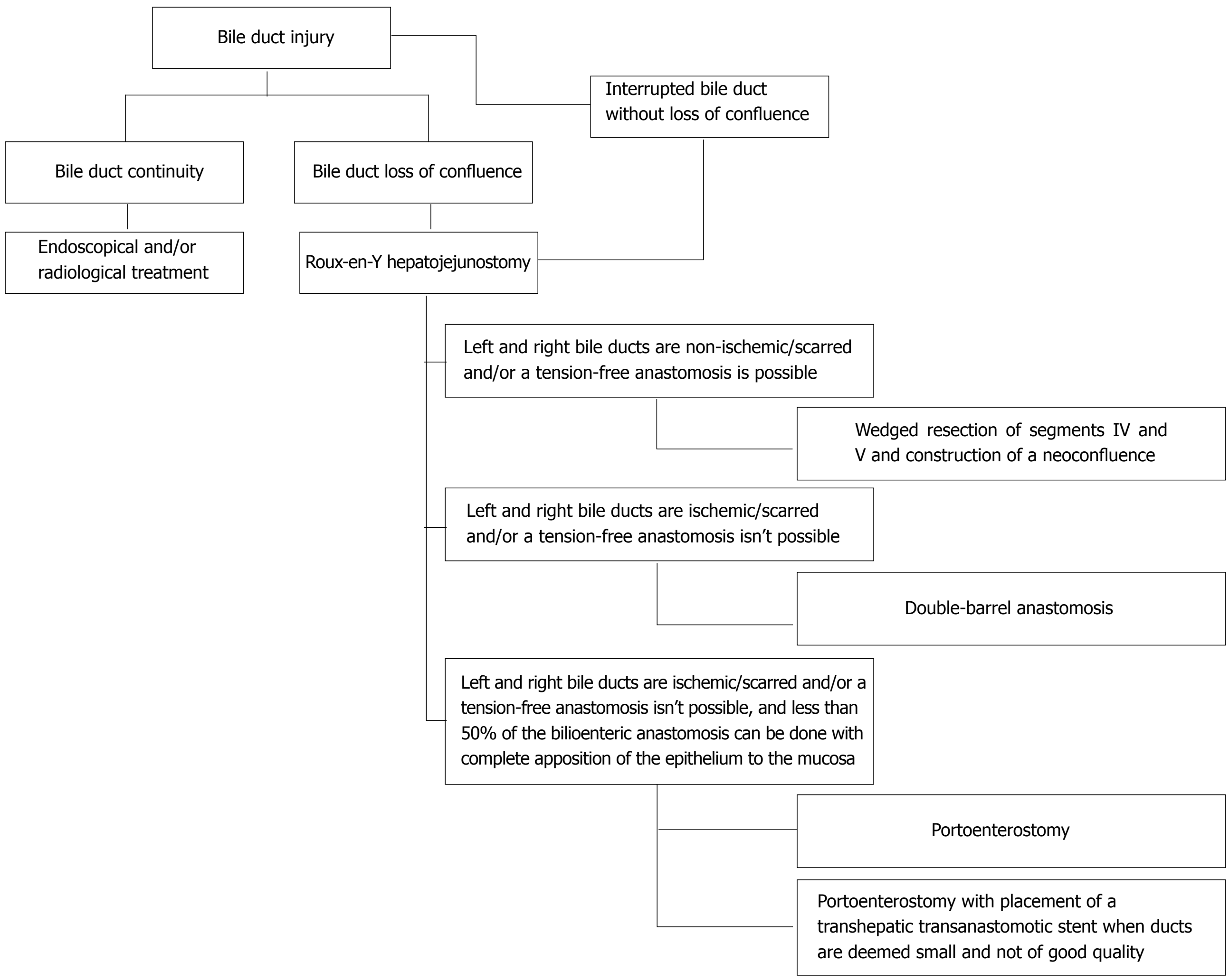

Figure 3 Surgical treatment strategy followed in patients with bile duct injury.

double-barrel anastomosis was performed. Three of these patients remained asymptomatic in the postoperative period (mean 6 years, range 3-12). Two cases required a right hepatectomy several months after the reconstruction because of persistent sectionary (unilobar) cholangitis. They are currently doing well, with patent bilioenteric anastomosis. One patient had persistent cholangitis and developed cirrhosis in the 4th postoperative year after one reoperation and attempts to perform radiological percutaneous dilation and surgical and radiological placement of stents (Figure 2C).

Figure 3 shows a summary of the surgical treatment strategy followed for bile duct injuries with loss of confluence.

Results after first reconstruction

The frequency of perioperative complications in patients treated by means of a Roux-en-Y portoenterostomy (group 2) was of 57.6%. The postoperative complications of these patients according to the Clavien-Dindo grading system are shown in Table 2.

Sixteen (61.5%) group 2 patients presented cirrhosis during follow-up, while 10 (38.4%) haven't developed cirrhosis to the last moment of follow-up. Thirteen patients (50%) have been referred for hepatic transplant evaluation, and 3 (11.5%) haven't been sent because of compensated cirrhosis.

On the other hand, 14 (53.8%) group 2 patients developed cholangitis. The cholangitis free survival rate was of 45 ± 9.17 mo (95%CI: 27.1-63) as shown in Figure 4.

Of these patients, 4 out of 9 patients in which a T-tube was placed (44.5%) required percutaneous interventions after their removal. Two patients (22.2%) needed the placement of an internal-external biliary drainage catheter after removal of the T-tube, while in the other 2 patients (22.2%) the T-tube was replaced with a percutaneous biliary catheter which wasn't removed until 11.1 mo after.

Four patients out of the 17 in which a T-tube wasn't placed (65.3%) required the placement of an internal-external biliary drainage. Only one of them (25%) is free of drainages at 63.7 mo.

Seven (77.8%) group 2 patients in which a T-tube was placed developed cholangitis during follow-up.

Table 2 Group 2 postoperative complications according to the Clavien-Dindo grading system

Classification	Frequency (%)	Description (frequency)
I	1 (3.8%)	Superficial surgical site infection (1)
II	7 (26.9%)	Intra-abdominal collection not requiring surgical intervention (5) Superficial surgical site infection not requiring surgical intervention (1) Cholangitis (1)
IIIa	0 (0%)	-
IIIb	3 (11.5%)	Intra-abdominal collection requiring surgical intervention (1) Biliary anastomosis remodeling (1) Intra-abdominal collection requiring transendoscopic ultrasound drainage (1)
IVa	3 (11.5%)	Septic shock (3)
IVb	0 (0%)	-
V	1 (3.8%)	Atrioventricular block (1)

Those in which a T-tube wasn't placed, 7 (41.2%) presented this complication. Nonetheless, there was no significant difference between these two subgroups (P = 0.075). Cholangitis free survival rate tended to be greater in those patients without placement of a T-tube (60.1 ± 11.6 mo, 95%CI: 37.4-82.9; *vs* 23.1 ± 8.6, 95%CI: 6.2-40; log-rank P = 0.056) (Figure 5).

DISCUSSION

Surgical treatment of bile duct injury is indicated when loss of duct continuity is found and endoscopic and/or radiological approach is ruled out[2]. Roux-en-Y hepatojejunostomy has been proven to be the best treatment option by several groups[3]. A high quality bilioenteric anastomosis, which is defined as tension-free, wide, with adequate suture material, done in healthy, non-scarred non-ischemic ducts that are anastomosized to an afferent Roux-en-Y jejunal limb, offers the best results[4]. There are several technical maneuvers that can be done in order to reach this goal, including the anterior opening of the confluence and the left duct, as well as partial removal of segments IV and V[5,6].

Our group has shown that an anastomosis done in a patient with preserved confluence offers the best results[7]. These results can be also optimized if the patient has no stones or sludge, usually the result of secondary colonization of bile.

Loss of confluence, depicted in Bismuth classification as IV and in Strasberg classification as E-4, is one of the most feared scenarios for surgeons, because of the technical challenge that it represents.

Loss of confluence can be the result of several issues. In some instances, it is the result of an anatomical variation in which the given patient has a low extrahepatic confluence that is injured during dissection, and also in subsequent section, transection or occlusion of the duct can be performed at this level. There is no available data on how many individuals have a low extrahepatic confluence. In the majority of people the confluence, although extrahepatic, is not low. In these cases, loss of confluence is the result of ischemic damage, thermal damage or both.

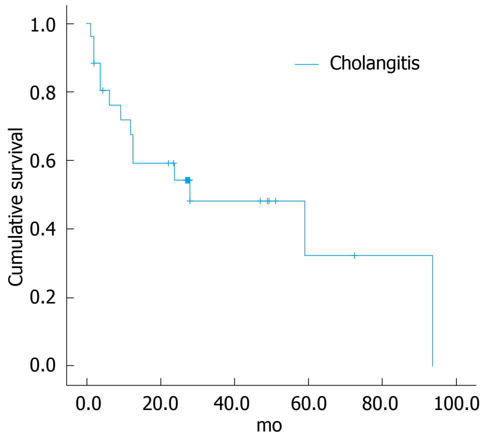

Figure 4 Group 2 cholangitis free survival rate.

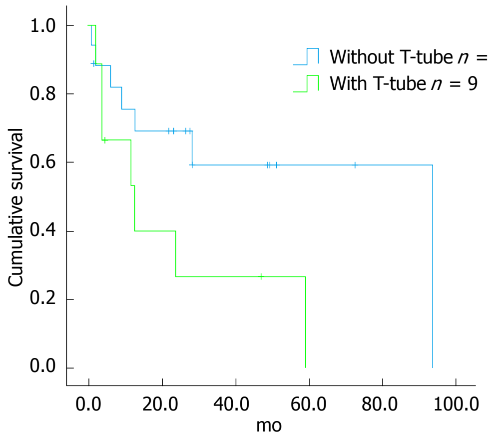

Figure 5 Group 2 cholangitis free survival rate in patients with and without T-tube placement. Log-rank P = 0.056.

After section of the common duct, the proximal stump (near to the plane of section) becomes ischemic. It has been stated by Strasberg *et al*[5] that one of the key features for successful repair and successful bilio-enteric anastomosis is to wait enough time, so that the injury stabilizes and the exact level of duct ischemia is reached[8]. So, in some cases the ischemia level reaches the confluence. Bismuth has also stated that the level of the injury is always higher than it is appreciated in the initial stump[9].

In other cases, loss of confluence is the consequence of the local inflammatory reaction produced by either bile leakage or drains placed for a long time in the common duct, which lead to consequent destruction. This is especially true when patients in whom a non-silastic drain is placed subhepatically and fixed to the bile duct, establishing an external fistula, are referred late. Right hepatic arterial injuries are usually seen in this type of injury. Stewart *et al*[10] have shown that the higher the injury the higher the probability of arterial damage. They have also shown that this has no impact in the final results of reconstruction, with the condition that the procedure is done by an interested and experienced hepatobiliary surgeon. In some cases, the artery can be reconstructed[11] by carrying out a primary anastomosis or planning an interposition graft. In our experience these arteries are not suitable for repair. The circulatory status of the ducts at the confluence level has a vascular net that allows a compensatory supply from the left to the right. This is why an anastomosis done at the confluence level warrants a good result, regardless of the patency of the right artery.

Ischemia of the duct is usually secondary to the type of the dissection inherent to the laparoscopic procedure. The common duct is easily confused with the cystic duct, and lateral traction of it causes damage to the small duct lateral vessels. Also, thermal injury is more likely because the higher the dissection goes, small bleedings can be found that are cauterized *via* thermal energy. In every repair, we do everything possible in order to cannulate the right and left hepatic ducts for identification purposes. In some of these cases we have found isolated right posterior injuries, with the right anterior duct reaching the left duct.

In some cases the separated duct can be reunited by removing the adjacent parenchyma and placing everted stitches that allow the construction of a neoconfluence. This could be done in 6 of the 37 cases (17%). There are other cases in which this maneuver could not be done and a portoenterostomy was constructed. Pickleman *et al*[12] published their experience obtaining good results with this type of approach. Some of our cases required placement of a transhepatic transanastomotic stent. The decision to place them was made according to the characteristics of the duct found at the time of operation. In our first three cases treated by means of portoenterostomy, we observed a difficult postoperative evolution. In other cases, it was deemed that a hepatectomy was necessary because of the characteristics of the duct and the lobe. In these two cases, a right hepatic injury was shown so that the lobectomy was done with a left duct jejunostomy. Laurent *et al*[13] have shown that in 15% of their cases with a complete injury a major hepatectomy was required, and resulted in excellent postoperative results. For cases with major vascular injury and bad quality major ducts, hepatectomy must be considered.

In other cases, the construction of two separated anastomosis could be done. This approach was selected when adequate separated ducts were found.

Rebuilding the confluence is not always possible. After removal of the liver parenchyma at the hilar level, both ducts are identified at the hilar plate. It is very important not to manipulate the ducts excessively because of the danger of devascularization. When both ducts are deemed "healthy", a tension free approximation of the posterior lateral edge of the left duct is done to the medial aspects of the right duct. Usually with three to four everted stitches the approximation is obtained. The anterior aspect of the left duct is opened and then an anastomosis to the jejunal limb (almost in a side to side fashion) is done. If the ducts are ischemic and/or the approximation of both foramens is not tension free, the surgeon must decide to do separate anastomosis of the ducts to the jejunum.

When a two anastomoses approach is decided, our preference is to open the anterior aspect of the left duct as well as right one in the same fashion, as described by Strasberg *et al*[5].

Portoenterostomy is decided when it is deemed that less than 50% of the anastomosis is done with complete apposition of the epithelium to the mucosa. Everted stitches are placed between the jejunal mucosa and the bile duct where it is possible and the remaining part of the anastomosis is done to the liver capsule and/or parenchyma.

The decision to place a transanastomotic stent is always difficult. When our group first started, we decided to place stents in all cases, but we evolved to selective placing when needed[14], specifically when ducts were deemed small and not of good quality. As we have stated, each patient has an individual type of injury and resulting anatomy.

Overall, considering all the treatments modalities, the procedure was successful in 88% of the cases, obtaining good postoperative results without cholangitis, good quality of life and without requiring reintervention.

In conclusion, an injury that includes the loss of confluence of the duct represents a surgical challenge. There are several options to be considered (neoconfluence, double-barrel anastomosis and portoenterostomy) that must be shaped and selected according to the individual characteristics of a given patient.

COMMENTS

Background

One of the most complex bile duct injuries is that which involves the loss of confluence of the right and left bile ducts, namely a Strasberg E-4 injury. Initially, the authors' team's surgical approach to this problem was the forming of a double-barrel anastomosis; however, it resulted in long term dysfunction. By descending the hilar plate, performing a partial resection of segment IV, and liberating both bile ducts so as to approximate them and include them in a single anastomosis, the outcomes seen in these patients became comparable to those in patients in which the confluence was preserved.

Research frontiers

Many surgical treatments for loss of confluence bile duct injuries have been proposed, including the creation of a two-barrel anastomosis, a portoenterostomy, or a neoconfluence. Few have described results regarding any of these reconstructions.

Innovations and breakthroughs

To our knowledge, this is the first retrospective study that analyzes long term outcomes of neoconfluences in iatrogenic bile duct injuries. They have only been described in Blumgart's textbook of hepatic and biliary surgery, although without mentioning the removal of segment IV, which the authors consider necessary to facilitate the construction of an anastomosis.

Applications

Roux-en-Y hepatojejunostomies offer the best outcomes in patients with bile duct injuries with loss of confluence, as reported in the authors' observations. Individual characteristics of the patient must be taken into account in order to decide the most suitable surgical approach, although creating a neoconfluence should be of top priority.

Terminology

Bile duct injuries represent all deleterious consequences on the intra- or extrahepatic bile ducts, as a result of the removal of the gallbladder or of any endoscopic and surgical instrumentation of the ducts. Cholangitis is one of the most important complications that arise from these injuries, usually due to inflammation and fibrosis caused by biliary leaks.

Peer-review

The manuscript is interesting and well written.

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ORIGINAL ARTICLE

Prospective Study

Obese patients have similar short-term outcomes to non-obese in laparoscopic colorectal surgery

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Abstract

AIM: To determine whether obese patients undergoing laparoscopic surgery within an enhanced recovery program had worse short-term outcomes.

METHODS: A prospective study of consecutive patients undergoing laparoscopic colorectal resection was carried out between 2008 and 2011 in a single institution. Patients were divided in groups based on body mass index (BMI). Short-term outcomes including operative data, length of stay, complications and readmission rates were recorded and compared between the groups. Continuous data were analysed using *t*-test or one-way Analysis of Variance. χ^2 test was used to compare categorical data.

RESULTS: Two hundred and fifty four patients were included over the study period. The majority of individuals (41.7%) recruited were of a healthy weight (BMI < 25), whilst 50 patients were classified as obese (19.6%). Patients were matched in terms of the presence of co-morbidities and previous abdominal surgery. Obese patients were found to have a statistically significant difference in The American Society of Anesthesiologists grade. Length of surgery and intra-operative blood loss were no different according to BMI.

CONCLUSION: Obesity (BMI > 25) does not lead to worse short-term outcomes in laparoscopic colorectal surgery and therefore such patients should not be precluded from laparoscopic surgery.

Key words: Laparoscopic surgery; Colorectal cancer; Obese: body mass index; Outcomes

Core tip: Laparoscopic colorectal surgery for cancer can be safely performed in obese patients without an increase in adverse events or outcomes. Patients should not be precluded from laparoscopy in such cases based on their body mass index. However it is important for the team to assess patients pre-operatively to decide on whether additional or more intensive peri-operative care is needed to ensure optimal outcomes.

Chand M, De'Ath HD, Siddiqui M, Mehta C, Rasheed S, Bromilow J, Qureshi T. Obese patients have similar short-term outcomes to non-obese in laparoscopic colorectal surgery. *World J Gastrointest Surg* 2015; 7(10): 261-266 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i10/261.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i10.261

INTRODUCTION

Obesity is a considerable and growing healthcare concern, and more patients treated for colorectal cancer are obese with a body mass index (BMI) of greater than 30. Historically, individuals with an increased BMI have been thought of as having a higher risk of poorer outcomes following surgery with an increased rate of peri-operative complications and longer hospital stays, however more recent studies have challenged this view[1-3].

The surgical management of colorectal cancer has shifted towards a minimally-invasive approach and the current expectation is that the majority of patients should undergo laparoscopic surgery. It is now recognised as a safe and more advantageous alternative to laparotomy for most patients as benefits include reduced morbidity and shorter hospital stays with comparable oncological outcomes to open surgery[4-7].

However, obesity has long been considered a relative contraindication to laparoscopic surgery due to the perceived associated technical difficulty and increased morbidity[8-10]. Despite more recent reports of good short-term outcomes in colorectal cancer resections[11-13], there remains a reluctance to offer laparoscopic surgery to obese patients. Consequently, an increasing number of patients with a high BMI are being denied the benefits of laparoscopic surgery.

The aim of this study was to determine whether obesity was an acceptable contraindication to laparoscopic colorectal surgery by comparing the short-term outcomes of patients with an increased BMI to those of a healthy weight-to-height ratio.

MATERIALS AND METHODS

Study design and setting

A prospective cohort study conducted between 2008 and 2011 at a single colorectal surgery institution in the United Kingdom.

Study population

All consecutive patients undergoing laparoscopic colorectal surgery were included. There were no exclusion criteria. Consistent with the surgical protocol of the unit, all individuals were enrolled into its enhanced recovery after surgery (ERAS) program. A standardised approach to both the anaesthetic and the surgery was performed in all patients.

Data collection

Data were collected prospectively on each individual patient and recorded anonymously on a database. These included patient demographics and BMI, The American Society of Anesthesiologists (ASA) grade, nature of surgery, operative and anaesthetic time, stoma formation, intra-operative blood loss, complications including anastomotic leak, unplanned high dependency unit (HDU) admission, length of hospital stay and readmission rates. Complications were recorded according to the Clavien-Dindo classification system.

The ERAS protocol

All patients were counselled by a nurse specialist prior to surgery and given a detailed explanation of what to expect throughout the course of their hospital stay. Each patient was given contact details for a member of the ERAS team.

Patients were admitted on the day of surgery. The evening before admission each patient received a 100 g of Pre-Load (96 g of carbohydrate; osmolarity of 285 mOsm) mixed in 400 mL of water. On the morning of admission, a further 50 g of Pre-Load in 400 mL of water was given 2 h before surgery. Following discharge, a dedicated nurse practitioner telephoned the patients at 48 h to enquire about any concerns. Patients were followed up in the out-patient department at 6 wk regardless of any concurrent oncological referral.

Peri-operative anaesthetic regime

A standardised anaesthetic protocol was used for all patients. This consisted of a spinal anaesthetic before induction using 2 mL 0.5% plain bupivacaine with 700 mcg of diamorphine. Routine doses of propofol and remifentanil were used for induction and atracurium for neuromuscular blockade. Intraoperative medication included 6.6 mg of dexamethasone, 4 mg of ondansetron, 1.5 g cefuroxime and 500 mg metronidazole. In addition to the intrathecal diamorphine, perioperative analegesia included 1 g Ⅳ paracetamol and 75 mg Ⅳ diclofenac. An orogastric tube and urinary catheter were sited with the former removed at the end of the procedure. Routine maintenance fluids during the procedure consisted of 1.5 L Hartmann's solution. Temperature was maintained using a Bair Hugger® blanket. Post-operative fluid regime included 1 L Hartmann's solution given over 10 h in addition to oral fluids and high calorie drinks. All patients were given oral paracetamol 1 g QD and Ibuprofen 400 mg TD.

Table 1 Patient characteristics *n* (%)

	All	BMI < 25	BMI 26-30	BMI > 30	*P* value
Number	254	106 (41.7)	98 (38.6)	50 (19.7)	< 0.001
Males	122 (48)	41 (38.7)	58 (59.2)	23 (46)	0.01
BMI	26 (23-30)	22.5 (2.1)	27.8 (1.5)	35.3 (5.9)	< 0.001
ASA grade	2 (0.6)	1.9 (0.6)	2.0 (0.6)	2.2 (0.6)	0.04
Previous abdominal surgery	80 (31.5)	34 (32)	30 (30.6)	16 (32)	0.972
Co-morbidities	187 (73.6)	76 (71.7)	75 (76.5)	36 (72)	0.789

Data presented as mean (standard deviation) unless otherwise indicated. Comparisons are between the three BMI groups. BMI: Body mass index; ASA: American Society of Anesthesiologists.

Patients were managed on an elective surgical ward and allowed oral fluids on the night of surgery. The urinary catheter was removed on the first operative day and patients were encouraged to take a solid oral diet and to mobilise.

Surgical technique

All surgical procedures were carried out using a standardised modular technique. Patients were placed in the modified Lloyd-Davies position for all resections with the legs in stirrups but with the femurs horizontal to the floor, the arms positioned by the sides and high-friction gel pads were used. Arm boards and shoulder supports were avoided. Routine port positions were used for left and right-sided procedures with the use of a 10 mm 30 degree camera. Dissection was predominantly performed using the "hook" with diathermy attached and occasional use of an energy device. Specimens were extracted through a wound protector device using either lower right- or left-sided transverse muscle splitting incisions for right and left-sided resections, respectively. Extraction sites were closed in layers making sure to avoid muscle in the suture line and infiltrated with maximal safe dosage of bupivacaine 0.375%. For left-sided resections a leak test was performed with a flexible sigmoidoscope which was also used to inspect the anastomosis, but was not passed through it.

Statistical analysis

Individuals were classified according to their BMI as healthy weight (< 25), overweight (26-30) and obese (> 30). Outcomes were compared between the three groups.

Continuous data are expressed as mean with standard deviation and categorical data as an absolute number and percentage. Continuous data were analysed using Analysis of Variance (ANOVA). Fisher's exact test or χ^2 test was used to compare categorical data. A two-sided *P* value of less than 0.05 was considered significant. All data analyses were performed using SPSS version 21 (SPSS Inc., Chicago IL).

RESULTS

Two hundred and fifty four patients were included over the study period. The majority of individuals (41.7%) recruited were of a healthy weight (BMI < 25), whilst 50 patients were classified as obese (19.6%). In all groups, there were more female patients than males. Overall, patients were well matched in terms of the presence of co-morbidities and previous abdominal surgery. Obese patients were found to have a statistically significant difference in ASA grade. Patient characteristics are shown in Table 1.

Anterior resection and right hemicolectomy were the two most frequently performed operations, accounting together for three quarters of the procedures undertaken (Table 2). There were no significant differences in the incidence and nature of operations across the BMI cohorts.

There were few significant differences in outcomes between obese patients and healthier weight individuals (Table 3). Only readmission rates with rectal bleeding were higher in the obese (2 patients in the obese group compared with none in the other groups), whilst there was a non-significant trend towards increasing anaesthetic time and length of stay associated with higher BMI. Unplanned HDU admission rates favoured patients with a higher BMI, whilst the rate of stoma formation was lower although not significant. Length of surgery and intra-operative blood loss were no different according to BMI.

DISCUSSION

This study revealed that obese patients with an increased BMI have comparable short-term outcomes to healthy weight individuals. Furthermore, outcomes of overweight patients with a BMI of between 26 and 30 were also similar. In particular, there was no significant increase in post-operative complications or length of stay, both of which are historically associated with obese patients. Additionally, the length of operating time and intra-operative blood loss were similar in all groups, suggesting a comparable degree of operative difficulty. Finally of note, all patients in the study underwent an ERAS protocol with no adverse outcomes as a result of this approach, in spite of the traditional caution in patients with an increased BMI.

The relationship between obesity and various conditions has been clearly established including with type

Table 2 Nature and number of operations

Operation	Total	BMI < 25	BMI 26-30	BMI > 30	*P* value
Anterior resection	107 (42.1)	46 (43.4)	37 (37.8)	24 (48)	0.462
Right hemicolectomy	82 (32.3)	32 (30.2)	34 (34.7)	16 (32)	0.789
Left hemicolectomy	7 (2.8)	3 (2.8)	2 (2.1)	2 (2)	0.787
Ileocaecal resection	10 (3.9)	5 (4.7)	5 (5.1)	0 (0)	0.277
Panproctocolectomy	7 (2.8)	5 (4.7)	2 (2.1)	0 (0)	0.209
Abdominoperineal resection	2 (0.8)	0 (0)	2 (2.1)	0 (0)	0.201
Sigmoid colectomy	5 (2)	1 (0.9)	3 (3.1)	1 (2)	0.553
Subtotal/total colectomy	11 (4.4)	6 (5.7)	3 (3.1)	2 (4)	0.426
Hartmann's	3 (1.2)	1 (0.9)	2 (2.1)	0 (0)	0.530
Miscellaneous	20 (7.9)	7 (6.6)	8 (8.2)	5 (10)	0.756

Data presented as absolute number (percentage). Comparisons are between the three BMI groups. BMI: Body mass index.

Table 3 Outcomes split by body mass index

	BMI < 25	BMI 26-30	BMI > 30	*P* value
Anaesthetic time, min mean (SD)	41.10 (50.9)	52.62 (62.6)	67.55 (70.9)	0.080
Length of surgery, min mean (SD)	181.1 (65.4)	177.8 (56.6)	192.63 (61.5)	0.421
Intra-op blood loss, mL mean (SD)	33.18 (31.9)	44.00 (67.1)	38.33 (33.6)	0.309
Stoma	22 (20.8)	22 (22.5)	8 (16)	0.600
LOS, d, mean (SD)	4.1 (4.1)	3.9 (3.9)	5.8 (7.7)	0.076
All complications	23 (21.7)	15 (15.3)	14 (28)	0.686
Anastomotic leak	2 (1.9)	0 (0)	1 (2)	0.771
Re-admission	8 (7.5)	12 (12.2)	3 (6)	0.984
Wound infection	1 (0.9)	1 (1)	1 (2)	0.609
Abdominal collection	1 (0.9)	5 (5.1)	0 (0)	0.859
PR bleeding	0 (0)	0 (0)	2 (4)	0.021
DVT/PE	0 (0)	1 (1)	0 (0)	0.769
Obstruction/ileus	3 (2.8)	2 (2)	0 (0)	0.254
Vomiting/diarrhoea	3 (2.8)	1 (1)	0 (0)	0.156
Non-specfic abdo pain	0 (0)	2 (2)	0 (0)	0.677

Data are presented as absolute number (percentage) unless otherwise indicated. LOS: Length of stay; BMI: Body mass index.

2 diabetes, cardiovascular disease, cerebrovascular disease, pulmonary disease, and more recently, cancer[14-17]. Therefore, it would be expected that more perioperative complications would be likely in the obese population consistent with associated co-morbidities. It has been well documented that wound complications are significantly more common in obese patients following, in particular, those receiving long midline incisions[18-20]. Given that this may be the case, it is even more important in this group of patients to limit the surgical stress, so it is felt that they may actually be better off undergoing laparoscopic rather than open surgery. The relationship between obesity and laparoscopic colorectal surgery has evolved over the years. Initial reports investigating the feasibility of laparoscopy in patients with an increased BMI resulted in worse outcomes compared to the non-obese. This included more post-operative complications, conversions to open procedures and an increased length of stay. In cases of cancer resections, however, this was shown to be oncologically safe. Nonetheless, as techniques have improved and there is greater familiarity and capability with laparoscopic surgery, short-term outcomes have become more comparable to open surgery[21-23]. Yet there remains a reluctance to offer laparoscopy to obese patients. It is important to recognise that open surgery in obese patients also takes longer and is more difficult.

Technically, the surgery can be demanding and has been shown repeatedly to lead to a higher learning curve[9]. A thicker, heavier mesentery creates difficulty in recognising the planes of dissection and causes limited space to operate within the abdomen. In those series which show comparable operating times and peri-operative outcomes such as blood loss, improved technology in the form of instruments and high-definition laparoscopes have been cited as factors. Classically, the obese male patient with a narrow pelvis has been considered the most challenging of surgery for colorectal surgeons.

The present study has shown that despite increased BMI, the intra-operative outcomes of blood loss and operating time are no different to non-obese patients. Previous reports have shown an increased operating time in obese patients which is most likely a reflection of the difficulty in operating in these patients[10]. Interestingly, studies which showed an increase in the number of complications in obese patients also reported an increased length of stay. However, these two outcomes are intrinsically linked. For example, ileus is the most common cause of prolonged hospital admission after colorectal surgery[24]. This can be attributed to longer operating time and post-operative complications which need resolution prior to discharge. Therefore, it is not surprising that if the number of complications is reduced, so is the length of stay.

The rate of stoma formation was similar across groups. Stomas may often be formed to protect an anastomosis which is at risk of leaking, a concern associated with technically challenging surgery. It must be noted that stoma formation is also technically more challenging in obese patients due to the increased distance from the abdominal cavity to the skin.

The peri-operative approaches to laparoscopic cases in our institution are identical regardless of whether the resection is right or left-sided. This includes anaesthesia, patient preparation and positioning, and post-operative care. Clearly, there will be modifications in the port positioning although for the vast majority of cases no more than 4 ports and a transverse incision extraction site are used. Using a standardised approach allows clarity for all staff involved in the peri-operative care of the patient.

This study has shown that using a standardised peri-operative protocol including anaesthesia and surgical technique, obese patients can safely be offered laparoscopic surgery for colorectal cancer resections. The short-term outcomes including post-operative complications and length of stay are comparable to non-obese patients. Consequently, obesity should not preclude laparoscopic surgery being offered to patients for colorectal cancer.

COMMENTS

Background

An increased body mass index (BMI) has been traditionally associated with a higher rate of complications. Initial reports on laparoscopy stated the increased BMI should be a preclusion for laparoscopic approaches in colorectal cancer surgery. However as techniques have improved and become more standardised it is possible to safely operate on patients with a high BMI.

Research frontiers

There is still some contention as to whether laparoscopic surgery can be safely performed for colorectal cancer without compromising oncological outcomes.

Innovations and breakthroughs

This study demonstrates that patients can undertake laparoscopy without additional complications and similar short-term outcomes as non-obese patients.

Applications

This study should allow clinicians to assess patients with a high BMI confidently and not preclude them from laparoscopy based solely on BMI.

Peer-review

The study is clear, well-written and easy to read.

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ORIGINAL ARTICLE

Prospective Study

Laparoscopic *vs* mini-incision open appendectomy

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Author contributions: Çiftçi F designed research; performed research; contributed to new reagents or analytic tools; analyzed data; wrote the paper; performed surgical operations.

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Abstract

AIM: To compare laparoscopic *vs* mini-incision open appendectomy in light of recent data at our centre.

METHODS: The data of patients who underwent appendectomy between January 2011 and June 2013 were collected. The data included patients' demographic data, procedure time, length of hospital stay, the need for pain medicine, postoperative visual analog scale of pain, and morbidities. Pregnant women and patients with previous lower abdominal surgery were excluded. Patients with surgery converted from laparoscopic appendectomy (LA) to mini-incision open appendectomy (MOA) were excluded. Patients were divided into two groups: LA and MOA done by the same surgeon. The patients were randomized into MOA and LA groups a computer-generated number. The diagnosis of acute appendicitis was made by the surgeon with physical examination, laboratory values, and radiological tests (abdominal ultrasound or computed tomography). All operations were performed with general anaesthesia. The postoperative vision analog scale score was recorded at postoperative hours 1, 6, 12, and 24. Patients were discharged when they tolerated normal food and passed gas and were followed up every week for three weeks as outpatients.

RESULTS: Of the 243 patients, 121 (49.9%) underwent MOA, while 122 (50.1%) had laparoscopic appendectomy. There were no significant differences in operation time between the two groups (P = 0.844), whereas the visual analog scale of pain was significantly higher in the open appendectomy group at the 1st hour (P = 0.001), 6th hour (P = 0.001), and 12th hour (P = 0.027). The need for analgesic medication was significantly higher in the MOA group (P = 0.001). There were no differences between the two groups in terms of morbidity rate (P = 0.599). The rate of total complications was similar between the two groups (6.5% in LA *vs* 7.4% in OA, P = 0.599). All wound infections were treated non-surgically. Six out of seven patients with pelvic abscess were successfully treated with percutaneous drainage; one patient required surgical drainage after a failed percutaneous drainage. There were no differences in the period of hospital stay, operation time, and postoperative complication rate between the two groups. Laparoscopic appendectomy decreases the need for analgesic medications and the visual analog scale of pain.

CONCLUSION: The laparoscopic appendectomy should be considered as a standard treatment for acute appendicitis. Mini-incision appendectomy is an alternative for a select group of patients.

Key words: Appendicitis; Surgical wound infections; Laparoscopic surgical procedure; Abdominal abscess; Mini-incision open appendectomy

Core tip: Acute appendicitis is mostly encountered disease in a daily routine. Researchs regarding decreasing morbidity and mortality are still needed, although it is very well known. Hospital stay, operation time, postoperative complication rates are important for the management of acute appendicitis. Therefore, we suggest that laparoscopic appendectomy should be accepted as a standard treatment for acute appendicitis. Mini-incision appendectomy is an alternative for a select group of patients.

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INTRODUCTION

The most common reason for admission to the emergency room is acute appendicitis (AA), and appendectomy is a daily surgical procedure performed around the world[1,2]. Open appendectomy (OA) is accepted as a standard treatment for (AA); its morbidity and mortality are very low[1,2]. However, laparoscopic appendectomy (LA) has recently become more accepted[1,2]. Many advantages of LA have been shown such as lower hospital stay, shorter recovery period, shorter period for returning to daily activities, lower postoperative pain, and lower postoperative infections[1-6]. In spite of these advantages, there is controversy over the best model of appendectomy techniques in the literature. Any extra potential advantages resulting from the laparoscopic approach are hard to prove because OA has the advantages of minimally invasive surgery such as a small incision, faster return to daily activities, and short hospital stays[3,7]. Moreover, there are some discouragements for LA such as longer operation time, higher intra-abdominal abscess, and higher failure rate in complicated appendicitis cases[2,4,5,8]. Therefore, there is no consensus in the literature about whether LA should be chosen as a routine procedure for all acute appendicitis cases or only for selected cases such as young women, obese patients, and professional workers[3,7,9].

MATERIALS AND METHODS

Our hypothesis is that for treatment of AA, whether complicated or not, in all adult patients, LA is superior to mini-incision open appendectomy (MOA) in terms of safety and effectivity. The longer operation time and higher intra-abdominal abscess rate in LA will improve in advanced laparoscopic surgical centres with increased laparoscopic experience. Therefore, we compared the shorter and longer outcomes of LA and MOA in patients with AA.

Patients

From January 2011 to June 2013, the data of patients who underwent MOA and LA were recorded at the general surgery department of Safa Hospital. Patients with completed follow-up were included in the study. Pregnant women and patients with previous lower abdominal surgery were excluded. The patients were randomized into MOA and LA groups a computer-generated number. Patients with surgery converted from LA to MOA were excluded. Patients were divided into two groups: LA and MOA done by the same surgeon. All patients gave their informed consent. Patients' demographic data, procedure time, histopathologic reports, the need for analgesics, postoperative visual analog scale (VAS) score at 1, 6, 12 and 24 h, the hospital stay period, the period of time to return to daily activity, morbidity, and mortality were recorded. The diagnosis of AA was made by the surgeon with physical examination, laboratory values, and radiological tests (abdominal ultrasound or computed tomography). All operations were performed with general anaesthesia.

Methods

LA was performed based on the three trocars technique: a 10 mm port was placed at the umbilical area for the scope; a 5 mm port was placed in the left lower quadrant; a 5 mm port was inserted in the suprapubic area. The mesoappendix was transected with ultrasonic energy, and the appendix was tied at the radix. Appendectomy was completed by endo scissors and was removed from the abdomen through a 10 mm port in the umbilical area in an endo-loop (EndoLoop, Vicryl Coated Ligature, Ethicon UK Ltd., Edinburgh, United Kingdom). The appendix stump was not embedded. A drain tube was placed in the rectovesical area when considered necessary.

MOA was performed as a standard treatment. A 3 cm Mc Burney incision was made to enter the peritoneum. Appendectomy was completed followed

Table 1 Patients' characteristics and operative data *n* (%)

	LA (*n* = 122)	MOA (*n* = 121)	*P* value
Age (yr)[1]	25.9 ± 9.6	28.8 ± 11.1	0.249
(median, range)	(26.91-99)	(29.81-97)	
Gender (F/M)	56/66	50/70	0.389[2]
ASA score	108/16/3	106/11/4	0.449
BMI[3] (kg/m^2)	24.1 ± 2.9	24.6 ± 3.1	0.998
Operative time (min)	51.0 ± 13.9	50.9 ± 19.9	0.844
Surgeon	122	121	
Appendix			
Normal	8 (6.5)	18 (14.8)	0.009
Gangrenous	14 (11.4)	11 (9.0)	0.149
Phlegmonous	93 (76.2)	86 (71.0)	0.079
Perforated	7 (5.7)	6 (4.9)	0.073

[1]Students' *t* test; [2]χ^2 test; [3]mean ± SD. BMI: Body mass index; ASA: American Society of Anaesthesiology; MOA: Mini-incision open appendectomy; LA: Laparoscopic appendectomy.

by tying off of the mesoappendix and radix of the appendix. The appendix stump was embedded. A drain tube was placed in the rectovesical area when considered necessary. All appendectomy specimens were sent for histopathological examination. All patients received intravenous 3rd generation cephalosporin as a prophylactic antibiotic (Seftriakson - Novosef, 1000 mg iv, Zentiva, İstanbul, Türkiye). Patients with complicated AA received both 3rd generation cephalosporin and metronidazole (Biteral, 500 mg iv, Deva, Istanbul, Turkey) as prophylactic antibiotics. All patients received a dose of analgesic medication (diclofenac sodium, 75 mg im, Deva, İstanbul, Turkey) prior to intubation in the operating room. In the postoperative period, patients received analgesic medication based on the need for pain medication. The postoperative VAS score was recorded at postoperative hours 1, 6, 12, and 24. Patients were discharged when they tolerated normal food and passed gas and were followed up every week for three weeks as outpatients. Sutures were removed one week after surgery. Follow-ups for complications occurred in postoperative weeks two and three. Patients with complications were admitted to the hospital.

Statistical analysis

Results for categorical variables are given as frequencies and proportions (%), and results for continuous variables are given as mean ± SDs. Results for categorical variables were compared by χ^2 tests; results for continuous, normally distributed variables were compared by student *t*-tests; and results for non-normally distributed continuous variables were compared using a Mann Whitney *U* test. Variables were considered statistically significant if the *P*-value $\leqslant$ 0.05 was in the 95%CI. Statistical analyses used SPSS for SPSS 16.0 software (SPSS Inc., Chicago, Illinois, United States).

RESULTS

The study's 243 patients were randomly divided into two groups, either MOA (*n* = 121) or LA (*n* = 122). Five patients who had undergone conversion from LA to OA were excluded from the study. As shown in Table 1, there were no statistical differences in demographics between the two groups. The data of the operations are shown in Table 1. The mean operating time was similar in both groups. Between the two groups, diagnoses of gangrenous, inflamed, and perforated appendicitis histopathologically were normally distributed. However, the rate of false appendicitis was statistically lower in the LA group (*P* = 0.009). The early postoperative VAS was statistically lower in LA, whereas the differences were similar at the postoperative 24 h mark (*P* = 0.056, Table 2). The need for analgesics in the LA group was lower in the postoperative period (*P* = 0.001). The length of hospital stay was lower in LA, but the difference was not statistically significant (*P* = 0.071, Table 2). The rate of total complications was similar between the two groups (6.5% in LA *vs* 7.4% in OA, *P* = 0.599). All wound infections were treated non-surgically. Six out of seven patients with pelvic abscess were successfully treated with percutaneous drainage; one patient required surgical drainage after a failed percutaneous drainage (Table 2). There were no other complications such as bowel obstruction or incisional hernia. The follow-up period was similar in both groups (14.7 mo for OA and 15.6 mo for LA, *P* = 0.449). No mortality was reported in the follow-up period.

DISCUSSION

As a minimally invasive technique, controversy regarding the superiority of LA over OA has existed for several years[1,9,10]. Because there are no differences in surgical outcomes between the two groups, OA is considered the better option due to lower cost[3]. However, lower postoperative pain, diagnostic accuracy, especially in women and the elderly, shorter periods of healing, and better cosmetic results have been considered advantages of LA over OA[2,4,9]. There were different protocols in previous studies, which resulted in various outcomes reported in the literature[3]. The longer operating time required for LA is a factor in comparing the two groups, and it extends farther in laparoscopic procedures done by inexperienced surgeons[1,4,9]. A previous study reported that operating time is shorter if the procedure is performed by an experienced surgeon due to better exposure[11]. Because our surgical team has laparoscopic procedure experience, we have concluded that the operating times for LA and MOA are similar. In our institution, ultrasonic energy is used for transsecting the mesoappendix. But it is not actually mandatory, electro-cautery and other devices can be preferred[12-14]. Moreover, the similar operating time should be considered a positive factor for LA. The hospital stay period is directly dependent on a patient's general condition[4], and a shorter hospital stay in LA has been shown in previous studies; this outcome was proven by meta-analysis studies[3,6,7,9].

Table 2 Result of mini-incision open appendectomy vs laparoscopic appendectomy *n* (%)

		LA (*n* = 122)	OA (*n* = 121)	*P* value
Hospital stay (h)[3]		25.61 ± 23.72	28.92 ± 21.93	0.071[4]
Return to daily activities (d)		4 (2–12)	5 (3-15)	
Overall morbidity		8 (6.5)	9 (7.4)	0.599[2]
Mortality		0	0	-
VAS score[3]	1st hour	7.1 ± 0.5	7.6 ± 0.7	0.001[1]
	6th hour	3.9 ± 1.1	4.5 ± 1.2	0.001[1]
	12th hour	2.6 ± 1.3	3.1 ± 1.4	0.027[1]
	24th hour	2.4 ± 0.7	2.9 ± 0.9	0.056[1]
Number of analgesics	1	33 (27.0)	18 (14.8)	
	2	46 (37.7)	42 (34.7)	
	3	25 (20.4)	27 (22.3)	0.00[4]
	4	17 (13.9)	33 (27.2)	
Postoperative complications	Pelvic abscess	4	3	
	Wound infection	1	5	
	Atelectasis	1	-	

[1]Student's *t* test; [2]χ^2 test; [3]mean ± SD; [4]Mann-Whitney test. LA: Laparoscopic appendectomy; OA: Open appendectomy.

The 48 h discharge policy recommended for both OA and LA by previous studies has caused confusion due to different policies of individual hospitals[3,9]. Many studies list hospital stay periods by the number of days *vs* hours because They may be affected by social standards, insurance systems, and hospital discharge policies[3,4,9,15]. In this study, we used hours to define hospital stay periods to reflect differences between the two groups. The hospital stay period was shorter by three hours in LA; it is unclear if this is clinically significant. A meta-analysis done by Cochrane Colorectal Cancer Group revealed that returning to daily activities in a shorter amount of time is considered as an advantage for LA[3,9,16]. Minimal trauma to the abdominal wall is considered the main reason for faster healing and lower pain for LA[3,11,17-28]. Early mobilisation after LA is another advantage, and this is achieved by minimal manipulation of the cecum and ileum during the procedure[3]. While the recovery period was shorter in LA, it was not considered significant.

Postoperative pain on day one was evaluated by the need for analgesics and VAS[3]. Evaluating pain was difficult due to the use of different analgesics, administration of those analgesics in different forms, and different cultures' perceptions of pain. Therefore, to obtain a better result in regard to pain evaluation, we used two methods. Many previous studies have shown lower needs for analgesics and VAS[3,9]. In this study, postoperative pain was measured by VAS, and the need for analgesics was statistically lower in the LA group. All of these results supported LA as the preferred option for AA. The presence and degree of postoperative complications are generally considered as safety indicators for a procedure. The most common complications of AAs are wound infections, intra-abdominal abscess, and ileus[9]. It has been shown that postoperative complications are lower in LA *vs* OA[3,4,7,9]. Lower complications in LA, as shown in this study, are due to the lower incidence of wound infections. There is considerable controversy regarding the occurrence of intra-abdominal abscess after appendectomy, which is a serious and life threating complication[9]. Some studies in the literature have shown that the rate of intra-abdominal abscess is higher in OA[1-3,5,15,16]. Moreover, some studies have favoured LA in terms of these complications. The laparoscopic technique has some advantages such as the removal of intra-abdominal infected fluid with suction. However, it can spread infected fluid into the peritoneum, especially in perforated appendicitis and when using more irrigation. Additionally, carbon dioxide insufflation can spread bacterial contamination into the peritoneum[3,9,13]. It is believed that using advanced surgical techniques and gaining more laparoscopic experience may decrease the intra-abdominal abscess rate in LA[3]. Overall, the lower rate of wound infection is an advantage for LA because the infected appendix can be removed from a small incision in an endobag[3,4,9]. The economical analysis of these two techniques is another issue that must be addressed. Although there are many studies about the cost analysis between LA and OA[29,30], we did not make an actual consideration, which needs to be addressed in further studies. In this study, pregnancy group was excluded, because we believe in that MOA *vs* LA in the pregnant should be evaluated in a separate study[31].

In conclusion, LA has a similar hospital stay, operating time, and rate of postoperative complications as MOA, yet decreases the need for analgesics and VAS. Therefore, LA should be the suggested treatment for AA. MOA is still a viable alternative for selected patients.

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COMMENTS

Background

Laparoscopic appendectomy is still not accepted as a standard management for acute appendicitis due to longer operation time and higher cost. In the literature, there are few studies on surgical treatment comparing laparoscopic and mini-incision open appendectomy.

Research frontiers

Hospital stay, operation time, postoperative complication rates are important for the management of acute appendicitis. It is important for the patient's comfort to understand the best technique with regard to mini-incision open and laparoscopic techniques.

Innovations and breakthroughs

Acute appendicitis is mostly-encountered disease in a daily routine. Researches regarding decreasing morbidity and mortality are still needed, although it is very well known. There were no differences in the period of hospital stay, operation time, and postoperative complication rate between the two groups. Laparoscopic appendectomy decreases the need for analgesic medications and the visual analog scale of pain. Therefore, the author suggests that laparoscopic appendectomy should be accepted as a standard treatment for acute appendicitis. Mini-incision appendectomy is an alternative for a select group of patients.

Applications

The author suggests that laparoscopic appendectomy should be accepted as a standard treatment for acute appendicitis. Mini-incision appendectomy is an alternative for a select group of patients.

Peer-review

The author describes the differences between two techniques about the acute appendicitis. This is an interesting issue.

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ORIGINAL ARTICLE

Prospective Study

Anal cushion lifting method is a novel radical management strategy for hemorrhoids that does not involve excision or cause postoperative anal complications

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Author contributions: Ishiyama G and Nishidate T designed the study; Ishiyama G, Ishiyama Y, Nishio A, Tarumi K and Kawamura M acquired the data; Ishiyama G, Nishidate T, Mizuguchi T, Fujimiya M and Hirata K analyzed and interpreted the data; Ishiyama G, Nishidate T, Mizuguchi T and Hirata K drafted this paper; Okita K provided the statistical advice.

Institutional review board statement: The study was reviewed and approved by the Ishiyama Clinic and Hospital Institutional Review Board.

Clinical trial registration statement: This study is registered at http://www.ishiyamahp.jp/index.html [Anorectal clinical trial registry (ACTR)]. The registration identification number is #IS 10012006.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (nisidate@sapmed.ac.jp). Participants gave informed consent for data sharing.

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Abstract

AIM: To describe the anal cushion lifting (ACL) method with preliminary clinical results.

METHODS: Between January to September 2007, 127 patients who received ACL method for hemorrhoid was investigated with informed consent. In this study, three surgeons who specialized in anorectal surgery performed the procedures. Patients with grade two or more severe hemorrhoids according to Goligher's classification were considered to be indicated for surgery. The patients were given the choice to undergo either the ACL method or the ligation and excision method. ACL method is an original technique for managing hemorrhoids without excision. After dissecting the anal cushion from the internal sphincter muscle, the anal cushion was lifted to oral side and ligated at the proper position. Clinical characteristics and outcomes of patients were recorded including complications after surgery.

RESULTS: A total of 127 patients were enrolled. Their median age was 42 (19-84) years, and 74.8% were female. In addition, more than 99% of the patients had grade 3 or worse hemorrhoids. The median follow-up period was 26 (0-88) mo, and the median operative time was 15 (4-30) min. After surgery, analgesics were used for a median period of three days (0-21). Pain control was achieved using extra-oral analgesic drugs, although some patients required intravenous injections of analgesic drugs. The median duration of the patients' postoperative hospital stay was 7 (2-13) d. A total of 10 complications (7.9%) occurred. Bleeding was observed in one patient and was successfully controlled with manual compression. Urinary retention occurred in 6 patients, but it disappeared spontaneously in all cases. Recurrent hemorrhoids developed in 3 patients after 36, 47, and 61 mo, respectively. No anal stenosis or persistent anal pain occurred.

CONCLUSION: We consider that the ACL method might be better than all other current methods for managing hemorrhoids.

Key words: Hemorrhoidectomy; Anal stenosis; Anal cushion lifting method

Core tip: Hemorrhoidectomy, *e.g.*, the ligation and excision method, is still the gold standard surgical technique for hemorrhoids. All of the classical surgical techniques for hemorrhoids are fundamentally based on the resectioning of the hemorrhoids, which can result in anal stenosis. We developed the anal cushion lifting method, in which the prolapsed anal cushion is restored to its original position, as a way of preventing various postoperative complications. We recruited 127 patients and conducted a prospective clinical study. By the end of the study, none of the patients had suffered anal stenosis or persistent anal pain.

Ishiyama G, Nishidate T, Ishiyama Y, Nishio A, Tarumi K, Kawamura M, Okita K, Mizuguchi T, Fujimiya M, Hirata K. Anal cushion lifting method is a novel radical management strategy for hemorrhoids that does not involve excision or cause postoperative anal complications. *World J Gastrointest Surg* 2015; 7(10): 273-278 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i10/273.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i10.273

INTRODUCTION

Hemorrhoids are the most common symptomatic disorder among adults, although its exact incidence is unclear[1-4]. In the Austrian national screening program, 39% of the adult population was found to have symptomatic hemorrhoids[5]. However, hospital-based proctoscopic studies have suggested that after including asymptomatic cases the prevalence of hemorrhoids is 86%[6]. Hemorrhoids can be caused by abnormal downward displacement of the anal cushions due to straining associated with constipation or traditional lifestyles. Thereafter, the hemorrhoids gradually enlarge until they become symptomatic[1-4]. Surgical management primarily aims to control hemorrhoid prolapse in cases in which conservative treatment has been ineffective[1-4,7]. In addition to symptom management, anal function should be maintained after surgery.

Hemorrhoidectomy is still the gold standard surgical procedure for hemorrhoids, and various techniques have been developed such as the Milligan-Morgan (MM), Ferguson, and stapled hemorrhoidectomy (procedure for prolapse and hemorrhoids) methods, *etc*[2]. All of the classical surgical techniques for treating hemorrhoids aim to resect the hemorrhoids together with the anoderm and the perianal epithelium, which occasionally causes anal stenosis and persistent anal pain[8]. In a previous study, anal stenosis occurred in 2.4%-5% of cases in which the Ferguson or MM method was employed[9,10]. Furthermore, severe anal stenosis was reported to occur in 1.8% of cases in which the MM method was performed[11]. In addition to anal stenosis, postoperative pain, bleeding, and long hospital stays are clinical problems that need to be overcome[1]. We developed a novel surgical method for treating hemorrhoids, in which the prolapsed anal cushion is returned to its native position and sutured, that does not involve any resectioning of the anoderm. The main advantages of this technique, which we have named the anal cushion lifting method [the anal cushion lifting (ACL) method], are that it is very simple and does not cause anal stenosis or persistent pain. Herein, we describe the ACL method in detail and report preliminary clinical results for the procedure.

MATERIALS AND METHODS

We used the ACL method to treat 127 patients who gave their informed consent from January to September 2007. In this study, three surgeons who specialized in anorectal surgery (board certified anorectal surgeons belonging to the Japan Society of Coloproctology; No. 1857 for Ishiyama G, No. 0021S for Ishiyama Y, and No. 1829 for Tarumi K) performed the procedures. Before the study, we decided that the study would be terminated if any of the patients suffered anal stenosis or persistent pain. Otherwise, it would be terminated

Table 1 Classification of internal hemorrhoids

Grade	Physical findings
I	Prominent hemorrhoidal vessels, no prolapse
II	Prolapse with Valsalva maneuver; spontaneous reduction
III	Prolapse with Valsalva maneuver; requires manual reduction
IV	Chronically prolapsed; manual reduction ineffective

at the end of the month in which the 100th patient was recruited. Patients with grade two or more severe hemorrhoids according to Goligher's classification were considered to be indicated for surgery (Table 1)[12]. The patients were given the choice to undergo either the ACL method or the ligation and excision (LE) method. During the study period, 189 patients selected the LE method. The study protocol was consistent with the Declaration of Helsinki, and all of the patients gave their informed consent.

Procedure of the ACL method

Caudal epidural anesthesia or low lumber anesthesia was used. The procedure was usually performed whilst the patient was in the prone position, but the Jack-knife position was sometimes selected in cases involving patients with muscular bodies. A good surgical field was obtained by taping and pulling using packing tape. The anal field was sterilized using disinfectant before the operation.

After careful assessment of any anal conditions or other disorders that the patient was suffering from, the anus was gently stretched using the fingers. Some patients had already suffered stenosis, which resulted in the internal sphincter exhibiting reduced elasticity muscle due to fibrosis. This manual manipulation procedure partially restored the hemorrhoids to their native position (Figure 1A and B).

Five to six small straight incisions of 1-2 cm in length were made in the swollen epithelium of the perianal skin (Figure 1C and D). Then, we dissected the tissue between the anal cushion and internal sphincter muscle (Figure 1E and F). No significant bleeding occurred, providing that the dissection was performed accurately. In most cases, the hemorrhoids were spontaneously restored to their native position after this part of the procedure.

Next, we sutured the cranial side and middle portion of the anal cushion to the internal sphincter muscles (Figure 1G and H) using 3-0 VICRYL® Rapide sutures (Ethicon Endo-Surgery Inc., Blue Ash, OH, United States). The anal cushion shrank after its circumferential ligation, and the anal prolapse was completely resolved (Figure 1I and J).

Postoperative medication

No antibiotics were administered after the surgery. Non-steroidal anti-inflammatory drugs (NSAID) were administered on the first three postoperative days unless the patient experienced pain. If the patient complained of pain, intravenous analgesic injections or extra-oral analgesic medication were administered, and NSAID were administered the next day.

Table 2 Clinical characteristics and outcomes of patients that underwent the anal cushion method (*n* = 127)

Characteristics and outcomes	Values (95%CI)
Age (yr)	42 (19-84)
Gender (male:female)	32 (25.2%): 95 (74.8%)
Grade (2:3:4)	1 (0.8%): 113 (89.0%): 13 (10.2%)
Follow-up time (mo)	26 (0-88)
Operative time (min)	15 (4-30)
Duration of analgesic treatment (d)	3 (2-13)
No. of intravenous analgesic injections	0 (0-9)
No. of doses of extra-oral analgesic medication administered	3 (0-21)
Duration of hospital stay (d) (Time to resumption of normal activity)	7 (2-13)
Total complications	10/127 (7.9%)
Bleeding	1 (0.8%)
Urinary retention	6 (4.7%)
Recurrence	3 (2.4%)
Anal stenosis	0
Infection	0
Persistent anal pain during hospital stay	0

Statistical analysis

All data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL). A statistical review of the study was performed by a biomedical statistician.

RESULTS

A total of 127 patients were enrolled in this study (Table 2). Their median age was 42 years old, and 74.8% were female. In addition, more than 99% of the patients had grade 3 or worse hemorrhoids. The median follow-up period was 26 mo, and the median operative time was 15 min. After surgery, analgesics were used for a median period of three days. Pain control was achieved using extra-oral analgesic drugs in most cases, and such drugs were administered a median of three times, although some patients required intravenous injections of analgesic drugs. The median duration of the patients' postoperative hospital stay was 7 d.

A total of 10 complications occurred. Bleeding was observed in one patient and was successfully controlled with manual compression. Urinary retention occurred in 6 patients, but it disappeared spontaneously in all cases. Recurrent hemorrhoids developed in 3 patients after 36, 47, and 61 mo, respectively. No anal stenosis or persistent anal pain occurred.

DISCUSSION

We developed a novel surgical procedure for hemorrhoids,

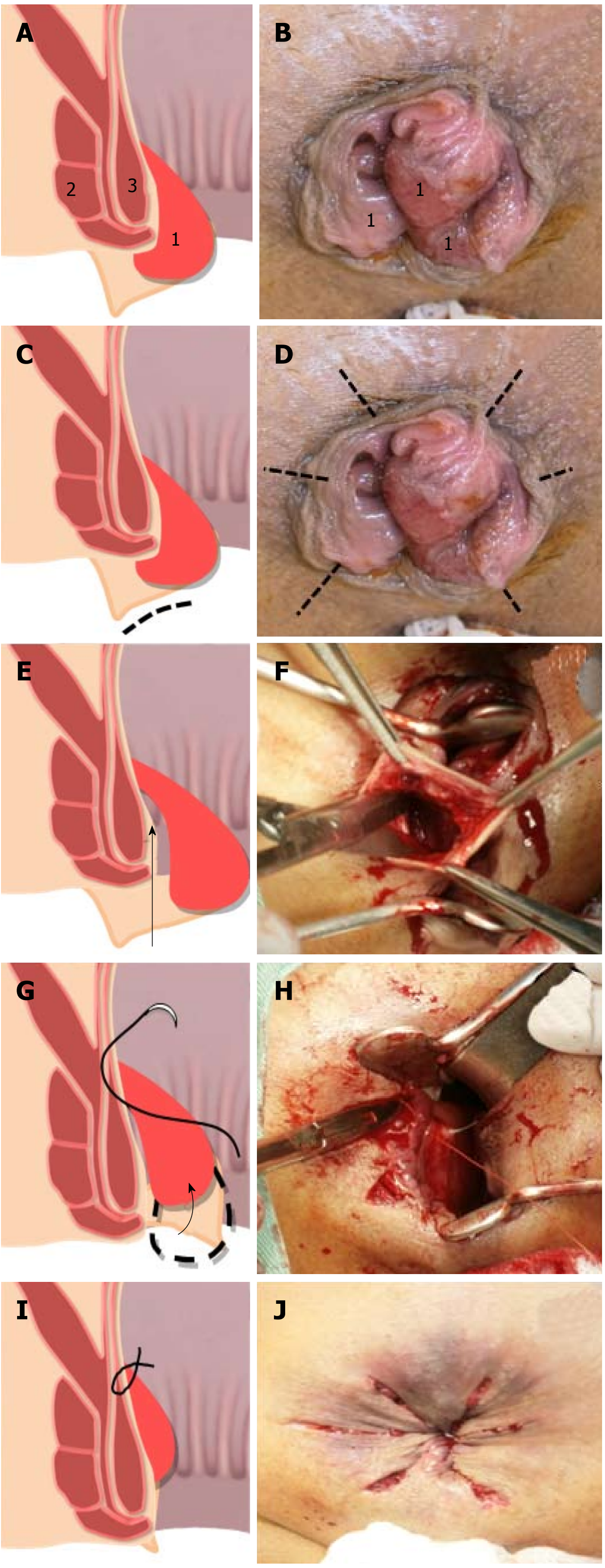

Figure 1 Sagittal diagrams (A, C, E, G and I) and intraoperative views (B, D, F, H and J) of the anus. Small incisions were made in the perianal skin (C), and several radial incisions were performed (D). The tissue between the internal sphincter muscle and anal cushion was dissected (E and F). The anal cushion was restored to its native position (G). The anal cushion was sutured from its middle portion to the cranial side using single stitches (G and H). All sutures were tied up circumferentially (I). The appearance of the anus after the completion of the ACL procedure (J). 1: Hemorrhoids; 2: External sphincter; 3: Internal sphincter. Dotted line: Incision; Arrow: Dissection.

which we named the ACL method. In the present study, the clinical outcomes of the ACL method; *i.e.*, its complications, the operative time, the number of postoperative analgesic injections required, the frequency of postoperative oral analgesic medication use, the duration of postoperative analgesic treatment, and the duration of the postoperative hospitalization period, were acceptable.

Classical hemorrhoidectomy and other surgical techniques for treating hemorrhoids basically involve the ligation of the feeding artery[1]. However, if the blood supply to the anoderm and perianal tissue is cut off due to arterial ligation then these tissues will become necrotic. On the other hand, the ACL method is based on the ligation of the superficial anal cushion and preserves the arterial supply. So, no necrosis occurs after surgery, and complete wound healing can be achieved. In addition, the importance of preserving the anoderm has been stressed in reports about various other techniques, and anoderm preservation has been reported to reduce the risk of anal stenosis and anal pain after surgery[13]. The ACL method does not involve any excision of the anoderm. Our only concern about the ACL method was whether the anal cushion would become congested after surgery, which could lead to a worsening of the patient's symptoms. However, the collateral venous plexus is preserved in the ACL method, so the anal cushion never becomes congested.

Recently, a similar technique, the Z-shaped ligation method for anal hemorrhoids, was reported by Gemici *et al*[14]. Their concept is derived from sclerotherapy, which aims to treat vascular structures alone. The difference between our ACL method and the Z-shaped ligation method is that we dissected the tissue between the anal cushion and internal sphincter muscle and they did not. Both procedures involve similar ligation sites and exhibited similar complications rates. Our ACL method might be more painful than the Z-shaped ligation method as it requires incisions and dissection. However, small radial incisions do not cause severe anal pain, and dissection itself does not cause anal pain. The recurrence rate of the ACL method seems to be lower than that of the Z-shaped ligation method, which is reasonable. As *en-bloc* ligation of the anal cushion can only be achieved after the dissection of the tissue, both methods prove that ligation of the anal cushion is sufficient for managing hemorrhoids.

The anal pain experienced after the LE method is considered to be caused by the anal duct being subjected to excessive tension after surgery[8]. Excision of the anoderm and perianal epithelium itself can also cause postoperative anal pain[13]. On the other hand, the ACL method causes minimal postoperative anal pain, as it does not involve the application of tension to the anal duct. In addition, the total length of the incisions made during the ACL method is shorter than the total length of the incisions made during classical methods. Furthermore, the better blood supply provided by the

Table 3 Perioperative and postoperative findings of conventional hemorrhoidectomy methods

Ref.	Bikhchandani *et al*[15]	Shalaby *et al*[10]	Bulus *et al*[16]	Correa-Rovelo *et al*[9]
Method	MM	MM	Ferguson	Ferguson
No. of patients	42	100	71	42
Operative time (min) (mean ± SD)	45.2 ± 5.4	19.7 ± 4.7	25.5 ± 7.7	38.1 ± 12.9
Complications (%)				
Bleeding	2.4	2.0	4.2	0
External tags	2.4	1.0	-	4.9
Anal stenosis	0	5.0	1.4	2.4
Infection	0	-	1.4	-
Urinary retention	16.7	14.0	28.2	7.1
Recurrence	5.0	2.0	8.5	0

MM: Milligan-Morgan.

ACL method helps to prevent persistent pain after surgery. In fact, the patients that underwent the ACL method did not have to stay in hospital for as long and were able to return to normal life faster than those that underwent the classical method. Also, the patients who underwent the ACL method required fewer analgesic injections, took analgesic medications less often and for shorter periods, and experienced less pain than those that underwent the LE method.

As we have shown, the ACL method is a very simple technique that does not cause significant bleeding. The classical surgical methods for hemorrhoids are based on the excision of the anoderm and ligation of the feeding artery[2,3]. In such procedures, the incisions have to be meticulously planned in order to prevent skin tags. However, the ACL method involves simple dissection of the tissue between the anal cushion and the inner sphincter muscle followed by the ligation of the anal cushion. Therefore, in the present study the total operation time for the ACL method was shorter than that for the LE method.

The most important aspect of the classical technique is the extent of the excision. In cases involving significant anal prolapse, a large amount of skin has to be excised to achieve good anal esthetics. However, the risk of postoperative stenosis is increased if the excision is too extensive. On the other hand, the ACL method is not affected by such concerns. The clinical outcomes of two excision methods, the MM and Ferguson methods, are summarized in Table 3. In the present study, the ACL method exhibited a lower complications rate than the abovementioned excision methods. Interestingly, all of the patients' anal cushions eventually shrank after the ACL method. This makes sense as the ACL method preserves collateral venous vessels, which facilitates anal cushion shrinkage and the restoration of normal function.

We consider that the ACL method might be better than all other current methods for managing hemorrhoids, including the Z-shaped ligation method. However, we could not prove that the ACL method has definitive clinical advantages in the present study. Therefore, a large prospective study should be designed to confirm the clinical advantages of the ACL method over other methods.

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COMMENTS

Background

Hemorrhoidectomy is still the gold standard surgical procedure for hemorrhoids, and various hemorrhoidectomy procedures, such as the ligation and excision method, *etc*., have been proposed. All of the classical surgical techniques for hemorrhoids are based on resecting the hemorrhoids together with the anoderm and the perianal epithelium, which occasionally causes anal stenosis and persistent anal pain. The authors present a novel surgical approach, in which the prolapsed anal cushion is restored to its native position that does not cause postoperative stenosis or persistent anal pain.

Research frontiers

Classical hemorrhoidectomy and other surgical techniques for treating hemorrhoids cause postoperative stenosis or persistent anal pain. On the other hand, the anal cushion lifting (ACL) method is based on the ligation of the superficial anal cushion and preserves the arterial supply. So, no necrosis occurs after surgery, and complete wound healing can be achieved.

Innovations and breakthroughs

The ACL method is an original novel surgical technique which causes no anal stenosis and persistent pain after surgery.

Applications

The ACL method might take place classical technique for surgical management of the hemorrhoids in future.

Terminology

Hemorrhoidectomy, *e.g.*, the ligation and excision method, is still the gold standard surgical technique for hemorrhoids. The ACL method is novel surgical technique for hemorrhoids.

Peer-review

The authors have presented interesting results on the development of a new surgical method for the management of hemorrhoid which shows superiority to the current surgical techniques in terms of operation time, post-operative pain and recovery.

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EDITORIAL

Pelvic radiation therapy: Between delight and disaster

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Abstract

In the last few decades radiotherapy was established as one of the best and most widely used treatment modalities for certain tumours. Unfortunately that came with a price. As more people with cancer survive longer an ever increasing number of patients are living with the complications of radiotherapy and have become, in certain cases, difficult to manage. Pelvic radiation disease (PRD) can result from ionising radiation-induced damage to surrounding non-cancerous tissues resulting in disruption of normal physiological functions and symptoms such as diarrhoea, tenesmus, incontinence and rectal bleeding. The burden of PRD-related symptoms, which impact on a patient's quality of life, has been under appreciated and sub-optimally managed. This article serves to promote awareness of PRD and the vast potential there is to improve current service provision and research activities.

Key words: Pelvic radiotherapy; Radiation; Toxicity

Core tip: Radical cancer treatments have come at a price. Radiotherapy carries the risk of pelvic radiation disease (PRD), a condition that can significantly reduce a patient's quality of life. We argue that PRD is a neglected problem that requires investment in service provision and research studies.

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INTRODUCTION

The last four decades have been a golden era for improving cancer survivorship. Three times as many people survive cancer than 30 years ago largely as a result of the increasingly potent, multi-modality treatment regimes[1]. Yet 20%-25% of cancer survivors report a decline in quality of life secondary to the physical consequences of treatment[2]. A sinister side to cancer research studies is the fixation on survival statistics and prevention of disease recurrence. Patient quality of life has been unacceptably neglected. Toxicity and debilitating short- and long-term complications are inevitable consequences of radical treatments. Patients who receive radiotherapy form a large cohort of patients who report side effects leading to a reduced quality of life[1]. Radiotherapy is a cornerstone treatment for pelvic tumours which includes those of gastrointestinal, gynaecological or urological systems[3].

Radiotherapy to organs of the pelvis renders the bowel at risk of radiation induced injury, a condition recently coined pelvic radiation disease (PRD)[4,5]. This term encapsulates conditions including radiation enteritis, radiation proctitis and radiation cystitis[6] which inaccurately depict the condition as an ongoing inflammatory process. In fact, after the initial three months the inflammation is largely replaced by progressive ischaemia and fibrosis of tissues. This radiation induced damage to healthy tissue around the tumour could be a major limiting factor to curative treatment of localised cancer as treatment regimes may be interrupted.

This editorial outlines the clinical presentation, pathophysiology, histopathological features, prevention and management of PRD and aims to shed light on the future direction of much needed research in this field.

THE MAGNITUDE OF THE PROBLEM

It is truly remarkable how common PRD is. Yet should we be surprised? More people with pelvic tumours are treated with radiotherapy than any other anatomical site and as more people live longer with cancer or indeed survive it the burden of PRD increases. A questionnaire investigating the opinion of clinical oncologists in the United Kingdom reveals that most believe it is a significant problem that is under recognised and inadequately managed[7]. An impasse has been reached: The magnitude of the problem significantly exceeds clinical and research provisions. In fact, the annual incidence of patients adversely affected by PRD with symptoms of gastrointestinal disturbance eclipses the number of patients diagnosed with Crohn's disease[8]. Numerous large studies have documented the rates of complications in patients with pelvic tumours treated with surgery alone or surgery combined with either preoperative or postoperative radiotherapy[9-19]. Yet the funding and service provisions for PRD are a fraction of those for Crohn's disease[8].

A remarkable nine out of ten patients who received pelvic radiotherapy experience chronic change to bowel habit with five out of ten reporting a significant change to their quality of life[20]. Despite this only one fifth of patients with PRD in the United Kingdom are reviewed by a gastroenterologist[2]. This figure is even more remarkable given the fact that the onset of PRD, unlike inflammatory bowel disease (IBD), is relatively predictable. Acutely PRD occurs simultaneously or within three months of radiotherapy. There should be a low threshold for suspecting chronic PRD in patients previously treated with pelvic radiotherapy. PRD thus represents a model of disease with a predictable onset and a large patient cohort.

Not all patients who receive radiotherapy directed at tumours within the pelvis develop PRD. The reason for this is unclear however evidence suggests it may be a multifactorial process involving patient-related and treatment-related factors. Indeed, there is still uncertainty regarding who are the most susceptible patients, even those that fall into similar cohorts. Consequently, there is major scope for future research to exploit this disease model to shed light on the pathogenesis, preventative measures and management of PRD[21].

THE CLINICAL PRESENTATION

There is a vast spectrum of clinical presentations of PRD owing to numerous influential variables such as timing since radiotherapy, site of the tissue damage, severity of tissue damage, side effects of medications, coexisting medical conditions and psychological issues. The clinical presentations can be crudely classified into three clinical phases: Acute, chronic and delayed (latent)[22]. The timing of gastrointestinal complications of PRD follows a relatively predictable pattern (Table 1). Within these groups the symptoms of PRD may manifest as a result of direct damage to pelvic structures or as secondary phenomena triggered by the radiotherapy. These include small bowel bacterial overgrowth, bile salt malabsorption, malabsorption of lactose and similar fermentable sugars[23].

The acute phase

Acute PRD is defined as an acute inflammatory reaction to radiation treatment that can occur during, immediately after or within the first three months of radiotherapy. It occurs in 60%-80% of patients treated with abdominal or pelvic radiotherapy and is a major risk factor for modification of the planned treatment regime. Such changes could have ramifications on local tumour control[3]. Common symptoms include nausea, diarrhoea, tenesmus, abdominal cramps, urgency, mucus discharge, faecal urgency, loss of appetite and bleeding. Such non-specific symptoms can overlap with differential diagnoses such as infection, which needs to be excluded. Bleeding occurs in 50% of patients who receive pelvic radiotherapy as a consequence of radiation induced telangectasia which usually form on the anterior rectal wall[5]. Symptoms of acute PRD most commonly manifest in the second week post-radiotherapy and peak in week four or five and resolve within two to six months[23]. Importantly, the occurrence of acute PRD does not increase the risk of developing chronic PRD later on and patients can be reassured that resolution of symptoms generally occurs with cessation

Table 1 The timing of gastrointestinal complications of pelvic radiation disease in relation to tissue type damage

Complication	Primary tissue type damage	Timing
Acute proctitis	Epithelial	0-4 wk
Acute enteritis	Epithelial	0-4 wk
Rectal bleeding	Vascular	4-12 mo
Anal/perianal pain	Stromal	6-9 mo
Chronic abscess	Stromal	9-15 mo
Fistula	Stromal	18-24 mo
Stricture/malabsorption	Stromal	2-20 yr
Rectal malignancy	Epithelial	5-30 yr

of radiotherapy[24].

The chronic phase

Chronic PRD is a progressive condition and major source of morbidity for cancer survivors. Symptoms of chronic PRD begin to develop after a period of 6 mo to 3 years but can occur up to three decades following treatment. Occasionally the onset of symptoms crosses over with the acute phase of PRD. Clinically the signs of chronic PRD are symptoms of bowel dysmotility such as urgency. Altered transit of faeces and malabsorption are other prominent features[3]. In fact, when treating rectal cancer with radiation, it has been estimated that the majority will suffer from faecal incontinence[25]. Vascular telangectasia often lead to bleeding in the chronic phase. The bowel has a limited range of symptoms and therefore PRD manifests similarly to other bowel conditions including celiac disease, IBD, infection, malignancy, diverticular disease. The timing of radiotherapy in relationship to symptom manifestation is key to raising clinical suspicion and providing tailored support for PRD.

Patients that experience long standing chronic PRD can also experience sudden complications. Radiotherapy increases the risk of bowel wall stricture formation, adhesions, fissures, severe bleeding and bowel wall perforation. Surgeons should be alert to the fact that PRD may be the cause of acute or sub-acute small bowel obstruction.

The latent phase

A third stage of the clinical pathological presentation of PRD is well recognised. Latent clinical symptoms first arise years or decades after the initial radiotherapy treatment. Latent phase symptoms are in fact those of secondary malignancies, which can arise within or outside of the irradiation field. Radiotherapy used to treat the first malignancy can induce minor alterations to the nuclear DNA that predispose the cellular DNA to novel mutations, carcinogenesis and teratogenesis[22]. Studies have shown patients treated with radiotherapy for cervical or ovarian cancer developed endometrial cancer between approximately 15 years later[26,27]. Importantly there was a preponderance for high-risk histological sub-types in endometrial cancers that develop after pelvic radiotherapy[27]. Prostate cacner not treated with RT is not associated with an increased risk of other malignancies. Bostrom and Soloway[28] (2007) showed that there is a slight increase in radiation-induced secondary malignancies after prostate radiotherapy. Approximately one in seventy of such patients who survive longer than ten years will develop a secondary malignancy. There is a predilection for secondary rectal or bladder tumours[28]. Despite the association between radiotherapy and secondary malignancies there is a lack of definitive evidence for a direct relationship.

Clinicians should be suspicious of a primary tumour in any patient who has received pelvic radiotherapy and has new onset red flag symptoms of cancer, such as *per rectum* bleeding. Furthermore, although the risk of secondary malignancies after pelvic radiotherapy is modestly above the overall population patients should be informed about the risk.

THE PATHOPHYSIOLOGY OF PRD

Cells exposed to ionising radiation experience oxidative stress injuries. The damage is widespread however the principle sub-cellular target is the nuclear DNA[29]. Both direct and indirect mechanisms inhibit DNA from fulfilling its function as a template for DNA transcription. The nuclear chromatin is directly targeted, causing DNA damage through the generation of inter- and intra-strand cross-linkages, breaks and mutations. The plasma membrane is directly affected as radiotherapy disrupts the rigidity of the phospholipid bilayer and electric gradient; injuries which challenge integrity of the cell. Indirect damage occurs secondary to the formation of free radicals from the ionisation of water molecules[22].

Intricate and coordinated DNA repair mechanisms have evolved to fix damage induced by ionising radiation, including strand breaks and replication errors. At low levels of radiation repair mechanisms in the cell can resolve injuries such as double strand breaks. With increasing amounts of radiation the damage inflicted overwhelms these systems and the cell either enters programmed cell death (apoptosis) or mitosis is inhibited. The amount of ionising radiation required to inflict cell inactivation and cell death varies between each tumour and its surrounding tissues[30]. A further variable that influences a cell's response to radiotherapy is whether adjuvant chemotherapy features in the treatment regime. Concomitant chemotherapy often leads to delay or prevention of the reparative process thus aggravating the disease. Chemotherapeutic agents may help to accumulate cells in the more radiosensitive stages of the cell cycle. Timing of radiotherapy in relation to chemotherapy is an essential consideration[31].

The damaging affect of radiotherapy is most potent against tissues with a high turnover, making it an ideal modality to treat typically rapidly proliferating tumour cells. This is because the potential cell injury is dependent not only upon the cellular repair processes but also the stage of the cell cycle that the cell is in. Certain stages within the cell cycle optimise the opportunity to repair damage. For example, ionising radiation damage results in cell cycle arrest and initiation of a temporary cell cycle check point. This aims to provide time to conduct repairs. A crucial protein in the checkpoint machinery is the tumour suppressor gene *p53*. Highly proliferative cells, such as those residing in the crypt epithelium of the bowel, are frequently in the more radiosensitive G_2-M phase[31]. Crypt cell death results in insufficient renewal of the villous epithelium. The mucosa and lamina propria become inflamed and the mucosal barrier breaks down[3]. In comparison slowly dividing tissues, such as those in vascular or fibrous tissue, spend more time in the less radiosensitive G_1 and S phases and damage to these tissues are usually not responsible for acute clinical presentations[22].

Impaired anorectal functionality

Maintenance of faecal continence is regulated by the tonic contractions of the internal and external anal sphincters. The former is a smooth muscle and is supplied by intrinsic myenteric innervation and has the chief role of maintaining a tonic contraction and thus continence whilst at rest. Comparatively the external sphincter is composed of striated muscle and is innervated by an extrinsic supply. In health these work together to provide an effective seal to solids, liquids and flatus. The anorectum has a rich nervous supply, which includes pain, temperature and touch sensory components, each of which aid the maintenance of continence through the ability to differentiate between solids and flatus. Impaired anal functioning can result from damage to the nerves of the pelvis including the pudendal nerve, the lumbo-sacral plexus and the myenteric plexus. The external anal sphincter is relatively radioresistant and it is postulated that faecal incontinence is strongly influenced by nerve damage. Case reports demonstrate that damage to the pudendal nerve may lead to morphological changes in the muscle. Some case reports have proposed that injury to the lumbo-sacral plexus can indirectly affect the external anal sphincter by causing perianal anaesthesia[32].

MICROSCOPIC CHANGES TO THE BOWEL MUCOSA

An appreciation of the radiation induced microscopic changes observed in patients with PRD is a window to understanding the clinical symptoms, stages of the disease and how best to manage the condition. The epithelial cells within the bowel wall, particularly those in the small bowel, have a high turnover rate which renders them vulnerable to ionising radiation. A fine balance lies between the dose tolerated by the epithelium and the dose that destroys the neoplasm. Histologically the damage inflicted upon surrounding healthy tissues has characteristic appearances depending upon the time interval since the radiotherapy. There are three main histological phases depending upon the tissue type that is predominantly affected. The epithelial phase generally correlates with acute phase clinical symptoms with vascular and stromal changes commence several weeks later (Table 1)[33].

In the epithelial phase damage to the epithelium, seen as sloughing of epithelial cells into crypt lumina, can be observed within eight hours of exposure to ionising radiation. Other characteristic acute phase histological changes include patchy fibroblastic changes to the submucosa, epithelial meganucleosis and significant eosinophilic infiltrate with formation of eosinophilic microabscesses. Caution and experience is required to interpret these morphological changes as they can resemble dysplasia. Nuclear and cytoplasmic early phase changes are usually reversible[33]. Mitosis is inhibited preventing epithelial re-growth and causing denudation of the underlying structures. Importantly, during the acute phase the vasculature appears normal[33,34].

Severe fibrovascular changes, depletion of goblet cells and atrophy are core features of chronic PRD and the vascular phase. Extensive fibrosis can be seen in submucosal arterioles and the lamina propria, which contributes to deformed architecture such as crypt distortion. Characteristic changes during the vascular are telangectasia of capillaries and post-capillary venules, fibrin deposition, subendothelial odema and platelet thrombi formation that can cause *per rectum* bleeding[33]. Ultimately there is significant narrowing of the vascular lumina that leads to ischaemia and further fibrosis. Macroscopically these microscopic changes correlate with a pale, non-compliant bowel wall with telangectasia[24]. The reversibility of the vascular phase morphological changes is unclear however the stromal phase which includes mesenchymal and stomal fibrosis is irreversible[33].

Despite these distinctions the bowel has a limited array of modifications in response to damage. In fact under a microscope a canny mimic of chronic PRD is the quiescent phase of IBD. Since chronic PRD can take months, if not years to develop, is quite possible that PRD is overlooked as a differential diagnosis and the histopathologist could remain oblivious to the patient's history of irradiation. Relevant clinical information is therefore essential for the histopathologist. As they trawl through mounds of rectal biopsies labelled with minimal clinical information the biopsy from the patient with chronic PRD could be mistaken for chronic IBD[35].

Importantly, a study profiling the time patterns of histological mucosal changes in relation to the clinical manifestation of PRD indicated that they do not always coincide. Microscopic evidence of inflammation in rectal biopsies precedes the onset of symptoms. Thus pathological changes do not always cause the symptoms but it is the disruption to normal physiological processes that results in the symptoms such as diarrhoea. These findings suggest that pre-emptive, prophylactic treatment that tries to prevent PRD may be a prudent way to tackle the condition[36].

HOW TO PREVENT PRD

Preventing the adverse impact of radiotherapy and development of PRD is a multi-disciplinary responsibility. Prior to receiving radiotherapy the patient should be optimised for treatment by attempting to control and treat pre-existing co-morbidities, such as hypertension and diabetes, and making lifestyle modifications like smoking cessation. Clinical oncologists have, over the decades, honed the radiotherapy regimes to try to reduce damage from too high doses or too large field sizes. Medical oncologists should liase closely with surgeons and clinical oncologists to attempt to minimise the increased toxic effects of concurrent chemotherapy.

Factors related to the host

Hypertension, arterial disease, IBD and diabetes mellitus are co-morbidities that predispose a patient to PRD. Previous abdominal surgery also increases the likehood of PRD owing to the tethering effect of adhesions that reduce bowel motility out of the radiation field[22]. Tobacco smoking is an independent risk factor for predicting the development of complications to radiotherapy. A body mass index greater than 30 is found to be protective against pelvic and abdominal radiotherapy whereas low body mass increase the risk of toxicity. Genetic predisposition is thought to explain the varying level of complications observed between patients who receive the same radiotherapy regime[3].

Factors related to therapy

When radiotherapy was initially used against tumours within the pelvis the development of resistance to the radiation was a common set back. This was especially problematic in patients with rectal cancer. Higher doses were discovered to overcome the resistance but are associated with higher collateral damage to surrounding healthy tissue in the radiotherapy beam[24].

High doses and large field sizes are associated with increased radiotherapy toxicity. Large doses per fraction facilitate a quicker completion of the radiotherapy regime and progression to surgery. Larger doses are believed to increase the chronic complications of radiotherapy as increase the safety problems of concurrent chemotherapy. These observations were particularly pertinent in the 1970s when patients with carcinoma of the uterine cervix were treated with > 1000 cGy/min over 2-3 min resulting in irreparable tissue damage. Modifications to radiotherapy doses have since resolved this risk[22]. Dose-volume histograms are routinely used by clinical oncologists to plot cumulative dose-volume frequency to help safeguard against toxicity and PRD[37].

Radiation therapy can be administered to a patient in two main ways: *Via* external beam radiation or brachytherapy (radioactive implants). The field size used in external beam radiotherapy is crucial to the level of exposure that surrounding healthy tissues receives. Large field sizes increase the acute side effects, in particular diarrhoea. Radiotherapy is delivered using an external photon generator that exposes the patient to X-rays, electron beams and gamma rays in a four beam approach which results in significant exposure to surrounding tissues[24]. Development of three dimensional conformal radiation therapy and intensity-modulated radiation therapy attempts to minimise the field size thus sparing non-cancerous tissue. Large field exposure can be avoided by limiting the field to 2-3 cm beyond the tumour margin on computed tomography (CT) or magnetic resonance imaging scans. This strategy accounts for natural bowel motility and infiltration of metastatic cells beyond tumour margins. Alternatively, surgical clips at sites of residual disease can be used as landmarks for post-operative radiotherapy although they are less reliable indicators than scans. Consequently, post-operative radiotherapy often utilises larger field sizes in comparison to pre-operative fields[22].

Post-operative radiotherapy is more toxic than preoperative radiotherapy due to disturbance to the natural reflections of the perineum and allowing it to enter the pelvis. Following surgery adhesions form around the bowel limiting its movement and tethering it in potential radiation fields. The Swedish rectal cancer trial involving 1168 patients randomly assigned to surgery alone or surgery with neoadjuvant radiotherapy showed five year survival rates as 48% and 58% (P = 0.004), respectively[38]. Studies comparing surgery with either pre-operative or post-operative radiotherapy for rectal cancer showed significant differences between the incidence of bowel habit disturbance (minimal *vs* 90% respectively)[11,39].

A retrospective study explored the use of non-absorbable mesh implanted during surgery which would act to protect the small bowel from radiation injury and suggests a reduction in chronic PRD from 90% to 3%[40]. Prophylactic surgical techniques such as pelvic reconstruction, omentoplasty and transposition of the large bowel can reduce the volume of bowel at risk of radiation exposure by 60%. Additionally clinical oncologists have developed a range of techniques to reduce PRD. Image guidance techniques such as megavoltage and kilovoltage cone beam CT performed immediately before radiotherapy can accurately assess location and mobility of the bowel. Manoeuvring the patient into the supine position during the radiotherapy has significantly reduced the incidence of PRD in patients treated for prostate, rectal, small bowel and bladder cancer[37].

MANAGEMENT

How to manage patients with PRD is a contentious subject. It was largely believed to be untreatable until a better understanding of the aetiology and pathogenesis paved the way for a paradigm shift in treatment. Medicines, dietary modifications and supportive measures are some of the components of current guidelines. In the majority of cases the cornerstone of management after prevention is symptom control. Symptoms can originate from a variety of affected sites therefore a crucial step in PRD management is the understanding that urological, gastrointestinal, gynaecological, dermatological, lymphatic, nervous, vascular structures and sexual organs can be involved. The severity of damage and whether the patient is in the acute or chronic phase of PRD are additional variables that make each patients case unique. A degree of flexibility is essential when approaching PRD to cater for this wide spectrum of clinical presentations. Several scoring systems have been developed or adopted from elsewhere to quantify and categorise a patient's symptoms and quality of life. The inflammatory bowel disease questionnaire-bowel subset score[2] and the Franco-Italian glossary which classifies symptom severity 0 to 4[41] are two such examples.

Additionally, the psychological impact of PRD should never be underestimated. Evidence shows that 24 mo after radiotherapy for cervical cancer disease-free patients have a reduced quality of life and experience psychological reactions such as inability to perform daily household tasks and making plans for the future[42]. Sexual functioning in both males and females, ejaculation disorders and erectile dysfunction are significantly more common in patients who have received pelvic radiation when compared to surgery alone[17]. Although the bowel is the most affected site radiotherapy to the pelvis can cause complications such as vaginal stenosis. The pathogenesis of this condition is akin to that in the bowel; inflammation within the connective tissues and blood vessels leads to fibrosis and a reduced blood supply. Consequently, the hypoxic conditions encourage loss of elastin, atrophy and collagen deposition[43]. A holistic approach addressing the physical, psychological, social and emotional hurdles of PRD is thus gold standard management.

Management during the acute phase

Treatment of acute PRD can take the form of supportive and/or dietary modifications. To tackle the problem of diarrhoea bulking agents and anti-kinetic drugs, such as fybogel, codeine and loperamide, are commonly prescribed to increase excess fluid absorption in the bowel and to reduce the peristaltic activity, respectively. Anti-cholinergic anti-spasmodics, anti-emetics and analgesia are other agents offering effective symptom control. Most patients respond to this regime however patients with profuse diarrhoea leading to malabsorption and dehydration require more intensive supportive measures with fluids and electrolyte balance support. The use of these measures is generally based on anecdotal evidence and experience of the attending healthcare professionals. A salient point about acute PRD is that symptoms often recede once the radiotherapy regime has ceased[23]. Transparency about the potential for chronic manifestations of PRD through education and counselling can encourage patients to seek medical attention if needed.

Management during the chronic phase

Making the diagnosis of chronic PRD can be a convoluted process. Irritable bowel syndrome is a common misdisgnosis. Once the diagnosis is made many patients symptoms improve with modification of their diet. Ionising radiation can cause damaged intestinal villi and insufficient enzyme production leading to malabsorption of nutrients. Low fat, low roughage and low residue diets are encouraged and adequate calorific and fluid intake is essential. Dietetic input can provided structured and targeted advice[23]. Should symptoms persist, medical management can be added to this conservative approach through the addition of anti-inflammatory agents. Steroid enemas or suppositories and oral 5 acetyl salicylic acid preparations may offer symptomatic relief of *per rectum* bleeding, tenesmus or urgency[22].

In 2010, the United Kingdom national cancer survivorship initiative vision was launched. Its aims were to stimulate development of new models of care to manage patients with chronic cancer related symptoms. The initiative came into being after the recognition that surviving cancer does not equate to a good quality of life. The consequences of cancer treatment can result in debilitating chronic symptoms[2]. In total 23 different gastrointestinal symptoms have been associated with chronic PRD. The cluster of symptoms, severity, frequency of symptoms all vary between individual patients making chronic PRD a highly heterogenous condition. Andreyev *et al*[1] (2013) devised an investigative and management algorithm to help improve the gastrointestinal symptoms of chronic PRD. Results of the randomised control trial showed that use of the algorithm-based care improved symptoms in patients with PRD. Additionally, the study indicated that nurse-led care is sufficient for the majority of patients with PRD[2].

Malabsorption of bile acids is believed to be the cause diarrheal symptoms in between 35%-72% of patients with chronic PRD[23]. Ninety-five percent of all bile acid salts are absorbed in the terminal ileum which means that damage to this area or decreased transit time leads to bile acid malabsorption[44]. The terminal ileum is the most commonly affected portion of small bowel affected by PRD. An important factor which determines the risk of radiation induced damage to the bowel is its mobility. An area that is not tethered and therefore mobile has a chance of migrating into areas outside the radiation field in the weeks between radiation fractions. The entire duodenum, the jejunum at the ligament of trietz and the terminal ileum are tethered in place making them vulnerable for repeated radiation exposure[34]. Cholestyramine, colestipol and colesevelam bind bile salts and have been administered to patients with PRD[23]. There is evidence that patients with PRD respond well to the former agent but palatability is an issue[45].

LATEST DEVELOPMENTS AND FUTURE RESEARCH PRIORITIES

Rather disturbingly, although there have been a plethora of expensive multi-centre studies into the treatment of cancer, there is scant evidence of how to optimally manage the debilitating consequences of treatment. Several strategies of PRD management are being researched and are potential avenues for future PRD management.

Antibiotics vs probiotics

As outlined above, ionising radiation modifies the intestinal muscosa, inducing changes to the vascular permeability of the mucosa and overall motility. These changes directly impact on the natural bacteria that colonise the bowel[46]. Specifically, dysmotility and stasis encourages bacterial overgrowth in the small bowel. In comparison to the colon the small bowel usually harbours few microorganisms. Jejunal cultures from one in three people detect no bacteria. Ionising radiation disturbs the homeostasis of indigenous intestinal microflora which directly influences bowel functions. For example, they have a role in processing unabsorbed dietary carbohydrates and converting them into fatty acids: An energy source for the colonic mucosa. Enteric bacteria contribute to their host's health by synthesising essential molecules such as vitamin K and folate. Commensal bacteria also interact with the host immune response inducing a state of controlled inflammation which maintains a fine homeostasis between protection against disease and chronic inflammation[47].

There is contradictory evidence of how to combat this radiotherapy - induced pathophysiological change. Broad spectrum antibiotics including co-amoxiclav, ciprofloxacin, tetracycline and rifaximim are frequently used but some patients require repeated courses or low dose, long-term maintenance therapy[48]. Understanding the pathophysiology led to studies into the use of probiotics which aim to restore the balance of the commensal microbiota. Trials have yielded mixed results with some heralding lactobacilli probiotics as a cheap, safe and feasible method of reducing diarrhoea in the acute phase[46,49] with others finding no significant reduction in diarrhoeal symptoms[50]. There is currently no evidence supporting their use in the prevention of chronic PRD. This remains an area for future research studies[51].

Medications

Patients who take angiotensin I-converting enzyme inhibitors (ACEi) and the cholesterol lowering statins have been observed to have fewer gastrointestinal complications from radiotherapy to the pelvis. *In vitro* studies have supported this by showing the anti-inflammatory, anti-thrombotic and anti-fibrotic properties of statins when administered to human cells treated with ionising radiation[52]. The mechanism of action of statins is to inhibit 3-hydroxymethylglutaryl co-enzyme A reductase whilst ACEi block the conversion of angiotensin Ⅰ to angiotensin Ⅱ, which influences blood pressure homeostasis. These drug-induced physiological changes have recently been shown to have a protective effect on the bowel when it is exposed to ionising radiation. Wedlake *et al*[53] (2012) showed that in a study of 308 patients the use of a statin or stain with an ACEi significantly reduced the incidence of gastrointestinal symptoms following radiotherapy. Further prospective, randomised, blinded, adequately powered and stratified by disease stage trials with adequate follow up are required to support the use of statins and ACEi in PRD management.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy has been utilised to treat chronic PRD for several decades[54] but with insufficient evidence of its exact mechanism of action or to support its use in clinical practice. More recently HBO has been found to decrease tissue hypoxia by inducing angiogenesis in bowel affected by the ischaemic and fibrotic changes associated with chronic PRD changes[55]. Clarke *et al*[56] (2008) conducted the first randomised control trial and provided support for its use in refractory PRD. Specifically, HBO induced healing responses and was associated with an absolute risk reduction of 32%. Furthermore, bowel specific quality of life was improved. HBO treatment does require a significant time commitment, logistical hurdles and is expensive to fund. A complete regime consists of eight weeks of daily treatment in a specialist unit that typically have vast catchment areas[5].

Argon plasma coagulation

Three main strategies for managing PRD exist: Medical, surgical and endoscopic. New techniques are emerging in the endoscopy arena, such as argon plasma coagulation (APC) therapy, which followed the limited success of treating vascular telangiectasia with locally applied formaline solution. APC therapy is a noncontact thermal coagulation technique on a probe that can be passed through the scope during endoscopy. The probe delivers argon gas to bowel mucosa targeted by the endoscopist. A high voltage filament then ionises the gas which heats the mucosa and results in coagulation of tissues damaged by PRD and aims to prevent them from bleeding. So far, several case series have shown that APC reduces rectal bleeding in 80%-90% of treated patients[57]. APC should be used with caution as serious complications have been documented in as high as 26% of patients[58]. A case series of 16 patients states that it is a safe, well tolerated treatment for rectal bleeding in PRD and should be considered as first line treatment[59]. However, currently the evidence for its use in clinical practice is insufficient. There is a need for large, prospective, blinded, randomised control trials to explore the use of APC in PRD management and to explore its safety and outcomes in the short- and long-term[12].

Key research priorities

An area that requires serious consideration is clarification of the most effective - by considering both survival and quality of life parameters - radiotherapy regime for mid and lower rectal carcinomas. There is wide variation between treatment centres across the world. Short course with immediate surgery, short course with delayed surgery, long course with neoadjuvant chemotherapy then surgery and chemoradiotherapy without surgery are some of the approaches utilised to treat patients with the same stage of disease. It is concerning that without a unified approach that some centres or clinicians may be basing their clinical decisions on anecdotal evidence. A consensus meeting to address the application and modality of radiotherapy to low and mid rectal cancers could be a key step in reducing the incidence of future PRD cases.

Key research priorities revolve around the need for randomised trials of best supportative care *vs* hyperbaric oxygen or argon plasma coagulation or intrarectal formalin for bleeding associated with PRD. A large multi-centre phase three study in the United Kingdom, the Hyperbaric Oxygen Therapy (HOT-Ⅱ) study is completed, the results of which are eagerly awaited.

Further research into service provision would shed light on how best to use the resources that are currently in place. Simple amendments and interventions have the potential to improve patient care. The findings of a trial conducted by Andreyev *et al*[1] (2013) provided evidence that the use of an investigative and management algorithm for practitioners to follow improves patient symptoms when compared to current care.

CONCLUSION

A crucial step in management planning for patients with cancer is consideration of the risk-benefit ratio. Clinicians are faced with the task of weighing up the benefit of prolonged survival following surgery and radiotherapy *vs* the risks of treatment related complications such as PRD. As the number of cancer survivors continues to increase the long-term outcomes related to health and well-being, exemplified by those patients who develop PRD, becomes an ever more significant health issue. However, striving to improve cancer survivorship has meant that the recognition and management of treatment associated complications has not been prioritised. Thousands of patients with PRD are poorly managed and denied a service that is tailored to meet their needs. Although it is an uncomfortable notion we must not shy away from iatrogenic causes of patient debility[4]. Effective methods to prevent PRD and an optimal, unified strategy to manage affected patients remain elusive making PRD a well-placed focus for future research[3].

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EDITORIAL

Anastomotic leakage in rectal cancer surgery: The role of blood perfusion

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Abstract

Anastomotic leakage after anterior resection for rectal cancer remains a common and often devastating complication. Preoperative risk factors for anastomotic leakage have been studied extensively and are used for patient selection, especially whether to perform a diverting stoma or not. From the current literature, data suggest that perfusion in the rectal stump rather than in the colonic limb may be more important for the integrity of the colorectal anastomosis. Moreover, available research suggests that the mid and upper rectum is considerably more vascularized than the lower part, in which the posterior compartment seems most vulnerable. These data fit neatly with the observation that anastomotic leaks are far more frequent in patients undergoing total compared to partial mesorectal excision, and also that most leaks occur dorsally. Clinical judgment has been shown to ineffectively assess anastomotic viability, while promising methods to measure blood perfusion are evolving. Much interest has recently been turned to near-infrared light technology, enhanced with fluorescent agents, which enables intraoperative perfusion assessment. Preliminary data are promising, but large-scale controlled trials are lacking. With maturation of such technology, perfusion measurements may in the future inform the surgeon whether anastomoses are at risk. In high colorectal anastomoses, anastomotic revision might be feasible, while a diverting stoma could be fashioned selectively instead of routinely for low anastomoses.

Key words: Anastomotic leakage; Blood perfusion; Rectal cancer; Anterior resection; Diverting stoma

Core tip: Anastomotic leakage after anterior resection for rectal cancer is still common. Several preoperative risk factors may inform the surgeon of the leakage risk. The surgeon might choose to perform a diverting stoma to mitigate this risk, or to construct an end colostomy and thus avoid an anastomosis altogether. Intraoperatively, clinical judgment of the viability of the anastomosis is not reliable. However, research using blood perfusion measurement technology has evolved in recent years; technology using near-infra red light seems to be promising, allowing assessment

of the bowel perfusion. In the future, such technology may aid in the decision-making concerning colorectal anastomoses.

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INTRODUCTION

Anterior resection is considered standard procedure for patients with cancer in the mid and high rectum. With the advent of the total mesorectal excision (TME) technique, complications such as anastomotic leakage have been increasing in frequency[1]; current population-based studies indicate rates of around 10%-11%[2,3]. The impact of anastomotic leakage is considerable, leading to major morbidity and mortality[4]. Anastomotic breakdown is a multifactorial event, influenced by patient factors as well as surgical technique[5,6], although the pathogenesis has not been clearly elucidated. Axiomatically, the fundamental principles of a successful anastomosis entail anastomosing two ends of healthy bowel with adequate blood supply and lack of tension after union. The former aspect has been the subject of considerable debate but perhaps less investigation. Surgeons' ability to predict anastomotic leakage by judging the appearance of the serosa has been shown to be highly unreliable[7]; in current practice, only risk factor appraisal is available to guide the surgeon when making decisions whether to, *e.g.*, perform a diverting stoma, revise the anastomosis, or fashion an end colostomy. However, the advent of new studies and technologies may soon provide surgeons with effective means of assessing anastomotic viability.

Blood flow measurement technology

A plethora of methods has been used to determine blood flow or oxygenation in general surgery[8]. The most commonly used method has been laser-Doppler flowmetry (LDF), the principle of which is to measure the Doppler shift - the frequency change that light waves undergo when reflected by moving objects, *e.g.*, red blood cells. Laser light is emitted and the backscattered light is collected, producing an output signal that is proportional to the number and velocity of the moving blood cells in the measured volume. The method has proven to be reproducible and has been correlated with other flow measurements, but LDF measurements are easily perturbed by motion artefacts and require direct tissue contact, which may disturb local blood flow. In order to measure oxygenation, visible light spectrophotometry offers shallow penetration of tissue at the capillary level, while near-infrared (NIR) light goes deeper and allows for a global oxygenation assessment. Spectrophotometry systems employ devices that emit light on or near the bowel wall - this light penetrates, diffuses and is subsequently analysed as it re-emerges variably coloured, according to the oxygenation level. In combination with injection of fluorescent agents, perfusion may also be evaluated by the NIR technique, which has lately been introduced into clinical studies[8].

Vascular anatomy and the anastomosis

The importance of the knowledge of gross vascular anatomy cannot be overstated. Much attention has been directed at the colonic limb of the colorectal anastomosis, as evidenced by the controversy surrounding high ligation of the inferior mesenteric artery - high arterial ligation may compromise blood supply to the oral part of the anastomosis, if the sigmoid or descending colon is used and the marginal artery is not present or patent.

A Japanese group performed LDF on patients operated for cancer of the rectum and the sigmoid colon; colonic measurements were made before and after clamping, and showed marked reductions in perfusion after clamping, particularly for high tie patients[9]. Similar methodology was used by a Dutch group, but these authors compared measurements made immediately after laparotomy to measurements made before fashioning the anastomosis, and found that there were blood flow reductions in high tie patients; however, low tie patients displayed an increase in blood flow, a difference between groups that was statistically significant[10].

Observational studies on the clinical impact of high ligation have not consistently shown that this is a risk factor for anastomotic leakage[3,11,12], while no randomized clinical trial data are available. It is entirely possible that any perfusion compromise is uncommon due to collateral networks and also that surgeons adjust the colonic resection margins when faced with perfusion loss; thus, any perfusion disadvantage rendered by the high tie on the oral part of the anastomosis might be mitigated.

Using the TME technique, dissection at the level of the pelvic floor is sometimes extensive. The rectal blood supply after anterior resection is dependent on the inferior and the variable medial rectal arteries, but perfusion to the different parts of the rectum is not equally distributed. Angiographic findings suggest that the lower rectum has a sparse network of intramural collaterals, in contrast to the more vascularized upper and mid rectum[13]; this might explain the lower leak rate when performing partial mesorectal excision (PME), an oncologically feasible alternative for tumours in the upper rectum[14]. Moreover, the dorsocaudal aspect of the rectum is sparsely perfused[15], lending biological rationale to the clinical experience that most anastomotic leaks are located in the posterior aspect of the rectum[16]. Furthermore, laser-Doppler blood flow measurements recently made by our group have indicated that TME surgery, as compared to PME, markedly reduces perfusion in the posterior quadrant of the rectum[17].

An Italian group considered both the proximal and distal circulations in surgery for rectosigmoid cancers, where TME surgery was performed for cancers in the middle and lower rectum. Low tie was routinely performed, and measurements were made at the colonic serosa in and at the rectal mucosa, after division of the artery and before fashioning the anastomosis. The authors noted that most patients displayed colonic as well as rectal blood flow reduction, but the latter was more predictive of anastomotic leaks[18].

More recently, there have been several studies on NIR with fluorescent agents in the setting of colorectal surgery in general, including anterior resection. In a large series of open colorectal procedures, imaging of the bowel serosa prompted surgeons to revise transection margins in 16% of cases; reoperation for anastomotic leakage was decidedly less common in the group using this technique, compared to matched but historical controls[19]. As the bowel wall is difficult to assess aborally to the anastomosis in particularly low anterior resection, mucosal evaluation might be more important. Initial experiences have shown that reliable imaging of the perianastomotic region could be achieved[20], and suggested that revision of anastomoses, which displayed questionable perfusion, decreased leak rates[21]; in another study on NIR, the perceived imaging results provided confidence to avoid a diverting stoma in low anterior resection cases[22]. These studies all share small sample sizes and results cannot be validly extrapolated. However, the largest and most recent study to date on NIR included 139 laparoscopic colorectal resections, where all anastomoses were evaluated; in eleven patients, poor perfusion changed operative strategy, in most cases leading to an altered transection margin. In these patients, no leaks were detected[23]. However, no control group was enrolled and most anastomoses were high, making even this study difficult to apply to low rectal cancer. Arguably, the very low anastomoses may be challenging to revise, as any attempt may lead to a short and possibly damaged rectal stump; this would subsequently demand a purse string suture, hand-sewn under pressure, in order to be able to insert another circular stapler.

Future implications

Preoperative risk factors for anastomotic leakage have been identified[24], and serve as a means to select patients to either anterior resection or operation with end colostomy. The unselected use of a diverting stoma in low anterior resections seem to reduce anastomotic leakage in a trial setting[25], while recent audits provide data that favour more selective use, tailored to the individual patient risk factor profile[26].

Ideally, the experimental data on rectal perfusion above could be translated into clinical practice. First, the anatomical knowledge on rectal vasculature may inform the surgeon that deep extensive dissection in the posterior aspect of the rectal stump may be potentially harmful. Second, blood flow measurements before and after the construction of the anastomosis could inform the surgeon that this particular anastomosis is at risk, and subsequently the case for anastomotic revision (for high anastomoses) or a diverting stoma (for low anastomoses) could be stronger. Presently, it seems that the evolving NIR methodology may offer such an opportunity in the near future. Naturally, such a strategy would need extensive support from more experimental and clinical data, but would provide a valuable tool for the colorectal surgeon.

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REVIEW

Evolution and advances in laparoscopic ventral and incisional hernia repair

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Abstract

Primary ventral hernias and ventral incisional hernias have been a challenge for surgeons throughout the ages. In the current era, incisional hernias have increased in prevalence due to the very high number of laparotomies performed in the 20th century. Even though minimally invasive surgery and hernia repair have evolved rapidly, general surgeons have yet to develop the ideal, standardized method that adequately decreases common postoperative complications, such as wound failure, hernia recurrence and pain. The evolution of laparoscopy and ventral hernia repair will be reviewed, from the rectoscopy of the 4th century to the advent of laparoscopy, from suture repair to the evolution of mesh reinforcement. The nuances of minimally invasive ventral and incisional hernia repair will be summarized, from preoperative considerations to variations in intraoperative practice. New techniques have become increasingly popular, such as primary defect closure, retrorectus mesh placement, and concomitant component separation. The advent of robotics has made some of these repairs more feasible, but only time and well-designed clinical studies will tell if this will be a durable modality for ventral and incisional hernia repair.

Key words: Evolution; Advances; Laparoscopic ventral hernia repair; Laparoscopic incisional hernia repair; Laparoscopic ventral incisional hernia repair; Ventral hernia repair; Incisional hernia repair; Ventral hernia; Incisional hernia

Core tip: This manuscript reviews the evolution and advances of laparoscopic ventral and incisional hernia repair. We discuss preoperative considerations,

intraoperative factors including the type of mesh in conjunction with placement and fixation of the mesh, as well as postoperative issues such as complications, recurrence and quality of life. New evolving techniques such as minimally invasive components separation and robotic surgery are reviewed. In addition, some of the future directions of this exciting and rapidly developing field are explored. We hope you find this review helpful in summarizing the past advances in hopes that it may illuminate new avenues of research in minimally invasive ventral and incisional hernia repair.

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BRIEF HISTORY ON THE EVOLUTION OF LAPAROSCOPY

The concept of minimally invasive surgery has been present for millennia, and started with the advent of endoscopy of the rectum, vagina, ear, and nose. Hippocrates first described a rectoscope in the 4th century[1]. Later in the 10th century, Albukasim, an Arab physician, developed methods of speculum illumination with candlelight and mirrors. In the early 19th century, Phillipp Bozzini utilized the centrally bored mirror for his cystoscope. In 1879, Maximilian Nitze improved the cystoscope, adding a platinum wire electric light source and developing the first endoscopic photographs[2].

In 1901, the German surgeon George Kelling insufflated a dog's abdomen and viewed the viscera with the Nitze style cystoscope. A Swedish surgeon, Hans Christian Jacobaeus, performed the same procedure that year and coined the term laparoscopy. The new procedure of diagnostic laparoscopy then spread around the world. Innovations were rapidly added, such as needle induced pneumoperitoneum, 45-degree laparoscopes, trocar insertion, and insufflation machines. In 1933, Heinz Kalk, a German gastroenterologist, pioneered many of these techniques. He developed a dual trocar technique and a wide-angle scope to obtain biopsies. Visualization improved remarkably in the 1950's with the Hopkins lens and fiberoptic cold illumination; however, interest in these techniques waned for several decades. Gynecologists began experimenting again in the 1970's with tubal ligation, oocyte harvesting, and tumor biopsies[3]. In 1971, Harrith Hasson developed a technique to safely enter the abdomen with his new trocar. Kurt Semm performed the first laparoscopic appendectomy in 1983, and went on to perform a total of 20000 procedures. The German surgeon Erich Muhe performed the first laparoscopic cholecystectomy in 1985, but was not initially received well by his peers. This was followed by an explosion of laparoscopic procedures, including the first laparoscopic ventral hernia repair done by LeBlanc and Booth[4] in 1993.

TRANSLATION TO HERNIA REPAIR

While the incidence of primary ventral hernias has been relatively static, the incidence of incisional ventral hernias has increased as abdominal surgery has become more prevalent. In the United States, 4 to 5 million laparotomies are performed each year, and it is estimated that three to as high as fifty percent of these patients develop incisional hernias, although the exact incidence is unknown[5-8].

Prior to 1993, all ventral and incisional hernias were repaired with open exposure. Primary suture repair remains one of the oldest techniques, but it has been shown to have a high recurrence rate with wide variability, ranging from 8% to 63%[8-10]. The invention of prosthetics has revolutionized ventral hernia repair, leading to a significant reduction in the recurrence rates, ranging as low as 1% to 14% in some studies[8,9]. In the best prospective, randomized controlled trial of mesh based ventral incisional hernia repair, the recurrence rate was 24% with an appropriate follow-up period of 3 years[10]. The gold standard repair widely reinforces or bridges the defect, with mesh placed posterior to the fascia either in a retrorectus, preperitoneal, or intraperitoneal anatomic space. This takes advantage of LaPlace's Law, distributing intra-abdominal pressure across the overlapping mesh instead of only at the hernia defect[7]. However, the need for an extensive dissection, which was associated with postoperative wound-related complications, has driven surgeons to search for new techniques. This was translated to laparoscopic surgery in hopes of decreasing the morbidity of open surgery, including wound complications, postoperative pain, hernia recurrence, and delayed return to normal function[7,11]. Nowadays, about 20% to 27% of repairs are performed laparoscopically[11,12]. One challenge for the minimally invasive approach has been creating a more anatomic, physiologic abdominal wall reconstruction.

The general steps in laparoscopic ventral and incisional hernia repair include safe entry into the peritoneum, insufflation, careful lysis of intra-abdominal adhesions, reduction of the hernia contents, wide, typically intraperitoneal mesh coverage of the defect, and mesh fixation[8,11]. Primary defect closure or concomitant component separation can be performed in selected patients[13,14]. There is wide surgeon variability in preoperative selection of patients for open *vs* laparoscopic repair. These clinical decisions are based on patient factors such as obesity, previous operative history, and size and location of the hernia defect. Furthermore, there are surgeon specific variations in mesh fixation techniques, and differences in the type and size of mesh used[8,11].

PREOPERATIVE CONSIDERATIONS

Any given patient with a ventral or incisional hernia must be evaluated for open *vs* laparoscopic repair. Past data has pooled primary ventral hernias with ventral incisional hernias; however, the behavior of these two types of hernias is most likely different, and should not be overlooked during preoperative assessment. For example, Stirler *et al*[15] showed that laparoscopic repair of incisional hernias on average results in more adhesiolysis, a higher conversion to open, longer operative times, and a higher recurrence rate when compared to primary ventral hernias.

For the majority of surgical specialties, it is well established that patients' preoperative health status can significantly impact postoperative outcomes. Laparoscopic ventral and incisional hernia repairs are not an exception to this principle. Known risk factors for incisional hernia include male sex, advanced age, obesity, tobacco use, chronic obstructive pulmonary disease, immunosuppression, diabetes mellitus, and history of an emergent operation[7,8,16]. All these factors should be addressed during preoperative counseling. Postoperative wound-related complications have also been identified as a major risk factor for recurrence after laparoscopic ventral hernia repairs[7]. Wound infections may increase the incidence of incisional hernias up to 80%[10,17]. Our institution has previously identified predictive factors for postoperative wound infections after ventral and incisional hernia repairs using the American College of surgeons national surgical quality improvement program (NSQIP) database[18]. We found several risk factors for postoperative wound infections after ventral/incisional hernia repair including high body mass index (*i.e.*, greater than 30 kg/m^2), tobacco use, high American Society of anesthesiologists class (*i.e.*, 3 or 4), open surgical approach, prolonged operative times, recurrent hernias, and inpatient status. In addition, with the widespread use of smartphones, other investigators created a smartphone application, which uses an externally validated formula to calculate the risk of wound related complications and the associated cost of care after ventral hernia repairs[19]. These novel methods of patient education may provide motivation to modify these risk factors.

Martindale and Deveney[20] provide an extensive review of perioperative interventions aimed at decreasing wound infection and recurrence. Smoking cessation, blood glucose control, and obesity are again reviewed. Smoking cessation for 4 wk is associated with a decrease in complication rate from 41% to 21%. Preoperative blood glucose control with hemoglobin A1c less than 7% is desired, and perioperative blood glucose should be between 140-160 mg/dL. Obesity is more difficult to control; however, body mass index correlates strongly with recurrence. Many surgeons will not electively repair ventral hernias in patients with a body mass index over 50. In this setting, it has been suggested that aggressive attempts at weight loss including weight loss surgery should precede a futile attempt at ventral hernia repair. Other interventions include preoperative antibiotics and optimizing nutrition. Ríos *et al*[21] showed prophylactic antibiotics decrease wound infection rates in incisional hernia repair from 26.3% to 13.6%. Nutrition is a vital part of healing, and preoperative nutrition may decrease recurrence. Arginine and fatty acid mixtures have been shown to decrease perioperative complications, infection related morbidity, and length of hospital stay[20].

INTRAOPERATIVE CONSIDERATIONS

Selection of mesh

An ideal mesh has sufficient strength, is chemically stable, is easily sterilized, resists infection, is non-carcinogenic, limits inflammatory foreign body reactions, and incorporates (heals) well into the abdominal wall[22]. The latter point is important as many ventral hernia recurrences occur at the interface of the mesh and the wounded abdominal wall, a form of acute wound failure[23,24]. Materials fitting these prerequisites were not developed until the 1900s. Silver was used first, followed by stainless steel and other metals[22]. Polypropylene mesh was not created until 1959. Since then, several categories have been produced: Non-absorbable synthetic meshes, composite meshes, absorbable meshes and tissue-based biologic implants.

Permanent meshes, such as polypropylene and polyester, were use when laparoscopic hernia repairs were first started. However, uncoated meshes were soon abandoned due to the large number of visceral adhesion related complications, such as fistula, bowel obstruction, and complications during re-operative adhesiolysis[24]. Table 1 summarizes some of the main advantages and disadvantages of these meshes.

Composite meshes were developed for laparoscopic intraperitoneal onlay placement, and are the ones usually used for laparoscopic hernia repair[24]. They combine the strength of permanent mesh with a bowel-protective anti-adhesion barrier. The parietal peritoneum side is composed of permanent mesh, usually polypropylene or polyester, which provides structural strength and promotes tissue inflammation and ingrowth. The visceral facing side of the mesh requires an anti-adhesion barrier. Most of these barriers are absorbable, with the exception of expanded polytetrafluoroethylene[25]. Table 2 provides a general overview of the most common composite meshes used for laparoscopic ventral and incisional hernia repair and relevant research. Unfortunately, there is a lack of high-level clinical evidence to direct surgeons and patients as to the safest and most effective material.

New meshes are being developed for potential use in laparoscopic ventral and incisional hernia repair (Table 3). Recently, absorbable synthetic meshes were developed to have a better infection resistance profile, but risk recurrence by weakening during the resorption process[37]. To date, at least 3 new, slow resorbing meshes have been developed, including

Table 1 Advantages and disadvantages of permanent synthetic mesh materials (polyester and polypropylene)

Advantages	Disadvantages
Permanent synthetic mesh, either woven or knit	Risk contraction, chronic inflammation, stiff abdominal wall, chronic pain especially with heavy weight PP
Provides strength by stimulating inflammation and abdominal wall ingrowth	PE with possible higher infection and recurrence *vs* PP
PE has less contraction than PP	Should not be placed in contact with bowel as inflammatory response increases adhesions to viscera
Lightweight PP has less foreign body response, more pliable, more ingrowth[25]	Increased risk of fistula, bowel obstruction, and re-operative complications[26]
Sometimes able to salvage lightweight mesh after infection due to improved antibiotic penetration[25]	Enterotomy and/or bowel resection upon re-operation are almost four times greater with prior use of mesh, with most of these being uncoated mesh[27]

PE: Polyester; PP: Polypropylene.

Table 2 Advantages and disadvantages of commonly used composite meshes

Mesh	Abdominal wall side/visceral side	Advantages	Disadvantages
Composite meshes[24]	Permanent mesh/anti-adhesion barrier	Permanent mesh for inflammation, fibrosis, and abdominal wall ingrowth and strength Visceral side designed to prevent adhesion related complications	No level Ⅰ evidence of the superiority of one mesh over another. Some differences have been noted in animal models, although adhesion prevention is similar for most[28]. A multi-center, human study is underway to better determine the characteristics of these composite meshes (NCT01355939)[29]
Dualmesh[25]	Micropore ePTFE/Macropore ePTFE	Minimal inflammatory reaction[22] Adhesions less tenacious than all other meshes[24,30] Less adhesiolysis time/mesh surface area compared to composix[24]	PTFE has higher rates of bacterial adherence and less resistant to colonization[31,32] Higher risk of explantation in open cases (14.2%), but not laparoscopic cases (4.6%)[32] Limited fibrous tissue ingrowth and incorporation[22]
Composix™[25]	PP/ePTFE	PP thought to promote better ingrowth and inflammation	Adhesions predominately found due to mesh eversion at periphery[24] Possible increased infection risk (8% in one series)[33]
Parietex[30]	PET/type Ⅰ collagen, polyethylene glycol, and glycerol	United States evaluation showed adhesions in 18% of patients, *vs* 77% when uncoated PE was used	Collagen film absorbed quickly (20 d)[34]
Proceed[30]	PP encapsulated by PDS/oxidized regenerated cellulose	Lightweight, macro-porous mesh[34]	Incomplete peritoneal mesothelialization over graft Induced dense adhesions in rabbit models[35]
C-QUR[30]	PP/omega 3 fatty acid gel	Less contracture in rabbit model[30]	Poor incorporation strength in rat model[28]
Sepramesh[25]	PP/sodium haluronate and carboxy - methylcellulose	Low adhesion coverage and good incorporation[28]	Inflammation induces breakdown of the coating, resulting in delayed adhesion formation[28]

ePTFE: Expanded polytetrafluoroethylene; PDS: Polydioxanone; PE: Polyester; PET: Polyethylene terephthalate; PP: Polypropylene.

BioA® tissue reinforcement by Gore®, TIGR® Matrix by Novus Scientific[38], and Phasix™ mesh by Bard[39]. These meshes might be used for laparoscopic repair in contaminated fields, including parastomal hernia repair.

Titanized mesh might help reduce inflammatory, foreign body reactions and reduce pain after laparoscopic repair, although results have yet to be confirmed in randomized or comparative studies[42]. A third kind of mesh helps prevent migration and reduces the amount of mesh fixation needed. Covidien created a new, self-gripping mesh currently being used in laparoscopic inguinal, as well as open ventral and incisional hernia repairs. ProGrip™ is a polypropylene mesh that includes small absorbable "hooks" designed to promote abdominal wall adhesion, prevent migration, and decrease the number of fixation points needed. One study asserts less postoperative pain after inguinal hernia repair, but this has not been observed in other studies[43,44]. This mesh might be used in order to decrease the number of tacks and sutures needed for fixation.

Placement and fixation of mesh

Laparoscopic lysis of adhesions is performed prior to mesh placement. Multiple instruments exist for this application, including newly developed ultrasonic shears and bipolar devices. However, there is currently no level Ⅰ data on the superiority of one over the other. Intraperitoneal mesh is placed once the hernia defect is identified and prepared, and there are many variations

Table 3 Advantages and disadvantages of newly developed meshes

Name	Materials	Properties	Current research
BioA® Tissue Reinforcement by Gore®[36,37]	3D matrix copolymer of polyglycolic acid and trimethyl carbonate	Absorbed in 6 mo	Prospective, observational study (NCT01325792) to evaluate single-staged open ventral incisional hernia repair with midline reinforcement in clean contaminated and contaminated wounds. Early one-year results demonstrated a hernia recurrence rate of 14% and an 18% infection rate[36]
TIGR® Matrix by Novus Scientific[38]	Knit mesh of fast absorbing and slow absorbing glycolide, lactide, and trimethylene carbonate fibers	First fiber retains strength for 1-2 wk Second fiber retains strength for 6-9 mo Stimulates neovascularization and a high level of type Ⅰ collagen ingrowth Absorbed in 3 yr	One case report of onlay use for open ventral hernia repair[38] Currently three-year safety and performance study showing use for inguinal hernia repairs in humans[40]
Phasix™ mesh by Bard[39]	Monofilament, knit mesh of poly-4-hydroxybutyrate	Minimal absorption in 12-26 wk Porcine model shows 18% strength than natural abdominal wall at 48 wk Manufacturer claims hernia repair support for 12-18 mo	Launched in 2013 and currently there are no published results in human subjects
Titanized mesh[41]	PP mesh with relatively inert titanium coating	Retains strength of PP mesh Titanium retards inflammation and decreases foreign body reaction[42]	Lower analgesic use (1.6 d *vs* 6.1 d, $P < 0.001$) and a quicker return to baseline activity (6.9 d *vs* 9.7 d, $P < 0.001$) when compared to parietex mesh. Also less postoperative pain at 1 mo, but no difference at 6 mo
Progrip by Covidien[43]	Self gripping PP mesh with small, absorbable hooks	Promotes abdominal wall adhesion, prevents migration, and decreases the number of tack or sutures fixation points	Has been used in laparoscopic inguinal, ventral, and incisional hernia repairs One study asserts less postoperative pain after laparoscopic inguinal hernia repair, but another shows no difference with open repair[43,44] Operative times may be less

PP: Polypropylene.

in the fixation of that mesh. Most surgeons cover the hernia defect with a 3 to 5 cm overlap circumferentially, and then secure the mesh in place with transfascial sutures and/or intra-abdominal peritoneal tacking[8,11]. Little is known about the physiologic movement of mesh *in vivo* during physiologic stress, however, the ideal technique would prevent migration and folding of the mesh[45].

Over the years, surgeons have varied greatly in the number of tacks, the number of sutures, as well as the materials of tacks and sutures used for fixation[46]. The goal has been to balance adequate fixation to prevent recurrence against excessive fixation that can lead to unnecessary pain. It is also important to minimize the amount of permanent component of mesh without sacrificing overlap, because large meshes require multiple, potentially painful fixation points, and have an increased risk of chronic pain from foreign body reaction[47]. The use of transfascial sutures may allow the surgeon to limit overlap to only 3 cm, whereas the use of tacks requires at least 5 cm of overlap[48]. An intuitive understanding of biomechanical forces suggests that transfascial sutures provide better fixation, as they are secured to the strong anterior fascia. Unfortunately, transfascial sutures risk abdominal wall nerve entrapment and muscle strangulation, which is thought to contribute to the significant postoperative pain[46]. Tacks provide a 3.8 to 6.8 mm posterior to anterior purchase of the abdominal wall and do not capture the anterior fascia[49]. The tensile strength of sutures was 2.5 times greater than that of tacks in a pig cadaver model; however, a laparoscopic pig model showed no signs of migration or recurrence, and no additional fixation strength at 4 wk when only tacks were used[46]. More tacks are used than suture, and increasing the number of tacks theoretically cause more pain. Schoenmaeckers *et al*[50] demonstrated that decreasing the average number of tacks to 20 from 40 significantly decreases their visual pain analog scale at 3 mo from 5.8 to 1.8 out of 100 ($P = 0.002$), which is not likely to be clinically significant. Of note, this study did not control for the type of mesh.

Recently absorbable tacks have been developed, with the objective of reducing pain, foreign body reactions, and adhesion formation. One porcine model proved similar tensile fixation strength between a 4.1 mm poly (glycolide-co-L-lactide) tacks and a control titanium tacks at 6 mo and less tensile strength with 6.8 mm poly (D,L)-lactide tacks[49].

Many studies compare sutures *vs* spiral tackers; however, many of these studies do not adequately control for patient demographics, hernia size, technical variations, suture type, and mesh size and type, to name a few. Multiple reviews largely showed no optimal technique to prevent recurrence and reduce pain. A recent systematic review by Reynvoet *et al*[46] grouped 25 prospective and retrospective studies from 1999 to 2011 into suture only repair, tack only repair, and both sutures and tacks. Other reviews included many of the same studies, however, this study used the DerSimonian-Laird random effects model to assign relative weights in relation to study sample size. The hernia recurrence rate for the suture only group (0.9%CI: 0%-1.7%) was less than the tacks only group (3.4%CI: 2.4%-4.5%) and the combination of suture and tack group (2.5%CI: 1.3%-3.7%). As the CIs were overlapping, there was no significant difference in recurrence rate between the three fixation techniques. This is consistent with other past reviews[46,48,51].

The review by Reynvoet *et al*[46] was unable to statistically analyze the outcome of pain following hernia repair, as there was not a standardized way between studies to report pain outcomes. Chronic pain was defined as pain anywhere from 4 wk to 6 mo. Narcotic use, pain analog scales, and quality of life surveys measured pain threshold. Despite these methodological variations between individual studies, Reynvoet *et al*[46] concluded that literature currently shows no significant difference in postoperative pain between suture and tack repairs.

In contrast, the WoW trial (with or without sutures), a randomized controlled trial from Belgium, showed significantly more pain with "sutures and tackers" *vs* a "double crown" tack arrangement[52]. Patients were asked to draw a line representing postoperative pain; significant pain was defined as a visual analog scale score greater than 1 cm. There was a significant difference at 4 h when coughing, and 3 mo at rest (31.4% *vs* 8.3%, P = 0.036). Secondary outcomes were reported, showing less operative time in the tacks only group and similar hernia recurrence at 24 mo. However, the main limitation was the somewhat arbitrary 1 cm visual analog scale for pain (VAS) cutoff for significant. A similar study by Wassenaar *et al*[53] used VAS mean scores instead of the 1 cm cutoff. It showed no difference between double crown tackers, absorbable suture and tackers, and non-absorbable suture and tackers.

New less invasive, less painful alternatives for mesh fixation have been developed for hernia repair. Fibrin sealant initially was used for inguinal hernia repair; however, it has also been studied for laparoscopic incisional repair[54]. In 2011, a randomized prospective study was performed comparing the use of fibrin sealant only to the use of titanium tacks only after laparoscopic umbilical hernia repair[55]. At 4 wk follow-up, there was significantly less acute postoperative pain both at rest and during activity, as well as shorter convalescence (median 7 d *vs* 18 d, P = 0.027) with use of fibrin sealant. At 1-year follow-up, these differences were not significant, and the hernia recurrence rate was predictably higher in the fibrin only group, though statistically insignificant (26% *vs* 6%, P = 0.18). Another study used fibrin sealant in the hernia sac after laparoscopic hernia reduction[56]. This showed a significant reduction in the incidence of seromas at 1 mo (72% control *vs* 28% with sealant, P = 0.002). Although promising for some limited applications, the current data does not show an advantage to routine use of fibrin sealant, and shows a trend toward increased recurrence rates if it is used alone for mesh fixation.

EVOLVING TECHNIQUES

Primary defect closure

Once the hernia contents are reduced, the defect is measured and prepared for mesh placement[11]. Traditionally, a tension free repair is created by placing mesh over the defect and securing it in place. Some surgeons prefer to close the hernia defect primarily prior to this step. Three main laparoscopic approaches have been described: (1) interrupted percutaneous closure with suture passer; (2) intra-corporeal suturing; or (3) Endo Stitch™ suturing with a knot pusher[13]. Barbed suture can be used for defect closure or mesh fixation in order to decrease the tension needed when placing each suture. Lyons *et al*[57] used a porcine model to show that barbed suture requires the application of 75% less force than conventional suture, while maintaining adequate mesh fixation strength.

There are many proposed advantages of performing primary defect closure before applying the mesh[13,58]. Re-approximating the abdominal fascia is thought to be a more physiologic repair, and thus stronger. Additionally, it provides a greater surface area of abdominal wall for the mesh to be in contact with. Furthermore, it prevents postoperative bulging of the mesh into the defect. Bulging is not ideal for cosmesis, and may allow mesh to come closer to the skin surface, which can increase the risk of mesh infection and erosion. Conversely, closing the defect increases tension, which may be counterproductive. Also, placement of extra suture in the abdominal wall increases the risk of postoperative pain. Many surgeons have yet to adopt this technique, most likely due to the technical difficulty, and the current lack of evidence suggesting its superiority when compared to mesh placement alone.

Current literature lacks randomized control trials examining the effectiveness of concomitant primary defect closure during laparoscopic ventral and incisional hernia repair. Nguyen *et al*[58] performed a systematic review of 11 studies, including case series and retrospective reviews. Recurrence rate ranged from 0% to 7.7%, and seroma rates were 0% to 11.4%. Three of the retrospective reviews included compared laparoscopic hernia repairs with and without primary defect closure. Clapp *et al*[59] was the only risk adjusted study and followed 72 cases for an average of 24 mo. Hernia recurrence was 16.7% in the group without primary defect closure, whereas no recurrences were seen in the group with primary defect closure. Bulging in this study was decreased from 69.4% in the non-closure group to 8.3% in the closure group. In addition, superficial wound infections were decreased from 13.9% to 8.3%, and the incidence of seroma was decreased from 27.8% to 5.6%. Another retrospective comparative review of 128 patients also reported low recurrence rates after concomitant primary defect closure (6.25%), but this was not significantly different when compared to the group without primary defect closure[13]. Interestingly, the incidence of seroma formation was higher in the group with primary defect closure than the group without primary defect closure (11.4% *vs* 4.3%).

Component separation

The separation of components technique includes various methods of dissecting the abdominal wall layers in order to advance facial edges and decrease physiologic tension. In 1990, Ramirez *et al*[60] first described releasing the external oblique aponeurosis alone, which allows approximately 5 cm of unilateral fascia advancement at the umbilicus, and 3 cm inferiorly and superiorly. The drawback is that it weakens the abdominal wall, especially laterally at the semilunar line[61]. In 2000, Lowe *et al*[62] combined an open technique with balloon dissection endoscopy. A few years later, Rosen *et al*[63] began separating the external and internal oblique muscles laparoscopically, followed by release of the external oblique aponeurosis. In the morbidly obese population, the presence of thick subcutaneous tissue can make this last technique challenging. After laparoscopic myofascial release, the overlying attached subcutaneous tissue limits movement of that fascia toward the midline[64]. This restricts the advancement to 86% of that of the open release[63].

Although minimally invasive separation of components provides less myofascial release, it avoids creating large skin flaps and spares vital perforating vessels[61,64]. On the other hand, open technique allows excision of dystrophic and tissue expanded skin in conjunction with the hernia sac. One could assume that subsequent advancement of normal skin into the wound may lead to better wound healing and cosmetic result. However, recent studies note a decrease in wound complications with the minimally invasive approach, without significantly affecting recurrence rates[64]. A systematic review comparing minimally invasive component separation with open component separation included 7 non-randomized controlled studies and 56 case series with a total of 3055 patients[61]. Minimally invasive component separation as compared to open component separation resulted in lower rates of total complications (20.6% *vs* 34.6%), superficial wound infection (3.5% *vs* 8.9%), necrosis (2.1% *vs* 6.8%), and hematoma/seroma (4.6 % *vs* 7.4%). Open component separation had a lower rate of recurrence (11.1% *vs* 15.1%), possibly due to a higher rate of simultaneous midline mesh repair in this group. They went on to perform a meta-analysis of the 7 non-randomized controlled studies, which included 387 patients. This showed a significant decrease in skin dehiscence (OR = 3.18) favoring minimally invasive component separation.

Most studies use variations of the Rosen anterior release technique. Posterior component release techniques have also been described, most notably the transversus abdominis muscle release[65]. This involves dissection in the retrorectus space to the semilunar line. The transversus abdominis muscle is then divided vertically that allows entry to the preperitoneal space below, dissection is carried laterally, and a mesh is placed as a sublay. This dissection is tedious and theoretically carries higher risk with a wider learning curve due to the presence of neurovascular structures. It is therefore rarely performed laparoscopically. However, the added dexterity of robotics make the minimally invasive technique feasible.

Multiple concomitant procedures

Ventral and incisional hernias are relatively common in patients requiring other procedures, such as cholecystectomy and bariatric procedures. Previous studies have shown a high recurrence rate and complications rate with ventral and umbilical hernia repair during bariatric procedures[66]. However, a recent retrospective review of 54 patients reported a favorable experience with laparoscopic mesh repair after gastric banding, sleeve gastrectomy, and Roux-en-y gastric bypass[67]. There were no mesh infections and only one hernia recurrence after 12 mo of follow-up. Eleven percent of patients had complications including leak, abdominal wall hematoma, and pulmonary embolism. This was consistent with expected outcomes for bariatric surgery.

Similar results were not obtained when ventral hernia repair was performed with cholecystectomy. Orr *et al*[68] queried the NSQIP database and found 357 cases of simultaneous cholecystectomy and ventral hernia repair. Stepwise multi-variable logistic regression analysis was performed for over 50 risk factors in the NSQIP database, comparing these to 74019 cases of cholecystectomy alone. This model determined that patients undergoing the combination procedure were 2.4 times more likely to have a wound complication, 3.1 times more likely to have sepsis or septic shock, and 2.8 times more likely to have pulmonary complications. The study was limited as it was only able to analyze 30-d outcomes. Also, it was not able to separate out which patients had mesh repair or suture repair. Nevertheless, this study gives great pause to surgeons promoting laparoscopic hernia repair during cholecystectomy.

Avoiding port site hernia

The rate of incisional hernias due to previous laparoscopic port placement is 1% to 22%, which has stimulated interest in more advanced minimally invasive options[69]. Bucher *et al*[69] also reported a case series of 52 patients undergoing single port ventral and incisional hernia repair through one 10-mm endoscope with a working channel. There were no conversions to open and no morbidity, with exception of two seromas. No recurrences were noted at 16 mo. Other surgeons seek to avoid 10-mm ports altogether. Agarwal *et al*[70] described a technique of introducing the mesh through a port placed in the hernia defect. This obviated the need for a 10-mm port in the flank.

Natural orifice transluminal endoscopic surgery

Natural orifice transluminal endoscopic surgery (NOTES) continues to be explored as a future option for general surgery. One case report describes repairing an umbilical port site hernia through a 2 cm incision in the posterior vaginal fornix[71]. Panait *et al*[72] reported a series of 107 patients undergoing transvaginal appendectomy, cholecystectomy, and ventral hernia repair. Proponents of this approach claim a potential benefit in cosmesis, decreased pain, early return to work, decreased port site complications, and specific advantages in the obese population. Most agree that NOTES operations for hernia repair increase the risk of a major complication, and these techniques should strongly be considered as experimental for now and performed under institutional research protocols.

Robotic surgery

The use of the da Vinci robot has expanded since its approval by the Food and Drug Administration in 2000[73]. Initially applied for hysterectomy and prostatectomy, it has recently been used for an increasing number of general surgery procedures, including Nissen fundoplication, single site cholecystectomy, colectomy, and ventral or incisional hernia repair. The magnified, three-dimensional high-definition view, computer-aided elimination of tremor, and seven degrees of freedom at the distal ends of the instruments with superior maneuverability, have led to its increasing adoption by several prominent surgeons[74]. In fact, LeBlanc *et al*[75] presented his early experiences with robotic approach at a recent American college of surgeons meeting, asserting its role in replicating open technique with minimally invasive methods.

Many surgeons are currently utilizing the robot simply to facilitate their ability to suture the hernia defect closed, and thus place the mesh as an intraperitoneal onlay. Gonzalez *et al*[76] compared a standard laparoscopic intraperitoneal mesh placement technique without defect closure, to a similar technique, which utilized the robot to close the hernia defect. They found an increased operative time for the robot with no difference in wound complications or recurrence. In our practice (AC-Greenville), we have developed a robotic approach to replicate the open Rives-Stoppa retromuscular incisional hernia repair technique. We are able to perform a retrorectus dissection, with or without the addition of a transversus abdominis release, or posterior component separation. We then suture the posterior rectus sheaths closed in the midline, followed by uncoated polypropylene mesh placement in the retrorectus space, and closure of the abdominal wall defect. A case controlled retrospective cohort study comparing our robotic Rives-Stoppa to the open technique favored the robotic approach with less blood loss and a shorter length of stay with no difference in operative time or direct hospital cost. Surgical site infection was 9.5% in the open group and 0% in the robotic group (P = 0.48)[77]. The sample size was small, which increased the likelihood of type Ⅱ statistical error. Like any new operation, there is a steep learning curve. On the other hand, the ergonomic nature of the robotic system may allow a novice user to rapidly progress. Initially, the robotic retrorectus mesh repair with simultaneous posterior component release was taking upwards of 6 h to perform. With some technique modifications and experience, we have been able to decrease operative times into the 2.5-4 h range depending upon the degree of intraperitoneal adhesions. Interestingly, the initial cost analysis suggests that this repair is equal to open repair. Decreased cost with robotic use is not unprecedented. In fact, one study in the United States showed decreased costs with robotic single site cholecystectomy *vs* laparoscopic cholecystectomy ($1319 *vs* $1710, P = 0.001), mostly due to decreased use of supplies[78].

POSTOPERATIVE CONSIDERATIONS: COMPLICATIONS, RECURRENCE, AND QUALITY OF LIFE

The patient centered outcome reporting initiative is a nonprofit organization in the United States authorized by congress in the patient protection and affordable care act. It is charged to "improve the quality and relevance of evidence available" on healthcare topics such as this[79]. They noted that a lack of convincing trials makes it difficult to develop and validate an ideal, standardized approach to laparoscopic ventral and incisional hernia repair. However, it is generally accepted that decreased risk of postoperative infection is the primary advantage, especially in the obese population[80-82].

Recently, there has been a movement to separate primary ventral and secondary incisional hernias into two different categories. Stirler *et al*[15] showed that laparoscopic repair of incisional hernias on average results in more adhesiolysis, a higher conversion to open, a longer procedure, and a higher recurrence rate when compared to primary ventral hernias. In 2014, Awaiz *et al*[83] performed a meta-analysis with strict exclusion criteria in order to evaluate elective repair of incisional hernias. There was a statistical reduction in bowel related complications favoring open repair *vs* laparoscopic repair. However, "bowel injury" included an aggregate of enterotomies, serosal tears, and small bowel obstructions. There was no difference in other postoperative morbidities. Arita *et al*[84] reviewed ventral and incisional hernias separately, and found that superficial surgical site infection rates were higher in open repairs for both hernia types, but there was no difference in recurrence rates between open and laparoscopic approaches.

There has also been an attempt to correlate the acuity of hernia presentation with outcomes. Our group used NSQIP database to determine propensity score adjusted OR in 26766 subjects undergoing open *vs* laparoscopic ventral and incisional hernia repair for reducible and incarcerated/strangulated hernias[85]. Laparoscopic repair was found to have a small but significant decrease of length of stay in both reducible (open = 2.79, 2.59-3.00; laparoscopic 2.39, 2.20-2.60; $P < 0.01$) and strangulated/incarcerated hernias (open = 2.64, 2.55-2.73; laparoscopic 2.17, 2.02-2.33; $P < 0.01$). Open repair of incarcerated/strangulated hernias increased the risk of superficial surgical site infection (OR = 3.1, $P < 0.01$), deep surgical site infection (OR = 8.0, $P < 0.01$), and wound disruption (OR = 9.3, $P < 0.01$) when compared to laparoscopic repair. Open repair had a lower risk of organ/space surgical site infection after repairing reducible hernias when compared to laparoscopic repair, but there was no increased risk of other infections.

Quality of life

As the incidence of recurrence decreases, there is an increasing focus on secondary patient reported outcomes that affect postoperative quality of life. Surrogates have been created because there is no consensus on how to measure pain, mobility, cosmesis, and length of convalescence. A 2011 Cochrane review found no significant differences in acute postoperative pain (mean difference 0.09, 95%CI: -0.45 to 0.62), and return to full activity (mean difference -0.70, 95%CI: -2.10 to 0.70)[81]. One study showed no difference in acute postoperative pain, but another study showed less chronic neuralgia in the laparoscopic group. Regarding return to full activities, Pring *et al*[86] revealed no difference between open and laparoscopic repairs. However, Itani *et al*[87] found a near significant advantage for laparoscopic repair (23 d *vs* 28.5 d, adjusted hazard ratio 0.54, 95%CI: 0.28-1.04; $P = 0.06$). The Cochrane review showed a significant difference in hospital stay (mean difference -4.63, 95%CI: -5.95 to -3.32); however, this was only if the open repair control group stayed longer than 5 d[81]. There was no significant difference in quality of life (mean difference 0.44, 95%CI: -0.24 to 1.11).

In 2014, Jensen *et al*[88] reviewed 26 articles for quality of life assessment methods. Fifty-four percent of these used the short-form 36 (SF-36), which is a non-surgery or hernia specific scoring of general physical and mental health. The physical component focuses on pain, energy/fatigue, and functional limitations. The mental health component focuses on social functioning, emotional wellbeing, and general perception of health. Two of the studies discussed found no difference when comparing open to laparoscopic repair[87-89]. On the contrary, some other authors showed better quality of life, and better short-term physical functioning with laparoscopic repair[90]. In addition, when tack and transfascial suture techniques were compared using the SF-36, no significant difference was noted between the two approaches[52,53,88].

Only two of the quality of life assessment methods are hernia specific. These include the Carolinas comfort scale and the hernia-related quality of life survey (HerQLes). The Carolinas comfort scale assesses pain, limitations in movement, and mesh sensation for eight daily activities. Colavita *et al*[91] assessed 710 patients and showed worse quality of life one month after laparoscopic repair when compared to open repair, but there was no long-term difference. Two other studies showed large hernia defects and the presence of preoperative pain to be strong predictors of a short-term decrease in quality of life, most likely due to pain[92,93]. The HerQLes is a newly developed assessment first reported by Krpata *et al*[94]. It associates hernia specific physical limitations with overall physical and mental effects on quality of life. It shows an advantage in laparoscopic repair at 4 wk, but no difference at 6 mo. Based on the available literature, it appears that there might be some improvement in short-term quality of life with the laparoscopic approach, but this benefit balances out in the long run.

FUTURE DIRECTIONS

Preoperative patient selection and risk modification

Most surgeons attempt to decrease modifiable risk factors through patient encouragement; however, there are very few multidisciplinary programs that actively and successfully accomplish this. Further research is required to validate methods to decrease known modifiable risk factors, such as obesity and smoking. Furthermore, only 20% to 27% of hernias are repaired laparoscopically, despite the benefits noted above[12,18].

Considering the plethora of procedural and equipment options, surgeons need criteria to develop a tailored surgical technique for each patient, including surgical approach, mesh material, fixation material, and fixation method. Several algorithms have been developed for operative planning, but no one method has become ubiquitous. Eid *et al*[95] developed an algorithm to stratify obese patients, taking into account body mass index, abdominal wall thickness, and presence of symptoms. Parker *et al*[96] proposed another algorithm to determine open *vs* laparoscopic component separation, and concomitant open *vs* laparoscopic ventral hernia repair. Further research is needed to create a reliable and validated algorithm for surgical selection.

Mesh selection

No one mesh has become dominant in intraperitoneal onlay repair. There is an ongoing study at Washington University determining the adhesion profile of these meshes[29]. Several other studies have attempted to stratify mesh characteristics, but the numbers are too small to draw definitive conclusions[24]. Mesh technology continues to develop ahead of validating research. Long-term absorbable meshes, self-gripping meshes, and titanium reinforced meshes are now available for use. The robotic platform increases the ability to place mesh in the retrorectus space, which may obviate the need for different mesh materials. Surgeons and patients would benefit from more level 1 clinical studies scientifically comparing the risks and benefits of evolving mesh technologies.

New techniques

Non-standard laparoscopic techniques are being increasingly utilized, such as simultaneous primary hernia closure, retrorectus mesh placement, concomitant component release, and mesh fixation, in order to decrease wound complications, postoperative pain, and hernia recurrence. Surgeons are more likely to attempt laparoscopic repair of more complex hernias, such as incarcerated/strangulated ventral hernias, as their collective experience grows. In the same way, newer fixation methods might decrease postoperative pain, such as barbed suture or fibrin sealant, but may risk re-herniation if they do not provide adequate fixation. Simultaneous component release has gained popularity as it allows reconstruction of the midline. Considering the relatively low incidence of complications, mesh registries may be useful to increase the power of future studies.

The robotic platform

The ease of robotics may decrease the learning curve for surgeons, making a good laparoscopic surgeon better able to replicate the tenets of open repair. It permits relatively easy access to the anterior abdominal wall, allowing the surgeon to perform the ideal repair for that patient - including possible primary defect closure, retrorectus mesh placement, intracorporeal suturing, and concomitant posterior component release. It also might allow for standardization of surgical technique in order to develop a reliable approach to hernia repair that can be offered to an increasing number of patients. Further research is needed to determine the ability to decrease patient morbidity *vs* the increased cost of technology.

Patient reported outcome measures

Patient reported outcome measures (PROM) are standardized measures used to assess symptom status, physical function, mental health, social function, and wellbeing, with the goal of patient centered improvement of care. This system has been implemented in the United Kingdom and the National Health Service for many years with variable success[97]. Previously discussed studies have attempted to assess quality of life using similar standardized measures for ventral hernia repair, such as the SF-36, Carolinas comfort scale, and the HerQLes. Thus far, these studies have been experimental and have not been used to guide treatment. Further research might develop specific PROM that may be used to enable cost analysis, standardization of treatment, and quality improvement.

CONCLUSION

Laparoscopic ventral and incisional hernia repair has evolved significantly since its roots in the crude endoscopy of Hippocrates. The experience of the last 25 years has allowed us to significantly decrease the morbidity of post-laparotomy incisional hernia and *de novo* ventral hernias. Preoperative risk factor modification and a useful diagnostic algorithm have a significant role in preparing a patient for the right operation. New hernia repair techniques have the potential to continue to reduce the associated morbidity, and perhaps robotic surgery will be the tool to accomplish the ideal hernia repair in the appropriate setting. Despite the advances noted above, open surgical technique is many times necessary and should not be overlooked. Improved postoperative evaluation is necessary to effectively weigh the results of our innovations, and continue to evolve solutions to ventral and incisional hernias.

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MINIREVIEWS

Watch and wait approach to rectal cancer: A review

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Abstract

In 2014, there were an estimated 136800 new cases of colorectal cancer, making it the most common gastrointestinal malignancy. It is the second leading cause of cancer death in both men and women in the United States and over one-third of newly diagnosed patients have stage Ⅲ (node-positive) disease. For stage Ⅱ and Ⅲ colorectal cancer patients, the mainstay of curative therapy is neoadjuvant therapy, followed by radical surgical resection of the rectum. However, the consequences of a proctectomy, either by low anterior resection or abdominoperineal resection, can lead to very extensive comorbidities, such as the need for a permanent colostomy, fecal incontinence, sexual and urinary dysfunction, and even mortality. Recently, trends of complete regression of the rectal cancer after neoadjuvant chemoradiation therapy have been confirmed by clinical and radiographic evaluation-this is known as complete clinical response (cCR). The "watch and wait" approach was first proposed by Dr. Angelita Habr-Gama in Brazil in 2009. Those patients with cCR are followed with close surveillance physical examinations, endoscopy, and imaging. Here, we review management of rectal cancer, the development of the "watch and wait" approach and its outcomes.

Key words: Rectal cancer; Watch and wait approach; Neoadjuvant chemotherapy rectal cancer; Nonoperative management rectal cancer

Core tip: Standard treatment for stage Ⅱ and Ⅲ rectal cancer includes neoadjuvant chemoradiation followed by radical surgical resection. Recent studies have demonstrated that a select population of patients will achieve a pathological complete response with the absence of residual cancer present after surgical resection. Preliminary attempts to identify those rectal cancer patients with a clinical complete response to neoadjuvant therapy, through various diagnostic modalities, may prevent future patients from having to undergo a very morbid operation.

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INTRODUCTION

Colorectal cancer is the most common gastrointestinal malignancy with an estimated 136800 new cases diagnosed in 2014 in the United States[1]. Over one third of colorectal cancers consist of Stage Ⅲ node-positive disease and rectal cancer accounts for approximately a third of these cases. Proctectomy has been the cornerstone of therapy to achieve long-term oncological results either *via* low anterior resection or abdominoperineal resection. Standard surgical technique involves total mesorectal excision as proposed by Heald *et al*[2] to achieve the lowest rates of regional recurrences with reported morbidity and mortality rates of 35% and 4%-5%, respectively and over a third of patients report some degree of urologic and sexual dysfunction, and fecal incontinence[3].

Additionally, landmark studies, like the Dutch trial and German trial CAO/ARO/AIO-94, have proven the beneficial effects of preoperative chemoradiation therapy (CRT)[4,5]. Locoregional failure rates are reported as < 10% and thus, neoadjuvant CRT plus radical surgical resection have become the standard of care for rectal cancer. Long-term results with this approach show stage-specific 5-year survival rates between 63% and 77.4%[6-8].

Despite excellent oncologic outcomes with neoadjuvant CRT followed by radical surgery, contemporary data is shifting the current paradigm of rectal cancer management towards nonoperative therapy. Multiple studies have shown an absence of viable malignant cells in surgical resection specimens after CRT, termed pathological complete response (pCR) in 18.1%-26% of cases[9]. Thus questions arise in colorectal surgery: Do patients benefit from radical surgery after an "adequate" response to CRT? How does one define an "adequate" response to neoadjuvant therapy? Do these patients achieve equivalent oncological long-term outcomes with reduced morbidity and mortality?

This paper reviews the non-operative treatment algorithm known as the "Watch and Wait" protocol, first proposed by Habr-Gama *et al*[10] in Brazil. Indications, treatment algorithms, outcomes, and areas of uncertainty are assessed from a worldwide perspective.

The utilization of an inaccurate staging system: Treating with uncertainty

According to the American joint committee on cancer, tumor depth is denoted by T; N is nodal metastasis, and M is distant metastasis - for evaluation of TNM cancer staging. Nodal positivity or a ≥ T3 tumor (stages Ⅱ and Ⅲ disease) qualifies a patient for neoadjuvant CRT prior to surgical resection[11,12]. Digital rectal examination (DRE) combined with imaging modalities including endorectal ultrasound (ERUS), magnetic resonance imaging (MRI) and/or positron emission tomography - computed tomography are utilized to determine TNM status. Staging determines prognosis and guides therapy.

The depth of tumor invasion can be determined with acceptable accuracy rates of > 90% with either ERUS or MRI, whereas lymph node (N) status is much less reliable with these imaging modalities. Accuracy rates have been determined to be between 60%-80%[13,14]. The evaluation of lymph node status is limited by the shortcomings of current diagnostic methods available in rectal cancer staging. Failure to identify up to 25% of malignant lymph nodes because of their size being less than 3 mm counters conventional beliefs that lymph node size must exceed 1 cm in order to be deemed positive for metastasis[15,16]. In other words, our current diagnostic imaging modalities understage N status. Furthermore, tumor response may not correlate with lymph node status in patients after CRT. Previous studies have shown that between 16.3%-28% of patients with complete clinical response (cCR) harbor nodal disease and its incidence is associated with initial T stage[17,18].

Defining response after CRT: Clinical complete response vs pathological complete response

pCR has been defined as the absence of neoplastic cells in the surgical resection specimen after neoadjuvant CRT and resection. Fifteen to forty percent of patients who receive neoadjuvant chemotherapy will have a pCR[19-21]. Tumor response is considered a marker of tumor biology. Patients with complete tumor response after neoadjuvant CRT have improved disease-free survival (DFS) and distant metastatic rates of 89.5% and 7%-10.5%, respectively, when compared to poor responders of neoadjuvant therapy (65% and 26%-31%, respectively)[9,22]. Variables such as sex, age and tumor location are not predictors of tumor response, whereas lymph node status is significantly associated with the risk of locoregional recurrence and subsequent distant metastases.

At present, no predictive factors exist to determine which patients will respond to CRT based on preoperative data. However, pCR is not an appropriate primary endpoint to guide clinical decision-making because it depends on the pathological results after radical surgery. Habr-Gama *et al*[10,23] developed the "watch and wait" protocol by creating a new endpoint: cCR. Based on a strict surveillance protocol, patients are determined to be responders once they have no evidence of tumor on: (1) DRE; (2) endoscopic assessment; and (3) imaging. When irregularities of the rectal wall (including mass, ulceration, or stenosis) are palpated on digital

Table 1 Watch and wait protocol surveillance schedule (adapted from Habr-Gama *et al*[10])

Assessment of complete response	Initial assessment	First year	Second year	Third year and after
DRE	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
CEA	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
Endoscopic assessment	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
MRI	10 wk	If 1st assessment normal with cCR, then every 6 mo	Every 6 mo	Every 6 mo

DRE: Digital rectal examination; CEA: Carcinoembryonic antigen; MRI: Magnetic resonance imaging; cCR: Clinical complete response.

rectal examination, it is concerning for residual cancer. Endoscopic assessment not only confirms DRE but identifies ulceration or mucosal irregularity that may have been missed during DRE. During flexible or rigid proctoscopy, the procurement of biopsies is helpful in verifying a cCR. MRI evaluates for mixed signal intensity of the rectal wall, in addition to malignant mesorectal lymph node involvement (Figures 1 and 2). Finally, carcinoembryonic antigen (CEA) levels are obtained pre- and post-neoadjuvant CRT. If abnormal CEA levels persist after CRT, this suggests an incomplete response to neoadjuvant therapy and/or distant metastatic disease.

As previously discussed, lymph node status is the most important prognostic factor in rectal cancer. The challenge of a nonoperative approach is determining whether contemporary imaging modalities adequately evaluates lymph node status in these patients; thus yielding an inferior oncological outcome compared to that of conventional operative management.

This is the basis of uncertainty and the main criticism to the "watch and wait" protocol. Deciding not to offer radical surgery based on inaccurate diagnostic tools that could potentially understage neoplastic process has been a deterrent to the acceptance of the "watch and wait" protocol in the United States. Studies are ongoing to determine whether this protocol is acceptable as standard of care.

Outcomes with watch and wait protocol: Brazil, Netherlands, United Kingdom, and United States

The "watch and wait" approach was first proposed by Habr-Gama[1] in Brazil in 2009. The current protocol by Habr-Gama[1], includes radiation therapy of 54 Gy with combination 5-fluorouracil and leucovorin chemotherapy, which extends for an additional 3 cycles beyond the neoadjuvant radiation period for a duration of 9 wk. At 10 wk, patients undergo an initial assessment with DRE, flexible sigmoidoscopy, and imaging for cCR. The patients then enroll in a vigorous surveillance program: DRE, CEA, and endoscopic assessment every 1-2 mo in the first year, every 3 mo in the second year, and every 6 mo in the third year and beyond. If the initial radiologic assessment shows cCR, then serial imaging may be performed every 6 mo (Table 1)[10]. Habr-Gama[1] prospectively studied 70 patients, of which one died due to cardiac complications from chemotherapy. On initial assessment, 68% of patients had cCR. After follow-up of 12 mo, 56% of patients had sustained cCR. For those who initially had cCR, the 3-year overall survival was 90% and DFS was 72%[24].

Another study from the Netherlands prospectively followed 192 patients with locally advanced rectal cancer who were treated with CRT[4,25]. Twenty-one patients had cCR and were followed for 25 ± 19 mo. The control cohort consisted of 20 patients who had a pCR after chemoradiation followed by surgical resection. Out of the twenty-one patients in the watch and wait protocol group, one patient developed a small endoluminal local recurrence without nodal recurrence at 22 mo follow-up. The remaining 20 patients neither had local nor distant recurrence of disease. DFS and overall survival did not statistically differ between both the watch and wait and control groups.

There are two retrospective studies from the United States and the United Kingdom which are concordant with the aforementioned prospective studies. Disease-free and overall survival rates are similar in patients with cCR, who undergo the watch and wait protocol *vs* conventional neoadjuvant chemoradiation therapy, followed by surgery (Table 2)[24-28].

In conclusion, advances in chemoradiation therapy for rectal cancer have delineated a select population of patients who have a pCR after surgical resection. Observation of this pCR led to the conception of the watch and wait protocol by Habr-Gama *et al*[24], in Brazil. Patients are identified as having a cCR and followed with close surveillance by physical examination, endoscopic assessment, and imaging studies. Thus far, they have followed prospectively, a highly selected patient population. This study has been confirmed by a study in the Netherlands[26,27].

However, the watch and wait protocol has not been widely accepted as standard of care. There are limitations for current data in the literature. First, only two prospective cohort studies exist with small sample sizes. No randomized controlled trials exist, comparing the watch and wait protocol with standard neoadjuvant chemoradiation therapy followed by surgery. Enrollment into these studies is biased by patient selection due to the lack of randomization. Despite close surveillance, no studies have delineated patient characteristics

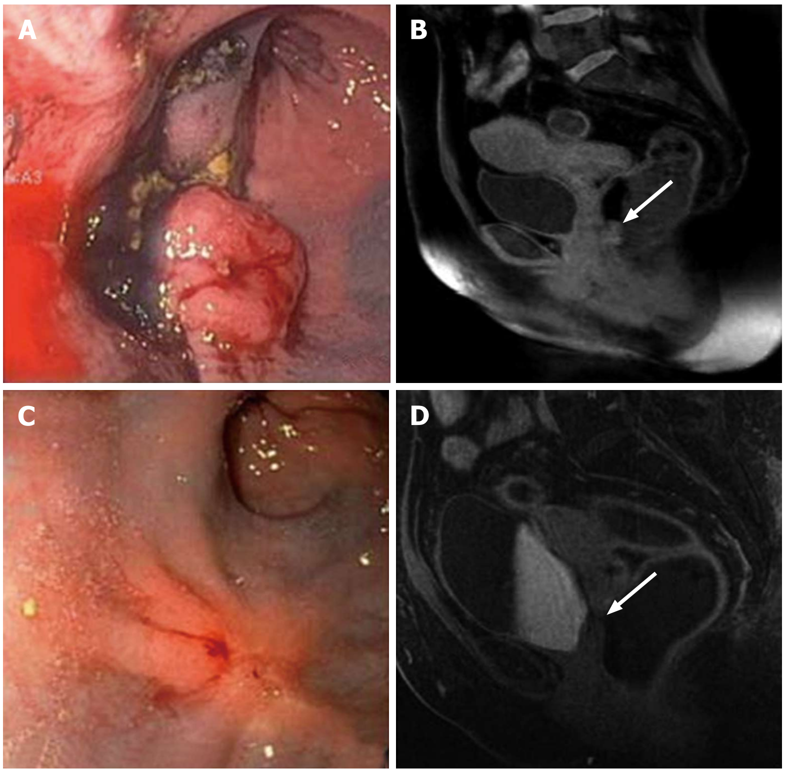

Figure 1 Clinical incomplete response. Evaluation of the rectal cancer prior to the initiation of neoadjuvant chemoradiation therapy by flexible sigmoidoscopy (A) and MRI (B, white arrow: Tumor). Evaluation of 7 wk after completion of neoadjuvant chemoradiation therapy. The tumor has decreased in size; however, it continues to be present as evidenced by flexible sigmoidoscopy (C) and MRI (D, white arrow: Tumor). MRI: Magnetic resonance imaging.

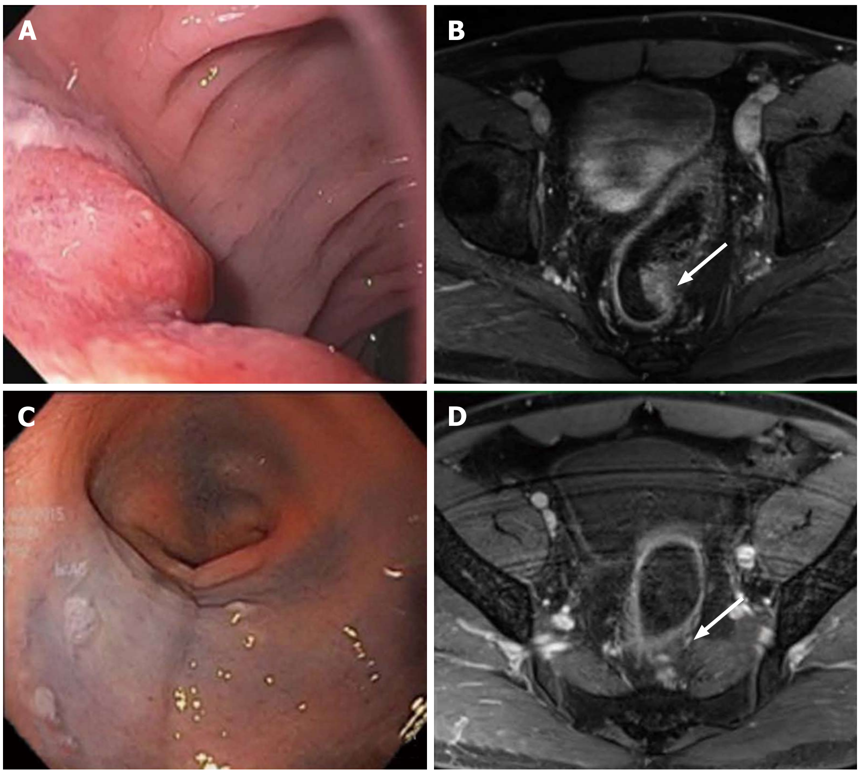

Figure 2 Complete clinical response. Evaluation of the rectal cancer prior to the initiation of neoadjuvant chemoradiation therapy by flexible sigmoidoscopy (A) and MRI (B, white arrow: Tumor). Evaluation of 7 wk after completion of neoadjuvant chemoradiation therapy showed no evidence of tumor by flexible sigmoidoscopy (C) and MRI (D, white arrow: Tumor). MRI: Magnetic resonance imaging.

or predictive factors that predict tumor response to chemoradiation therapy. Though patients undergo a

Table 2 Studies evaluating the watch and wait protocol

Study	Patients (*n*)	Neoadjuvant therapy		Details	Outcomes/endpoints
		Radiation	Chemotherapy		
Prospective					
Habr-Gama *et al*[24] (Brazil)	69	54 Gy radiation (45-Gy delivered as 3-field approach with daily doses of 1.8 Gy on weekdays to pelvis, followed by 9-Gy boost to the primary tumor and perirectal tissue)	3 cycles of 5-FU (450 mg/m^2) bolus and a fixed dose of 50 mg leucovorin for 3 consecutive days every 3 wk. After completion of radiation, patients received 3 additional identical cycles of chemotherapy every 3 mo	Assessment after CRT: 10 wk; assessment for sustained cCR: From 10 wk to 12 mo after CRT; patients with local recurrences after sustained cCR classified as LR	3-yr OS for patients with initial cCR = 3-yr DFS for patients with initial cCR = 72%
Lambregts *et al*[25] and Maas *et al*[26] (Netherlands)	21	28 fractions of 1.8 Gy = 50.4 Gy	Ⅳ oxaliplatin and capecitabine	Assessment after CRT: 6-8 wk; evaluation for cCR: MRI and endoscopy; operative management with CRT and resection (control group): 20 patients with pCR after surgery	Nonoperative management group; 1 patient developed LR and had surgery as salvage treatment; 20 patients are alive without disease; no difference in 2-yr DFS and OS between the watch and wait and the CRT and resection groups
Smith *et al*[27] (United States)	32	External beam radiation over 5-6 wk, median dose 50.4 Gy (range 45-56 Gy)	5-FU or capecitabine	Assessment after CRT: 4-10 wk; evaluation for cCR: DRE, endoscopy ± biopsy; evaluation for cCR at 1-yr: DRE, flexible sigmoidoscopy every 3 mo; evaluation for cCR subsequent years: DRE, flexible sigmoidoscopy every 4-6 mo; operative management (control group): 256 patients, 57 (22%) with pCR; median follow up: 28 mo	Nonoperative management group had a higher rate of LR (21% *vs* 0%, P = 0.001): 6 recurred locally (median 11 mo), 3 had concurrent DR; 2-yr DR (8% *vs* 2%, P = 0.30), DFS (88% *vs* 98%, P = 0.27), and OS (97% *vs* 100%, P = 0.56) were similar for nonoperative management and rectal resection/pCR groups
Dalton *et al*[28] (United Kingdom)	12	45 Gy in 25 fractions over 5 wk	Concurrent capecitabine	Assessment after CRT: 8 wk; evaluation for cCR: MRI complemented with EUA/biopsy and PET/CT if tumor regression is suspected; cCR patients are followed with repeat EUA at 3 mo and 12 mo, and 6-monthly PET/CT and MRI; median follow up 25.5 mo	cCR in 12/49 (24.4%); 6/12 patients with cCR without evidence of disease

LR: Local recurrence; DR: Distant recurrence; DFS: Disease-free survival; OS: Overall survival; Gy: Gray; CRT: Chemoradiation therapy; DRE: Digital rectal examination; EUA: Examination under anesthesia; 5-FU: 5-fluorouracil; cCR: Clinical complete response; pCR: Pathological complete response; PET/CT: Positron emission test/computerized tomography; MRI: Magnetic resonance imaging.

very strict surveillance protocol, the ultimate question arises as to whether cancer remains in the rectum and whether they exist in the lymph nodes. The inaccuracies of current imaging modalities limit the accurate staging of rectal cancer. Further precision in rectal cancer staging would require innovative advances in diagnostic technologies in order to avoid radical surgery.

The uncertainty of outcomes of a cCR after chemoradiation therapy for rectal cancer continues to exist. Further randomized controlled trials are required to validate the watch and wait protocol. As nonoperative management for rectal cancer advances, we predict that the evolution of rectal cancer treatment will mimic that of anal cancer. Prior to the 1970's anal cancer management was purely surgical. However, with the ground-breaking work of Nigro *et al*[29], the anal cancer treatment paradigm has shifted to a nonsurgical approach with primary treatment consisting of multi-modality therapy with chemotherapy and radiation. Further changes in the standard of care to nonoperative management will be dependent on the identification of patient factors that can predict a pCR. The introduction of molecular techniques that allow the identification of high-risk patients could play a substantial role in the creation of a genetic profile that would funnel a highly selected group of rectal cancer patients into the watch and wait protocol.

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MINIREVIEWS

Natural history of uncomplicated sigmoid diverticulitis

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Author contributions: Buchs NC and Gervaz P designed the research; Buchs NC, Ris F and Gervaz P performed the research (acquisition of data); Buchs NC, Mortensen NJ and Morel P analyzed and interpreted the data; Buchs NC and Gervaz P wrote the article; Mortensen NJ, Ris F and Morel P revised the article; all the authors gave the final approval.

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Abstract

While diverticular disease is extremely common, the natural history (NH) of its most frequent presentation (*i.e.*, sigmoid diverticulitis) is poorly investigated. Relevant information is mostly restricted to population-based or retrospective studies. This comprehensive review aimed to evaluate the NH of simple sigmoid diverticulitis. While there is a clear lack of uniformity in terminology, which results in difficulties interpreting and comparing findings between studies, this review demonstrates the benign nature of simple sigmoid diverticulitis. The overall recurrence rate is relatively low, ranging from 13% to 47%, depending on the definition used by the authors. Among different risk factors for recurrence, patients with C-reactive protein > 240 mg/L are three times more likely to recur. Other risk factors include: Young age, a history of several episodes of acute diverticulitis, medical *vs* surgical management, male patients, radiological signs of complicated first episode, higher comorbidity index, family history of diverticulitis, and length of involved colon > 5 cm. The risk of developing a complicated second episode (and its corollary to require an emergency operation) is less than 2%-5%. In fact, the old rationale for elective surgery as a preventive treatment, based mainly on concerns that recurrence would result in a progressively increased risk of sepsis or the need for a colostomy, is not upheld by the current evidence.

Key words: Diverticulitis; Colon; Cohort; Recurrence; Natural history

Core tip: The natural history of sigmoid diverticulitis is poorly understood. While there is a clear lack of uniformity in terminology, which results in difficulties interpreting and comparing findings between studies,

this comprehensive review demonstrates the benign nature of simple sigmoid diverticulitis. The overall recurrence rate is relatively low. Several risk factors are found to be associated with recurrence.

Buchs NC, Mortensen NJ, Ris F, Morel P, Gervaz P. Natural history of uncomplicated sigmoid diverticulitis. *World J Gastrointest Surg* 2015; 7(11): 313-318 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i11/313.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i11.313

INTRODUCTION

Colonic diverticulosis is an increasingly common condition in the Western world. Half of the population is affected by the 6th decade and two-thirds by the 9th decade[1,2]. Fortunately, the majority of patients with diverticulosis remains asymptomatic; diverticulitis, the most common presentation of diverticular disease, has a life time prevalence of 25%[3,4]. The diagnosis of sigmoid diverticulitis is usually suspected clinically in a patient presenting with acute lower abdominal pain, associated with an inflammatory syndrome. The preferred imaging modality is computed tomography (CT)[5] scan, which may also demonstrate complicated diverticulitis (abscess, fistula or peritonitis)[6]. A full colonoscopy once the acute inflammatory process has resolved[5] is recommended in order to exclude cancer or inflammatory bowel disease[7]. Most patients presenting with simple diverticulitis will be successfully managed symptomatically or with antibiotics alone[8-11].

Whilst diverticular disease is extremely common, there are few prospective series documenting the natural history (NH) of sigmoid diverticulitis[12,13]. Studies from the 1960s had suggested that a recurrent episode of diverticulitis occurs in > 40% of patients, and that these are complicated in up to 60%[14]. However, recent series suggest that the NH of sigmoid diverticulitis, in the era of modern antibiotics, is more benign[15,16], as shown in our prospective cohort study[17]. A few have looked at the incidence and severity of recurrent diverticulitis but with the diagnosis based upon clinical parameters only[18]. Without a CT scan it is difficult to differentiate between simple and Hinchey Ⅰ-Ⅱ diverticulitis[10,19,20]. So, the existing studies probably do not provide reliable information regarding the NH of simple diverticulitis.

The object of this review is to evaluate the NH of simple sigmoid diverticulitis.

DEFINITIONS

There is a clear lack of uniformity in terminology resulting in difficulties interpreting and comparing findings between studies[10,18].

NH can be defined as the longitudinal outcomes for patients whose disease was managed non-operatively[21]. In our own cohort (NCT01015378), we chose a definition of simple diverticulitis, which comprised 4 criteria[22]: (1) Clinical: Acute lower abdominal pain or discomfort; (2) Biological: Inflammatory syndrome [C-reactive protein (CRP) > 50 mg/L or white blood cell count > 11000 G/mm^3]; (3) Radiological: Signs of inflammation of the sigmoid and/or descending colon on a CT scan ideally performed with triple contrast injection (oral, rectal, and intra-venous); and (4) Endoscopic: To document the presence of diverticula (*i.e.*, confirming the diagnosis) and rule out another associated condition.

All patients are usually encouraged to undergo routine colonoscopy six to twelve weeks after the first attack, in order to rule out malignancy, although the evidence supporting this practice is weak[10,18].

Regarding outcomes, a diagnosis of recurrent diverticulitis implied that the patient has completely recovered from their first episode. An interval of 12 wk without symptoms in between two attacks was required. All the aforementioned criteria were required to confirm a recurrent diverticulitis (including an abdominal CT). The Hinchey classification[23], or its modified versions[24], was used to stage complicated diverticulitis. In addition, we considered a fistula and a stenosis as a complicated attack[18].

NH OF SIMPLE DIVERTICULITIS

Recent advances in the understanding of diverticular pathophysiology and NH have led to substantial changes in diverticulitis treatment guidelines[21].

We have recently published a large prospective single center cohort study focusing on the NH of sigmoid diverticulitis[17]. We demonstrated that, after a first episode of simple diverticulitis, the overall recurrence rate was 16%, and that 87% of recurrences were of similar severity (Figure 1). Of note, four patients only (1.4%) underwent emergency surgery for complicated (Hinchey stages Ⅲ/Ⅳ) diverticulitis. The main predictor of recurrence after a first attack was a serum CRP > 240 mg/L. Subsequently, 23 (8.2%) patients proceeded to an elective laparoscopic sigmoid colectomy because of chronic symptoms. In addition, as reported by others, the highest risk of recurrence was within the first year (10%) and dropped to approximately 3% in the years thereafter[25,26].

In series without adequate imaging with CT scan as a prerequisite for inclusion, recurrence rates ranged from 13% to 47% (Table 1), depending on the definition used by the authors. Two United States series using large administrative databases have reported recurrence rates between 13% and 19%, which is in accordance with the results from our institution[17] and from other centers[27,28]. Indeed, in a study population of 3165 patients with acute diverticulitis, Broderick-Villa *et al*[28] reported a recurrence rate of 13.3% after a follow-up of 8.9 years. Less than 4% presented with a second recurrence, as others have shown[26].

The emerging picture is then that recurrence is relatively rare, and that recurrent diverticulitis is rarely

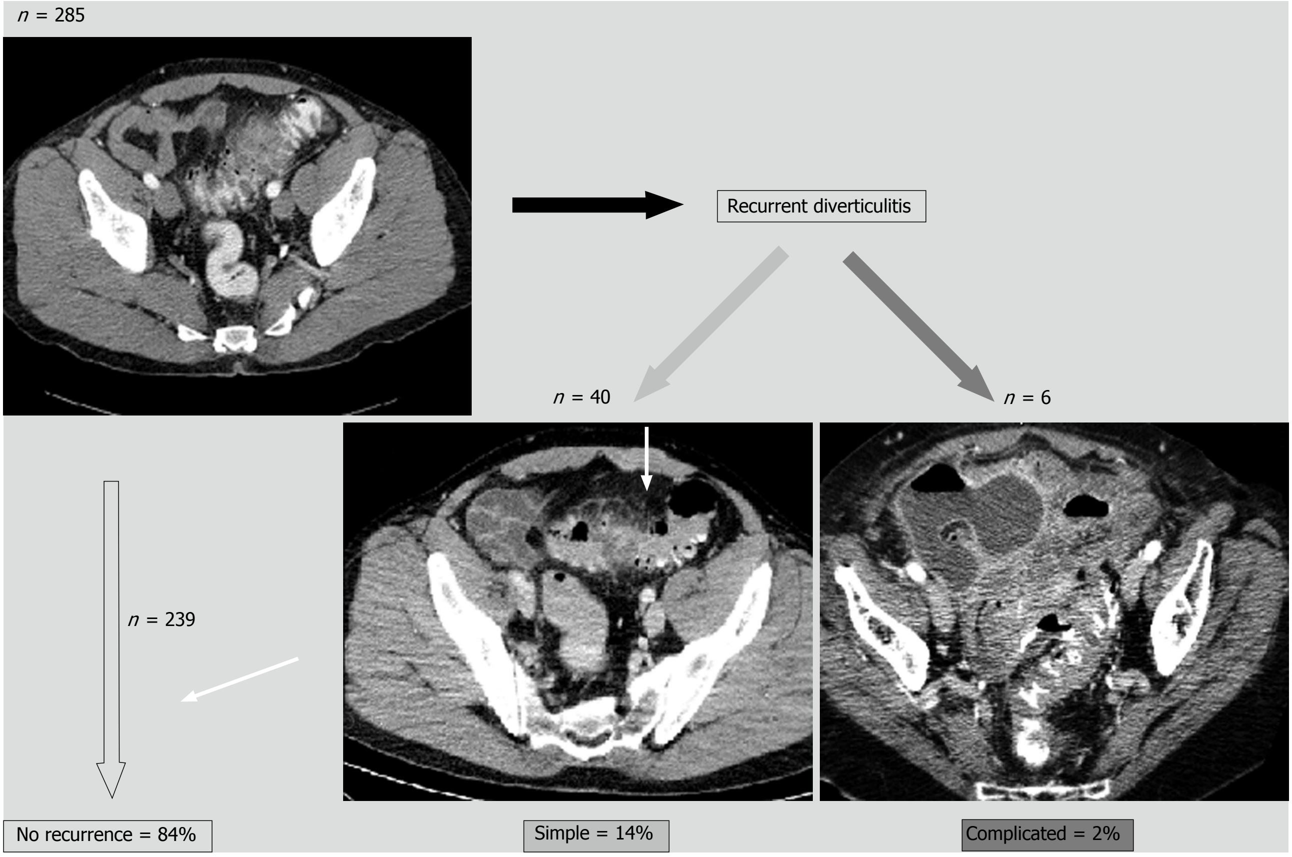

Figure 1 Flow chart of patients' outcome. Simple: Uncomplicated acute attack (Hinchey Ⅰa) (no abscess, no perforation); Complicated: Presence of abscess (Hinchey Ⅰb and Ⅱ) or peritonitis (Hinchey Ⅲ and Ⅳ).

severe[16,26]. The results of our study[17] confirm that a non-surgical strategy for the treatment of uncomplicated diverticulitis is safe in the long term[29]. They also contradict the once popular view that diverticulitis is a progressive disease[30]. Out of the 6 patients (2.1%) who developed complicated diverticulitis during follow-up, four (1.4%) patients developed peritonitis (Hinchey Ⅲ/Ⅳ) and underwent emergency Hartmann operation. A conservative policy after a first episode of simple diverticulitis is thus associated with a colostomy rate, which is similar to the risk of anastomotic dehiscence after an elective sigmoid colectomy[31]. Eglinton *et al*[26] found a risk of 5% for developing complicated disease after a first episode of uncomplicated diverticulitis. The risk of stoma formation was only 0.9%, all of which were temporary and subsequently reversed. Most perforations do not occur after recurrences, but after the first attack of acute diverticulitis[19,30,32-34]. Humes and West[35] however showed that, although most patients in their study (72.3%) had suffered no prior episodes of acute diverticulitis, further episodes of acute diverticulitis were associated with an increased risk of developing a fistula (OR = 1.54, 95%CI: 1.08-2.19), but there was no clear relationship with perforation or abscess.

Among the different risk factors for recurrence, age has often been mentioned (Table 1)[15,36]. In the past, sigmoidectomy was advocated in young patients (< 50 years at the first episode)[37]. But, younger patients have a similar absolute risk of recurrence, and a higher lifetime risk[10]. Buchs *et al*[17] do not agree with the general thought that younger patients has more aggressive diverticulitis, as suggested by others[26,36,38-40]. We agree the recent shift towards a more conservative management of diverticulitis is effective for all the different age groups. There is no evidence that younger patients should be treated differently from older patients[5,18].

The gravity of inflammation (measured by the CRP level) is associated with a higher probability of recurrence, as shown in our series[17]. The risk of recurrence at 6 mo was 22% for patients with CRP > 240 mg/L during their initial episode. Recently, CRP was seen as an interesting marker in simple cases of sigmoid diverticulitis. A level higher than 200 mg/L can be associated with local complication[41,42]. We recently proposed that the diagnostic criteria for diverticulitis should include CRP[22]. In our series, free pelvic fluid seen on CT was not associated with further recurrence. However, the discovery of a pneumoperitoneum was of borderline significance. Others groups have reported risk factors for recurrence, including: Age younger than 40 (or 50), a history of a least 3 episodes of acute diverticulitis, medical *vs* surgical management, male patients, radiological signs of complicated first episode

Table 1 Studies evaluating the natural history of acute diverticulitis

Ref.	No. of patients	Type of study	FU	Recurrence rate	Comments
Lahat *et al*[38], 2013	261	Prospective	88 mo	21.5%	21% operated, 46.6% asymptomatic
Buchs *et al*[17], 2013	280	Prospective	24 mo	16.4%	RF: CRP > 240
Humes and West[35], 2012	2950	Population-based cohort study	7.99 yr	-	Risk of fistula correlates to the number of prior episodes of diverticulitis
Binda *et al*[36], 2012	743	Multicenter, retro-prospective	10.7 yr	17.2%[1]	RF: < 40 yr, 3 episodes
Hall *et al*[16], 2011	672	Retrospective	42.8 mo	36%	RF: Family history, length of involved colon > 5 cm, retroperitoneal abscess
Mäkelä *et al*[20], 2010	555	Retrospective	-	42%	38% of recurrence diagnosed on clinical findings
Eglinton *et al*[26], 2010	320	Retrospective	101 mo	18.8%	4.7% more than one recurrent episode
Pittet *et al*[19], 2009	271	Retrospective	-	25%	Similar severity
Mueller *et al*[48], 2005	252	Retrospective	89 mo	47% (with 10% readmitted)	Based on symptoms
Anaya and Flum[27], 2005	25058	Cohort study, retrospective	-	19%	RF: < 50 yr, number of recurrent episodes
Broderick-Villa *et al*[28], 2005	3165 (2366 managed conservatively)	Cohort study, retrospective	8.9 yr	13.3%	RF: < 50 yr, charlson comorbidity index ≥ 1
Biondo *et al*[40], 2002	327	Retrospective	24-90 mo	15.9%	Age not a RF
Chautems *et al*[15], 2002	118	Prospective	9.5 yr	31%	Considering only patients undergoing an operation
Somasekar *et al*[34], 2002	108	Two-center, retrospective	-	2.7%[1]	Only patients with complicated disease
Mäkelä *et al*[43], 1998	366	Retrospective	-	22%	RF: < 50 yr, male
Ambrosetti *et al*[44], 1997	300	Prospective	46 mo	2%	RF: Radiological signs of complicated first episode
Parks[14], 1969	317	Retrospective	-	24.6%	Only readmitted patients

[1]If medically treated (*vs* 5.8% if surgically treated; $P < 0.001$); 22.7% of the studied population (complicated diverticulitis) was known for a previous acute diverticulitis. FU: Follow-up; RF: Risk factor; CRP: C-reactive protein.

(abscess formation and extra-colonic contrast or gas), higher comorbidity index, family history of diverticulitis, and length of involved colon > 5 cm[16,27,28,36,43,44].

In addition, risk factors for the development of complicated diverticulitis include smoking, non-steroidal anti-inflammatory drugs use, renal failure, organ transplants and steroid use[10].

After the resolution of an episode of diverticulitis, a variety of medical therapies have been used to prevent future attacks. Supplemental fiber, antispasmodics, rifaximin, Mesalamine 5-aminosalicyclic acid (5-ASA), and probiotics have all been studied. These studies included heterogeneous patients however the history of diverticulitis was poorly characterized[5]. 5-ASA has been reported to reduce the risk of recurrent symptomatic diverticular disease[10], but there is no evidence that it may prevent recurrent diverticulitis. A recent randomized controlled trial showed that 5-ASA did not reduce the risk of recurrence or time to recurrence. The proportion of patients requiring surgery was comparable among 5-ASA and placebo groups[45]. Whilst a protective benefit for these agents has been suggested, their role in prevention of diverticulitis remains to be properly defined[5,46].

This review has some limitations. First, most of the studies consider only individuals who received in-hospital treatment, and it is known that 50% of diverticulitis patients are safely managed in an outpatient setting[18,47]. There is a risk of bias in considering for inclusion the most severe cases of diverticulitis. Second, longer follow-up is needed to draw definitive conclusions. Finally, the clear lack of uniformity in terminology results in difficulties interpreting and comparing findings between studies.

In conclusion, we have demonstrated the benign nature of simple sigmoid diverticulitis in the vast majority of cases, with a low rate of recurrence, and most importantly a very low rate of subsequent peritonitis requiring emergency surgery. The risk of complication after sigmoidectomy for simple diverticulitis is probably superior than the risk to develop a complication related to the disease itself. And surgery does not completely protect against recurrence[36]. The old rationale for elective surgery as a preventive treatment, based mainly on concerns that recurrence would result in progressively increased risk of sepsis or the need of colostomy[21], is thus not supported by current series.

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MINIREVIEWS

Role of laryngeal mask airway in laparoscopic cholecystectomy

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Abstract

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures and the laryngeal mask airway (LMA) is the most common supraglottic airway device used by the anesthesiologists to manage airway during general anesthesia. Use of LMA has some advantages when compared to endotracheal intubation, such as quick and ease of placement, a lesser requirement for neuromuscular blockade and a lower incidence of postoperative morbidiy. However, the use of the LMA in laparoscopy is controversial, based on a concern about increased risk of regurgitation and pulmonary aspiration. The ability of these devices to provide optimal ventilation during laparoscopic procedures has been also questioned. The most important parameter to secure an adequate ventilation and oxygenation for the LMA under pneumoperitoneum condition is its seal pressure of airway. A good sealing pressure, not only state correct patient ventilation, but it reduces the potential risk of aspiration due to the better seal of airway. In addition, the LMAs incorporating a gastric access, permitting a safe anesthesia based on these commented points. We did a literature search to clarify if the use of LMA in preference to intubation provides inadequate ventilation or increase the risk of aspiration in patients undergoing laparoscopic cholecystectomy. We found evidence stating that LMA with drain channel achieves adequate ventilation for these procedures. Limited evidence was found to consider these devices completely safe against aspiration. However, we observed that the incidence of regurgitation and aspiration associated with the use of the LMA in laparoscopic surgery is very low.

Key words: Laryngeal mask airway; Laryngeal mask airway Proseal; Laryngeal mask airway Supreme; I-gel; Laparoscopic cholecystectomy; Oropharyngeal leak pressure; Ventilation

Core tip: Use of the laryngeal mask airway (LMA) in laparoscopy is controversial, largely because of a concern about increased risk of regurgitation and aspiration, also due to an inadequate or suboptimal ventilation of the patient during these procedures. We performed the first review of this topic and we found evidence to recommend the LMA with gastric access in laparoscopy for selected patients based on its ability for optimal ventilation. A potential risk of aspiration cannot be totally rejected, however, clinical performance using these devices has reported a very low incidence of aspiration-related morbidity, so future research may provide some evidence about this topic.

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INTRODUCTION

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures in the world, in fact, it is the most frequent laparoscopic procedure performed. Over one million cholecystectomies are performed in the United States annually, with over 96% of those being performed laparoscopically[1].

It is common practice in most of the countries for anesthesia to be carried out with the use of the laryngeal mask airway (LMA), the most important and popular supraglottic airway device (SAD).

This device has several advantages when compared to tracheal intubation (TI), in particular avoidance of complications associated with TI, quick and ease of placement of the airway device itself, a lesser requirement for neuromuscular blockade, as well as a lower incidence of postoperative adverse events such as sore throat, dysphagia and dysphonia (based on its design to be a minimally stimulating to the airway)[2-4].

However, the use of the LMA in this context is controversial, the main concern being that it does not offer definitive airway protection from pulmonary aspiration of potential regurgitated gastric contents. The other controversial point is the ability of the LMA to provide correct ventilation in patients undergoing laparoscopic procedures. Laparoscopy is thought to increase the risk of aspiration due to the pneumoperitoneum-induced, which increase intra-abdominal pressure and it is accompanied by high peak airway pressure[5-7].

Therefore, many anesthesiologists advocate TI and mechanical ventilation for this kind of procedures.

When LMA is fully inserted using the recommended insertion technique, the distal tip of the cuff is at the upper esophageal sphincter, its sides face into the pyriform fossae and the upper border rests against the base of the tongue[8]. In this position, the LMA create an airway sealing, which permit a correct ventilation of the patient as well as a protection of airway against aspiration. We usually measure this sealing pressure or oropharyngeal leak pressure (OLP) in order to know how capable the LMA is to protect airway against potential aspiration of gastric contents. Different types of airway seal pressure tests can be performed using different test, it is commonly done by the anesthetist after general anesthesia induction for assessing OLP with the LMA prior to the beginning of the surgery[9].

The classical laryngeal mask airway (LMA-C) is the most widely studied SAD and in the last 15 years, several devices have been incorporated in order to improve the SAD's indications, these devices have bigger and better cuff, some of them with gastric access incorporation.

These designs offers a cuff that allows a higher seal pressure than the LMA-C and a drain tube that allows venting of the stomach contents and blind insertion of standard gastric tubes. Therefore, these new generation LMAs provides certain protection against regurgitation and prevents gastric insufflation when correctly placed.

These devices are a reasonable choice when performing anesthesia for procedures accompanied by high peak airway pressure, such as laparoscopy.

There are six SADs with a drain tube available in the market at this moment: Laryngeal Tube Suction™ (LTS or LTS-D if disposable), LMA Proseal™ (LMA-P), LMA Supreme™ (LMA-S), i-gel™ and recently the Guardian CPV™, the Baska Mask™ and the Ambu AuraGain™. LMA-P, LMA-S and i-gel are the most commonly used devices with gastric access in clinical anesthesia.

LMA was evaluated in laparoscopic cholecystectomy for the first time in 1996[10]. Between 2000 and 2002, a few studies reported the use of LMA-C and LMA-P for this kind of procedures[11-14]. Since 2010, several clinical studies have investigated the use of LMA with drain channel for laparoscopic cholecystectomy[2,15-19].

We will try to clarify if evidence-based medicine guides us to choose a LMA instead of an endotracheal tube (ETT) when performing a general anesthesia for laparoscopic cholecystectomy. And also what is the most appropriate airway device for this laparoscopic procedure. This review is an approach based on defining a specific and clinically relevant question, followed by a systematic search for evidence about the appraised topic.

Table 1 Summary of the studies investigating ventilation and aspiration with the laryngeal mask airway

Ref.	Group	*n*	Ventila-tory efficiency (%)	No. of insertion attempt ($1^{st}/2^{nd}/3^{rd}$)	Airway insertion time (s)	OLP (cm H_2O)	Peak airway pressure before pneumoperi-toneum (cm H_2O)	Peak airway pressure after pneumoperi-toneum (cm H_2O)	Blood on mask (%)
Lu *et al*[12], 2002	LMA-P	40	100	33/7/0	-	29 ± 6	18.3 ± 3	24.1 ± 2	15
	LMA-C	40	80	40/0/0	-	19 ± 4	17.6 ± 2	22.7 ± 3	
Maltby *et al*[13], 2002	LMA-P	50	92	-	-	34 ± 4	18 ± 5	25 ± 5	-
Sharma *et al*[15], 2010	LMA-P	30	100	24/5/1	14.2 ± 5.5	38.9 ± 3.2	15.9 ± 3.2	21.5 ± 3.2	26.6
	i-gel	30	100	28/2/0	13.6 ± 4.2	35.6 ± 4.8	14.9 ± 2.9	20 ± 3.7	10
Beleña *et al*[16], 2011	LMA-S	100	100	91/0/0	12 ± 4.6	28.8 ± 5.2	17.5 ± 3.3	22.9 ± 1	0
Hoşten *et al*[17], 2012	LMA-P	29	100	27/2/0	15.6 ± 6	27 ± 4.7	-	-	6.8
	LMA-S	30	100	28/2/0	12.5 ± 6	27 ± 2.9			3.3
Beleña *et al*[18], 2013	LMA-P	60	100	51/9/0	11.2 ± 4	30.7 ± 6	19 ± 3	26 ± 5	3.3
	LMA-S	60	100	55/5/0	11.8 ± 2	26.8 ± 4	18 ± 4	24 ± 4	0

Values are presented as numbers, mean ± SD, numbers or percentage. LMA-C: Laryngeal mask airway classic; LMA-P: Laryngeal mask airway Proseal; LMA-S: Laryngeal mask airway Supreme; OLP: Oropharyngeal leak pressure.

LITERATURE SEARCH QUESTION

The search question was clarified to "In healthy patients with no risk factors for regurgitation, undergoing elective laparoscopic cholecystectomy, does the use of the LMA in preference to tracheal intubation provide inadequate ventilation or increase the risk of pulmonary aspiration?"

Search methods

The ideal study design to answer this question is a randomized, controlled trial that compares ventilatory efficacy and the incidence of aspiration between LMA and tracheal intubation in patients undergoing laparoscopic cholecystectomy. We did not limit this search to those articles dealing with ventilatory efficacy and the incidence of aspiration, but we included all studies about LMA for laparoscopic cholecystectomy. A search was performed in MEDLINE, EMBASE, CENTRAL and Google Scholar in November 2014, and updated in February 2015. Search terms used in various combinations were: "laryngeal mask airway", "LMA", "laparoscopic cholecystectomy" and "laparoscopy".

All studies that met these criteria were included regardless of publication language. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, comparative studies using manikins, and any other non-relevant studies were excluded.

Summary of findings

The search identified ten randomized controlled trials, case series and large prospective observational studies (Table 1).

There was no meta-analysis on the specific subject of our appraised topic but a meta-analysis of trials, other studies and cases reporting the use of the LMA, involving 706 patients, reported optimal ventilation in 99.5% of the patients and no aspiration was identified[2,11-19]. The vast majority of the patients were successfully ventilated through the assigned laryngeal mask [LMA-C (*n* = 120), LMA-P (*n* = 306), LMA-S (*n* = 250), i-gel (*n* = 30)]. We excluded 62 patients ventilated with the streamlined liner of the pharynx airway (SLIPA™), because this SAD is not really considered a LMA[19].

Four of 16 obese LMA-P patients (BMI > 30 kg/m^2) crossed over to ETT because of respiratory obstruction or airway leak (0.5%)[13]. In 3 patients treated with LMA-C, ventilation failed but was subsequently optimal with the LMA-P[12].

Sharma *et al*[15] reported only 3 cases of regurgitation in patients ventilated with LMA-P, although no cases of aspiration were recorded. No more cases or regurgitation nor aspiration were found among the 706 patients studied.

Most of the studies analyzing and comparing the use of LMA in laparoscopy have focused on gynecological patients. Therefore, most part of LMA data were derived from gynecological laparoscopic procedures[5,20-39]. These data are not comparable with ours because gynecological laparoscopic has some differences when compared to cholecystectomy, such as higher intra-abdominal pneumoperitoneum pressure, trendelenburg position and all patients are women.

Other studies included different types of laparoscopic procedures apart from cholecystectomy (gynecological, appendicectomy or nephrectomy) and they were also excluded from our analysis[10,40,41]. We only found two studies involving the use of LMA for pediatric laparoscopic procedures and they were as well excluded[42,43].

Maltby *et al*[11] studied 101 adult American society of anesthesiologists (ASA) 1-2 patients scheduled for elective laparoscopic cholecystectomy using LMA-Classic or ETT, focused on gastric distension and ventilation parameters. They concluded that positive pressure ventilation with LMA-C of permitted adequate pulmonary ventilation and gastric distension occurred with equal frequency with either airway device. These authors, conducted another similar study in 2002[13] comparing LMA-P with ETT. They included 109 patients stratifying them as non-obese or obese (BMI > 30 kg/m^2) and stated that LMA-P provided a correct ventilation without clinically significant gastric distension in all non-obese patients. Four of 16 obese LMA-P patients crossed over to TI because of failed ventilation, so the recommended that further studies were required to determine the use of the LMA-P for laparoscopic cholecystectomy in obese patients.

The third study, conducted by Lu *et al*[12], tested the hypothesis that the LMA-P was a more effective ventilatory device than LMA-C for laparoscopic cholecystectomy in 80 ASA 1-2 patients. Ease of insertion, efficacy of seal, peak airway pressures and oxygenation were recorded. These authors determined that LMA-P was a more effective ventilatory device for laparoscopic cholecystectomy than the LMA-C. Although first-time insertion success rates were higher for the LMA-C, OLP was higher for the LMA-P and ventilation was suboptimal less frequently with the LMA-P under pneumoperitoneum condition. In 3 patients receiving LMA-C, ventilation failed but was subsequently optimal using the LMA-P.

This is an important work, because it was the first one considering that LMA-P is a better device than LMA-C for laparoscopy and they did not recommend the use of the LMA-C for laparoscopic cholecystectomy.

Natalini *et al*[14], compared the frequency of airway seal and sore throat with the LMA-P and the LMA-C in a study involving 60 ASA 1-3 patients for laparoscopic cholecystectomy. Patients were ventilated adding positive end-expiratory pressure 10 cm H_2O through the proseal or the standard LMA, in order to improve ventilation. Both devices showed similar ventilatory efficiency during laparoscopy. The sore throat evaluation performed in recovery room was scored as mild and there were no differences between the groups.

The fifth research, involved 60 patients and compared respiratory mechanics in laparoscopic cholecystectomy using LMA-P and i-gel[15]. They observed that OLP was higher in LMA-P group, however, dynamic compliance was higher with the i-gel. They performed a fibreoptic evaluation of positioning of the devices, showing a higher malrotation for i-gel. Although regurgitation occurred in 3 cases (LMA-P), aspiration was not reported. Both devices provided optimal ventilation and oxygenation.

Another prospective observational study was performed in 100 patients undergoing laparoscopic cholecystectomy with LMA-S[16]. This device was successful inserted in all patients (first attempt n = 91 and second attempt n = 9) and mechanical ventilation was adequate in all cases. Gastric tube insertion was successful in all patients and graded as easy in 97% of the cases. Mean OLP was 28.8 cm H_2O (± 5.2; range 18-40 cm H_2O) and median (range) of stomach size on entry of the laparoscope, and change in stomach size during surgery (scored by the surgeon on an ordinal scale of 0-10) did not interfere with the procedure in any patient. The study concluded that supreme is an easy to insert and effective ventilatory device for laparoscopic cholecystectomy that provided an optimum airway seal with minimum adverse events.

A prospective randomized study conducted in 2012[17], compared the safety and efficacy of supreme and proseal during laparoscopic cholecystectomy. LMA-S was easier device to insert, as well as its drainage tube which was more quickly inserted. Seal pressure was similar in both groups and they did not find differences regarding the degree of gastric distension. Therefore, the study stated that both devices provided optimal ventilation and LMA-S is a good alternative to LMA-P for laparoscopy in suitable patients and experienced users.

The next publicated study was conducted at Sureste University Hospital in Madrid (Spain)[18] and it is the largest comparison performed between two LMA for laparoscopic cholecystectomy. This prospective randomized single-blind study, tested the efficacy and safety of the LMA supreme *vs* the LMA proseal in 120, ASA 1-3 patients undergoing elective laparoscopic cholecystectomy. These authors found that the LMA-S has a lower OLP and achieves a lower maximum tidal volume compared to the LMA-P. The success rate of the first attempt insertion was higher for the LMA-S group and this could have important implications when using the LMAS as an airway rescue device. The easy of insertion of the drain tube, adequacy of ventilation and complication rates are comparable for the two airway devices.

Aydogmus *et al*[2], studied a small sample of 60 patients wondering if LMA-S can be an alternative to endotracheal intubation in laparoscopic surgery. They focused on ventilation efficacy, ease of insertion, hemodynamic response (heart rate and mean arterial blood pressure) during insertion and removal of the mask and postoperative adverse events. In the end, they concluded that this device can be a suitable alternative to intubation for laparoscopy in selected patients.

Our last selected article, compared the quantitative clinical performances of the SLIPA and the LMA proseal regarding intensity of gastric distension in 124 anesthetized and paralyzed patients undergoing laparoscopic cholecystectomy. Secondary outcomes were the fiberoptic bronchoscopic view of the glottis, the severity of blood stain, and postoperative sore throat. There were no statistically significant differences between groups for each of these parameters[19].

DISCUSSION

In summary, in our review involving 706 patients undergoing laparoscopic cholecystectomy, ventilation was optimal in almost all the cases (99.5%) and it only failed in 4 obese patients (in the other 3 patients it was not considered as a failure because it was solved using another kind of LMA), which underlines the importance of a good selection of the patients. As showed in this review, the use of LMAs (particularly those LMA with gastric access) for these laparoscopic procedures provided an adequate tidal volume and it was consistent with an optimal ventilation and oxygenation. Moreover, most of the studies performed with LMA involving gynecological laparoscopy or other kind of surgical procedures, permitted adequate ventilation in nearly 100% of the patients.

The studies reviewed also included capnography measurement during surgery as an important parameter to control hypercapnia in laparoscopic procedures. Mean $EtCO_2$ was maintained between 30-36 mmHg and it always remained < 45 mmHg[12-18].

These studies suggested a safe pneumoperitoneum pressure even using a relatively high peritoneal insufflation pressure of 15 mmHg used in the early studies[12,13]. Recent articles also found safe pressure when using lower values of 12-13 mmHg[16-18].

Regarding the risk of aspiration when using a LMA for general anesthesia during laparoscopic cholecystectomy, we observed a very low incidence of regurgitation and aspiration. This review found only 3 cases of regurgitation out of 706 patients studied (0.4%) and no cases of pulmonary aspiration were reported. Our results coincide with other authors; the largest study ever performed using LMA conducted by Chandi Verghese and Joseph Brimacombe[10] in 11910 patients for conventional and nonconventional usage, including 1534 laparoscopies (1469 gynecological and 65 cholecystectomies), only found four cases of regurgitation and one aspiration case. This patient was a female undergoing spontaneous ventilation anesthesia for an elective non-laparoscopic surgery who aspirated gastric contents during the procedure. She experienced an initial adverse outcome but with full recovery. These authors used LMA-C, because at that time, LMA with gastric access had not been introduced yet.

Brimacombe[44], stated that the LMA-C was used in 3000 selected women undergoing gynecological laparoscopy without serious morbidity. This suggests that the true risk of aspiration is likely to be less than 1 in 1000 (using 3/n to estimate the upper limit of a 95%CI).

Finally, a meta-analysis by Brimacombe and Berry[45] in 1995 about the incidence of aspiration associated with the LMA, involving 12901 patients, gave a final incidence of 2 aspiration in 10000 and case reports showed that most cases has one or more predisposing factors.

These three articles stated a very low incidence of aspiration over large series of patients when using the classic LMA (this device has not gastric access). We must have into account that, our review was performed over a sample mostly constituted by LMA with drain channel and this device is more appropriate for nonconventional usage such as laparoscopy than LMA-C. Based on the characteristics of these devices, its better airway seal pressure and the incorporation of a gastric access that allows the insertion of a gastric tube and the aspiration of gastric contents if necessary, makes this masks the optimal device to use for laparoscopic cholecystectomy.

The presence of gastric drainage channel should be mandatory for these procedures, because a common situation is the need for aspiration of gastric contents (including air) in order to properly expose the surgical field (gastric distention may impair the exposure of the triangle of Calot).

CONCLUSION

The published evidence does not allow us to totally answer the question we posed for this appraised topic. On the one hand, mechanical ventilation has been proved to be adequate when using LMA for laparoscopic cholecystectomy in selected patients. Although we do not recommend the use of the classic LMA for these procedures, only LMA with gastric access are advised. We do not either recommend the use of any type of LMA in laparoscopy for spontaneously breathing patients.

On the other hand, there is limited evidence to support the use of the LMA for laparoscopy. In particular, it is not completely clarified that the use of the LMA is not associated with an increased risk of pulmonary aspiration. We found, however, that the reported incidence of aspiration associated with the use of the LMA in laparoscopic surgery is very low. Moreover, we have found a non-existent incidence of aspiration when using LMA with drain channel for laparoscopic cholecystectomy in selected patients.

Based on our findings, we suggest the following inclusion criteria for using LMA in laparoscopic cholecystectomy: ASA 1-3 patients scheduled for elective laparoscopic cholecystectomy, non-obese patients (BMI < 30 kg/m^2), pneumoperitoneum pressure value lower than 13 mmHg, always using a LMA with drain channel and maybe performing a prophylactic routine gastric aspiration in order to minimize the risk of regurgitation and properly expose the surgical field.

Future research should focus on actual adverse outcomes and morbidity of these devices. A randomized comparison of tracheal intubation and LMA, investigating the risk of aspiration laparoscopy (assuming an incidence of 1 in 1000), would require a sample size of more than 30000 to find a twofold increase in risk. Such a trial is not feasible, but every year, hundreds of patients are successfully anesthetized using these devices with no morbidity. Clinical practice and the performance of more studies could provide satisfactory evidence in the future for anesthesiologists and patients.

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MINIREVIEWS

Endoscopic surgery - exploring the modalities

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Abstract

The adoption of endoscopic surgery continues to expand in clinical situations with the recent natural orifice transluminal endoscopic surgery technique enabling abdominal organ resection to be performed without necessitating any skin incision. In recent years, the development of numerous devices and platforms have allowed for such procedures to be carried out in a safer and more efficient manner, and in some ways to better simulate triangulation and surgical tasks (*e.g.*, suturing and dissection). Furthermore, new novel techniques such as submucosal tunneling, endoscopic full-thickness resection and hybrid endo-laparoscopic approaches have further widened its use in more advanced diseases. Nevertheless, many of these new innovations are still at their pre-clinical stage. This review focuses on the various innovations in endoscopic surgery, with emphasis on devices and techniques that are currently in human use.

Key words: Transanal total mesorectal excision; Natural orifice transluminal endoscopic surgery; Endoscopic surgery; Submucosal tunneling technique; Endoscopic submucosal dissection; Endoscopic full-thickness resection; Endo-laparoscopic

Core tip: This article is a comprehensive review of endoscopic surgery. It analyses the different types of endosurgery from endoscopic submucosal dissection, endoscopic full-thickness resection and natural orifice transluminal endoscopic surgery. This article highlights the relevant topics and recent advances in this area. In addition all the latest procedural devises such as the master and slave transluminal endoscopic robot endoscopic robot, multitasking endoscopes and other examples are described. Finally a clear and comprehensive review of the latest human clinical trials and their outcomes are outlined. Hence overall, readers will have a full understanding of endosurgery, the currently available as well as upcoming technology and their safety profiles.

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INTRODUCTION

Endoscopic resection has emerged as an alternative to many cases that were traditionally managed by surgery alone. Natural orifice transluminal endoscopic surgery (NOTES) has now offer truly scarless minimally invasive procedures for resection of abdominal organs. Since its introduction in 2000, more than 1000 reports have been published describing various applications NOTES in both animal and human[1]. The concept is continuously expanding in parallel to the advancement in technology and innovation of mechanics.

Endoscopic surgery is becoming increasingly popular among surgeons especially in Asian countries because many surgeons here were capable of performing flexible endoscopy. The Asia Pacific NOTES working group was formed in 2006 by a group of endoscopists and laparoscopic surgeons from Hong Kong, China, South Korea, Japan, Singapore, India and Malaysia. Since its establishment, many collaborative efforts between these countries have produced innovative developmental breakthroughs that address the barriers faced and clinical application in NOTES[2]. One example is the robotic endoscopic prototype named master and slave transluminal endoscopic robot (MASTER) that was developed in Singapore to perform complicated NOTES procedure.

Many novels endoscopic interventions have been described over the past decade, but none has have been formally approved as standard of care. There are many preliminary data that suggest its feasibility and safety, but there are still at preclinical stage. This article aims to provide a comprehensive review on endoscopic surgery, focuses on various innovations in endoscopic surgery, with emphasis on devices and techniques that are currently in human use.

Endoscopic submucosal dissection

Endoscopic resection was first reported by Hirao *et al*[3], a surgeon, for the treatment of early gastric cancer using local injection of hypertonic saline-epinephrine. The ideal result of endoscopic submucosal dissection (ESD) is that the specimen is resected *en bloc* and has sufficient depth to ensure accurate histopathological assessment and achieve R0 resection, while avoiding hazardous complications, mainly perforation and bleeding. Colonic ESD is technically more difficult because of the colon has thin wall, narrow lumen, and acute bends. At times, this is further complicated with the lesions being situated at proximal colon or behind a mucosal fold[4,5]. Various advances in the knives and other accessories have been developed to overcome these challenges (Table 1).

The devices used are generally divided into two broad categories: The needle-knife type and the grasping (scissors) type[6,7]. The most commonly used are the Dual knife and the insulated-tipped knife. The grasping scissors may be used when there is inadequate elevation of the submucosa plane to allow safe dissection. EndoLifter is a novel innovation in which an additional external grasping forceps is used to provide countertraction and make the submucosal plane wider. This is widely used in gastric ESD.

One of the disadvantages of ESD is that it can be time consuming. To reduce procedure time by eliminating the need for frequent switching of instrument, a new hybrid knife that combines both submucosal injection and dissection facilities into a single instrument has been developed (HybridKnife by ERBE, Tübingen, Germany). HybridKnife allow fluid injection into submucosal plane under safe and preselected pressure *via* the tip of the knife. The operators can perform marking, circumferential cutting and submucosal dissection with just one instrument. This device have shown to decrease procedure time, perforation rate and increase the rate of en bloc resection[8]. Another new water-jet system that also combines both submucosal injection and dissection known as the ENKI-2 has also recently been developed in France (by NESTIS, Lyon). The water jet is produced by a high pressure chamber. It is delivered *via* a flexible catheter hence enable ESD in retroflexion position. This system has proven its safety and efficiency in an animal study when compared to Dual knife[9]. A prospective human trial is currently underway.

Endoscopic full-thickness resection

Endoscopic full-thickness resection is a new technique that involves en bloc resection of the tumor which resulting in perforation, and closure of the defect. Initial experience with endoscopic full-thickness resection (EFTR) involves secondary defect closure using either over-the-scope-clip (OTSC), conventional clipping, T-tags or endoloops[10-12]. This may potentially cause peritoneal contamination or seedling of early cancer. Sarker *et al*[13], Fähndrich and Sandmann[14] have separately reported the successful use of grasp-and-snare techniques with preresection closure using OTSC system in human studies. The key aspect of this technique is to apply the clip at the base of the target lesion, and followed by resection above the ensnared lesion (Figure 1). There was no complication reported in their case series and all specimens had achieved complete resection margin. A significant disadvantage of using the OTSC system is that the size of the cap limits the size of the lesion that can be resected. Schmidt *et al*[15] described another preresection closure method using suturing devices (Plicator and GERDIX) in which it was found feasible for tumor of approximately 4 cm.

EFTR procedure still need to be investigated as current available evidence is mainly of animal models or from small series of human studies. EFTR could have a great impact in management of gastrointestinal stromal tumour and neuroendocrine tumor that would currently

Table 1 Characteristic of various endoscopic submucosal dissection knives

Type	Manufacturer	Description	Comments
Needle-knife type			
Insulated tip knife	Olympus	Ceramic ball attached to the tip of the knife	Insulator helps to prevent perforation. Small ceramic ball is suitable to operate on thinner submucosal plane; *e.g.*, in the esophagus and colon
Hook knife	Olympus	Tip of the knife is right-angled	Submucosal tissue is hooked and pulled before incision, lessen the risk of perforation
Flex knife	Olympus	Knife formed by soft, flexible loop cutting wire with adjustable length	Less risk of perforation. Distal end of the sheath is thick to serve as stopper to allow precise control of incision depth
Dual knife	Olympus	Small ball-like process on the tip, knife can be fixed in two positions - retracted or extended	Ball tip prevents slipping
Flush knife	Fujinon	Short needle knife that comes in 5 different projection lengths Water emission through the lumen of the needle	Water jet is activated by a foot pedal, helps to washout blood at operative field and debris at the tip of knife. Provide better visualization and less time consuming without having to switch instruments
Splashneedle	Pentax	Similar to Flush knife	
Mucosectomy	Pentax	Circumferentially insulated knife with single cutting wire on the side of the tip	Insulated plastic sheath can lie on the muscular layer, allowing safe dissection by cutting wire on the submucosal plane
Grasping type scissor forceps			
SB knife	Sumitomo Bakelite	Rotatable monopolar scissors, surrounded with no-conductive coating. Clawed and curved tip	Large insulated claw prevents injury to the muscular layer
Clutch Cutter	Fujinon	Thin serrated cutting scissor, insulated on the outer forcep, rotatable	Serrated edges help to grasp tissue better

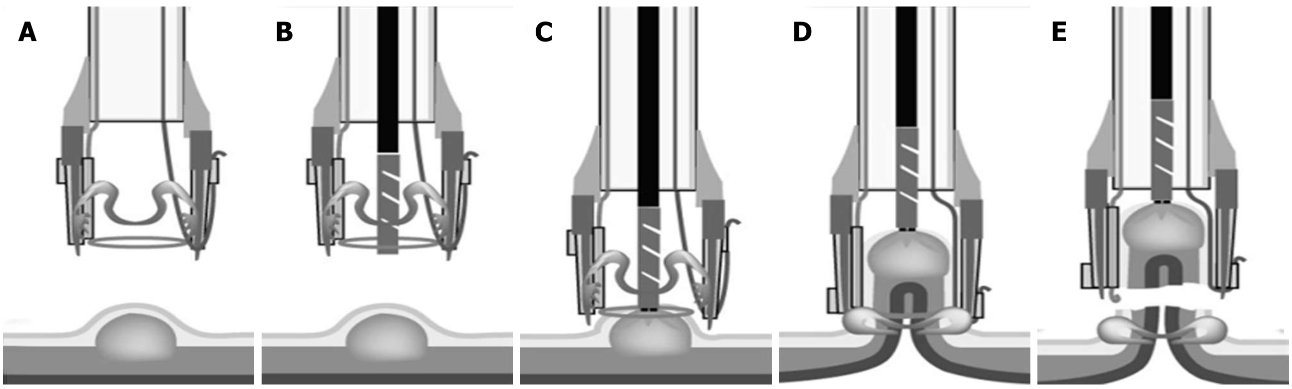

Figure 1 Endoscopic full-thickness resection of a submucosal lesion by application of an over-the-scope-clip followed by snare polypectomy. A: Endoscope is equipped with a cap mounted with clip; B: Identified lesion grasped; C: Pulled into the cap; D: Clip applied at the base; E: Full-thickness of the targeted lesion resected with closure of snare.

be treated by surgical resection.

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

Endoscopic surgery has in recent years achieved yet another breakthrough, going beyond the boundaries of the gastrointestinal lumen, and entering into the peritoneum to perform intra-abdominal intervention. This concept, widely known as NOTES, was first introduced by Kalloo *et al*[16]. In 2004 whereby he reported the success of transgastric peritoneoscopy using a flexible endoscope in an animal model 3 years later, Rao *et al*[17] performed the first ever human NOTES procedure, which was a transgastric appendicectomy. Since then NOTES has been increasingly adopted to perform intra-abdominal exploration and extraction of various organs.

One of the most common NOTES access route is transvaginal access. Its accessibility and safety has long been proven through the use of culdoscopy in gynaecology and of the vaginal route to extract surgical specimen. However, in clinical practice, transvaginal NOTES is mostly facilitated with the help of abdominal wall entry, hence these surgeries are sometime known as hybrid procedures. One of the most studied procedures is transvaginal cholecystectomy (TVC). To date, TVC has been put up against laparoscopic cholecystectomy on a few prospective studies, and the results have favor TVC being associated with decreased risk of port site hernia, less postoperative pain and shorter recovery time (Table 2)[18-20]. Many intra-abdominal operations have now been undertaken *via*

Table 2 Randomised controlled trials that reported on no significant difference in major outcomes between transvaginal cholecystectomy and conventional laparoscopic cholecystectomy

Ref.	Study type	Type of TVC	Outcome					
			Median/min Duration of surgery (min)		Median/min Length of stay (d)		Median/min Pain score	
			TVC	CLC	TVC	CLC	TVC	CLC
Kilian *et al*[18]	RCT	Hybrid	68	55	3	4	1	3
Noguera *et al*[19]	RCT	Hybrid	64.85	47.04	1	1	3.94	4.65
Borchert *et al*[20]	RCT	Hybrid	65.1	64.2	2.81	2.81	1.81	2.03

These studies proved that TVC is not inferior to CLC. RCT: Randomised controlled trials; TVC: Transvaginal cholecystectomy; CLC: Conventional laparoscopic cholecystectomy.

this route. The drawbacks to transvaginal access are its associated risk of bladder and urethra injury, potential risk of infertility, and it is only applicable to female. It may be less acceptable in Asian countries due to cultural differences[21].

NOTES *via* gastrointestinal lumen have been proven to be virtually possible for every type of surgery in animal models. Despite this breakthrough, there are reservations of utilizing this route among patients mainly due to fear of introducing infection from gut wall penetration. A transcolonic approach carries the highest risk, followed by transgastric, transesophageal, transvaginal and transvesical approaches. Over the past years, evidence from experimental and clinical studies have shown that infectious complication from NOTES is low (< 3%)[22-24]. At present, the transvaginal and transgastric approaches are the most relevant for intraperitoneal NOTES procedures in human.

Pure NOTES is technically challenging. Conventional flexible endoscopes are inadequate to perform complex transluminal surgical procedures. They lack a multitasking platform that allows more variety of surgical manipulation. Like in any laparoscopic procedures, the key element to successful pure NOTES is triangulation. The evolution of NOTES devices has seen many efforts put into developing devices and platforms that simulate triangulation and surgical tasks (*e.g.,* suturing and dissection) in a laparoscopic procedure. Presently, all multitasking system developed for NOTES procedures can be broadly classified into two different types: (1) Mechanical platforms, which includes the dual channel endoscope (DCE) (Olympus, Japan), R-Scope (Olympus, Japan), the ANUBISCOPE (Karl-Storz, Germany), the EndoSAMURAI (Olympus, Japan), incisionless operating platform (IOP) (USGI Medical, United States), and DDES system (Boston Scientific, United States). DCE, R-Scope (a modified DCE), EndoSAMURAI and the ANUBISCOPE are integrated system comprising of the visual and the instrument manipulation function. The IOP and DDES systems serve as multitasking platforms that have multiple operating channels and they rely on conventional endoscopes for visualization. Generally, these systems have an average diameter of not more than 22 mm in order to be able to intubate pass the pharynx. Triangulation is achieved by having two or more working arms and therefore increases the degree of freedom of the end effectors. To date, DCE, R-scope and the IOP have data published on human studies. The EndoSAMURAI, the more advanced platform, has two independently movable arms with an additional non-articulating arm. The moveable arms are mechanically cable actuated. They serve to provide traction and counter-traction on dissecting tissue, and perform more advanced maneuvers such as suturing. The non-articulating arm allows insertion of generic endoscopic instruments meant dissection, cautery and clipping. This system has console very similar to conventional laparoscopic instruments. During the early stage, Spaun *et al*[25] compared between DCE and EndoSAMURAI, and found that EndoSAMURAI has significant advantage over the conventional endoscopes in regards to accuracy and efficiency in performing complex surgical task. This device has been used successfully to perform transgastric small bowel full thickness resection in animal studies[26,27]. Another promising multitasking endoscope prototype is the ANUBIScope, which has a special tulip shaped tip that allow two deflectable instrument channels to be positioned for instrument triangulation, and a third central channel for suction. These instruments are controlled through a trigger handle that is similar to that seen in laparoscopic instruments. In 2012, Perretta *et al*[28] successfully completed a cholecystectomy on a human in 60 min using the ANUBISCOPE. Of the available integrated endoscope platforms, the ANUBIScope is likely to be the most successful.

IOP is another promising device which was first designed specifically to perform intraperitoneal NOTES procedures. One of the unique features of this multi-lumen access device is that its flexible over-sheath is equipped with ShapeLock function. ShapeLock function is formed by a series of titanium rings that are connected by wire, and the rings lock into position when the connecting wires are tightened. The stiffened over-sheath ensures a stable platform while articulating the instruments. As such, many extralumenal intraperitoneal procedures including those that require significant retroflexion such as transgastric cholecystectomy, fundoplication, gastric restriction and diaphragmatic repair have been performed in animal and human cadaveric study[29]. The IOP has since been used by surgeons in the Europe and Middle East for the novel primary obesity surgery

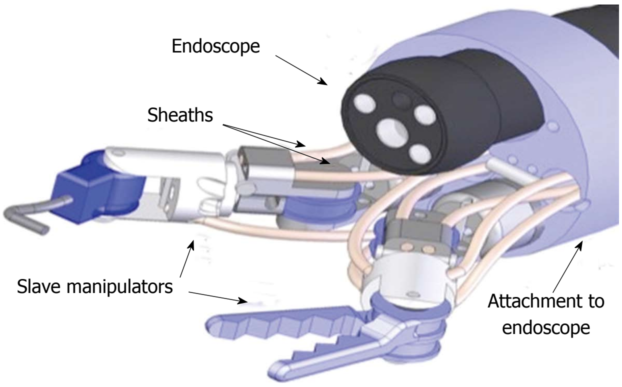

Figure 2 Design of prototype slave manipulator.

Figure 3 Master console controlled by surgeon.

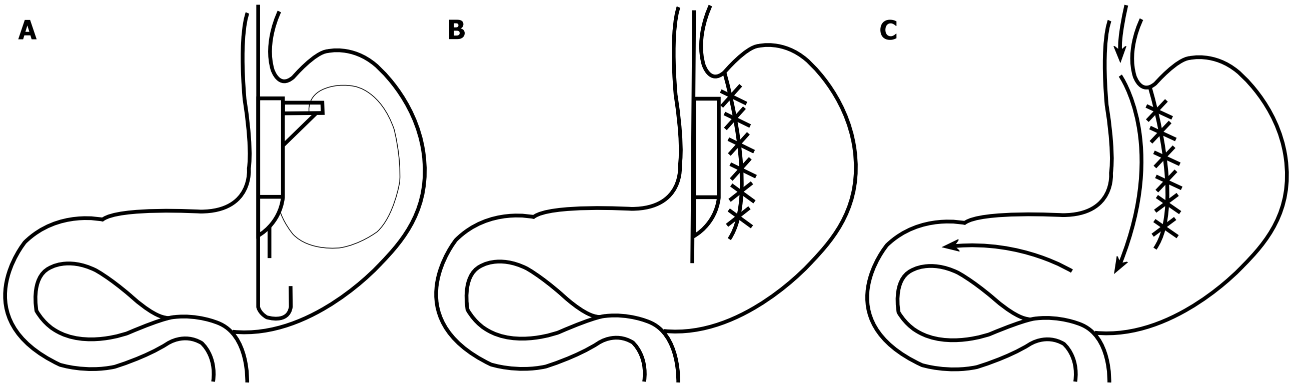

Figure 4 Endoscopic creation of restrictive pouch with transoral gastroplasty device. A: TOGA system deployed within the stomach, and having the endoscope at retroflex view; B: Anterior and posterior gastric mucosa brought into the suction chamber and stapled on; C: A restrictive luminal tube created within the stomach. TOGA: Transoral gastroplasty.

endoluminal (POSE) procedures. With this technique, multiple transmural plications are placed in the fundus and the distal body using specialized suture anchors that is facilitated by the IOP device. Espinós *et al*[30] has demonstrated clinical safety and effectiveness of POSE with IOP in 45 obese patients; (2) Robotic platforms: At present, two state-of-the-art robotic systems have been developed, namely the MASTER (Nanyang University, Singapore) and the ViaCath (Hansen Medical, United States). Master and slave translumenal endoscopic robot is an endoscopic robotic platform that is composed of a human-master robotic interface, a telesurgical workstation, and slave manipulator. This system works with a front-viewing endoscope equipped with two cable-actuated robotic arms (Figures 2 and 3). The robotic arm prototypes are designed with four "joints" which allows them to supinate, pronate, hyperextension, and flexion. One arm has a grasper and the other arm a cauterizing hook. The MASTER robotic system requires an endoscopist and a surgeon to operate. Once the endoscopist had positioned the endoscope, the surgeon then controls the finer motion of the robotic arms to perform surgery (Figure 4).

The MASTER system has been used to perform ESD in *ex vivo* and *in vivo* porcine models and was found to be comparable to standard endoscopic therapy in terms of operation time[31]. In 2014, Chiu *et al*[32] demonstrated that full thickness resection with MASTER for the treatment of gastric submucosal tumors in animal models with and closure of the defect with Overstitch is safe and feasible. First reported use of MASTER in clinical setting was a multicenter prospective study of 5 patients with early-stage gastric neoplasia[33]. All submucosal dissections were performed using the MASTER system, and no perioperative complications encountered. The resection margins were clear of tumors in all 5 patients. From these studies, the MASTER system has shown to have met its objectives on successfully performing true NOTES procedures. We are still awaiting further studies to assess its capability and safety to perform other surgical procedures.

ViaCath system is another robot driven actuator that consists of a flexible overtube that runs alongside a standard endoscopes with two distal articulated robotic instruments. It functions similar to the IOP except it is robotic assisted hence allow more precise manipulation of the operating arms. ViaCath is yet to be fully utilized for NOTES procedures in human.

Although the most common access route for NOTES procedures is the vagina, selective indications have emerged for each different access techniques, including submucosal tunneling techniques *via* the transesophageal approach, staging, gastric restriction and small tumor resection *via* the transgastric approach, and colorectal resections *via* the transanal/transcolonic approach.

Transeophageal approach: Submucosal tunneling techniques

Submucosal tunneling technique was first developed at the Mayo clinic with the intention to create a mucosal flap prior to penetration through the deeper layer and subsequent entry into the peritoneal cavity[34]. In this technique, the submucosal layer is endoscopically tunneled into with the resulting space that can be used either for dissection onto the deeper layer, or an offset exit into the peritoneal cavity. The mucosal flap serves as a sealant valve that minimizes the risk of intraperitoneal soiling with the luminal contents. Experimental studies on animal models have shown safe entry *via* the submucosal tunnel into the mediastinum and peritoneum, resulting in successful transesophageal approach for epicardial coagulation and transgastric cholecystectomy, respectively[35,36].

This submucosal tunneling technique has been adapted into the esophageal myotomy procedure to treat achalasia. The procedure, first introduced in 2008 by Inoue *et al*[37] as per oral endoscopic myotomy (POEM), involves dissection and division of the inner circular muscle layer of the esophagus through a submucosal tunnel created endoscopically by a small proximal opening in the esophageal mucosa. The submucosal entry point is usually created at 10-15 cm from the gastroesophageal junction (GEJ). Once the subumucosal layer is exposed, the dissection is carried out using electrosurgical ESD technique. The mucosal layer is separated from the underlying circular muscle fibers, and this dissection is extended until the endoscope is 2-3 cm beyond the GEJ. Myotomy then begins from 2 cm distal to the entry point up to the GEJ. Once completed, the mucosal closure can easily be performed with clips or endoscopic suturing device. Five years later, Inoue *et al*[38] published the largest series of POEM with overwhelming success. Out of 300 patients, dysphagia was relief following one session of POEM in 98.2% of the subjects. There were only 2 patients with perforation that resulted in pneumomediastinum and pneumoperitoneum, one each respectively. In another prospective, multicentre study, 6 and 12 mo symptom remission rates was reported as 89% and 82%, respectively[39]. All current studies have indicated that POEM is a safe and effective treatment for esophageal achalasia.

The success in POEM has led to the further use submucosal tunneling technique for resection of subepithelial tumor. Usually, the submucosal tunnel begins at 5 cm proximal to the lesion. A short tunnel approaching the lesion is created by additional submucosal dissection with CO_2 or air insufflations. Subepithelial tumour is excised using needle-knife and removed completely through the tunnel. Mucosal entry flap is then approximated using endoclips. To date, successful attempts were reported for submucosal tumors in the esophagus and cardia that is ≤ 4 cm in size[40-42]. Resection of gastric lesion distal to cardia appears to be technically difficult, and endoscopic full thickness resection, as described above is the more preferred treatment of choice.

Transgastric access: Peritoneoscopy, gastric restriction surgery, full-thickness gastric tumor resection

Transgastric NOTES access is typically *via* gastrostomies performed in the anterior stomach with needle knife puncture and balloon dilation. Currently, its role in clinical practice is mainly for staging peritoneal exploration, small bowel tumor resection and gastric tumor resection. A study involving a series of 130 patients who underwent transgastric NOTES by Nau *et al*[43] found that endoscopic peritoneoscopy is not inferior to laparoscopic exploration for assessment of peritoneal metastasis. Interestingly, the former was also found to be equally effective and safe in a subgroup of patients with previous abdominal surgery. Transgastric peritoneoscopy can be performed with conventional flexible endoscopes, but the gastrotomies would require a specialized closure device. Since the development of abovementioned multitasking platforms, full thickness resections of gastric and small bowel tumors are currently performed *via* transgastric route.

Novel endoscopic gastric restriction surgery is the new frontier in bariatric surgery, to offer a less invasive approach which can be performed without general anesthesia. In theory, this may potentially reduce the risks commonly associated with laparoscopic bariatric surgery such as cardiopulmonary event, anastomotic leak, marginal ulcer formation and wound related complications. Endoscopic approach can serve either as a bridge to surgery or as "stand-alone" procedure for patients who are poor surgical candidates especially in super-obese (BMI > 50). Currently, there are two established techniques and, known as the transoral gastroplasty (TOGA™) and endoluminal vertical gastroplasty. Table 3 provides a summary of reported outcome for these endoscopic restrictive gastroplasty procedures. TOGA uses an endoscopic full-thickness stapling device to create a pouch along the lesser curve. The device uses vacuum suction to oppose the anterior and the posterior gastric wall prior to deploying the staplers. A restrictor is used to clamp the gastric folds, and the process can be repeated to achieve the desired luminal narrowing (Figure 4). A multicentre trial of 67 patients showed that this procedure resulted in substantial weight loss after 1 year without severe complications and no mortality[44]. Endoluminal vertical gastroplasty uses a endoscopic suturing device (Bard EndoCinch) to create a sleeve intraluminally. The suturing device is contained within a capsule that is attached at the end of the gastroscope. Tissue is sucked into the capsule and a needle is advanced through the captured tissue. Several sutures are deployed in a

Table 3 Summary of reported outcome data for endoscopic restrictive gastroplasty

Technique	Study design	Excess BMI/weight loss (%)	Effects of comorbidities	Postoperative complications
Transoral gastroplasty[44]	Prospective multicentre study with 67 patients enrolled Average BMI: 41.5 (range 35.0-52.7) Follow up period: 12 mo	52.2% for patients with baseline BMI < 40; 41.3% for patients baseline BMI > 40	Successful reduction of HbA1c to 5.7% (baseline of 7%), improvement in triglyceride level	2 patients had respiratory insufficiency and asymptomatic pneumoperitoneum, respectively. Both were successfully managed conservatively
Endoluminal vertical gastroplasty using Bard EndoCinch suturing system[45]	Prospective, single centre observational study Average BMI: 39.9 (range 28.0-60.2) Follow up period: 12 mo	Overall EWL of 58.1% Patients with BMI < 35 have highest EWL of 85.1%	NE	No serious adverse events reported
Endoscopic transmural gastric plication using Incisionless Operating Platform[30]	Prospective single centre Average BMI: 36.7 (range 28.1-46.6) Follow up period: 6 mo	49.4% EWL at 6 mo	NE	Minor postoperative side effects, *i.e.*, fever, sore throat, stomach pain, nausea, vomiting and chest pain

NE: Not evaluated; BMI: Body mass index; EWL: Excess weight loss.

continuous and cross-linked fashion from the proximal fundus to the distal stomach. Once the suture is fixed, a vertical sleeve is created. Fogel *et al*[45], the first to describe the use of EndoCinch for this procedure, reported a 12 mo excess weight loss of 58.1 ± 19.9 in 64 patients. The main concern with this technique is its durability, for which additional studies are needed to evaluate its long-term efficacy. Recent modifications to this technique is the use of the restoring suturing system that enabled suture reloading without device withdrawal and provide greater depth of suturing. The incisionless operating platform has also being used for this procedure.

Transanal/transcolonic natural orifice transluminal endoscopic surgery: Transanal endoscopic microsurgery

From experience derived from transanal endoscopic microsurgery (TEM), surgeons have expanded the utilization of the transanal route for complete rectal and colonic resection. In 2007, Whiteford *et al*[46] described the first transanal NOTES radical sigmoidectomy in human cadavers. Various attempts by others were successful in swine and cadaveric models, but all has found significant technical difficulty for dissection of the mesentery and more proximal colon using solely the TEM platform. This has led to the use hybrid technology that uses transabdominal laparoscopy to provide camera visualization, triangulation by assisting grasper, dissection with energy source device. Ever since, this approach has made it to clinical application for treating rectal cancer and inflammatory bowel disease[47-49]. Transanal approach has two distinct techniques: (1) Using origin TEM technique to dissect the lower rectum and perform colorectal resection and rectal anastomosis; and (2) abdominal cavity is entered *via* transanal route or *via* transcolonic approach at the desired anastomotic site. Currently, pure transanal NOTES colorectal resection is still at preclinical stage.

CONCLUSION

The innovation in endoluminal techniques and development of endoscopic instruments encouragingly implies that it is now possible to perform fully incisionless surgery. The progress of endoscopic surgery is still at an experimental stage. Further development of multitasking platforms and surgical instruments is necessary to allow safe and widespread application of endoscopic surgery for more complex procedures, especially for malignant tumors. Despite its current limitations, endoscopic surgery has met with considerable success and has proven to be not inferior to conventional laparoscopic surgery in numerous areas. The future of NOTES seems promising and may one day provide the ultimate version of minimally invasive surgery.

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ORIGINAL ARTICLE

Retrospective Study

Application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy

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Abstract

AIM: To investigate the simplicity, reliability, and safety of the application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy.

METHODS: A retrospective analysis was performed on the data of patients who received pancreaticoduodenectomy completed by the same surgical group between January 2011 and April 2014 in the General Hospital of the People's Liberation Army. In total, 51 cases received single-layer mucosa-to-mucosa pancreaticojejunal anastomosis and 51 cases received double-layer pancreaticojejunal anastomosis. The diagnoses of pancreatic fistula and clinically relevant pancreatic fistula after pancreaticoduodenectomy were judged strictly by the International Study Group on pancreatic fistula definition. The preoperative and intraoperative data of these two groups were compared. χ^2 test and Fisher's exact test were used to analyze the incidences of pancreatic fistula, peritoneal catheterization, abdominal infection and overall complications between the single-layer anastomosis group and double-layer anastomosis group. Rank sum test were used to analyze the difference in operation time, pancreaticojejunal anastomosis time, postoperative hospitalization time, total hospitalization time and hospitalization expenses between the single-layer anastomosis group and double-layer anastomosis group.

RESULTS: Patients with grade A pancreatic fistula accounted for 15.69% (8/51) *vs* 15.69% (8/51) (P = 1.0000), and patients with grades B and C pancreatic fistula accounted for 9.80% (5/51) *vs* 52.94% (27/51) (P = 0.0000) in the single-layer and double-layer anastomosis groups. Although there was no significant difference in the percentage of patients with grade A pancreatic fistula, there was a significant difference in the percentage of patients with grades B and C pancreatic fistula between the two groups. The operation time (220.059 ± 60.602 min *vs* 379.412 ± 90.761 min, P = 0.000), pancreaticojejunal anastomosis time (17.922 ± 5.145 min *vs* 31.333 ± 7.776 min, P = 0.000), postoperative hospitalization time (18.588 ± 5.285 d *vs* 26.373 ± 15.815 d, P = 0.003), total hospitalization time (25.627 ± 6.551 d *vs* 33.706 ± 15.899 d, P = 0.002), hospitalization expenses (116787.667 ± 31900.927 yuan *vs* 162788.608 ± 129732.500 yuan, P = 0.001), as well as the incidences of pancreatic fistula [13/51 (25.49%) *vs* 35/51 (68.63%), P = 0.0000], peritoneal catheterization [0/51 (0%) *vs* 6/51 (11.76%), P = 0.0354], abdominal infection [1/51 (1.96%) *vs* 11/51 (21.57%), P = 0.0021], and overall complications [21/51 (41.18%) *vs* 37/51 (72.55%), P = 0.0014] in the single-layer anastomosis group were all lower than those in the double-layer anastomosis group.

CONCLUSION: Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis appears to be a simple, reliable, and safe method. Use of this method could reduce the postoperative incidence of complications.

Key words: Pancreaticojejunal anastomosis; Pancreatic fistula; Pancreaticoduodenectomy

Core tip: Pancreaticoduodenectomy is a complex surgical procedure with a high perioperative complication rate and a high mortality rate, therefore, pancreaticoduodenectomy is considered a dangerous surgery. Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. In our study, there was a significant difference in the percentage of patients with grades B and C pancreatic fistula between the two groups. Single-layer anastomosis was better than double-layer anastomosis when the pancreatic texture was soft. The use of this method could reduce the rates of postoperative pancreatic fistula, abdominal infection and peritoneal catheterization.

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INTRODUCTION

Pancreaticoduodenectomy is the primary surgical method for the treatment of pancreatic head tumors, distal bile duct tumors, ampullary tumors, duodenal tumors, and duodenal papilla tumors. However, because it is a complex surgical procedure with a high perioperative complication rate and a high mortality rate, pancreaticoduodenectomy is considered a dangerous surgery. In the literature, the reported incidence of postoperative pancreatic fistula associated with this procedure differs due to the use of different definitions of pancreatic fistula; overall, the incidence ranges from 10% to greater than 30%[1-4]. Pancreatic fistula was associated with delayed gastric emptying, intra-abdominal abscess, local infection at the incision site, sepsis, and blood loss after pancreaticoduodenectomy[5-8]. Although the complication and mortality rates associated with pancreatic fistula have decreased due to improvements in perioperative management, surgical techniques and timely and proper management of postoperative complications[5,9,10], the incidence of postoperative complications during the perioperative period is still 30%-60%[11-15].

Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. Currently, pancreaticojejunal anastomosis is considered a weak link in pancreaticoduodenectomy[16,17]. Although several advocated methods of pancreaticojejunal anastomosis are considered to be able to reduce the occurrence of pancreatic fistula, the question of which pancreaticojejunal anastomosis method is best is still debatable[18-25]. This study describes a new, safe, simple, easy-to-suture, and reliable method for pancreaticojejunal anastomosis.

MATERIALS AND METHODS

General information

This study retrospectively analyzed data on pancreaticoduodenectomies completed by the same surgical group between January 2011 and April 2014 at our hospital. In these surgeries, a variety of pancreaticojejunal anastomosis methods were used, including single-layer mucosa-to-mucosa pancreaticojejunal anastomosis (referred to hereafter as single-layer anastomosis) and double-layer mucosa-to-mucosa pancreaticojejunal anastomosis (referred to hereafter as double-layer anastomosis). Patients whose surgery involved either of these two pancreaticojejunal anastomosis methods in pancreaticoduodenectomy were enrolled, and patients who did not meet the inclusion criteria for the study were excluded. There were 102 patients in the two groups, with 51 cases in each group. Of these patients, 19 had hypertension, 14 had a history of diabetes mellitus, 30 had a past history of drinking, 27 had a history of smoking, and 14 cases had a history of abdominal surgery. There were 62 males and 40 females. Other general information on these patients is presented in Tables 1 and 2. All 102 cases were confirmed by postoperative pathology (Table 3).

Double-layer anastomosis group

General information: There were 51 patients in

Table 1 General information on patients in the single-layer anastomosis group

Item	Mean value	Standard deviation	Minimum value	Maximum value
Age (yr)	58.804	9.466	38.000	79.000
BMI (kg/m^2)	22.866	2.755	17.900	29.400
Albumin (g/L)	38.039	3.891	26.100	45.000
Blood glucose (mol/L)	6.472	2.540	3.960	16.610
Total bilirubin (μmol/L)	122.618	122.204	6.400	412.600
Alkaline phosphatase (u/L)	359.631	258.629	39.900	1396.900
r-GT	620.853	522.464	7.000	2503.200
Operation time (min)	220.059	60.602	135.000	480.000
Pancreaticojejunal anastomosis time (min)	17.922	5.145	11.000	40.000
Amount of blood loss (mL)	292.549	146.940	100.000	800.000
Pancreatic duct diameter (mm)	4.863	2.322	1.000	12.000
Hospitalization time (d)	25.627	6.551	15.000	49.000
Postoperative hospitalization time (d)	18.588	5.285	7.000	33.000
Hospitalization expense (yuan)	116787.667	31900.927	64874.000	237762.000

BMI: Body mass index.

Table 2 General information on patients in the double-layer anastomosis group

Item	Mean value	Standard deviation	Minimum value	Maximum value
Age (yr)	58.020	12.820	18.000	78.000
BMI (kg/m^2)	23.858	3.272	13.360	32.690
Albumin (g/L)	39.480	4.182	29.600	50.000
Blood glucose (mol/L)	6.482	2.228	4.120	13.550
Total bilirubin (μmol/L)	73.510	78.244	3.500	313.000
Alkaline phosphatase (u/L)	303.245	268.287	42.000	1105.600
r-GT	533.655	631.956	5.800	2744.000
Operation time (min)	379.412	90.761	210.000	570.000
Pancreaticojejunal anastomosis time (min)	31.333	7.776	16.000	47.000
Amount of blood loss (mL)	482.353	293.909	50.000	1500.000
Pancreatic duct diameter (mm)	3.961	2.362	1.500	12.000
Hospitalization time (d)	33.706	15.899	16.000	105.000
Postoperative hospitalization time (d)	26.373	15.815	11.000	101.000
Hospitalization expense (yuan)	162788.608	129732.500	84497.000	968534.000

BMI: Body mass index.

the double-layer anastomosis group. Sixteen of these received pancreaticoduodenectomy (PD); of these, 3 also received combined portal vein resection and reconstruction. Thirty-five patients received pylorus-preserving pancreaticoduodenectomy (PPPD); of these, 2 also received combined portal vein resection and reconstruction.

Surgical method: The pancreas was transected at the left side of the portal vein using a surgical knife. The bleeding points on the pancreatic resection surface were sutured and ligated using 6-0 PDS Ⅱ for complete hemostasis. An appropriate pancreatic duct supporting tube was placed in the pancreatic duct. The pancreatic head was resected, and the duodenum and lymph nodes were completely cleaned. Approximately 2-3 cm of the pancreatic stump was freed, and an incision approximately 0.5 cm in length was made on the jejunal wall 4-5 cm from the jejunal stump. The distal end of the pancreatic duct supporting drainage tube was placed into the jejunum loop. The pancreatic parenchyma and the jejunal seromuscular layer were intermittently sutured using 4-0 Vicryl sutures; surgical knots were not made at this point. Next, 6-0 PDS Ⅱ absorbable thread was used to intermittently penetrate the pancreatic duct and the jejunal opening to form the mucosa-to-mucosa pancreaticojejunal anastomosis using intermittent sutures for 6 stitches. One suture on the middle of the posterior wall was reserved to fix the pancreatic duct supporting tube. The intermittent suture between the pancreatic parenchyma and the jejunal seromuscular layer was ligated to complete the anastomosis. After the cholangioenteric anastomosis and gastrointestinal anastomosis were completed, two abdominal drainage tubes were inserted, one before and one after the pancreaticojejunal anastomotic site to facilitate postoperative observation and conventional monitoring of the quantity and properties of the drainage fluid and to provide samples for the measurement of indicators such as bilirubin and amylase.

Single-layer anastomosis group

General information: There were 51 patients in the single-layer anastomosis group. Twenty of these received

Table 3 Pathology data

Pathological type	Number of cases
Distal bile duct adenocarcinoma	29
Chronic inflammation at the end of the distal bile duct mucosa combined with moderate atypical dysplasia	3
Villous adenoma at the end of distal bile duct mucosa and moderate-severe atypical dysplasia of some glands	1
Ampullary adenocarcinoma	14
Duodenal stromal tumors	1
Adenocarcinoma of the descending duodenum	3
Duodenal papilla adenocarcinoma	20
Duodenal neuroendocrine tumors	2
Tubulovillous adenoma of duodenal papilla with severe atypical dysplasia of some epithelia	1
Duodenal papilla adenocarcinoma	1
Chronic pancreatitis	1
Pancreatic head adenocarcinoma	22
Solid-pseudopapillary tumor of pancreatic head	1
Neuroendocrine tumor of pancreatic head	2
Neuroendocrine carcinoma of pancreatic head	1

PD; of these, 1 also received combined portal vein resection and reconstruction. Thirty-one of the patients in this group received PPPD; 1 of these also received combined portal vein resection and reconstruction.

Surgical method: The pancreas was transected at the left side of the portal vein using a small knife. The bleeding points on the pancreatic resection surface were sutured and ligated using 5-0 prolene sutures for complete hemostasis. Appropriate pancreatic duct supporting tubes were placed in the pancreatic duct. The pancreatic head was resected, and the duodenum and lymph nodes were completely cleaned.

Step 1: The pancreatic stump was freed for approximately 3-4 cm of its length. At 1-2 cm from the pancreatic stump, the anterior wall of the pancreatic duct and the anterior wall of the pancreas were intermittently penetrated and sutured using 4-0 absorbable Vicryl sutures for 3-4 stitches; surgical knots were not made at this point, and the suture was reserved for suturing the anterior wall of the jejunal incision and for suspension of the anterior wall of the pancreatic duct. The needling direction was from the whole layer of the anterior wall of the pancreas to the inside of the anterior wall of the pancreatic duct (Figure 1A).

Step 2: The proximal jejunum was lifted, and a 0.5-0.8 cm incision was made at the jejunal wall 4-5 cm from the jejunal stump. A 4-0 absorbable Vicryl suture was used to intermittently penetrate and suture the whole layer of the posterior-lateral wall of the jejunum, the posterior-lateral wall of the pancreatic duct, and the whole layer of the posterior-lateral wall of the pancreas for a total of 5-7 stitches (3-5 stitches in the posterior wall and 1 stitch in each lateral wall). Surgical knots were not made at this point. The needling was conducted from outside the jejunum to the inside of the jejunal section for suturing; then, the posterior-lateral wall of the pancreatic duct and the whole layer of the posterior-lateral wall of the pancreas were penetrated and sutured. The knot was tied at one side. It is important to ensure that this knot is tied properly; if it is too tight, the pancreas and the pancreatic duct may be cut; if it is too loose, the attachment will be insufficient (Figure 1B).

Step 3: A supporting tube was placed in the jejunum with its distal end projecting over the mouth of the cholangioenteric anastomosis by approximately 5-8 cm. The anterior wall suspension suture was used to intermittently suture the whole layer of the anterior wall of the jejunum section; knots were then tied one by one to create an anastomosis between the pancreatic duct mucosa and the jejunal mucosa. After the pancreaticojejunal anastomosis was finished, the suture was ligated; at this point, an excellent attachment of the jejunum to the whole pancreatic stump could be observed (Figure 1C). After the cholangioenteric anastomosis and gastrointestinal anastomosis were completed, abdominal drainage tubes were placed at the inferior-posterior and superior-anterior sides of the pancreaticojejunal anastomotic site to facilitate postoperative observation and conventional monitoring of the quantity and properties of the drainage fluid and to provide samples for the measurement of indicators such as bilirubin and amylase.

Postoperative treatment

After surgery, conventional infection prevention, nutrition, rehydration, and maintenance of water-electrolyte and acid-base balance were provided. All patients in both groups received total parenteral nutrition support. Conventional drugs for inhibition of pancreatic secretion were not administered after surgery. The amylase level in the drainage fluid at the pancreaticojejunal anastomotic site was measured 1, 3, 4, 5, 6, 7, and 10 d after surgery. On postoperative day 7, abdominal computed tomography (CT) was conventionally performed. If no pancreatic fistula was present 10 d after surgery, the peritoneal drainage tube at the pancreaticojejunal anastomotic site was removed. In patients with pancreatic fistula, the peritoneal drainage tube was removed after the pancreatic fistula had healed.

Observation indicators

Intraoperative blood loss, pancreaticojejunal anastomosis time, operation time, pancreatic fistula rate, abdominal infection rate, peritoneal catheterization rate, total complication rate, total hospitalization time, postoperative hospitalization time, and hospitalization expenses were recorded.

Diagnosis of pancreatic fistula

Pancreatic fistula was defined according to the ISGPF as output *via* operatively or postoperatively placed drains of any measurable volume of drainage fluid with amylase content greater than three times the upper

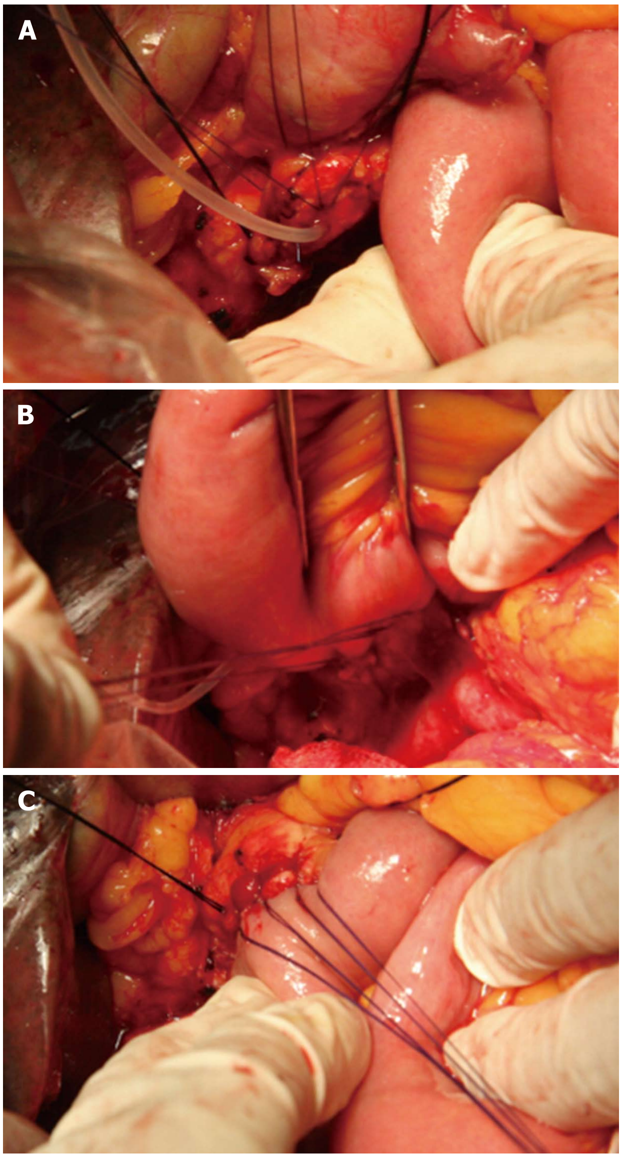

Figure 1 Surgical method using in single-layer anastomosis group. A: The pancreatic stump was freed for approximately 3-4 cm of its length; B: The proximal jejunum was lifted, and a 0.5-0.8 cm incision was made at the jejunal wall 4-5 cm from the jejunal stump; C: A supporting tube was placed in the jejunum with its distal end projecting over the mouth of the cholangioenteric anastomosis by approximately 5-8 cm.

normal serum value on or after postoperative day 3. Three grades of pancreatic fistula were determined according to the clinical severity of the individual cases. The grades were determined only after complete healing of the fistula had occurred[26].

Statistical analysis

Statistical analyses of the data on the patients in the two groups were performed using SPSS 17.0 software. Quantitative data that did not conform to a normal distribution or that had heterogeneous variances were examined using the non-parametric rank sum test. Qualitative data were examined using the χ^2 test or the Fisher exact probability test. The examination level was α = 0.05. P < 0.05 indicated that the difference was statistically significant.

RESULTS

Comparison of preoperative and intraoperative patient data in the two groups

Gender, age, hypertension history, diabetes mellitus history, drinking history, smoking history, abdominal surgery history, preoperative biliary drainage, body mass index, total bilirubin, albumin, blood glucose, disease composition, surgical methods, jejunum-jejunum anastomosis (Braun anastomosis), pancreatic texture, and pancreatic duct diameter did not show significant differences in the two groups (Table 4).

Comparison of complications

Abdominal CT examination of 51 patients in the single-layer anastomosis group after surgery showed that the mouth of the pancreaticojejunal anastomosis and the surroundings did not have effusion. Abdominal CT examination of 51 patients in the double-layer anastomosis group after surgery showed that 6 cases had effusion surrounding the mouth of the pancreaticojejunal anastomosis. Table 5 shows the incidences of postoperative complications such as pancreatic fistula, peritoneal catheterization, abdominal infection, and total complications in the single-layer and double-layer anastomosis groups.

In the single-layer anastomosis group, patients with pancreatic fistula accounted for 25.49% (13/51), patients with grade A pancreatic fistula accounted for 15.69% (8/51), and patients with grade B pancreatic fistula accounted for 9.80% (5/51); there were no patients with grade C pancreatic fistula. In the double-layer anastomosis group, patients with pancreatic fistula accounted for 68.63% (35/51), patients with grade A pancreatic fistula accounted for 15.69% (8/51), patients with grade B accounted for 45.10% (23/51), and patients with grade C accounted for 7.84% (4/51). In the single-layer anastomosis group, 10 of the 27 patients with soft pancreas had pancreatic fistula, 2 of the 14 patients with normal pancreatic texture or mild fibrosis of the pancreas had pancreatic fistula, and 1 of the 10 patients with hard pancreas had pancreatic fistula. In the double-layer anastomosis group, 21 of the 24 patients with soft pancreas had pancreatic fistula, 10 of the 17 patients with normal pancreatic texture or mild fibrosis of the pancreas had pancreatic fistula, and 4 of the 10 patients with hard pancreas had pancreatic fistula. A comparison of the incidence of pancreatic fistula in patients with different pancreatic textures is presented in Table 6.

Comparison of intraoperative operation time, pancreaticojejunal anastomosis time, postoperative hospitalization time, total hospitalization time, and hospitalization expenses in the two groups

Because the intraoperative operation time, pancreatico-

Table 4 Comparison of patient data in the two groups, *n*

Item	Single-layer anastomosis group	Double-layer anastomosis group	*P*-value
Gender	Female: 21 Male: 30	Female: 19 Male: 32	0.6850
Age	> 60 yr: 24 ≤ 60 yr: 27	> 60 yr: 25 ≤ 60 yr: 26	0.8429
Hypertension	Yes: 6 No: 45	Yes: 13 No: 38	0.0750
Diabetes mellitus	Yes: 10 No: 41	Yes: 4 No: 47	0.0843
Drinking history	Yes: 14 No: 37	Yes: 16 No: 35	0.6638
Smoking history	Yes: 13 No: 38	Yes: 14 No: 37	0.8224
Abdominal surgery history	Yes: 5 No: 46	Yes: 8 No: 43	0.3731
Preoperative biliary drainage	Yes: 13 No: 38	Yes: 10 No: 41	0.4772
BMI	> 25: 13 ≤ 25: 38	> 25: 17 ≤ 25: 34	0.3847
Total bilirubin	> 171 μmol/L: 16 ≤ 171 μmol/L: 35	> 171 μmol/L: 10 ≤ 171 μmol/L: 41	0.1728
Serum albumin	≥ 35 g/L: 40 < 35 g/L: 11	≥ 35 g/L: 47 < 35 g/L: 4 cases	0.0503
Blood glucose	> 6.1 mmol/L: 19 ≤ 6.1 mmol/L: 32	> 6.1 mmol/L: 24 ≤ 6.1 mmol/L: 27	0.3161
Disease composition	Pancreatic head: 11 Duodenum and papilla: 16 Ampulla: 5 Distal bile duct: 19	Pancreatic head: 16 Duodenum and papilla: 14 Ampulla: 5 Distal bile duct: 14	0.5418
Surgical method	PD: 20 PPPD: 31	PD: 16 PPPD: 35	0.4072
Braun anastomosis	Yes: 5 No: 46	Yes: 2 No: 49	0.2400
Pancreatic texture	Soft: 27 Normal or mild fibrosis: 14 Hard: 10	Soft: 24 Normal or mild fibrosis: 17 Hard: 10	0.7918
Pancreatic duct diameter	> 3 mm: 30 ≤ 3 mm: 21	> 3 mm: 26 ≤ 3 mm: 25	0.4261
Intraoperative blood transfusion	Yes: 4 No: 47	Yes: 1 No: 50	0.3590

BMI: Body mass index; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy.

Table 5 Comparison of postoperative complications, *n*

Complication	Single-layer anastomosis group	Double-layer anastomosis group	χ^2	*P*-value
Pancreatic fistula	Yes: 13 No: 38	Yes: 35 No: 16	19.0463	0.0000
Peritoneal catheterization	Yes: 0 No: 51	Yes: 6 No: 45	4.4271	0.0354
Abdominal infection	Yes: 1 No: 50	Yes: 11 No: 40	9.4444	0.0021
Total complications	Yes: 21 No: 30	Yes: 37 No: 14	10.2320	0.0014

jejunal anastomosis time, postoperative hospitalization time, total hospitalization time, and hospitalization expenses in the quantitative data of these two groups did not show normal distributions and/or exhibited heterogeneous variances, the data regarding these parameters were examined using the rank sum test to determine whether there were differences in these parameters between the two groups (Table 7).

DISCUSSION

The most important factor resulting in complications and deaths after pancreaticoduodenectomy was pancreatic fistula[13,26-28]. The tightness of the pancreaticojejunal anastomosis to a large extent determines the success of pancreaticoduodenectomy. The modification of the pancreaticojejunal anastomosis method and the

Table 6 Comparison of the incidence of pancreatic fistula in patients with different pancreatic textures in the two groups

Pancreatic texture	Single-layer anastomosis group	Double-layer anastomosis group	χ^2	*P*-value
Soft	10/27	21/24	13.5737	0.0002
Normal or mild fibrosis	2/14	10/17		0.0245
Hard	1/10	4/10		0.3034

Table 7 Comparison of intraoperative and postoperative conditions in the single-layer anastomosis group and the double-layer anastomosis group

Item	Single-layer anastomosis group	Double-layer anastomosis group	Mann-Whitney	*P*-value
Operation time (min)	220.059 (± 60.602)	379.412 (± 90.761)	179.000	0.000
Pancreaticojejunal anastomosis time (min)	17.922 (± 5.145)	31.333 (± 7.776)	185.000	0.000
Postoperative hospitalization time (d)	18.588 (± 5.285)	26.373 (± 15.815)	854.500	0.003
Total hospitalization time (d)	25.627 (± 6.551)	33.706 (± 15.899)	841.000	0.002
Hospitalization expense (yuan)	116787.667 (± 31900.927)	162788.608 (± 129732.500)	800.000	0.001

improvement in surgical techniques described here can be used for pancreaticojejunal anastomotic leakage to reduce the incidence of pancreatic fistula. The single-layer pancreaticojejunal anastomosis method is a simple, reliable, and safe method for pancreaticojejunal anastomosis[29,30].

The single-layer mucosa-to-mucosa pancreaticojejunal anastomosis elucidated in this study is associated with pancreatic duct diameters ranging from 1-12 mm and a mean pancreatic duct diameter of 4.863 mm. We considered that when the pancreatic duct diameter was greater than 2 mm, single-layer pancreaticojejunal anastomosis was a better choice.

Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple and time-saving anastomosis method. It should be emphasized that during the process of pancreaticojejunal anastomosis, the suturing between the anterior wall of the pancreatic duct and the whole layer of the anterior wall of the pancreas, involving 3-4 stitches, should be conducted first, together with the suspension and opening of the pancreatic duct; this sequence is conducive to posterior wall suturing. During the suturing process, the distribution of needling should be even to prevent the formation of large spaces and the occurrence of non-strict pairing in some regions, which may cause pancreatic leakage. During the suturing of the anterior, lateral, and posterior walls of the duct, the needling site was approximately 1-2 cm from the pancreatic stump. To prevent damage to the pancreas and to small branches of the pancreatic ducts by multiple needling, which may cause pancreatic leakage, the needling for suturing the pancreas and the pancreatic duct should be conducted only once. The suturing method described here is simple and does not require sophisticated suturing techniques. The pancreaticojejunal anastomosis time in the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis was 17.922 ± 5.145 min, and the pancreaticojejunal anastomosis time in the double-layer mucosa-to-mucosa pancreaticojejunal anastomosis was 31.333 ± 7.776 min. The Mann-Whitney value for comparison of this parameter between the two groups was 185.000 (*P* = 0.000); thus, the difference in anastomosis time between the two groups was statistically significant, indicating that the single-layer anastomosis time was significantly lower than the double-layer anastomosis time.

Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a reliable pancreaticojejunal anastomosis method. The 51 patients in the single-layer anastomosis group received conventional upper abdominal CT examination 1 wk after surgery to determine the condition of the mouth of the pancreaticojejunal anastomosis and its surroundings; the results showed that neither the mouth of the pancreaticojejunal anastomosis nor the surrounding area had effusion in any of the 51 patients. The 51 patients in the double-layer anastomosis group received conventional upper abdominal CT examination after 1 wk of surgery to display the condition of the mouth of the pancreaticojejunal anastomosis and its surroundings; the results showed that 6 patients had effusion at the mouth of pancreaticojejunal anastomosis and/or in the surrounding area. A χ^2 test of the data for the two groups yielded a χ^2 value of 4.4271 (*P* = 0.0354); thus, the difference in the incidence of effusion in the two groups was statistically significant. In the single-layer anastomosis patients, the suture used for the anastomosis was tight, and the mouth of the pancreaticojejunal anastomosis and its surroundings did not show effusion after surgery. In the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis, the jejunum completely covered the pancreatic section, and the resulting pressure on the pancreatic section and on the small pancreatic ducts within the pancreatic section contributed to hemostasis and thus reduced the risk of postoperative pancreatic section bleeding and pancreatic fistula. These results indicate that the application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy is reliable.

The application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy was shown to be safe. The pancreatic fistula rate in the single-layer anastomosis group was 25.45% (13/51), whereas the pancreatic fistula rate in the double-layer anastomosis group was 68.63% (35/51). A χ^2 test of the data regarding the incidence of pancreatic fistula in the two groups yielded a χ^2 value of 19.0464 (P = 0.0000). Thus, the difference between the two had statistical significance; the pancreatic fistula rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group.

Lin *et al*[31] summarized data from 1891 pancreaticoduodenectomy patients and concluded that soft pancreatic texture was the most important reason for the occurrence of pancreatic fistula. In our study, when the pancreatic texture was soft, the postoperative pancreatic fistula rate in the single-layer anastomosis group was 37.03% (10/27), whereas the rate of postoperative pancreatic fistula in the patients in the double-layer anastomosis group who displayed soft pancreatic texture was 87.50% (21/24). Comparison between the values obtained for the two groups yielded a χ^2 value of 13.5737 (P = 0.0002). The difference was statistically significant, indicating that single-layer anastomosis was better than double-layer anastomosis when the pancreatic texture was soft. The use of single-layer anastomosis reduced the time needed for suturing the pancreas, reduced the damage to the pancreas, and decreased the incidence of pancreatic fistula. When the pancreatic texture was normal or the pancreas displayed mild fibrosis, the incidence of postoperative pancreatic fistula was 14.28% (2/14) in the single-layer anastomosis group and 58.82% (10/17) in the double-layer anastomosis group. Comparison of the difference between the two groups using the χ^2 test and the Fisher exact probability test showed that the P-value was 0.0245, indicating that the difference between the two groups was statistically significant. For normal or mild fibrosis pancreatic texture, the pancreatic fistula rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group. In the single-layer anastomosis group, there were 5 cases of grade B pancreatic fistula, and the pancreatic fistula rate was 9.80%; there was no grade C pancreatic fistula in this group. In the double-layer anastomosis group, there were 23 cases of grade B pancreatic fistula, with a rate of 45.10%; in this group, there were 4 cases of grade C pancreatic fistula, with an incidence rate of grade C pancreatic fistula of 7.84%. Comparison of the incidences of grade B and grade C pancreatic fistula in the two groups yielded a χ^2 value of 22.0393 (P = 0.0000), indicating that the difference between the two groups was statistically significant. The incidence of grade B and grade C pancreatic fistula in the single-layer anastomosis group was significantly lower than that in the double-layer anastomosis group.

In the single-layer anastomosis group, the rate of postoperative peritoneal catheterization was 0/51, and that of abdominal infection was 1/51. In the double-layer anastomosis group, the rate of postoperative peritoneal catheterization was 6/51, and the rate of abdominal infection was 11/51; the differences in these two parameters in the two groups were statistically significant (P < 0.05). The rates of postoperative peritoneal catheterization and abdominal infection in the single-layer anastomosis group were significantly lower than those in the double-layer anastomosis group. The total postoperative complication rate in the single-layer anastomosis group was 41.17% (21/51) and the total postoperative complication rate in the double-layer anastomosis group was 72.55% (37/51). A χ^2 test comparing the data for the two groups yielded a χ^2 value of 10.232 (P = 0.0014); thus, the difference between the two groups was statistically significant. The postoperative complication rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group. In summary, the foregoing data show that the application of the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy is safe.

Patients who experienced pancreatic fistula after pancreaticoduodenectomy had prolonged hospitalization time and increased hospitalization expenses[32]. The pancreatic fistula rate in the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis group was lower than that in the double-layer mucosa-to-mucosa pancreaticojejunal anastomosis group. In addition, postoperative hospitalization time, total hospitalization time, and hospitalization expenses were all lower in the single-layer anastomosis group than in the double-layer anastomosis group. The rank sum test results showed that the P-values for all of these comparisons were < 0.05; thus, the differences were statistically significant. These results indicate that postoperative hospitalization time, total hospitalization time, and hospitalization expenses were all lower in the single-layer anastomosis group than in the double-layer anastomosis group.

In summary, the results of this study show that single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple, reliable, and safe anastomosis method. The use of this method could reduce the rates of postoperative pancreatic fistula, abdominal infection and peritoneal catheterization, overall complication rate, postoperative hospitalization time, total hospitalization time, and hospitalization expenses.

COMMENTS

Background

Pancreaticoduodenectomy is a standard treatment for various tumors of peri-ampullary region and pancreatic head. Pancreaticoduodenectomy is a difficult surgery with a high perioperative complication rate and a high mortality rate. Pancreatic fistula is associated with delayed gastric emptying, intra-abdominal abscess, local infection at the incision site, sepsis, and blood loss postoperation. Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery.

Research frontiers
Although the complication and mortality rates associated with pancreatic fistula have decreased due to improvements in surgical techniques, the incidence of postoperative complications during the perioperative period is still high. There are various pancreaticojejunal anastomosis procedures in pancreaticoduodenectomy, but so far none of the pancreaticojejunal anastomosis procedures is regarded as best. No matter what kind of way of pancreaticojejunal anastomosis use in pancreaticoduodenectomy, pancreatic fistula is still high.

Innovations and breakthroughs
In this study, single-layer anastomosis group applied single layer mucosa-to-mucosa pancreaticojejunal anastomosis to pancreaticoduodenectomy. It should be emphasized that during the process of pancreaticojejunal anastomosis, the suturing between the anterior wall of the pancreatic duct and the whole layer of the anterior wall of the pancreas, involving 3-4 stitches, should be conducted first, together with the suspension and opening of the pancreatic duct; this sequence is conducive to posterior wall suturing. There was no knots inside of pancreaticojejunal anastomosis. During the suturing process, the distribution of needling should be even to prevent the formation of large spaces and the occurrence of non-strict pairing in some regions, which may cause pancreatic leakage.

Applications
Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple pancreaticojejunal anastomosis. Surgeons can apply it to pancreaticoduodenectomy, especially when the pancreatic texture is soft. It can reduce the incidence rate of grade B and C pancreatic fistula and may reduce the mortality.

Terminology
Pancreaticojejunal anastomosis is essential and crucial anastomosis in pancreaticoduodenectomy. It plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis could help the surgeon to enhance the reliability of pancreaticojejunal anastomosis.

Peer-review
The article is an helpful and original research paper. It provides a new way of pancreaticojejunal anastomosis to surgeon in pancreaticoduodenectomy. The study is well designed, and the retrospective study was carried out at a very high accuracy and quality.

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CASE REPORT

Gastric remnant twist in the immediate post-operative period following laparoscopic sleeve gastrectomy

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Informed consent statement: The patient involved in this study has given her written informed consent authorizing use and disclosure of her protected health information.

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Abstract

Twist of stomach remnant post sleeve gastrectomy is a rare entity and difficult to diagnose pre-operatively. We are reporting a case of gastric volvulus post laparoscopic sleeve gastrectomy, which was managed conservatively. A 38-year-old lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy. Sleeve gastrectomy was performed over a 32 French bougie using Endo-GIA tri-stapler. On post-operative day 1, patient had nausea and non-bilious vomiting. An upper gastrointestinal gastrografin study on post-operative days 1 and 2 revealed collection of contrast in the fundic area of stomach with poor flow distally, and she vomited gastrograffin immediately post procedure. With the suspicion of a stricture in the mid stomach as the cause, the patient was taken back for a exploratory laparoscopy and intra-operative endoscopy. We found a twist in the gastric tube which was too tight for the endoscope to pass through. This was managed conservatively with a long stent to keep the gastric tube straight and patent. The stent was discontinued in 7 d and the patient did well. In laparoscopic sleeve gastrectomy the stomach is converted into a tube and is devoid of its supports. If the staples fired are not aligned appropriately, it can predispose this stomach tube to undergo torsion along its long axis. Such a twist can be avoided by properly aligning the staples and by placing tacking sutures to the omentum and new stomach tube. This twist is a functional obstruction rather than a stricture; thus, it can be managed by endoscopy and stent placement.

Key words: Gastric remnant; Stent; Sleeve gastrectomy; Volvulus; Obesity

Core tip: Twist of the stomach remnant post sleeve gastrectomy is a rare entity. We are reporting a case of gastric twist post laparoscopic sleeve gastrectomy.

This was managed conservatively with a long stent for 7 d. In laparoscopic sleeve gastrectomy the stomach is converted into a tube and is devoid of its supports, making it prone for twisting. Such a twist can be avoided by properly aligning the staples and by placing tacking sutures to the omentum. This twist is a functional obstruction rather than a stricture; thus, it can be managed by endoscopy and stent placement.

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INTRODUCTION

Laparoscopic sleeve gastrectomy is a restrictive bariatric surgical strategy. Compared to other bariatric surgeries, this procedure has relatively lower surgical risk in patients with extreme obesity. However sleeve gastrectomy does have complications which includes leaks, bleeding, splenic trauma, sleeve stenosis, and gastroesophageal reflux[1].

Gastric volvulus is a rare condition which involves the rotation of all or part of the stomach around the anatomic axes[1]. We would like to report a case of twist of the gastric remnant in the immediate post laparoscopic sleeve gastrectomy period, done for morbid obesity. This was managed non operatively with stent placement.

CASE REPORT

A 38-year-old morbidly obese lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy. Sleeve gastrectomy which was performed over a thirty two french bougie using Endo-GIA stapler with the tri staple purple load (Covidien Tri-Staple™, Mansfield, MA). Intraoperatively, post application of stapler, there was a bleeding from the stapled line at the mid stomach which was managed by a single imbricating stitch. On post-operative day 1, patient had persisting nausea and non bilious vomiting. An upper gastrointestinal (GI) gastrografin study revealed collection of contrast in the fundic area of stomach with poor flow distally; she vomited gastrografin immediately post procedure (Figure 1). She was kept nil per os (NPO) and the upper GI gastrografin study was repeated on post-operative day 2. Similar findings of collection of contrast in the fundic region of stomach with very little filling distally were noted. This raised a suspicion of stricture in the mid stomach. With a suspicion of the imbricating stitch in the mid stomach as the cause, the patient was taken back for a exploratory laparoscopy and intra operative endoscopy.

During exploratory laparoscopy, the stitch did not seem to be causing any constriction. The stitch was cut and no bleeding was noted. An intraoperative endoscopy showed complete obstruction in the mid stomach with inability pass the scope beyond the obstruction. Manipulation of stomach laparoscopically with simultaneous scope manipulation was needed to negotiate the narrowed mid stomach. A diagnosis of twist of the stomach along the long axis of the tubular remnant was made. She was kept NPO and started on total parenteral nutrition.

A long esophageal 18 mm × 15 cm long, fully silicone covered stent (WallFlex™, Boston Scientific, Natick, MA) was placed endoscopically on post-operative day 6 (Figure 2). She was able to tolerate liquid diet and was discharged home. The stent was removed endoscopically a week after its placement. She was put on a liquid diet for 2 wk and advanced to soft diet subsequently, which she tolerated well. Patient was seen to be doing well on a 6-mo follow-up visit.

DISCUSSION

Sleeve gastrectomy is a safe, reproducible technique with a relatively low rate of complications. Benefits of sleeve gastrectomy include the lower complications, the maintenance of normal gastro-intestinal continuity, the absence of mal-absorption and the ability to convert to multiple other operations. Excising the ghrelin producing stomach mass plays a significant role compared to other gastric restrictive procedures[2]. Laparoscopic sleeve gastrectomy is still associated with complications, these include, but are not limited to: Staple line leak (1.17%), post-operative hemorrhage (3.57%), and the irreversibility of gastrectomy[3].

Gastric volvulus is a rare condition which involves the rotation of the stomach around the anatomic axes. There are two forms of gastric volvulus, organo-axial (axis is longitudinal and passes through the pylorus and gastroesophageal junction) and mesenteric-axial (axis is transverse and passes through the middle of stomach). Gastrosplenic, gastrophrenic, gastrocolic, and gastrohepatic ligaments hold the stomach in anatomotical position. Stomach can be prone for volvulus whenever there is laxity in the gastric fixation or incorrect positioning of the stomach post surgical manipulation[1]. Twist of the gastric remnant is a condition similar to the organo-axial gastric volvulus.

Sleeve stenosis, which is currently seen in 0.2% to 4% of laparoscopic sleeve gastrectomies, can occur due to the intentionally creating a narrow tube of the stomach[4]. A twisted or spiral sleeve caused by the progressive rotation of the staple line in an anterior to posterior plane can lead to a functional narrowing despite a fairly normal luminal diameter, and is another cause of symptomatic stenosis. This functional stenosis makes it difficult for gastric contents to pass through, in spite of easy passage of the endoscope or balloon dilator through the narrowed area. This can be equated

Figure 1 Oral gastrograffin swallow showing poor flow distally.

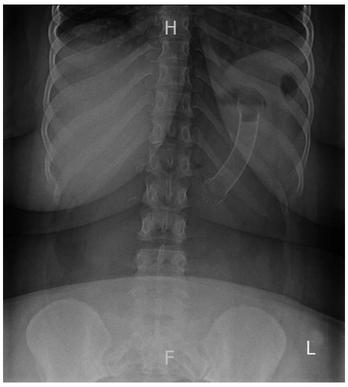

Figure 2 Abdominal X-ray showing stent placement.

to twisting a straight balloon wherein there is a twist at the incisura (Figure 3). An endoscope can be made to pass through by twisting in the same direction, which will undo the twist. Unless supported by a stent, the twist recurs on withdrawal of the endoscope. Scarring caused by hematomas can also lead to sleeve stenosis. Mechanical short-segment stenosis may be treated successfully with single or multiple endoscopic balloon dilation. But mechanical long-segment stenosis may ultimately require conversion to Roux-en-Y gastric bypass[4].

The dissection performed during sleeve gastrectomy including separation of greater omentum from the greater curvature of the stomach, makes the remnant stomach prone for volvulus as there are no fixations along the entire greater curvature[1]. Cases of organoaxial gastric volvulus have been reported after laparoscopic gastric banding, due to excessive dissection of the posterior wall of the stomach, which makes it mobile[5,6]. It is recommended to do a proper posterior dissection of the stomach in sleeve gastrectomy in order to achieve a symmetric stapling of the posterior and anterior wall to avoid twisting of the remnant stomach tube[7]. Pexy of omentum to the gastric remnant may also help to avoid such a twist in the remnant stomach after sleeve gastrectomy.

Flexible covered stents use has been described for patients with suture line leaks and strictures following

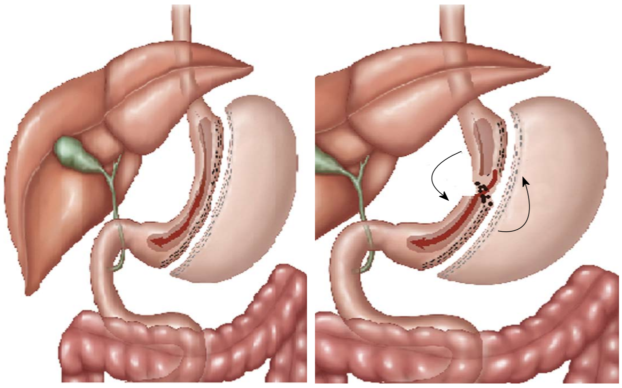

Figure 3 Animated diagram of the volvulus.

sleeve gastrectomy[4,8]. Following stent placement, patients may experience nausea, hypersialysis, early satiety and mild retro-sternal discomfort, which usually disappear in the first few days. Stent removal is not always easy, due to scarring around the stent, and mucosal injury and bleeding are frequently seen after removal. Another complication is stent migration, which can be seen in up to one third of cases[8].

Our patient developed obstruction due to torsion along the long axis of the remnant stomach on post operative day 1. There is a possibility of asymmetrical staples leading to initiation of the twist but completion of twist to an extent of obstruction as in a volvulus is attributed to a long tubular remnant with no supports. We feel that in this patient, creation of a longer stomach tube post removal of ligaments namely gastrosplenic and gastrophrenic made the tubular stomach devoid of its support, which then became susceptible to torsion. Some degree of a twist is seen in every stomach post laparoscopic sleeve gastrectomy but none of these cause functional stricture. These twists can be managed non-operatively with placement of covered stent. Also, mobilized omentum can tacked to the gastric tube on the stapled side and this could help in prevention of rotation by virtue of its weight.

The tubular gastric remnant is devoid of its supports and is predisposed to volvulus. In this present case we feel that a twist could have been initiated by asymmetrical staples which then progressed to a complete torsion in the organo-axial axis with functional stricture due to a long tubular remnant without anatomical support. We currently tack the mobilized omentum to the stapled side of gastric tube to help prevent post-operative twist. This condition can be managed non-operatively with placement of covered stent. There is always an option of converting it to a Roux-en-Y gastric bypass if the non-operative management fails.

COMMENTS

Case characteristics

A 38-year-old morbidly obese lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy and presented with post-operative gastric remnant twist.

Clinical diagnosis
Post-operative gastric remnant twist.

Differential diagnosis
Stricture, post-operative edema, hematoma.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Upper gastrointestinal gastrograffin study showed collection of contrast in the fundic area of stomach with poor flow distally.

Treatment
Placement of a long stent endoscopically.

Related reports
Most of the reports are of gastric volvulus which was managed by operative intervention.

Experiences and lessons
During laparoscopic gastric sleeve resection the authors currently tack the mobilized omentum to the stapled side of gastric tube to help prevent post-operative twist and post-operative gastric twist can be managed non-operatively with placement of covered stent.

Peer-review
This is a nice and well documented case report.

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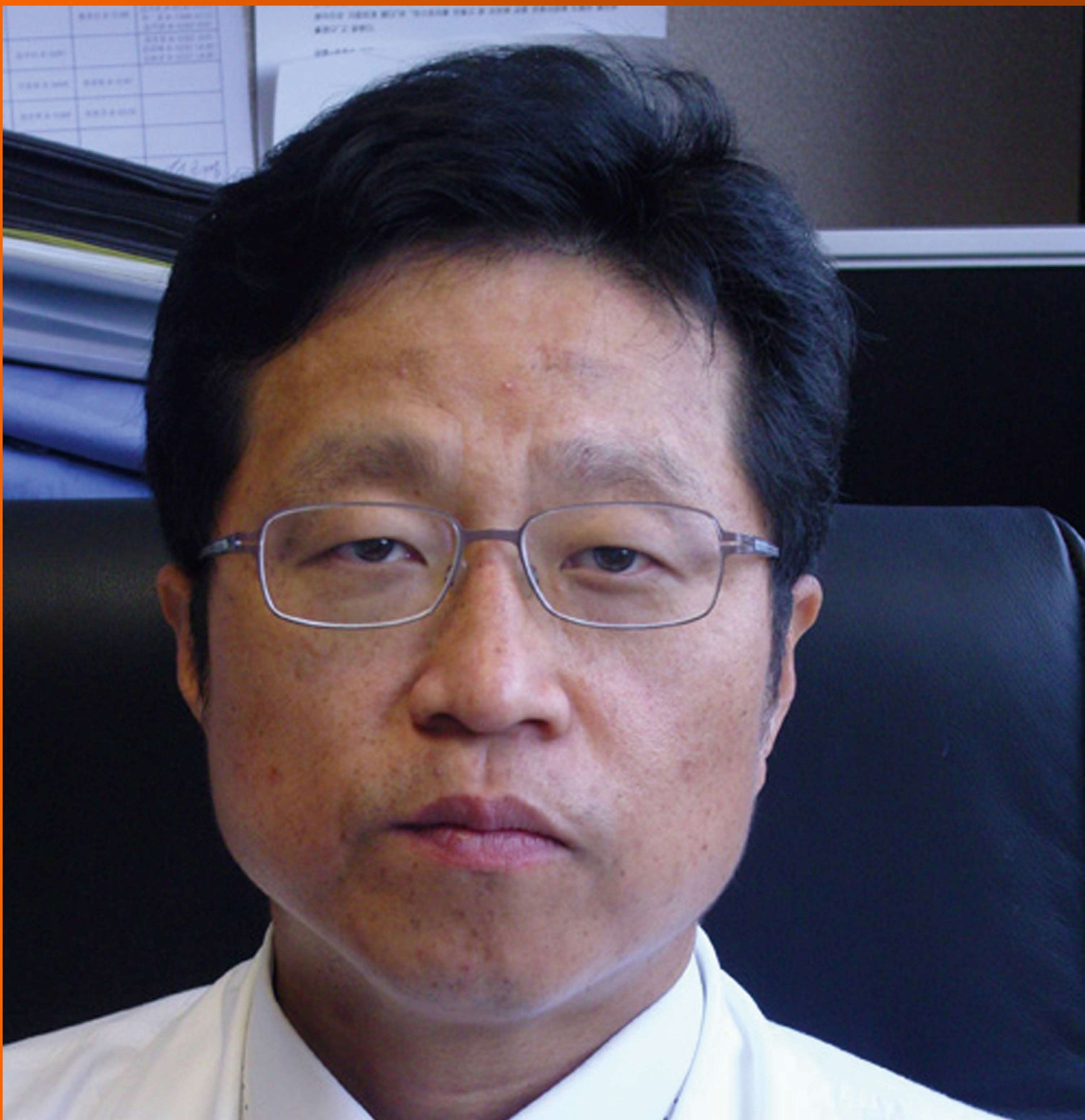

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EDITORIAL

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

Giovanni D De Palma, Gaetano Luglio

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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

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 someway 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 firs 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 Denonviellier'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-tickness 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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EDITORIAL

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 folfiri 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 reitroduced 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

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 Folfox6 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 microenvironment 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 lattest 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 (≥ 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/m^2 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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REVIEW

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

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.

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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 *et al*[11]	RCT comparing AZA *vs* 5-ASA	Steroid dependent UC	72	No difference in colectomy rates at 6 mo between AZA and 5-ASA groups
	Kaplan *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[26]	RCT comparing IFX rescue therapy *vs* placebo	Acute severe UC	45	3 yr colectomy free survival 50%
	Laharie *et al*[29]	Head to head RCT comparing IFX *vs* CSA as rescue therapy	Acute severe UC	115	No significant differences in colectomy rates between two therapies at 3 mo
	Sandborn *et al*[19]	ACT 1 and 2 RCT of IFX *vs* placebo	Moderate to severe UC	728	Colectomy rate significantly lower in IFX group (10% *vs* 17%) at 54 wk
	Feagan *et al*[41]	ULTRA 1 and 2 RCT of ADA *vs* 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 *et al*[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 *et al*[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 ⩽ 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*[8] 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 multicentre retrospective analysis of 211 aTNF-naive 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 sub group 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 heterogenous 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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 tria; 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 TPs 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 thiopuriness 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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MINIREVIEWS

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

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-1β, 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 founds 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 ^{131}I-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 carcinogen embryonic 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 *et al*[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 *et al*[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 *et al*[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% *vs* 78%) and 5-yr RFS (73.5% *vs* 78.9%) in low compared to normal ALB group	No difference in short-term postoperative GI and cardiovascular complications
Cengiz *et al*[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 *et al*[37]	Retrospective cohort study	Pretreatment ALB's prognostic value in rectal cancer following curative surgery	226 patients	Lower 5-yr OS (47% *vs* 69%) and RFS (69.7% *vs* 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 *et al*[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 *vs* 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: $\alpha1$, $\alpha2$, 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 *et al*[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 *et al*[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, P = 0.03) and PFS (HR = 2.66, P = 0.03) than low AGR group on multivariate analysis	No statistically significant difference in ORR between high and low AGR groups
Suh *et al*[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 *et al*[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 *et al*[51]	Systematic review	Relationship between mGPS and cancer outcome	60 studies with 18 on CRC	Higher mGPS in CRC predicted numerous worse outcomes (*e.g.*, postoperative infections, toxicity, survival, *etc.*)	Study looked at all cancer patients. CRC studies were geographically restricted to the United Kingdom and Japan
Richards *et al*[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 *et al*[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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MINIREVIEWS

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

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 sytem using a nitinol clip loaded at the tip of the endoscope (OTSC, Ovesco, endoscopy, Tubingen, 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. Enoscopic 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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ORIGINAL ARTICLE

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

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.

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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]Incsional 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-incisonal 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

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

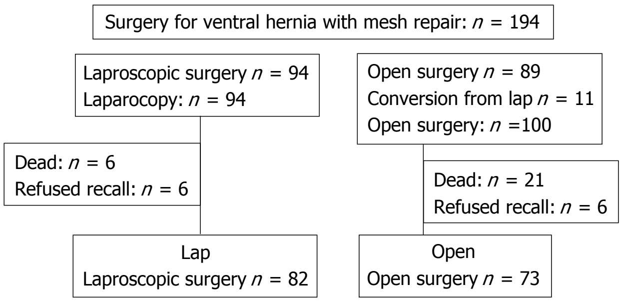

Figure 1 Consort diagram.

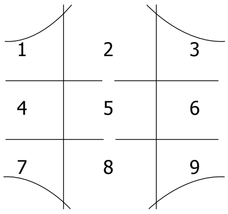

Figure 2 Sectoral map of the abdominal wall.

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 × A × B, where A and B are the two diagonals. Due to small numbers of patients in the 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 cm^2) and large sized hernias (≥ 70 cm^2). Non-incisional hernia size was categorised into ordinal variables as small/medium sized (< 13 cm^2) and large sized hernias (≥ 13 cm^2) (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	*P* value
Operative time, min, mean ± SD	117 ± 54	92 ± 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 tackers	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 ± 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 precentages 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 witch 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

[1]Correction for 3 false positive recurrences; [2]No 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

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

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

[1]Hernia area < 58 cm^2 small, reference category > 58 cm^2 large; [2]Operative 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

[1]1 missing value with recurrence; 3 missing values without recurrence. COPD: Chronic obstructive pulmonary disease.

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

In the present study, the overall recurrence rates 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 incisonal 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 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 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 *n* = 81	Open *n* = 72	OR[1] (95%CI)	*P* 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

[1]Referes 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

[1]Referes to LVHR when OVHR is excluded; [2]Referes male; [3]Referes age > 60; [4]Referes 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)	*P* value
Clinical recurrence	11.67 (2.00-68.24)	0.006
Late complications	5.47 (1.1-27.09)	0.037
Gender (referes 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 13 Predictors for satisfaction after laparoscopic mesh repair-multivariate analysis (*n* = 79)

	OR (95%CI)	*P* 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

[1]Chronic 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.

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

	OR (95%CI)	*P* 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 14 Predictors for satisfaction after open mesh repair-multivariate analysis (*n* = 71)

	OR (95%CI)	*P* 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

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

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 $\geqslant$ 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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CASE REPORT

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

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, Rahnemai-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

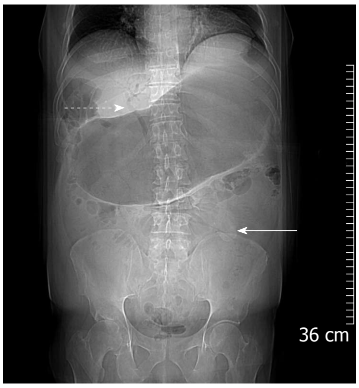

Figure 1 Scout film. Pneumobilia (dotted arrow) and ectopic gallstone (solid arrow). Marked gastric distention, with small bowel obstruction less clearly seen.

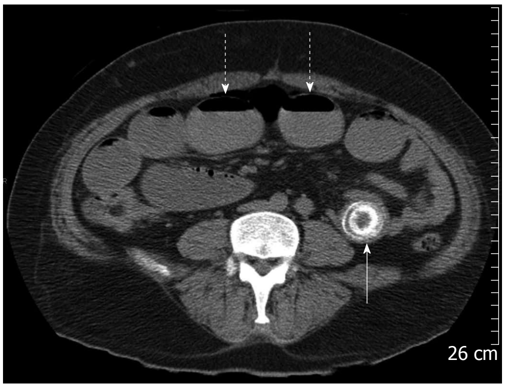

Figure 3 Small bowel obstruction with multiple dilated loops with air fluid levels (dotted arrows), ectopic gallstones in left lower quadrant is seen (solid arrow).

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.

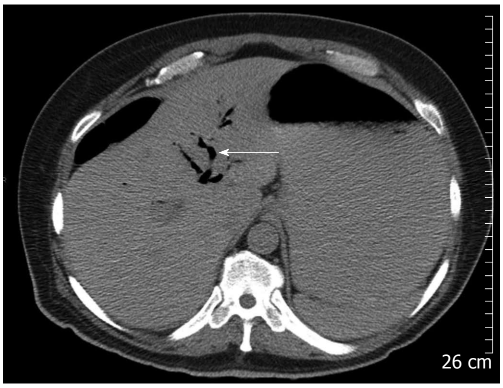

Figure 2 Pneumobilia clearly demonstrated.

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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CASE REPORT

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

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 cholecy-stectomy. 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

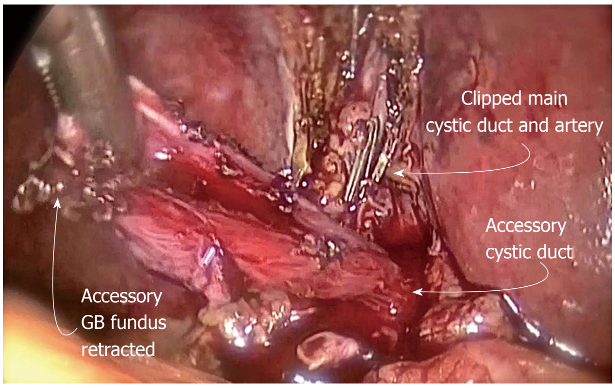

Figure 1 The accessory gallbladder shown here is dissected of the shared liver bed with the main gallbladder. Clips are placed on the divided main cystic duct and artery. GB: Gallbladder.

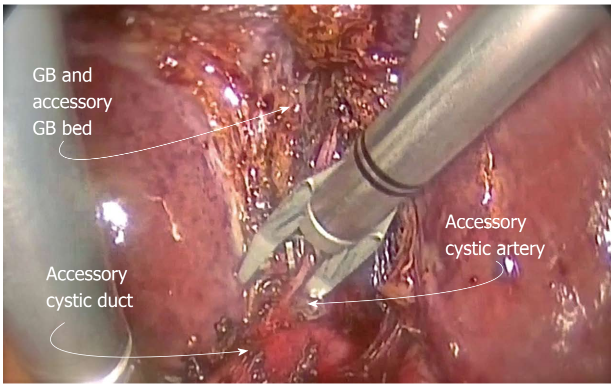

Figure 2 Further dissection of the accessory gallbladder revealed the accessory cystic artery, which helped in the identification of the cystic structure as an accessory gallbladder. The accessory cystic artery is dissected off the accessory cystic duct situated below, clipped and divided. A cholangiogram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

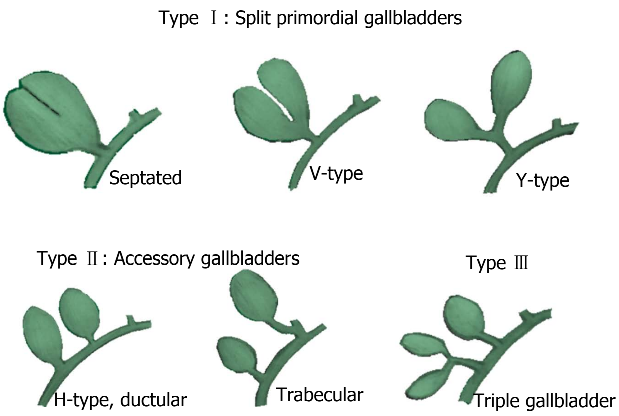

Figure 3 Harlaftis's classification of anatomical variations of accessory gallbladders.

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 Steenbergen *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. Postoperative 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 cholecystits.

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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CASE REPORT

Laparoscopic management of a two staged gall bladder torsion

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Author contributions: Sunder YK and Akhilesh SP contributed equally to this work; Sunder YK, Akhilesh SP and Raman G designed the research; Sunder YK, Akhilesh SP and Shantilal MH performed the research; Deborshi S analyzed the data; and Akhilesh SP wrote the paper.

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Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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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

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

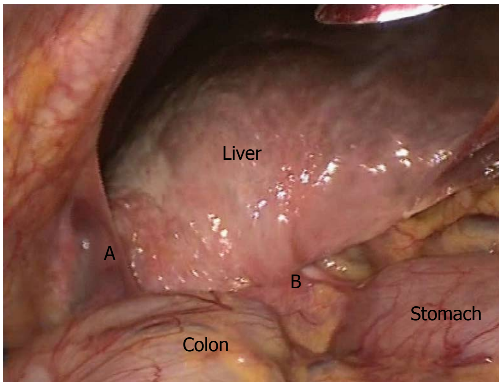

Figure 3 Laparoscopic view showing distorted anatomy. A: Adhesions between the gall bladder and the lateral abdominal wall; B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

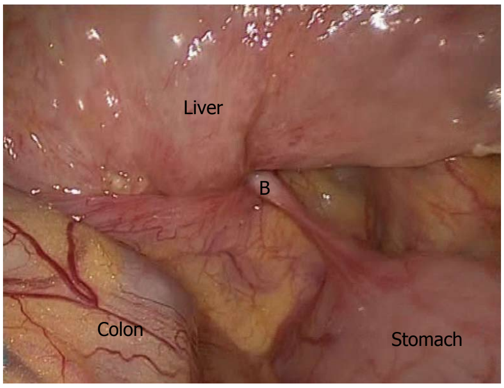

Figure 4 Zoomed in view of Calot's region. B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

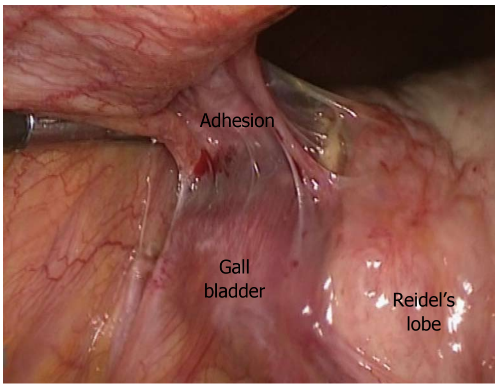

Figure 5 Adhesions between the gall bladder and the lateral abdominal wall.

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

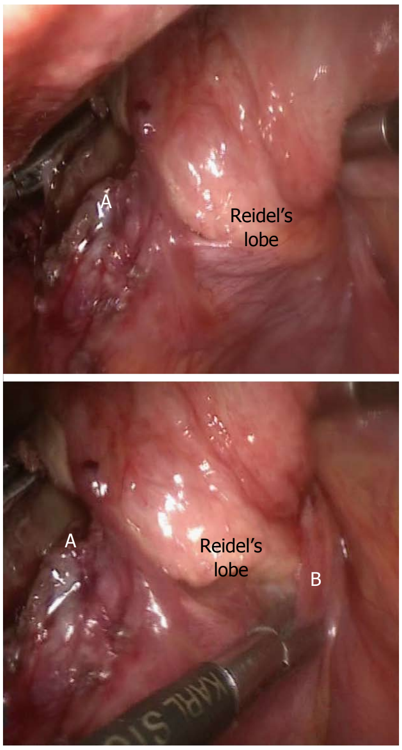

Figure 6 Rotated Riedel's lobe. A: Gangrenous fundus of the gall bladder; B: Pulled in peritoneal fold from the pylorus of the stomach and the hepatic flexure.

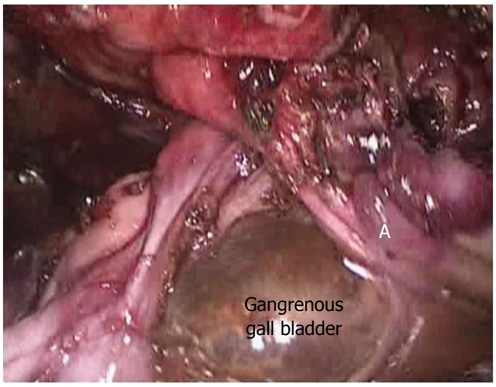

Figure 7 Gangrenous gall bladder after adhesiolysis. A: Adhesive band between the neck of the gall bladder and the Riedel's lobe.

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

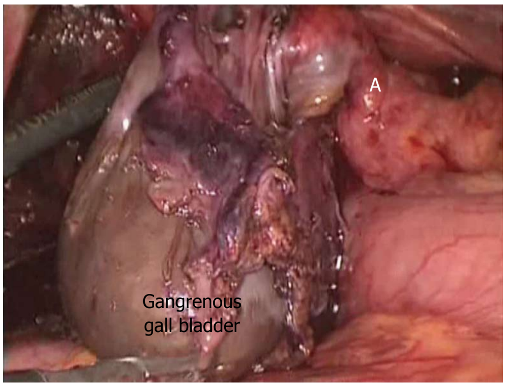

Figure 8 Gall bladder found gangrenous till its neck.

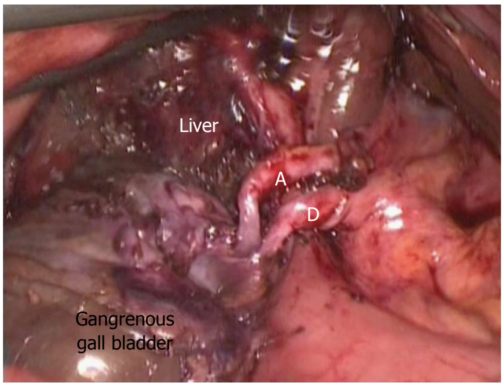

Figure 9 After derotation, the gall bladder in its normal position with the long and twisted cystic artery (A) and cystic duct (D).

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
Laproscopic 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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