ISSN 1948-9366 (online)

WJGS World Journal of Gastrointestinal Surgery

World J Gastrointest Surg 2010 September 27; 2(9): 275-298

A peer-reviewed, online, open-access journal of gastrointestinal surgery

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WJGS

World Journal of Gastrointestinal Surgery

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World Journal of Gastrointestinal Surgery

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NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

LAUNCH DATE
November 30, 2009

SPONSOR
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http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited, Room 1701, 17/F, Henan Bulding, No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: 00852-3115-8812
Telephone: 00852-5804-2046
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Beijing Baishideng BioMed Scientific Co., Ltd., Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
September 27, 2010

CSSN
ISSN 1948-9366 (online)

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World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i9.275

World J Gastrointest Surg 2010 September 27; 2(9): 275-282
ISSN 1948-9366 (online)

EDITORIAL

Laparoscopic surgery for rectal cancer: The state of the art

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Author contributions: Staudacher C wrote the manuscript; Vignali A co- wrote and reviewed the paper critically.

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Received: January 28, 2010 Revised: September 14, 2010
Accepted: September 21, 2010
Published online: September 27, 2010

Abstract

At present time, there is evidence from randomized controlled studies of the success of laparoscopic resection for the treatment of colon cancer with reported smaller incisions, lower morbidity rate and earlier recovery compared to open surgery. Technical limitations and a steep learning curve have limited the wide application of mini-invasive surgery for rectal cancer. The present article discusses the current status of laparoscopic resection for rectal cancer. A review of the more recent retrospective, prospective and randomized controlled trial (RCT) data on laparoscopic resection of rectal cancer including the role of trans-anal endoscopic microsurgery and robotics was performed. A particular emphasis was dedicated to mid and low rectal cancers. Few prospective and RCT trials specifically addressing laparoscopic rectal cancer resection are currently available in the literature. Improved short-term outcomes in term of lesser intra-operative blood loss, reduced analgesic requirements and a shorter hospital stay have been demonstrated. Concerns have recently been raised in the largest RCT trial of the oncological adequacy of laparoscopy in terms of increased rate of circumferential margin. This data however was not confirmed by other prospective comparative studies. Moreover, a similar local recurrence rate has been reported in RCT and comparative series. Similar findings of overall and disease free survival have been reported but the follow-up time period is too short in all these studies and the few RCT trials currently available do not draw any definitive conclusions. On the basis of available data in the literature, the mini-invasive approach to rectal cancer surgery has some short-term advantages and does not seem to confer any disadvantage in term of local recurrence. With respect to long-term survival, a definitive answer cannot be given at present time as the results of RCT trials focused on long-term survival currently ongoing are still to fully clarify this issue.

Key words: Postoperative complications; Recurrence rate; Transanal endoscopic microsurgery; Robotics; Long-term outcome; Prognosis; Rectal cancer; Laparoscopy

Peer reviewers: Tsukasa Hotta, MD, PhD, Department of Surgery, Wakayama Medical University, School of Medicine, 811-1, Kimiidera, Wakayama 641-8510, Japan; Tsuyoshi Konishi, MD, PhD, Department of Gastroenterological Surgery, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan

Staudacher C, Vignali A. Laparoscopic surgery for rectal cancer: The state of the art. *World J Gastrointest Surg* 2010; 2(9): 275-282 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i9/275.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i9.275

INTRODUCTION

Proven advantages of the short-term and similar long-term oncological outcome of laparoscopic surgery (LPS) for colorectal cancer when compared to open surgery have facilitated its wide diffusion[1]. The adoption of the laparoscopic approach for the management of rectal cancer has been more limited and controversial and is still considered investigational in the United States. This has been due to several concerns: the fact that laparoscopic total mesorectal excision (TME) has obvious technical difficulties: it mandates dissection to the pelvic floor; it is technically demanding, especially when performing stapled low-rectal division and anastomosis with the possible increase of the rate of anastomotic dehiscence; and it is characterized by a steep learning curve with protracted operating times. Furthermore, most surgeons are skeptical about the oncological value of laparoscopic TME, the adequacy of cancer margins and because of the limited amount of available data in the literature. Due to the aforementioned reasons, rectal cancer patients were excluded from the majority of randomized clinical trials or represented only a small proportion of patients recruited; to date, the number of prospective randomized trials specifically focusing on mid to low rectal cancer is limited[2,3]. The aim of the present review is to analyze the current role of mini-invasive surgery in the treatment of rectal cancer with emphasis on mid to low rectal cancer and in particular to TME and its related the technical and functional implications.

FEASIBILITY AND SHORT-TERM OUTCOMES

The feasibility of any laparoscopic procedure is reflected by the associated conversion rate. Figures ranging from 0 to 33% have been reported in the scientific literature[2-17]. This great variability in terms of conversion rate should be attributed to different variables such as the type of operation, distance of the tumor from the anal verge, previous surgeries, fixity of the tumor, experience of the surgical team or single surgeon, surgical volume of the center and the related learning curve. The UK MRC CLASICC trial is the only multicenter randomized controlled trial (RCT) published on rectal cancer. All the participating surgeons were required to have completed only 20 laparoscopic colorectal resections before entering in the study and thus had not gone through the whole learning curve before starting the study. Therefore, the data from this trial might be biased in the results of the intention-to-treat analysis which seem to support this hypothesis, reporting an initial phase with a conversion rate of 45% which declined to 15% in the last year of the study[7]. Different figures were reported when high volume centers or single experience of highly trained and experienced colorectal surgeons were considered. Recently, Milsom *et al*[9] reported a 2.9% conversion rate on 185 patients who underwent hand assisted or pure LPS for rectal cancer. Similar findings were reported by highly experienced surgeons with figures ranging between 0 and 15.5%[4,8,10,12,15]. Moreover, these data are in line and reflect the experience of mono-institutional randomized trials with figures ranging between 0 and 9.8%[2-7]. Thus, the way in which these results will ultimately translate into care in common daily practice remains unclear.

The safety of laparoscopic rectal cancer surgery has been extensively reported in the literature. In a recent Cochrane review of 4424 patients from 48 studies comparing laparoscopic *vs* open TME for rectal cancer, Breukink reported no significant differences in morbidity and mortality rate with several short-term advantages in favour of laparoscopic resection such as less blood loss, quicker return to normal diet, less pain as measured by narcotic use and reduced length of hospital stay[18]. On the other hand, a longer operating time and higher cost of the surgical procedure have been reported by a recent meta-analysis focused on the management of rectal cancer[18-21]. Some caution and criticism is recommended in the interpretation of these data as the majority of the studies included in the meta-analysis were small series or case-control studies and only three RCT trials. Moreover, in one of the three RCT analyzed in the meta-analysis, the distance of the tumor from the anal verge was not reported making it possible that recto-sigmoid cancer was also included[18]. These tumors generally behave similarly to colon cancer but have great technical differences in their management.

Nevertheless, more recently data from non-randomized comparative studies and RCT trials including the CLASICC MRCT trial, reported no differences in term of overall morbidity and mortality despite a trend toward a lower wound infection rate reported by other RCTs and most comparative series as shown in Table 1.

In particular, no differences of anastomotic leak rate have been reported between the LPS and open group. Data from CLASICC RCT reported a 10% leakage rate in the LPS and 7% in the open group. Similar findings were reported in comparative studies and the majority of non-randomized series showing either similar or lower anastomotic leak rates with figures ranging from 3.5% to 16.8%; it was most commonly reported to be approximately 10% as it emerged in two recent reviews and a meta-analysis on this subject[19-21]. This is a relevant issue in terms of safety and in favor of laparoscopic rectal surgery which has been previously hypothesized to increase the anastomotic leak rate of coloanal anastomosis following TME. In fact, transection of the rectum in the deep pelvis and anastomosis are considered two limiting factors due to the technical limitations of the currently available staplers which require multiple firing with possible increase of anastomotic leak[22]. A virtual simulation recently published in the literature has shown that the current stapler has to go through the iliac bone in order to achieve a 90° angle at the levator ani[23]. This situation could be partially overcome by the insertion of a conventional stapler through a supra-pubic port or alternatively by the insertion of a dedicated curved stapler. This latter stapling device has been recently reported in a RCT trial to be a safe alternative to a conventional stapler to secure the distal rectum during low anterior resection (LAR) in mid to low rectal cancers. However, this is the only study currently available in the literature on this subject and due to the high cost of the stapling machine[24] and the fact that differences in the devices are relatively minor factors that could affect leakage rates[18-21], further RCT studies are needed to justify the routine use of a curve stapler or supra-pubic port during laparoscopic TME.

PORT SITE METASTASIS

The actual overall incidence of port-site metastasis is a rare event and is about 0.1% from reviews and meta-analysis on this subject[19-21]. This figure is comparable to that of

Table 1 Short-term outcome after laparoscopic total mesorectal excision in randomized controlled trials and comparative series

Author	Morbidity		Mortality		Wound infection rate (%)		Leak rate (%)	
	Open	LPS	Open	LPS	Open	LPS	Open	LPS
Lujan *et al*[3] (TME)	33	33.7	2.9	1.9	1.9	0	12	6
Braga *et al*[5] (LAR/TME)	40	29	0	0	13	6	10.6	9.6
Ng *et al*[6] (APR)	52.1	45.1	0.2	0.2	8.3	0	NA	NA
Strohlein *et al*[28] (LAR/TME)	NA	NA	3.3	0	5.3	4.5	15.3	10
Gouvas *et al*[34] (LAR/TME)	36	63	1	0	31	9	10	16
Jayne *et al*[33] (TME/APR/LAR)	37	40	5	4	12	13	7	10
Laurent *et al*[10] (TME/APR)	37.7	32	0.8	2.6	NA	NA	12.9	11.8
Staudacher *et al*[8] (TME)	27.8	29.6	0	0	13.9	4.6	12.6	14.8
Rullier *et al*[46] (TME)	11.6	21.9	0	3.1	NA	NA	-	0
Zhou *et al*[2] (TME)	12.4	6.1	0	0	NA	NA	3.4	1.2

LPS: Laparoscopic surgery; TME: Total mesorectal excision; LAR: Low anterior resection; APR: Abdominoperineal resection.

wound recurrence following open surgery[25,26]. According to these findings, port-site metastasis is not an inherent drawback of LPS for rectal cancer.

ONCOLOGICAL OUTCOME

The current evidence for laparoscopic resection for rectal cancer is based mainly on several case series, case-matched studies and non-randomized studies, the majority of which have a relatively short follow-up period. Only a few randomized studies are available in the literature. To our knowledge, only 6 studies have been published so far on rectal cancer only. An additional RCT trial was also published, but in this study, recto-sigmoid tumor were considered with different technical and functional consideration when compared to low and mid rectal tumors[27]. The results of the aforementioned studies are influenced by different factors such as tumor height, experience of the surgical team, surgical approach (i.e. TME *vs* abdominoperineal amputation of the rectum) and use of neoadjuvant chemoradiation. In particular, many series report results for selected patients with early stage tumors reasonable given the technical issues of laparoscopic manipulation of neoplasms. However, such reports are not useful in making generalizations about the appropriateness of the technique for all patients with rectal cancer.

With respect to lymph nodes harvested intraoperatively, with the exceptions of Srohlein *et al*[28] who reported a difference in favor of open surgery (laparoscopic 13.5/open access 16.9; P = 0.001) and Lujan who reported a difference in favor of laparoscopic TME in a RCT trial[3], all the other comparative series and RCT trials analyzed in the present review reported no difference in the mean numbers of lymph-nodes harvested with laparoscopic or open rectal cancer resection, which varied considerably from 5 to 25[2-7,18-21,29]. Moreover, concerns have been recently raised by West *et al*[30] about an adequate distal resection margin and a cylinder without a waist both for low anterior and abdominoperineal resection. Lateral and distal margins are critical components of oncological proctectomy. Heald *et al*[31] and Quirke *et al*[32] demonstrated the need to achieve a wide lateral (radial) margin in order to avoid local recurrence of the neoplasm in the pelvis. In non randomized comparative studies, laparoscopic and open excision for rectal cancer were found to be equivalent in achieving distal and radial margin[8-10,13,14]. Different results were obtained when only RCT trials were considered. In single RCT center experience, good results were obtained with figures ranging between 1 and 4% involvement of radial and distal margin with no difference in respect to laparoscopic and open surgery[3,5,6]. When a RCT multicenter trial is considered, laparoscopic anterior resection resulted in a higher rate of radial margin involvement when compared to open resection (6% open *vs* 12% for LPS; P = 0.19) although this difference failed to reach statistical significance[7]. These latter data, however, referred to a center where surgeons are not solely dedicated to rectal surgery and have not completed their learning curve of laparoscopic rectal resection before starting the trial. Due to the mentioned findings, a trial promoted by the American College of Surgeons Oncology Group (ACOSOG) is currently ongoing. This trial will only consider patients with mid and low position, stage Ⅱ and Ⅲ rectal cancer. Operations will only be performed by surgeons who demonstrate expert abilities in both laparoscopic and colon rectal surgery before enrolling patients. Moreover, a more recent report analyzing data from the CLASICC RCT trial showed no impact of the high rate of radial margin involvement observed in the laparoscopic group on local recurrence rate[33]. In addition, results from other recent non randomized series found no differences in radial margins involvement between the laparoscopic and open group[10,34].

Local recurrence

Local recurrence is a key indicator of oncological adequacy in rectal cancer surgery which varies dramatically among surgeons, the surgical technique being a major determinant. In open surgery, the standard for local recurrence has been set by Heald *et al*[31] who reported a 4% local recurrence rate following LAR of the rectum with TME with a 10 years follow-up. According to these findings, in order for the laparoscopic approach to rectal cancer to be widely accepted, the proof of oncological equivalence is of paramount importance. Although most series and RCTs excluded T4 lesions and adopted neoadjuvant chemora-

Table 2 Local recurrences rates after laparoscopic rectal cancer surgery

Author/year	Operation	No. of patients		Follow-up (mo)	Local recurrence rate (%)	
		LPS	Open		LPS	Open
Hartley *et al*[11] (2001)	TME	21	22	38	5	4.5
Laurent *et al*[10] (2009)	LAR/TME	238	233	52	3.9	5.5
Bretagnol *et al*[13] (2005)	TME	50	-	18	0	NA
Fleshman *et al*[14] (1999)	APR	42	152	23.8	19	14
Araujo *et al*[4] (2003)	APR	13	13	47.2	0	15.4
Ng *et al*[6] (2008)	APR	51	48	87.2	5.9	4.2
Law *et al*[17] (2006)	LAR/TME	98	167	21	4.9	3.3
Staudacher *et al*[8] (2007)	TME	108	79	27.6	6.4	5.1
Leroy *et al*[12] (2004)	TME	102	-	36	6	NA
Milsom *et al*[9] (2009)	TME/LAR	103	-	42	5	NA
Jayne *et al*[33] (2005)	TME/APR	128	253	36.8	11.4	14.05

LPS: Laparoscopic surgery; TME: Total mesorectal excision; LAR: Low anterior resection; APR: Abdominoperineal resection.

diation for locally advanced rectal cancer, data from large series report local recurrence rates after laparoscopic TME ranging between 2.9% and 7.7%, with a mean recurrence rate of about 5% with no significant differences between laparoscopic and open resection as shown in Table 2. Different figures are reported when laparoscopic abdominoperineal resection (APR) is considered. A higher local recurrence rate is in fact reported following laparoscopic APR when compared to laparoscopic sphincter saving surgery[4,6,7,14,35-38]. Local recurrence rates after LPS varied considerably from 0 to 25% with contrasting results in series. When only comparative studies are considered, the majority of the studies found no differences in term of local recurrence rates between laparoscopic and open rectal resection[35-37] with the exception of two early comparative studies which demonstrated higher recurrence rates compared with open surgery but the difference was not significant[14,38]. In particular, Fleshman *et al*[14] reported a 19% recurrence rate in LPS *vs* 14 % in open group while Feliciotti *et al*[38] found a 20.8% and 18.2% recurrence rate in laparoscopic and open groups respectively. This difference however, failed to reach statistical significance in both studies.

Data from CLASICC MRCT trial showed a 15.1% local recurrence rate following LPS abdominoperineal excision and a 21.1% local recurrence rate following open APR[7]. Araujo, comparing laparoscopic *vs* open APR in a RCT trial, reported a 0% local recurrence rate following laparoscopic APR and a 15.4% local recurrence after conventional surgery. However, the study was a small series of only 13 patients per group[4]. Similar findings were also reported by Ng *et al*[6] who reported a 5% local recurrence rate after laparoscopic APR *vs* 11% local recurrence rate after open APR.

A significantly higher local recurrence rate was also observed after curative open APR when compared to conventional anterior resection. Wibe *et al*[39] in a prospective, cohort study involving 47 hospitals and 2136 patients reported a 15% local recurrence rate after APR *vs* 10% following LAR ($P = 0.008$). Similar findings were also reported by Heald *et al*[31] who found a 33% and 1% local recurrence rate after APR and conventional anterior resection of the rectum respectively. The higher incidence of local recurrence after APR compared to LAR with sphincter salvage could be ascribed to the higher prevalence of T4 disease and the higher incidence of positive radial margin which usually requires sphincter ablation and use of neoadjuvant therapy[29,32,39].

Long-term outcome

Long-term survival data following laparoscopic resection of the rectum are scanty in the literature. The majority of long-term outcome data refer to a single surgeon experience series or comparative studies and only five RCT studies focusing on this subject are currently available with different length of median follow-up period with figures ranging from 33.1 to 87.2 mo[2,3,5,6,33]. Data from these series reported no difference in terms of local recurrence, overall and disease free survival between groups. Similar findings of overall and disease free survival are reported by small comparative series but the follow-up time period is too short in all these studies to draw any conclusions[11,13,14,38]. In contrast, Laurent *et al*[10] reported a better survival rate in laparoscopic stage Ⅲ tumors with no difference in term of local recurrence and cancer-free survival between laparoscopic and open surgery with similar quality of surgery in a mono-centric comparative study with over 400 patients with mid and low rectal cancer. A better survival rate in patients with stage Ⅲ tumor was also reported by Lacy *et al*[40] in a RCT trial in patients with colon cancer and by Morino *et al*[41] in a prospective comparative study which focused on patients with extraperitoneal rectal cancer treated with laparoscopic or open surgery. More recently, Law *et al*[42] reported in a comparative monocenter series with a median follow-up of 34 mo in patients with stage Ⅱ and Ⅲ rectal cancer, a 5 year actuarial survival of 71% in the laparoscopic group compared to a 59% survival rate in the open group, also identifying laparoscopy as one of the independent significant factors associated with better survival at the multivariate analysis.

The positive impact of the laparoscopic approach on survival is still unclear. Supporting evidence of the beneficial oncological role of laparoscopy includes its impact on surgical stress response, cellular immunity, cytokine release, intraoperative tumor manipulation and blood transfusion rate. Moreover, during the early postoperative period, laparoscopic patients seem to display decreased levels of pro-inflammatory and vascular endothelial growth factor (VEGF) compared to open[18,21,43,44].

In summary, based on the available data in literature, the mini-invasive approach to rectal cancer surgery does not seem to confer any disadvantage in term of local recurrence. With respect to long-term survival a definitive answer cannot be drawn at present and the results from the RCT trials focused on long-term survival currently on-going are needed.

GENITOURINARY FUNCTION

Bladder and sexual function are recognized complications of open TME resulting from injury to the autonomic nerves. The real incidence of such complications following laparoscopic TME is still an unresolved issue due to controversial and limited data in the international literature. In a small series of laparoscopic TME including only 7 patients, Watanabe *et al*[45] reported no genitourinary dysfunction and only 9.5% erectile dysfunction. Similarly Rullier *et al*[46] reported only 3.1% long-term bladder dysfunction in patients who underwent laparoscopic intersphincteric resection. On the other hand, Quah *et al*[47] reported a significant increase of impotence or retrograde ejaculation in sexually active men after laparoscopic rectal surgery. Similar findings were reported by Jayne *et al*[48] in the only RCT trial available in the literature on this issue. In this RCT trial, more than 50% of both men and women reported no sexual activity. Among the sexually active patients, the author found no difference in bladder function between the laparoscopic and open group while in erectile and overall sexual function, only men perceived a significant decrease of their overall level of sexual function after laparoscopic TME when compared to open. No difference in overall sexual function was observed in women. The authors attributed the poorer sexual function observed in the laparoscopic group to the fact that TME was more commonly performed in the laparoscopic than open group. Moreover, TME and conversion to open were identified as independent predictors of postoperative male sexual function at multivariate analysis.

Currently, it remains unclear how the mini invasive approach to rectal surgery affects genitourinary function. This is not only because the limited available data show conflicting results, but mainly because different criteria and methods of measurements have been adopted. Future studies with the possible use of urodynamics and standard questionnaires are warranted.

TRANS-ANAL ENDOSCOPIC MICROSURGERY

Trans-anal endoscopic microsurgery (TEM), a technique initially developed for the excision of benign polyps not amenable by endoscopic resection[49], has recently gained a place in the universe of the mini invasive approach to rectal cancer. However, the widespread acceptance of TEM has been a very slow process due to its elevated starting cost and, most of all, for its limited caseload in non specialized centers. Only recently in fact, TEM has been proposed as an alternative safe and successful approach to major surgery in particular for well differentiated T1 rectal tumors and carcinoid tumors while controversy still exists in the treatment of more advanced tumors like poor differentiated T1 or T2. Moreover, TEM might be employed for non curative intent or pain relief in advanced tumors in patients with severe co-morbidities which preclude a major resection or in the salvage resection of local recurrence[50]. The main advantages of TEM are less blood loss, reduced operating times, shorter postoperative length of stay, less use of analgesia during postoperative course, earlier recovery and lower rate of major complications[50-52]. The occurrence of major complications in the case of TEM is mainly represented by perforation with entry in the peritoneum; occurrence of a recto-vaginal fistula and hemorrhage with figures ranging from 0 to 28% has been reported in a recent review by Middleton *et al*[53]. However this great variability is mainly influenced by the surgeon or team experience and hospital caseload.

When compared to traditional trans-anal excision, TEM provides several advantages such as better visualization, higher likelihood of achieving clear resection margins, lower recurrence rates and a higher rate of clear resection margins[54]. The main disadvantage of TEM is a significant change in continence in particular with respect to anorectal dysfunctions such as tenesmus and fecal soilage measured either by manometry or surveys. These symptoms seem to be significantly ameliorated or return to preoperative levels at 6 wk to 3 mo following the operation with minimal impact on clinical incontinence[55,56].

With respect to oncological outcome, comparative series and RCT trials reported recurrence rates and long-term survival similar to those with open resection for T1 rectal cancer[53,54,57]. However, when more advanced tumors are considered, local recurrence rates significantly increase to 14% for PT2 cancer and to 20% in patients with PT3 lesions as reported in a recent meta-analysis by Suppiah *et al*[57] which includes 28 studies. With respect to T2 tumors, in which management using TEM is the object of major controversy in the literature, recently Tsai *et al*[54] in reported a 23.5% local recurrence rate in a single center prospective study with 269 patients with a mean follow-up of 49.5 mo. This result is in accordance with the reported 6% to 80% local recurrence rate for T2 tumors in previous TEM series[58-60]. Different results were reported by Lezoche *et al*[61] who reported a 5% recurrence rate in both study arms and a similar distant metastasis rate (5% in each arm) after a median follow-up period of 56 mo in 40 patients preoperatively staged UT2NO who had preoperative neoadjuvant chemoradiation and were randomized to TEM or laparoscopic resection.

In conclusion, TEM is a safe and effective technique for curative resection with good short- and long-term outcomes when used for benign tumors, select T1 adenocarcinoma, carcinoid tumors or when adopted for palliative resection and salvage surgery for a more advanced tumor stage in patients medically unfit or unwilling to undergo radical resection. However, some criticism is required in the analysis of data on oncological outcome as the majority of available data come from retrospective series with a significant patient and tumor heterogeneity and with different surgical indications.

ROBOTICS

The wide diffusion of the mini invasive approach to rectal cancer has been hampered mainly by the availability of nonwristed instruments which make the operation technically demanding, especially while working in the confined space of the pelvis and in particular during the maneuver of transecting the rectum and fashioning the anastomosis. Recently, a hybrid technique has been introduced named as "robotics"[62-66]. This technique has the potential to overcome the obstacles of the standard laparoscopy by introducing wristed instruments which allow the surgeon to regain the two lost degrees of freedom. The value of using six degrees of freedom is of particular relevance when operating in a confined space such as the pelvis[63,64]. Moreover, the three-dimensional visualization offered by the robot provides a better visualization of depth in the pelvis to the surgeon. In addition, the higher magnification of the robotic camera system might be helpful in the identification and preservation of small anatomic structure like pelvic autonomic nerves. The potential advantages of robotics in confined spaces are well known by urologists and in a recently published consensus statement it is estimated that robotics prostatectomy in the United States has a penetration of 60% with more than 50 000 prostatectomies performed in 2007[65].

The experience of the adoption of robotics in rectal cancer surgery is, however, very limited[62-66] mainly because of the high cost of robotic platform and most of all by its costs of maintenance. The current available data from the literature show that robotic TME is feasible and safe with similar conversion, morbidity and mortality rates when compared to laparoscopic TME. Moreover, no differences were observed in the number of lymph-nodes harvested intraoperatively and to the distal margin involvement at the specimen analysis when compared to conventional laparoscopy[62-66]. Operative time is increased by the use of robotics probably due to the need for splenic flexure mobilization and high ligation of the inferior mesenteric artery and vein which mandate the repositioning of the robot and its operating arms. However**,** a totally robotic surgery technique for rectal cancer has recently been developed using a six-port system including a camera port to perform rectal cancer surgery from the splenic flexure to the pelvic diaphragm in one setup[67]. This technique was successfully adopted in 45 patients with very low conversion rate (2.2%).

At the present time, laparoscopic proctectomy is not yet cost-effective over standard laparoscopy, as it emerged in a comparative study by Delaney who reported his experience on a very small series with only six patients with different types of operations[67]. A more accurate visualization of pelvic nerves has been now advocated by the use of robotics with potential advantages on genitourinary function. Future RCT on this subject will clarify this point.

ACKNOWLEDGMENTS

A special thank goes to Maria Chiara Salandini MD for her precious help in redrafting the manuscript.

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S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Yang C

WJGS World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i9.283

World J Gastrointest Surg 2010 September 27; 2(9): 283-290
ISSN 1948-9366 (online)

REVIEW

Role of staging laparoscopy in peri-pancreatic and hepatobiliary malignancy

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Received: June 21, 2010 Revised: September 18, 2010
Accepted: September 24, 2010
Published online: September 27, 2010

Abstract

Even after extensive preoperative assessment, staging laparoscopy may allow avoidance of non-therapeutic laparotomy in patients with radiographically occult metastatic or locally unresectable disease. Staging laparoscopy is associated with decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy compared to laparotomy but its yield has decreased with improvements in imaging techniques. Current uses of staging laparoscopy include the following: (1) In the staging of pancreatic adenocarcinoma, laparoscopic staging allows for the identification of sub-radiographic metastatic disease in locally advanced cancer in approximately 30% of patients and, in radiographically resectable cancer, may identify metastatic disease in 10%-15% of cases; (2) In colorectal liver metastases, selective use of laparoscopic staging in patients with a clinical risk score of over 2 identifies unresectable disease in approximately 20% of patients; (3) In hepatocellular carcinoma, laparoscopic staging could be selectively used in high-risk patients such as those with clinically apparent liver cirrhosis and in patients with major vascular invasion or bilobar tumors; and (4) In biliary tract malignancy, staging laparoscopy may be used in all patients with potentially resectable primary gallbladder cancer and in selected patients with T2/T3 hilar cholangiocarcinoma. Because of the decreasing yield of SL secondary to improvements in imaging techniques, staging laparoscopy should be used selectively for patients with pancreatic and hepatobiliary malignancy to avoid unnecessary non-therapeutic laparotomy and to improve resource utilization. Each individual surgeon should apply his or her threshold as to whether staging laparoscopy is indicated according to the quality of preoperative imaging studies and the availability of resources at their own institution.

Key words: Pancreatic cancer; Liver metastasis; Staging laparoscopy; Cholangiocarcinoma; Gallbladder cancer; Hepatocellular carcinoma

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Gaujoux S, Allen PJ. Role of staging laparoscopy in peri-pancreatic and hepatobiliary malignancy. *World J Gastrointest Surg* 2010; 2(9): 283-290 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i9/283.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i9.283

INTRODUCTION

Resection remains the only treatment that can lead to cure and long-term survival in patients with peri-pancreatic or hepatobiliary malignancy. The majority of these patients, however, will present with metastatic disease and surgical resection in this setting is generally contraindicated. Despite continuous improvements in preoperative staging techniques, some patients will present with radiographically occult metastatic disease and will be identified with locally unresectable or metastatic disease at the time of operation.

Staging laparoscopy (SL) has been proposed as a minimally invasive technique for the identification of radiographically occult metastatic or locally unresectable disease. The benefit of this approach is in avoidance of non-therapeutic laparotomy. SL, in comparison to non-therapeutic laparotomy, has been reported to result in decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy[1]. Previously published work by our group[2] reported that laparoscopic staging compared to laparotomy did not significantly increase the operative time (83 ± 22 min *vs* 91 ± 33 min) but significantly decreased length of hospital stay (2.2 ± 2 *vs* 8.5 ± 8.6) and the total hospital charge. Controversy over the use of SL exists because the yield of this approach has decreased as imaging techniques have improved. The yield of SL is directly related to the quality of imaging as well as the likelihood that a given lesion will metastasize.

The aim of this report is to review the current yield of SL and assess the role and indication of SL in peri-pancreatic and hepatobiliary malignancy with a special attention to pancreatic cancer, colorectal liver metastasis, hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer.

LAPAROSCOPIC TECHNIQUE

The yield of laparoscopic staging depends on the quality of preoperative imaging studies and also the thoroughness of the laparoscopic technique. Briefly, and as previously reported by our group[3,4], SL is performed under general anesthesia typically at the time of planned resection. A 10mm trocar is inserted under direct vision along the anticipated laparotomy incision. Under 15 mmHg pressure pneumoperitoneum, the abdomen is evaluated with a 30° angle laparoscope. The whole abdomen is inspected including the parietal and visceral peritoneum from every quadrant, the pelvis, the anterior and posterior surface of the liver, the porta hepatitis, the gastrohepatic omentum, the duodenum, the transverse mesocolon and celiac region. Typically, two additional 5 mm ports are necessary for exposure. Any lesions likely to be metastases are sampled and analyzed by frozen section. When no metastatic lesions are found or if there is doubt about locally advanced disease, laparoscopic ultrasound can be performed using 7.5 MHz flexible probe placed through a 10-mm port. Ultrasonic examination of the whole liver (including hepatic vein, portal pedicle with a special attention to hepatic artery, portal vein or biliary involvement), lymph nodes and superior mesenteric artery can be readily performed.

SL has its greatest yield in the identification of superficial metastatic disease and is less accurate in identifying deep liver metastases, local vascular involvement or lymph node metastases. Some have advocated the routine use of laparoscopic ultrasonography to enhance the accuracy of the staging procedure with respect to the primary tumor relationship to the major blood vessels, the presence of enlarged peripancreatic lymph nodes or small deep liver metastasis[5]. In this setting, laparoscopic ultrasonography may identify additional disease in approximately 10% of patients[6,7] but whether it should be routinely or selectively used is controversial. Laparoscopic ultrasound probes are not widely available and thus the surgeon's familiarity with the findings is limited.

ISSUE OF PORT-SITE RECURRENCE

Initial reports of laparoscopy in cancer patients expressed concern about the oncological safety of laparoscopy with special attention to port-site recurrence and oncological outcome. Large series of oncological laparoscopic procedures have now been reported including randomized data in colon cancer[8] that have confirmed the safety of this approach with respect to disease recurrence and disease-specific survival. The rate of port-site recurrence does not seem to differ from the rate of incisional recurrence observed after open exploration for cancer. This has been specifically studied in laparoscopic staging for pancreatic cancer and has not been found to be associated with an increased risk of port-site recurrence or peritoneal progression[9,10]. Overall, no difference in survival has been observed between patients with pancreatic cancer who had a diagnostic procedure but no pancreatic resection with or without a laparoscopic approach[10].

OVERALL MORBIDITY AND MORTALITY

The overall reported mortality of SL is < 1% and the reported morbidity is very low with the majority of reported complications minor and usually related to the general health status of the patient. Potential complications due to the laparoscopic procedure include general surgical complications such as port-site bleeding, wound infection and the general risks associated with a general anesthetic. The most significant risk is from a missed colonic or small bowel injury occurring at the time of port insertion or during adhesiolysis from previous surgery and care must be taken during SL to evaluate for these injuries.

STAGING LAPAROSCOPY IN PANCREATIC MALIGNANCY

Adenocarcinoma

Accurate staging is essential in the treatment planning for patients with pancreatic cancer. Non-invasive staging has seen a dramatic improvement over the past few decades with improvements in cross-sectional imaging techniques. Since the purpose of SL is to supplement and not replace non-invasive imaging techniques, extensive preoperative assessment remains mandatory. As recently stated in a expert consensus statement[11], the current state-of-the–art imaging modality is multidetector CT with advanced volumetric processing techniques. In the case of equivocal imaging, magnetic resonance imaging may be considered but has not demonstrated a clear advantage over CT[12]. Endoscopic ultrasound (EUS) may also be useful for the evaluation of local resectability however it has been the authors' expe-

Table 1 Studies assessing the role of staging laparoscopy in pancreatic adenocarcinoma

Study/years	Time period	No. of patient	Contraindication found during laparoscopy (%)	Contraindication found during laparotomy[a] (%)	Morbidity/ Mortality of LAP	Note
Conlon *et al*[4]/1999	1992-1994	115	38	8	0/0	Extended laparoscopy only
Jimenez *et al*[18]/2000	1994-1998	125	31	3	0.8/0	+ cytology
Schachter *et al*[5]/2000	1996-1999	67	45	12	-	+ LAPUS
Doran *et al*[45]/2004	1997-2002	305	15	20	-	+ LAPUS
Maithel *et al*[46]/2008	2000-2006	491	14	1.5	-	+ CA 19-9[b]

[a]On remaining patients; [b]On metastatic spread only. LAPUS: Laparoscopic ultrasonography; LAP: laparoscopic staging.

rience that EUS may over interpret the extent of vascular involvement and triple-phase CT imaging is considered the most accurate in assessment of the local vasculature. Recently, FDG-PET/CT has been advocated to be more sensitive than conventional imaging in the diagnosis of both primary and metastatic pancreatic adenocarcinoma[13] and may be warranted in the high-risk patient to rule out radiographically occult or equivocal stage IV disease.

Laparoscopic staging: Even in the setting of high-quality preoperative imaging, up to a third of patients will be found to have radiographically occult distant metastatic or locally unresectable disease at the time of SL. To decrease patient discomfort and potential morbidity due to exploratory laparotomy, SL for this disease has been advocated since 1978 when Cuschieri reported his experience of 23 cases of pancreatic cancer[14]. Despite this relatively high yield for SL, the indications for SL have not been widely accepted and continue to evolve as the ability to non-invasively identify disease stage evolves[15]. Table 1 presents the main studies assessing the role of SL in pancreatic cancer.

The initial report from our institution of 115 patients undergoing SL for radiographically resectable pancreatic and peripancreatic malignancy included patients evaluated between 1992 and 1994[4]. Adequate SL was feasible in 94% of patients and findings that precluded resection were found in 38% of patients. Findings included liver metastasis (50%), extrapancreatic/peritoneal disease (39%), vascular encasement (35%) and celiac or portal lymphatic metastasis (20%). In 9% of patients who were deemed resectable by SL, there was disease identified at laparotomy that rendered the patient unresectable. In this series, there was no peri-operative complications reported to SL. At the time this study was performed, the positive predictive index, negative predictive index and accuracy of SL were 100%, 91% and 94% respectively.

With improvements in cross-sectional imaging and evaluation, we believe that the current yield of SL for peripancreatic and pancreatic malignancy has decreased. We recently reported an updated[16] review of 1045 patients who had undergone SL between 1995 and 2005. The yield of SL for pancreatic malignancy in this more contemporary series was 14%. Factors associated with radiographically occult unresectable disease included SL performed before 1999 (the year that multi-detector CT became available at our institution), imaging not performed at our institution, pancreatic primary site, adenocarcinoma (*vs* other type of tumor) and symptoms (weight loss, jaundice). Primary site (pancreatic versus nonpancreatic) was identified as the strongest predictor of yield. In patients with nonpancreatic tumors, the yield of laparoscopy was 4% *vs* 14% in patients with pancreatic tumors. Because of these findings, our general approach toward SL for these disease sites is to routinely generally perform SL only in patients with pancreatic adenocarcinoma.

The results noted above highlight the need to identify factors associated with the likelihood of sub radiographic metastatic disease. This likelihood is inversely proportional to the quality of imaging (higher quality imaging, lower likelihood of sub-radiographic metastatic disease) and proportional to the biology of the disease (increased metastatic potential, increased likelihood of sub-radiographic metastatic disease). Through an awareness of the quality of imaging and an understanding of the biology of the specific disease, the surgeon can have a better estimate of the yield of SL in the individual patient. With this knowledge, the surgeon may then utilize SL at whatever threshold they feel is beneficial. Some surgeons may feel SL is warranted if the likelihood of sub-radiographic disease is 5%, others 10%, but only with an understanding of the yield of SL can surgeons appropriately utilize this procedure.

In 2005, Karachristos *et al*[17] reported on the relationship between CA 19-9 and the likelihood of sub-radiographic metastatic disease. In their study, patients with higher CA 19-9 levels had significant higher odds of having metastasis identified by laparoscopy (odds ratio, 1.83; P = 0.04) and no patient with a CA 19-9 level below 100 U/mL had metastatic disease identified during SL. Similar results have been reported from our group in a study of 491 patients in which a CA 19-9 over 130 U/mL was associated with sub radiographic unresectable pancreatic adenocarcinoma in 26% of patients *vs* 11% when CA 19-9 was below 130 U/mL. CA 19-9 when combined with the previous factors identified, i.e. nonpancreatic primary site, adenocarcinoma (*vs* other type of tumor), weight loss and jaundice, may provide an improved ability to identify subgroups of patients both at very high-risk and at very low-risk for sub-radiographic metastatic disease. In patients at very high-risk of sub-radiographic disease, SL alone may be warranted with the anticipation that resection would be scheduled only in those patients with negative findings. In patients at very low-risk for sub-radiographic disease SL may not be indicated.

Peritoneal cytology performed at the time of SL has also been reported as a minimally invasive approach to identify sub-radiographic metastatic disease[18-20]. The current AJCC classification stages positive peritoneal cytology as stage IV disease with median survival reported between 6 and 12 mo. Positive cytology rates in those presenting with radiographically resectable disease vary and range from 3% to 10% of cases[18,19,21]. In our experience, patients who have undergone resection in the setting of positive peritoneal cytology and absence of other identifiable metastatic disease had a similar survival as patients with stage Ⅳ disease[22]. Nevertheless, the utility of peritoneal cytology remains controversial[21] and, overall, many remain reluctant not to perform resection when the tumor is resectable and without macroscopic metastatic disease.

Overall, it is difficult to precisely assess the sensitivity, specificity, positive and negative predictive value of SL for pancreatic and peri-pancreatic malignancy as studies are not easily comparable due to various approaches for preoperative imaging (and their constant improvement) and intraoperative assessment (cytology, laparoscopic ultrasonography, *etc*.). As stated in a recent expert consensus statement, laparoscopic staging could be selectively used in locally advanced pancreatic cancer and in apparent resectable cancer localized in the pancreatic body or tail and larger than 3 cm with equivocal findings on CT scan or in the setting of a high CA 19-9 level (> 100-200 U/mL). Given our findings of an overall yield of 14% in patients with pancreatic adenocarcinoma, it is our general approach to perform SL on all patients with pancreatic adenocarcinoma and selectively in patients with peri-ampullary malignancy.

Endocrine and other tumors

The yield of SL in patients with pancreatic endocrine neoplasms has not been clearly reported. In the report from our institution noted above, we found that the overall yield of laparoscopy was 8%[16] in non-adenocarcinoma tumors (endocrine tumor, mucinous cystic and Intraductal Papillary Mucinous Neoplasms). This yield was significantly less than in patients with pancreatic adenocarcinoma. In patients with pancreatic endocrine tumors, distant metastases do not necessarily contraindicate resection and therefore SL should be used in selected patients where findings of radiographically occult metastatic disease would alter the operative approach.

STAGING LAPAROSCOPY IN HEPATOBILIARY MALIGNANCY

Similar to pancreatic cancer, operative resection in hepatobiliary malignancy is associated with improved survival only in selected patients in which complete tumor resection can be performed with an adequate hepatic remnant for recovery. The presence of sub-radiographic metastatic disease is also of concern in certain patients with hepatobiliary malignancy. In a study by D'Angelica *et al*[23] of 410 patients with radiographically resectable hepatobiliary malignancy, SL was completed in 73% of patients and, in 84 (55%) of the 153 evaluated patients, SL identified disease that precluded resection. In this group of patients, SL was valuable in identifying unsuspected cirrhosis, peritoneal disease and additional hepatic tumors but it commonly failed to identify extra-regional lymph node metastases and vascular invasion. The addition of laparoscopic ultrasonography identified clinically important additional disease in 4.8% of patients and was responsible for approximately 10% of the findings of unresectability. In this study, laparoscopy spared one in five patients a laparotomy while reducing hospital stay and morbidity.

Liver metastasis

Colorectal: The decision to perform hepatic resection in patients with metastatic colorectal cancer to the liver remains challenging and SL with or without addition of ultrasonography has been advocated as a minimally invasive approach to identify those with liver confined and resectable disease. Initial publications in the 1990s identified SL with intraoperative ultrasonography of the liver as a valuable tool to assess the resectability of hepatic metastases. In the setting of radiographically resectable metastatic colorectal disease, Rahussen *et al*[24] reported a 38% yield of SL with intraoperative ultrasonography. Later, those results were confirmed by Thaler *et al*[25] who identified a 25% yield of SL in identifying radiographically occult disease which led to the decision of resection or no resection.

Limitations of the use of SL with laparoscopic ultrasonography for metastatic colorectal cancer often include extensive adhesions following previous primary surgery and again the ability to thoroughly and accurately assess the liver with laparoscopic ultrasound. The study of segment Ⅶ and Ⅷ seems more difficult with laparoscopic ultrasound compared to open ultrasonography even after division of the falciform ligament. Similarly, definitive evaluation of the caudate lobe and retroperitoneal lymph nodes remains challenging. Even if laparoscopic ultrasound is added, the yield in the detection of nodal disease seems to be comparable to laparoscopy alone[25].

Laparoscopic staging should be considered the first step of a laparoscopic liver resection. Indeed, laparoscopic liver resection is now increasingly utilized[26-29] and studies from several centers attest to its technical feasibility and safety with oncological results comparable to open resection[27-32]. Recent international consensus positions such as the Louisville Statement[31] have stated laparoscopic liver surgery as a safe and effective approach to the management of surgical liver disease. It now seems possible to perform laparoscopic major hepatectomy following SL.

With optimal preoperative evaluation including ultrasound, modern triphasic helical CT and MRI[33], the yield of laparoscopic staging has decreased and the majority of patients with potentially respectable hepatic colorectal metastasis may not benefit from SL[34]. We previously reported[23] that the yield of laparoscopy staging was lowest for metastatic colorectal cancer compared to other hepatobiliary malignancies. These data suggest that a selective approach to SL in these patients may improve resource

Table 2 Studies assessing the role of staging laparoscopy in colorectal liver metastasis

Study/years	Time period	No. of patient	Contraindication found during laparoscopy (%)	Contraindication found during laparotomy (%)	Morbidity/Mortality of laparoscopy	Note
Rahusen *et al*[24]/1999	1991-1997	50	38	13	-/0	+ LAPUS
Jarnagin *et al*[34]/2001	1997-1999	104	14	13	NA	
Grobmyer *et al*[37]/2004	1997-2002	264	10	8	NA	
Thaler *et al*[25]/2005	1996-2004	136	25	11	2%/0	+ LAPUS
Mann *et al*[36]/2007	2000-2004	200	20	17	NA	+ LAPUS

LAPUS: Laparoscopic ultrasonography.

utilization and decrease cost. Using a previously published Clinical Risk Score (CRS)[35], i.e. lymph node positive primary tumor, disease free interval below 12 mo, number of hepatic metastasis over 1, CEA over 200 ng/mL and size of the larger tumor over 5 cm (previously shown to predict survival after hepatic resection), we identified a group of high risk patients most likely to benefit from laparoscopy. In this study the likelihood of occult unresectable disease was 12% in patients with CRS < 2 and 42% with CRS > 2. These results have been validated in a study by Mann *et al*[36] and, due to the very low yield of laparoscopy in patients with a CRS of 1 or less, it should not be routinely performed in these patients[37]. Table 2 presents the main studies assessing the role of SL in colorectal liver metastasis.

Non colorectal metastases: Estimates have suggested that half the number of liver metastasis from neuroendocrine tumors are undetectable on preoperative imaging despite extensive imaging[38]. SL with ultrasonography could be performed at the first step of the intervention to rule out additional metastatic disease. Nevertheless, due to the indolent nature of these tumors and the association between cytoreduction and long-term survival, SL to exclude additional disease may not result in a change in management. Therefore we do not routinely perform SL prior liver resection for liver metastasis from neuroendocrine tumors.

Primary hepatic malignancy

Hepatocellular carcinoma: The use of SL has been advocated to select patients with hepatocellular carcinoma for resection. The literature evaluation of SL for hepatocellular carcinoma is not as extensive as for other malignancies. Peritoneal spread is relatively rare in hepatocellular carcinoma, however, the risks of laparotomy in patients with altered liver function subject to postoperative ascites should be considered as increasing the potential benefit of SL. In addition to tumor assessment, SL in patients with hepatocellular carcinoma provides a minimally invasive assessment of the severity of cirrhosis and the size of the liver remnant which is critical for the assessment of resectability. Lo *et al*[39] reported that SL and laparoscopic ultrasonography allowed for the avoidance of laparotomy in 63% of patients with unresectable disease. In their experience, the accuracy of SL was decreased in tumors > 10 cm and in the evaluation of tumor thrombi in major vascular structure and/or the invasion of adjacent organs. In patients who were spared laparotomy, a faster postoperative recovery and an earlier initiation of nonoperative treatment was observed and the authors suggest that the procedure should be performed routinely before laparotomy for hepatocellular carcinoma. Our group[40] has proposed a more selective approach and generally recommends SL only in high-risk patients such as those with clinically apparent liver cirrhosis and in patients with major vascular invasion or bilobar tumors. Table 3 presents the main studies assessing the role of SL in hepatocellular carcinoma.

Biliary malignancy: Preoperative assessment of resectability of biliary tract tumors is challenging since, in addition to metastatic spread, the resectability of a given tumor is predicated on hilar vascular and biliary involvement which is often not accurately assessed by preoperative imaging. Despite extensive preoperative evaluation, less than half of patients who undergo exploration are amenable to a potentially curative resection and the issue of resectability is usually resolved at laparotomy, often after an extensive dissection of the portal vascular and biliary structures.

The exact yield of SL is difficult to assess for cholangiocarcinoma since it depends of the quality of preoperative assessment as well as the willingness to attempt resection based on the surgeon's experience.

In the Beaujon experience[41], SL avoided unnecessary laparotomy in a third of patients with potentially resectable biliary carcinoma who had undergone extensive preoperative imaging. Nevertheless, contraindications found during laparoscopy were mainly due to peritoneal and liver metastasis and vascular and lymph node invasion were not diagnosed well by this procedure. The authors concluded that the yield of SL was more important in gallbladder cancer and in intrahepatic cholangiocarcinoma than in hilar cholangiocarcinoma where non-resectability is mainly due to vascular and biliary involvement that is best assessed after dissection.

Similarly, in the MSKCC experience, Jarnagin *et al*[2], in a prospective analysis of SL of 186 patients with primary and secondary hepatobiliary malignancies found that laparoscopy failed to identify non-resectability because of lymph node metastases, vascular involvement or extensive biliary involvement. Nevertheless, in 100 patients with extrahepatic biliary carcinoma prospectively analyzed[42] (gallbladder cancer, 44 and hilar cholangiocarcinoma, 56), they reported that SL identified the majority of patients with unresectable disease. In this study, the yield of lapa-

Table 3 Studies assessing the role of staging laparoscopy in hepatocellular carcinoma

Study / years	Time period	No. of patient	Contraindication found during laparoscopy (%)	Additional contraindication found during laparotomy (%)	Morbidity/Mortality related to laparoscopy	Note
Lo *et al*[39]/1998	1994-1996	110	16	12	0	+ LAPUS
Lai *et al*[47]/2008	2001-2007	122	37	3	NA	+ LAPUS
Montorsi *et al*[48]/2001	1998-2000	70	57[a]	NA	NA	+ LAPUS
Weitz *et al*[40]/2004	1997-2002	60	23	11	NA	

[a](1) Additional in; and (2) Formations found during laparoscopy and laparoscopic ultrasonography. LAPUS: Laparoscopic ultrasonography.

Table 4 Studies assessing the role of staging laparoscopy in biliary tract tumor

Study/years	Time period	No. of patient	Contraindication found during laparoscopy (%)	Contraindication found during laparotomy (%)	Morbidity/ Mortality	Note
Weber *et al*[42]/2002	1997-2001	100	35	52	0	Extrahepatic biliary carcinoma
Tilleman *et al*[44]/2002	1993-2000	110	41.8	47	3%/0	Malignant proximal bile duct obstruction with ultrasonography
Connor *et al*[43]/2005	1992-2003	84	41.5	48	NA	Hilar cholangiocarcinoma with ultrasonography
Goere *et al*[41]/2006	2002-2004	39	36	37	6%/0	

roscopy was lower for hilar cholangiocarcinoma compared to gallbladder cancer and the main cause of failure of laparoscopic staging was the assessment of local resectability. Overall, they advocate the use of SL in all patients with potentially resectable primary gallbladder cancer and patients with T2/T3 hilar cholangiocarcinoma[42].

Regarding the differential use of SL in cholangiocarcinoma and gallbladder cancer, most of the authors observed a higher yield of SL in gallbladder cancer. This is likely due to a more frequent early dissemination in gallbladder cancer, cholangiocarcinoma, especially hilar cholangiocarcinoma, being more likely to be locally invasive and having a slightly longer survival. Nevertheless, the use of laparoscopic ultrasonography increased the yield laparoscopic of staging from 24.3% to 41.5% as reported by Connor *et al*[43] but this remains controversial since Tilleman *et al*[44] reported a very limited value of laparoscopic ultrasound in patients with malignant proximal bile duct obstruction. In our experience, laparoscopic ultrasound does not detect any patient with unresectable disease that was not already found at laparoscopy and the interpretation of the findings is often difficult to interpret. Table 4 presents the main studies assessing the role of SL in biliary tract tumors.

CONCLUSION

Even after extensive preoperative assessment, SL may allow for avoidance of non-therapeutic laparotomy in patients with radiographically occult metastatic or locally unresectable disease. Laparoscopy is associated with decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy compared to laparotomy without significantly increasing the operative time. The yield of SL has decreased with improvements in preoperative imaging techniques. Currently, to improve resource utilization, SL should be used selectively for patients with pancreatic and hepatobiliary malignancy to avoid unnecessary non-therapeutic laparotomy.

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S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Yang C

WJGS World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i9.291

World J Gastrointest Surg 2010 September 27; 2(9): 291-294
ISSN 1948-9366 (online)

CASE REPORT

Gastroduodenal artery aneurysm rupture in hospitalized patients: An overlooked diagnosis

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Received: March 11, 2010 **Revised:** September 15, 2010
Accepted: September 22, 2010
Published online: September 27, 2010

Abstract

Gastroduodenal artery (GDA) aneurysm rupture is a rare serious condition. The diagnosis requires a high level of suspicion with specific attention to warning signs. Early diagnosis can prevent fatal outcomes. In this report, we describe a case of GDA aneurysm rupture presenting as recurrent syncope and atypical back and abdominal discomfort. The rupture manifested as hemorrhagic shock. The diagnosis was made by computed tomography of the abdomen which showed acute peritoneal and retroperitoneal bleeding. Angiographic intervention failed to coil the GDA and surgery with arterial ligation was the definitive treatment.

Key words: Gastroduodenal; Hemorrhage; Life-threatening; Embolization; Surgery

Peer reviewer: Paolo Massucco, MD, Department of Surgical Oncology, IRCC, Str Stat 142, Candiolo 10060, Italy

Harris K, Chalhoub M, Koirala A. Gastroduodenal artery aneurysm rupture in hospitalized patients: An overlooked diagnosis. *World J Gastrointest Surg* 2010; 2(9): 291-294 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i9/291.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i9.291

INTRODUCTION

Gastroduodenal artery (GDA) aneurysms are extremely rare, potentially serious conditions. They account for about 1.5% of all visceral arterial aneurysms which by themselves represent rare conditions with a reported incidence of 0.01% to 0.2% at best[1].

GDA aneurysm is usually diagnosed by ultrasound (US), endoscopic ultrasound (EUS), computed tomography (CT) or angiography depending on the presenting clinical scenario.

We describe a case of GDA aneurysm with onset of warning signs and symptoms 2 d prior to rupture with massive intra-abdominal bleed and resulting hemorrhagic shock.

CASE REPORT

A 64-year-old man was hospitalized 2 d post elective total knee replacement for recurrent syncopal episodes. His cardiac workup was negative on the telemetry floor with a negative echocardiogram and no evidence of arrhythmias. He was transferred to a rehabilitation ward 2 d later. The patient was doing very well with physical therapy and his knee pain was controlled using acetaminophen and opioids as needed. He was complaining of some back pain and mild epigastric discomfort with a negative physical exam. The patient has no significant past medical history and no previous surgeries. His social history was negative except for a remote smoking history and occasional alcohol use. The patient was on Coumadin postoperatively for DVT prophylaxis with therapeutic INR.

On his second day of rehabilitation, rapid response was called after he was found unresponsive in his chair. His blood pressure was undetectable with a regular heart rate at 120 per minute. Physical exam showed tender bilateral flanks with mild abdominal distension. INR was 2.9 and Hg was 9.8. Hg level was 11.3 five days prior to this event. Prior to this event and at all times, his vitals were stable with no tachycardia and normal blood pressure readings.

The management started with hemodynamic resuscitation with aggressive intravenous fluid management. He was given vitamin K intravenously and 4 units of FFPs were transfused immediately. The patient was transferred to the critical care unit with the diagnosis of hemorrhagic shock secondary to intra-abdominal bleed. CT scan of the abdomen/pelvis was ordered and done after hemodynamic stabilization (Figure 1). In addition to the below findings, there was an extensive inflammatory change surrounding the duodenum and pancreatic head that suggested these locations as the bleeding source.

The CT abdomen/pelvis was repeated the next day with IV contrast (Figure 2). It showed a retroperitoneal aneurysm suspected to be arising from the gastroduodenal artery or one of its branches. There was evidence of a retroperitoneal bleed in addition to the intraperitoneal bleed shown on previous CT scan.

The patient underwent urgent angiographic embolization the same day with coiling of the gastroduodenal artery (Figures 3 and 4). It was successful and without any complications. A follow up bleeding scan was negative. Three days later, an abdominal CT angiogram was performed as a follow up study. There was evidence of pulmonary embolism. Intravenous contrast filled the previously described aneurysm in the region of the gastroduodenal artery, measuring 1.6 cm × 1.5 cm. There was a slight increase in size of the retroperitoneal bleed. After placing a Greenfield filter, another attempt by intervention radiology to coil the aneurysm failed. Surgical intervention was the last resort with an exploratory laparotomy and successful ligation of the aneurysm. A 1 wk follow up CT abdomen showed shrinkage of the retroperitoneal hematoma.

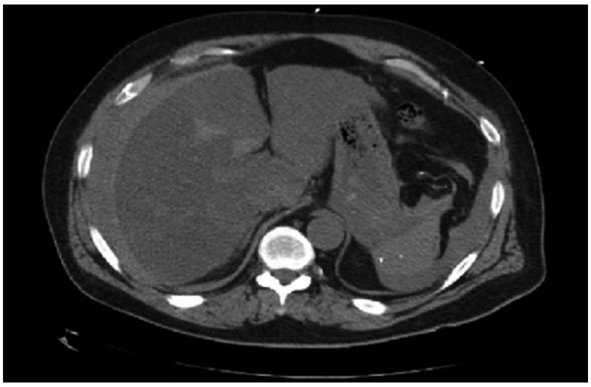

Figure 1 Computed tomography showing acute peritoneal hemorrhage. Fluid is prominent surrounding the second and third portions of the duodenum and pancreatic head, and perihepatic regions.

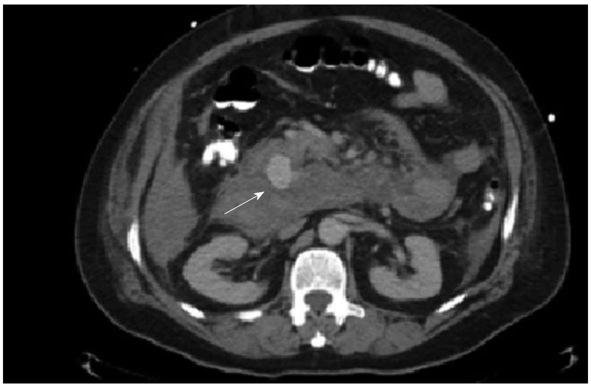

Figure 2 Abdominal contrast enhanced computed tomography showing retroperitoneal aneurysm which is suspected to be arising from the gastroduodenal artery or one of its branches (arrow). Aneurysm measures 3.1 cm × 2.5 cm.

DISCUSSION

Gastroduodenal artery aneurysm has always been reported in the literature as rare case reports. Therefore, there is no clear evidence concerning the best time to diagnose it or a clear algorithm of how to manage it. GDA aneurysm is a rare potential life-threatening condition reported in 0.5% of all visceral aneurysms[2]. In a routine autopsy series, visceral artery aneurysms were reported in 0.01% to 0.2%[1]. In other series, GDA aneurysms account for 1.5% of all visceral aneurysms[1,3,4]. Depending on the studied population, the mean age was between 50 and 58 years[5,6]. The male/female ratio is 4.5:1 and the mean size 3.6 cm[5]. The most common identified condition associated with GDA aneurysm is chronic pancreatitis[7]. Other associated conditions are liver cirrhosis[8], other vascular abnormalities such as fibro-muscular dysplasia and poly-arteritis nodosa and predisposing events such trauma and septic emboli[9]. The pathogenesis of GDA aneurysm is not well known with trauma, hypertension and atherosclerosis as possible risk factors[10]. Abdominal pain is the main symptom which can occur with or without rupture. Other symptoms include hypotension, gastric outlet obstruction[11] and other nonspecific symptoms such as vomiting, diarrhea and jaundice[12,13]. The most serious clinical scenario is upper gastrointestinal hemorrhage which occurs in about 50% of ruptured GDA aneurysms with retroperitoneal and intraperitoneal bleeds occurring less frequently[11,12,14]. In other cases, the presence of a pulsatile abdominal mass with a bruit could be the presenting warning sign[11]. The risk of rupture is high at up to 75% of cases with a mortality rate of about 20%[5]. Therefore, early diagnosis with a high level of suspicion can prevent the worst outcomes in this group of patients. Prior to the era of sophisticated imaging modalities, GDA aneurysms were diagnosed after rupture in the majority of cases. At this time, various imaging modalities are available with more cases diagnosed in asymptomatic patients.

The Gold standard diagnostic test is visceral angiography[15]. It is usually performed for diagnostic and therapeutic purposes. Plain X-ray of the abdomen is rarely helpful in suspected visceral aneurysms with shell-like calcification

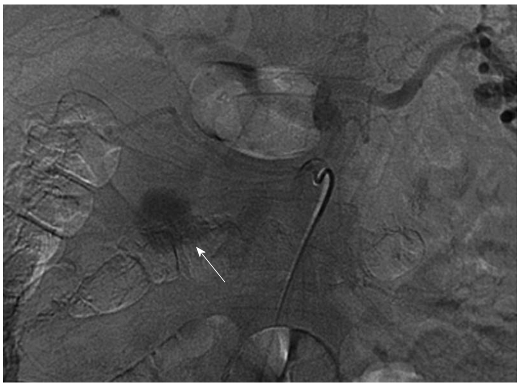

Figure 3 Abdominal angiography, selective superior mesenteric artery angiography showing the gastroduodenal artery aneurysm (arrow).

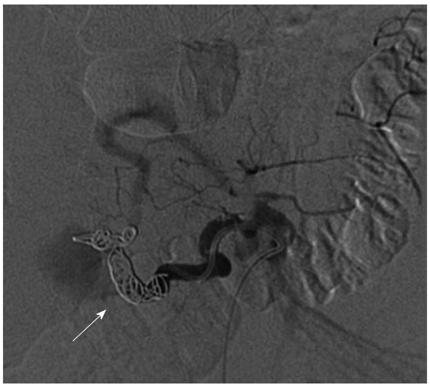

Figure 4 Post embolization angiography (arrow) showing no residual filling of the gastroduodenal artery aneurysm.

in an atherosclerotic aneurysm as the usual possible finding[2]. Among all diagnostic modalities, angiography is the most sensitive (100%) followed by computed tomography (67%) and ultrasonography (50%). Upper endoscopy has a sensitivity of about 20%[15].

Recently, other diagnostic modalities are available including Pulse Doppler US, color Doppler US, endoscopic ultrasound and magnetic resonance imaging[16-18]. Three dimensional CT has been reported to be an accurate diagnostic especially in locating the aneurysm and its relations to adjacent vasculature[6].

It has an advantage of being less invasive and therefore more useful than angiography to diagnose the location of the aneurysm.

Therapeutic modalities depend of the type of presentation and are usually made on individual basis. Endovascular trans-catheter embolization is the most popular despite the potential risk of visceral ischemia and organs embolization[19]. In our case, this was complicated by pulmonary embolism in a patient with a ruptured GDA aneurysm. The patient required GFF placement and eventually required surgical ligation of the aneurysm. Endovascular embolization is considered the treatment of choice for hemodynamically stable patients. Surgical intervention is usually reserved for actively bleeding patients and when embolization fails[20].

In conclusion, GDA aneurysm rupture is a serious fatal manifestation of a rare condition. It requires a high level of suspicion and warning signs and symptoms warrant further investigation with computed tomography being the most useful available test. Prompt diagnosis before rupture can change the course of this condition and prevent potential lethal complications. The prognosis of GDA aneurysm is generally excellent when diagnosed before rupture and treatment is usually definitive. Giving the rarity of this condition, there are no clear screening or follow-up guidelines. Decisions about diagnostic and therapeutic procedures should be made on an individual basis.

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S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Yang C

WJGS World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
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doi:10.4240/wjgs.v2.i9.295

World J Gastrointest Surg 2010 September 27; 2(9): 295-298
ISSN 1948-9366 (online)

CASE REPORT

Successful embolization assisted by covered stents for a pseudoaneurysm following pancreatic surgery

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Received: March 11, 2010 Revised: July 12, 2010
Accepted: July 19, 2010
Published online: September 27, 2010

Abstract

Delayed intra-abdominal hemorrhage after pancreatic surgery is a potentially lethal complication. Transarterial coil embolization and/or the placing of an endovascular stent are minimally invasive and effective procedures. An artery that is extensively eroded and rendered friable due to operative skeletonization or postoperative inflammation sometimes contributes to delayed intra-abdominal hemorrhage or rebleeding after coil embolization. This report presents a case of successful management of postoperative hemorrhage in a-74-year-old Japanese male. He experienced bleeding from a pseudoaneurysm of the brittle hepatic artery following total pancreatectomy. Initially the pseudoaneurysm was successfully treated with covered coronary stent-grafts, but rebleeding occurred 1 mo later due to the brittleness of the artery. Rebleeding was definitively managed by the complete packing of the stent by coil embolization. He remains stable at 18 mo following the final embolization. A stent graft can be used for protecting a brittle artery to avoid injury by coil embolization.

Key words: Covered stent; Hemorrhage; Pancreatic surgery; Hepatic artery; Pseudoaneurysm

Peer reviewer: John P Hoffman, MD, Department of Surgery, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, United States

Tanaka K, Ohigashi H, Takahashi H, Gotoh K, Yamada T, Miyashiro I, Yano M, Ishikawa O. Successful embolization assisted by covered stents for a pseudoaneurysm following pancreatic surgery. *World J Gastrointest Surg* 2010; 2(9): 295-298 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i9/295.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i9.295

INTRODUCTION

Perioperative mortality of pancreatic surgery has declined to between 0% and 5% due to advances in surgical techniques and critical care management[1]. Delayed massive intra-abdominal hemorrhage is one of the most serious complications and occurs in 1% to 8% of all pancreatic resections and accounts for 11% to 38% of the overall mortality[2-4]. Though transarterial embolization has been advocated as a minimally invasive treatment for a ruptured pseudoaneurysm with a high success rate, unsuccessful hemostasis or rebleeding after embolization are not rare[5,6]. The artery is occasionally damaged by surgical skeletonization or postoperative inflammation due to an abdominal abscess or pancreatic leakage. An artery that is extensively eroded and rendered friable cannot withstand pressure from the packing of an aneurysm lumen using endovascular coils and the brittle arterial wall may prevent a successful hemostasis and lead to death resulting from uncontrollable bleeding. This report presents a case of a bleeding from a pseudoaneurysm of the hepatic artery. The pseudoaneurysm and friable common hepatic artery were successfully treated with a covered coronary stent-graft, and then were definitively managed 1 mo later by the complete packing of the stent in order to treat a recurrence of bleeding.

CASE REPORT

A 74-year-old Japanese male presented with acute abdominal pain 10 mo after undergoing a total pancreatectomy for pancreatic adenocarcinoma. An intra-abdominal tumor was suspected. He was transferred to our hospital for further examination. Computed tomography revealed a narrow and irregular common hepatic artery and a 7.0 cm × 7.0 cm huge mass with no contrast extending into the ventral and cranial aspect of the constriction of the common hepatic artery (Figure 1). The diagnosis was a pseudoaneurysm arising at the common hepatic artery with no active bleeding. The following 6 d were uneventful, but he developed a melena and experienced a sudden drop of blood pressure on the 7th day. The patient was thought to have severe damage to the arterial wall because a digital subtraction angiogram revealed a pseudoaneurysm arising at the common hepatic artery (Figure 2A) and the arterial lumen was markedly irregular and enlarged,. A balloon-expandable coronary stent-graft was placed in the common hepatic artery to avoid unsuccessful hemostasis with endovascular coils. A guide wire was advanced past the pseudoaneurysm and a 4 mm × 14 mm covered stent (Jostent Graft master, Abott vascular) was deployed (Figure 2B). An additional stent-graft was considered because the extravasation of contrast medium from the proximal edge of the covered stent continued. A 3 mm × 19 mm covered stent (Jostent Graft master, Abott vascular) was placed in the friable hepatic artery partly under lapping the first stent (Figure 2C and D). His blood pressure recovered and angiography confirmed that the two covered stents had arrested the hemorrhage in the common hepatic artery and preserved the blood flow to the liver (Figure 3). No liver damage, such as an elevation of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and total bilirubin, was seen after stent grafting.

One month later, he presented with melena and hemodynamic shock. Emergency angiography revealed a pseudoaneurysm arising at the bifurcation of the common hepatic artery and proper hepatic artery (Figure 4A). Therefore, the aneurysm was packed with micro coils (3 Trufill coils; Cordis Endovascular Systems, Johnson & Johnson). Additional coiling was performed in the proper hepatic artery, because extravasation of the guide wire occurred at the distal portion of the hepatic artery during the coiling procedures. The blood flow *via* the hepatic artery was blocked by Microcoil embolization (10 Trufill coils and 6 Diamond coils; Cordis Endovascular Systems, Johnson & Johnson) in the lumen of the covered stent because of the vulnerability of the proper hepatic artery and the strong possibility of rebleeding. An arteriogram confirmed the complete exclusion of the common hepatic artery, cessation of bleeding and blood flow to the liver *via* the anastomotic branch of the left gastric artery (accessory left gastric artery) (Figure 4B). There was no liver damage after arterial embolization.

Figure 1 Abdominal computed tomography. Narrowing of the common hepatic artery and a 7.0 cm × 7.0 cm huge mass with no contrast (arrowheads) extending into the ventral and cranial aspect of the constriction of the common hepatic artery (arrows).

The patient was thereafter discharged and remains stable at 18 mo following the final embolization.

DISCUSSION

Massive arterial bleeding can occur late in the postoperative course of patients undergoing hepatobiliary pancreatic surgery. Delayed bleeding occurs mainly due to a pseudoaneurysm of a major visceral arteries or gastroduodenal arterial stump[6,7]. An urgent laparotomy to control bleeding is rarely successful due to the extensive inflammation, thus it has a high mortality rate and does not eliminate the risk of rebleeding[8,9]. Alternatively, selective angiography and transarterial embolization is now considered the standard therapeutic management. Angiography enables the precise localization of the pseudoaneurysm, which allows selective microcoil embolization[7]. The reported success rate of transarterial embolization for a visceral artery pseudoaneurysm is 63% to 100%, with a morbidity of 14% to 25% and a mortality of 0% to 14%[6-8]. Either recanalization or rebleeding may occur in up to 37% of the patients[5,6] and an interruption of the hepatic arterial flow is usually warranted for effective hemostasis[7,9,10].

Recently, stent grafts have been employed for the treatment of pseudoaneurysms[11-14]. This technique has the advantage of providing continued perfusion to the end-organ. Therefore, it seems to be safer to manage bleeding from the common hepatic artery after a pancreaticoduodenectomy by a stent graft rather than coil embolization especially when the collateral arteries cannot be confirmed.

The collateral arteries were available in the current case, and the patient was a candidate for embolization with coils. However, angiography showed an irregular and dilated arterial lumen which suggested the artery was extensively eroded and friable. Embolization with endovascular coils in a friable artery can consequently cause a rupture of the artery or subsequent rebleeding can occur after temporary hemostasis. In our hospital, incomplete hemostasis or rebleeding was experienced in cases who were treated by embolization with endovascular coils alone when irregular and enlarged artery or extravasation of the guide wire were

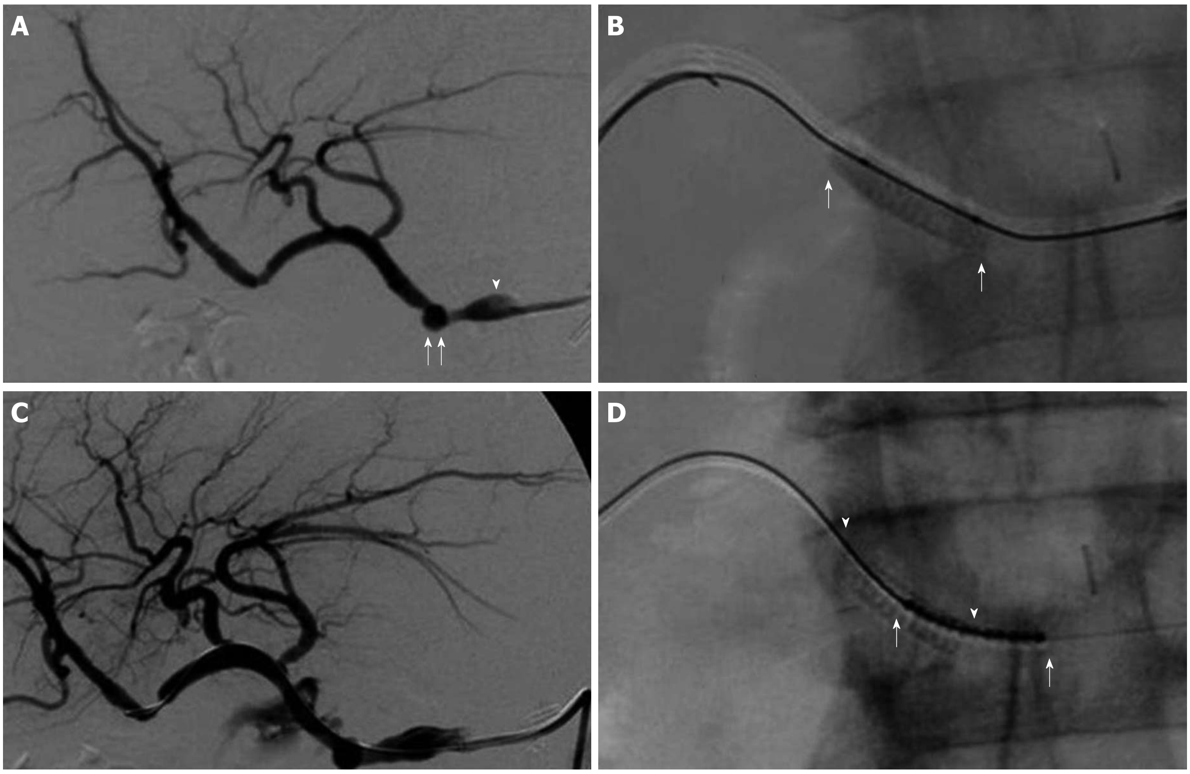

Figure 2 Placement of covered stent graft for pseudoaneurysm of common hepatic artery. A: Angiography revealed a pseudoaneurysm arising at the common hepatic artery (white arrows) and the dilated lumen of the common hepatic artery (arrowheads); B: A guide wire was advanced past the pseudoaneurysm and a 4 mm x 14 mm covered stent was deployed (arrows); C: Angiography revealed extravasation of contrast medium from the proximal edge of the covered stent (arrow). A dehiscence seemed to occur at the fragile arterial wall; D: An additional covered stent (arrows) was placed partly under lapping the first stent (black arrows).

Figure 3 Both hemostasis and blood flow to the liver was confirmed by angiography.

revealed by angiography. This case suggests that a stent may therefore be effective for protecting the fragile artery rather than for preserving the blood flow to the liver. The placement of stent-grafts following coiling should therefore be considered in some selected cases when the arterial wall appears to be fragile.

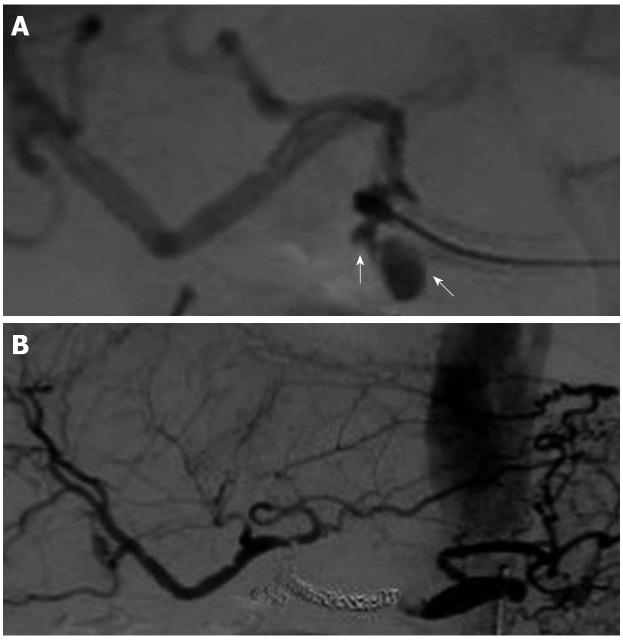

Figure 4 Microcoil embolization in the lumen of the covered stent. A: Angiography revealed a pseudoaneurysm in the proper hepatic artery at the distal edge of the covered stent (arrows); B: Arteriogram shows the complete exclusion of the common hepatic artery, complete cessation of bleeding and blood flow to the liver *via* the anastomotic branch of the left gastric artery.

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World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
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World J Gastrointest Surg 2010 September 27; 2(9): I
ISSN 1948-9366 (online)

ACKNOWLEDGMENTS

Acknowledgments to reviewers of *World Journal of Gastrointestinal Surgery*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Surgery*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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World J Gastrointest Surg 2010 September 27; 2(9): I
ISSN 1948-9366 (online)

Meetings

Events Calendar 2010

January 15-16, 2010
AGA Clinical Congress of Gastroenterology and Hepatology
The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinical-congress

January 27-31, 2010
Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
http://www.alpshpbmeeting.soton.ac.uk

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 4-7, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
http://www.surgonc.org/

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
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The International Liver Congress™ 2010
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May 1-5, 2010
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World J Gastrointest Surg 2010 September 27; 2(9): I-V
ISSN 1948-9366 (online)

Instructions to authors

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

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

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

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

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

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

Conference paper

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

Electronic journal (list all authors)

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

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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

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