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AIM AND SCOPE

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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TOPIC HIGHLIGHT

2016 Laparoscopic Surgery: Global view

Laparoscopic complete mesocolic excision with central vascular ligation in right colon cancer: A comprehensive review

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Abstract

Aim of the study is to comprehensively review the latest trends in laparoscopic complete mesocolic excision (CME) with central vascular ligation (CVL) for the multimodal management of right colon cancer. Historical and up-to-date anatomo-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind Laparoscopic CME with CVL is thoroughly investigated and explained. Attention is paid to the current surgical techniques and the quality of the surgical specimen, yielded through mesocolic, intramesocolic and muscularis propria plane of surgery. We evaluate the impact on long term oncologic outcome in terms of local recurrence, overall and disease-free survival, according to the plane of resection achieved. Conclusions are drawn on the basis of the available evidence, which suggests a pivotal role of laparoscopic CME with CVL in the multimodal management of right sided colonic cancer: performed in the right mesocolic plane of resection, laparoscopic CME with CVL demonstrates better oncologic results when compared to *standard* non-mesocolic planes of surgery, with all the advantages of laparoscopic techniques, both in faster recovery and better immunological response. The importance of minimally invasive *meso-resectional* surgery is thus stressed and highlighted as the new frontier for a modern laparoscopic total right mesocolectomy.

Key words: Right sided colonic cancer; Complete mesocolic excision; Central vascular ligation; Laparoscopy; Quality of surgical specimen; Oncologic outcome

Core tip: Laparoscopic complete mesocolic excision

(CME) with central vascular ligation (CVL) is based on resection of the colon within its intact and inviolate mesocolon with high tie ligation, so to improve the quality of the resection specimen produced; up-to-date anatomo-embryological concepts are analyzed in detail, focusing on the latest studies of the mesenteric organ, its dissection by mesofascial and retrofascial cleavage planes, and questioning the need for a new terminology in colonic resections. The rationale behind the CME with CVL is explained and particular attention is paid to the current surgical techniques. The impact on local recurrence, disease-free and overall survival is reviewed. Current literature about laparoscopic CME with CVL demonstrated better quality of the surgical specimen produced and significant survival advantage when compared to standard non-mesocolic resections, stressing the importance of meso-resectional surgery, especially when performed with minimally invasive techniques: higher surgical quality, faster recovery and better immunological response may in fact contribute to better long term oncologic outcome.

Siani LM, Garulli G. Laparoscopic complete mesocolic excision with central vascular ligation in right colon cancer: A comprehensive review. *World J Gastrointest Surg* 2016; 8(2): 106-114 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i2/106.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i2.106

INTRODUCTION

At the end of the 19th century, Emil Theodor Kocher[1,2], was the first to theorize oncologic resections based on removal of the involved organ along with its lymphatic drainage; this concept was shortly after substantiated by Miles *et al*[1] and Jemison *et al*[2] for rectal and colonic cancer respectively. Yet, the real revolution in oncologic surgery was performed seventy years later by Heald *et al*[3], who introduced the concept of total excision of the mesorectum (TME), the primitive embryological dorsal mesentery of the rectum: Dissection in the mesorectal plane yields an intact fascial-lined specimen containing all the vasculo-lymphatic pathways and lymph nodes, and reduces the risk of an involved circumferential resection margin (CRM)[3,4]. The embryological right plane of dissection, graded by the pathologist, has been shown to be independently related to the risk of local recurrence, disease free and overall survival[5,6], so to promptly became the central part of any multimodal treatment of rectal cancer[7].

In 2009, Hohenberger *et al*[8] translated the concept of TME to colonic cancer, noting that traditionally more favorable oncologic results of colon neoplasia was eventually overtaken by rectal cancer: Multimodal strategies, not yet applied to colonic tumors, and a more radical surgical approach performed along embryonic planes of development with higher quality specimens, produce better oncologic outcome; thus, complete mesocolic excision (CME) with central vascular ligation (CVL) was theorized, standardized and eventually validated by several studies[9,10].

The concept of complete excision of the involved organ along with its primitive mesentery, associated to central ligation of the supplying blood vessels, is progressively gaining acceptance as the next step towards a modern surgical oncology; surgical resection of the primitive embryological mesenterium is in fact pivotal for optimal local clearance. The primitive mesenterium is the embryological envelope where the neurolymphovascular structures develop within a double-layered mesenchymal fibrofatty tissue and the initial pathway for cancerous diffusion: Its intact, complete excision is thus essential to clear residual disease in the surgical field, with consequent impact on local control.

Furthermore, CVL allows for an extensive lymph node dissection along the feeding vessels, with significant effect on regional recurrence and systemic dissemination, as shown by improved survival in stage I-III colonic cancers treated with enhanced lymph node harvesting[11,12].

Blending Complete Mesocolic Excision with CVL is thus the logical step in gaining the highest loco-regional control, removing both the intact mesocolon and the apical nodes, with relevant impact on long term outcome. To take advantage of minimally invasive techniques, laparoscopic approach to CME with CVL seems the natural consequence in the evolution of this procedure.

ANATOMO-EMBRYOLOGICAL CONCEPT OF THE MESOCOLON

The mesocolon is the adult remnant of the primitive dorsal mesentery[13-19]. In the 5 mm embryo (approximately 32 d), the colon develops within a dorsal mesentery for all its length; an approximately 270° counterclockwise rotation of the primitive mid-gut along the axis of the superior mesenteric artery (SMA) causes the folding of the dorsal mesentery, originating the future mesocolon[13-19].

In 1885, Treves[20] stated that the right mesocolon fuses with the primitive posterior parietal peritoneum, with the consequent obliteration of the space between these embryonic structures. This view of mesenteric obliteration through a process of fusion was than refuted in the early '900 by the study of Carl Toldt[21] and Congdon[22], who affirmed that the mesentery of the colon persists in adulthood not only at the level of the transverse and sigmoid colon, but all along its length, being separated from the posterior parietal peritoneum by a loose areolar connective plane referred to as Toldt's fascia. Later on, Goligher[23] described the possibility of stripping back the colon and its meso towards the midline, restoring the primitive embryological disposition

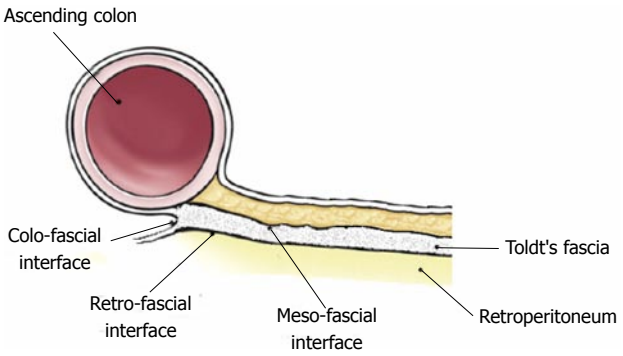

Figure 1 Depiction illustrating the relationships between the mesocolon, Toldt's fascia (schematically exaggerated for descriptive purpose) and the retroperitoneum. Meso-fascial interface is the apposition between the Toldt's fascia and the overlaying mesocolon; Retro-fascial interface is the apposition between the Toldt's fascia and the underlying retroperitoneum.

before its rotation, confirming the Toldt's and Congdon's remarks.

Contemporary view of the mesenteric organ

The increasing focus on the quality of the surgical specimen as an independent variable in the outcome of cancer surgery stresses the need for a more detailed knowledge of the mesocolon anatomy.

Recent papers demonstrated that the mesocolon persists in adulthood as a distinct anatomic structure, continuous from the ileocecal valve to the rectosigmoid junction, with well defined mesocolic, fascial, and retroperitoneal components and related mesofascial (the apposition between the Toldt's fascia and the overlaying mesocolon) and retrofascial (the apposition between the Toldt's fascia and the underlying retroperitoneum) interfaces (Figure 1): These latter are crucial for surgical planes in mesocolic and colonic mobilization[24,25].

Furthermore, recent studies[26,27] investigated the mesocolon by light and electron microscopy: Its structure is homogeneous across all locations and is composed of adipocyte lobules separated by thin fibrous septae layered by mesothelium, with lymphatic channels within this lattice; unexpectedly, a further connective, highly cellular submesothelial layer exists between surface mesothelium and the adipocytes.

A detailed appraisal of the lymphatic network within the mesocolon by immunohistochemical analysis[28], showed that lymphatic vessels occur within both submesothelial connective tissue and interlobular septations, on average every 0.14 mm and within 0.1 mm from the mesocolic surfaces, generating a rich lymphatic network; the authors stressed that breaching the mesocolic surface extensively disrupts this lymphatic network. In the same study, lymphatic vessels were also identified within the Toldt's fascia, with no direct communication with those in the mesocolon, and whose clinical significance (independent or integral part of the mesocolon) should be investigated with further dedicated works: In fact, in mesofascial separation, mesocolon and fascia are surgically separated with the Toldt's fascia left *in situ* (Figure 2A), whereas in retrofascial separation the mesocolon/fascia complex is separated from the underlying retroperitoneum (Figure 2B); both separations are integral to CME as shown by Hohenberger *et al*[8], but the exact role of lymphatic channels within the Toldt's fascia could define only retrofascial separation as an oncologically correct plane of resection.

Time for a new terminology?

Some authors[29-32] advocated the need for a new terminology in describing the mesocolon and its related surgical procedures: Visceral and parietal fascia, pre-renal fascia, parietal plane, somatic fascia may ingenerate confusion and should be standardized in the modern view of the mesenteric organ.

A surgical plane is defined as the interface between two contiguous structures, and in resectional colonic surgery the planes are (1) mesofascial; (2) retrofascial; and (3) colofascial, as shown in Figure 1. In keeping with this, a terminology of total or partial right (left) mesocolectomy has been proposed, being more informative than right (left) hemicolectomy or ilecocolic resection because entirely derived for the current anatomical appraisal of the mesenteric organ anatomy.

THE RATIONALE BEHIND

There are three essential components of CME with CVL: (1) development of a mesofascial or retrofascial plane to mobilize an intact and inviolate mesocolon as an intact package; (2) CVL with high tie to maximize the vertical lymph node dissection (central spread); (3) adequate length of bowel to remove pericolic lymphnodes, maximizing the longitudinal lymphnode harvesting (longitudinal spread).

CME allows for removal of the entire envelope of the primitive dorsal mesentery along the anatomo-embryological avascular cleavage planes, and is therefore fundamental for a true radical R0 resection, as the meso contains the whole potential routes of metastatic spread through lympho-vascular, neuro-perineural and fibro-fatty tissues[8-10]. The mesocolon must be excised as an intact, inviolate package as any breach of its surface and underlying structures threatens the radial margin and disrupts the lymphatic network of the meso-structure with consequent *spillage* of neoplastic cells within the surgical field, enhancing the risk of local recurrence. This concept stresses further the need for a correct surgical plane of resection to maximize the local clearance, exactly the same way we conceptually perform TME for rectal cancer: To reduce to reduce the risk of an involved CRM and minimize the risk of local failure[7].

CVL is essential in obtaining an adequate regional control and impact on survival. The latest 2010 JSCCR guidelines recommends D2 dissection for clinically

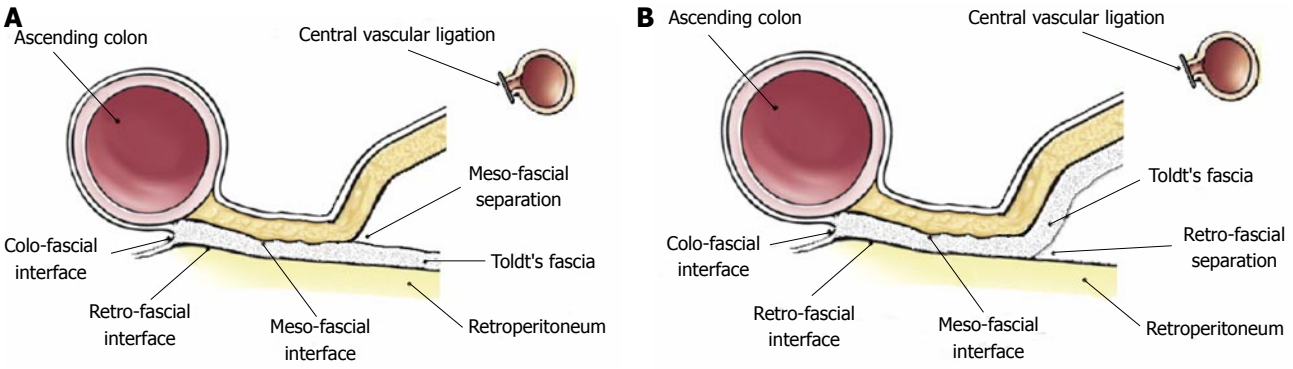

Figure 2 Depiction illustrating the meso-fascial (A) and retro-fascial (B) separation performed in the medial to lateral approach for laparoscopic right meso-colectomy. In Meso-fascial separation (A), the plane of dissection lies between the inferior leaf of the mesocolon and the underlying Toldt's fascia (schematically exaggerated for descriptive purpose), separating both components of the meso-fascial interface. In Retro-fascial separation (B), the plane of dissection lies between the Toldt's fascia and the posterior parietal peritoneum covering the retroperitoneum, separating both components of the retro-fascial interface. Both dissections end with colo-fascial separation.

early stages colorectal cancers and D3 dissection for more advanced disease: Impressive results in terms of local recurrence and patients survival have been reported[33,34], also by Western authors who claim CME with CVL for right colonic cancer as oncologically effective as D3 right hemi-colecomy performed in Eastern Countries[8,35,36]. CVL could be crucial in micro-metastatic clearance of central nodes, which are frequently missed by routine histological examination[37], and thus responsible for loco-regional recurrence and systemic dissemination[34]. For cancers located in the hepatic flexure and proximal transverse colon, possibly because of an embryological coalescence of mesenteric fascia, metastatic nodes incidence of about 5% for subpyloric station and about 4% for right gastroepiploic arcade has been reported[38]: Central transection of middle colic vessels, ligation of right gastroepiploic vessels at the origin, 10 to 15 cm of greater omentectomy off the tumor and removal of subpyloric nodes could be beneficial, especially in advanced stages (clinically T3c-d and T4)[8,39], as shown in Figure 3.

Blending CME with CVL is thus the logical step to ensure the best loco-regional control: CME maximizes the local clearance of the surgical field both increasing the chance for an uninvolved CRM and limiting any neoplastic spillage; CVL enhances regional control, removing apical nodes along the surgical trunk of the superior mesenteric vein (SMV), preventing regional recurrence and systemic dissemination: This is probably plausible for cancer without spread beyond the primitive *meso-structure*, as macroscopic involvement of apical nodes carries a poor outcome, independently from the extension of the surgical resection[40].

SURGICAL TECHNIQUE OF LAPAROSCOPIC COMPLETE RIGHT MESO-COLECTOMY

Patient is administered general anesthesia and placed in the supine or lithotomy position; a pneumoperitoneum is maintained at 10-12 mmHg using CO_2. The first step is always a thorough exploration of the abdominal cavity and peritoneal washing for cytology.

Once created the working space, a medial to lateral technique is generally adopted: The ileocolic vessels are stretched so to delineate the Treves arcade, and peritoneal incision is commenced at the base of the created peritoneal fold; dissection of the anterior peritoneal leaf is performed along the left margin of the SMA, with transection of the ilecocolic and of the inconstant right colic vessels at their roots. An *en-bloc* lymphadenectomy of the anterior aspect of the SMV from the ileocolic vessels to the gastro-colic trunk of Henle is preformed (D3 lymph node dissection).

The anatomo-embryological plane along the Toldt's fascia is sharply divided from medial to lateral and from bottom to top along the meso-fascial or retro-fascial plane, sometime mobilizing the duodenum, as suggested by Hohenberger *et al*[8], but usually dissecting along the plane between the intact dorsal mesocolon of the hepatic flexure and the Fredet's pre-duodenopancreatic fascia*;* the meso-fascial or retro-fascial interface must be carefully identified and components separated without breaching of either, respecting the integrity of the right mesocolon and of the retroperitoneal structures such as right ureter and gonadal vessels. The dissection stops at the lateral aspect of the right colon (right lateral peritoneal fold) exposing the colo-fascial interface, which will be separated later.

In case of caecum or ascending colon cancer, the stretched transverse mesocolon is progressively transected with central ligation of the right branch of the middle colic vessels and the colon is stapled 10 cm off the tumor (Total Right Meso-colectomy; Figure 3, blue lines); for hepatic flexure or proximal colon transversum cancers, middle colic and right gastroepiploic vessels are ligated at their roots, subpyloric lymph nodes are removed, 10 to 15 cm of greater omentum off the tumor is excised and colon stapling is carried out just

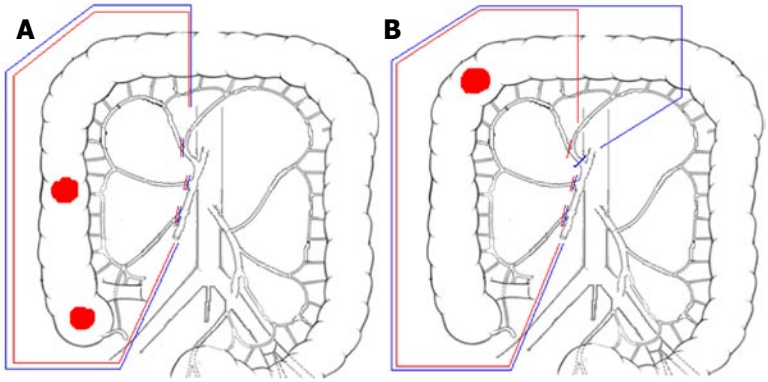

Figure 3 Schematic drawing illustrating the difference between extent of colon resection and lymph node harvesting between D3 right hemicolectomy accordingly to 2010 JSCCR guidelines (red lines) and complete mesocolic excision with central vascular ligation accordingly to Hohenberger's rules (blue lines). A: Cancer located in the caecum or ascending colon; B: Cancer located in the right (hepatic) flexure.

proximal to the splenic flexure (Total Extended Right Meso-colectomy; Figure 3, blue lines).

The hepatic flexure is mobilized by severing the lateral hepatocolic peritoneal fold, with the double components of the superior attachment (right phreno-colic ligament) and the medial attachment (cholecysto-duodeno-colic ligament); division of these peritoneal folds demonstrate the colo-fascial interface at this level, which can be easily mobilized.

The right lateral peritoneal fold and the ileocecal peritoneal folds (caecal ligaments) are progressively severed to obtain complete mobilization of the specimen.

The ileum is stapled at 10-15 cm from the ileocaecal valve and the specimen is extracted within a plastic bag through a protected mini-Pfannestiel incision; side-to-side mechanical intracorporeal or extracorporeal anastomosis is fashioned.

Variants to laparoscopic classic CME with CVL

Some authors proposed their experience with modification of the classical approach in CME and CVL: Cho *et al*[41], adopted a modified CME in respect to 3 major aspects: (1) non performance of kocherization as described in the original paper of Hohenberger *et al*[8]; (2) clearance of the pre-renal soft tissue behind Gerota's fascia for T3/4 cancer; and (3) tailored resection of the mesentery and mesocolon according to tumor location.

Feng *et al*[42] proposed a hybrid medial approach prospectively compared to a completely medial approach: The hybrid approach is based on a first up-to-bottom dissection (section of the gastrocolic ligament and dissection of the middle colic vessels and Henle's trunk) blending with a subsequent classical medial-to lateral bottom-to-top approach; the study demonstrated less time for CVL and fewer vessel-related complications, especially for the pancreatico-duodenal vessels.

Matsuda *et al*[43] also stressed a cranio-to-caudal approach for total right meso-colectomy, noting that lymph node dissection around the middle colic vessels is technically demanding and potentially exposed to severe intra-operative bleeding: The author suggests a caudal traction of the mesocolon to detect the origin of the middle colic vessels, maneuver suitable for detecting easily various types of middle colic vein branching and thus reducing the risk of Henle's trunk and/or pancreatico-duodenal vessels injury.

QUALITY OF THE SURGICAL SPECIMEN

Laparoscopic CME with CVL, when performed in the right mesocolic plane, produces high quality surgical specimens. A grading system was developed in the CLASICC trial[44], with the aim to compare laparoscopically assisted surgery with open resection for colorectal cancer; it was based on translation of the grading system used in the MRC CR07 trial for rectal cancer[45]: (1) mesocolic plane of resection ("good" plane of surgery; intact, inviolate mesocolon with a smooth peritoneal-lined surface); (2) intramesocolic plane of resection ("moderate" plane of surgery; irregular breaches in the mesocolon, none reaching down to the muscularis propria of the viscus); and (3) Muscularis propria plane ("poor" surgical plane; disruption of the mesocolon down to the muscularis propria).

In the initial study of West *et al*[46], the *mesocolic plane* translated into a higher quality of the surgical specimen: Wider cross-sectional tissue around the muscularis propria (mean 2181 ± 895 mm^2 compared to muscularis propria plane with a mean of 1447 ± 913 mm^2; $P = 0.0003$), longer distance between the tumor and the mesocolic/retroperitoneal resection margin (44 ± 21 mm *vs* 21 ± 12 mm for muscularis propria plane, $P < 0.0001$), longer distance between the tumor and the high vascular tie and greater lymph node yield. The same group, in 2010 compared the quality of specimen between the Erlangen and Leeds experience, by precise tissue morphometry and grading of the surgical plane, concluding that CME with CVL routinely performed in Erlangen yields wider mesocolic area (19657 mm^2 *vs* 11829 mm^2; $P < 0.0001$), longer large bowel (median, 314 mm *vs* 206 mm; $P < 0.0001$) and ileal (median, 83 mm *vs* 63 mm; $P = 0.003$) segment, higher distance between the tumor and the high vascular ties (131 mm *vs* 90 mm; $P < 0.0001$) and more lymph nodes harvested (median, 30 *vs* 18; $P < 0.0001$), reflecting in higher quality of the surgical specimens and better oncologic outcome[9]. In 2012, CME with CVL was compared to Japanese D3 resection,

Table 1 Pathological data and oncologic outcome of the principal studies in literature

Ref.	Plane of surgery		High tie		LN harvested		R0		5y LR		5y OS		5y DFS	
West *et al*[9]	Ms	90%	CVL	13 cm	CVL	30	Ms	94%	Ms	4.90%	Ms	85%	Ms	NR
	NMs	40%	Ctl	9 cm	Ctl	18	NMs	85%	NMs	NR	NMs	70%	NMs	NR
Hohenberger *et al*[8]	Ms	100%	CVL	13 cm	CVL	32	Ms	97.40%	Ms	4.90%	Ms	85%	Ms	NR
	NMs	0%												
Siani *et al*[40]	Ms	65%	CVL	13 cm	CVL	30	Ms	97%	Ms	NR	Ms	82.60%	Ms	73.80%
	NMs	35%	Ctl	9 cm	Ctl	18	NMs	85%	NMs	NR	NMs	60%	NMs	59.70%
Kanemitsu *et al*[34]	Ms	100%	CVL	NR	CVL	31	Ms	NR	Ms	6%	Ms	84.50%	Ms	91.60%
	NMs	0%												
Liang *et al*[48]	Ms	100%	CVL	NR	CVL	34 ± 8	Ms	NR	Ms	2%	Ms	NR	Ms	NR
	NMs	0%												
Feng *et al*[53]	Ms	94%	CVL	NR	CVL	19	Ms	NR	Ms	NR	Ms	NR	Ms	NR
	NMs	6%	Ctl	NR	Ctl	14	NMs	NR	NMs	NR	NMs	NR	NMs	NR
Gouvas *et al*[55]	Ms	68.70%	CVL	8.7 cm	CVL	33	Ms	85.70%	Ms	NR	Ms	NR	Ms	NR
	NMs	31.20%	Ctl	NR	Ctl	NR	NMs	NR	NMs	NR	NMs	NR	NMs	NR
Adamina *et al*[54]	Ms	100%	CVL	NR	CVL	22	Ms	100%	Ms	NR	Ms	NR	Ms	NR
	NMs	0%												
Bertelsen *et al*[57]	Ms	82%	CVL	NR	CVL	36	Ms	97%	Ms	11.30%	Ms	74.90%	Ms	85.80%
	NMs	18%	Ctl	NR	Ctl	20	NMs	95%	NMs	16.20%	NMs	69.80%	NMs	75.90%
Shin *et al*[51]	Ms	100%	CVL	NR	CVL	27.8 ± 13.6	Ms	NR	Ms	3.60%	Ms	NR	Ms	88%
	NMs	0%												
Bae *et al*[52]	Ms	100%	CVL	NR	CVL	28	Ms	NR	Ms	NR	Ms	90.30%	Ms	83.30%
	NMs	0%												

Ms: Mesocolic plane; NMs: Non-mesocolic planes; CVL: Central vascular ligation; Ctl: Control; NR: Not reported.

benchmark for highest survival reported in worldwide literature: Even in this case, CME with CVL showed wider mesocolic area (17957 mm^2 *vs* 8309 mm^2, $P < 0.001$), longer bowel segment (324 mm *vs* 162 mm, $P < 0.001$) and greater nodal yield (32 *vs* 18, $P < 0.001$), but equivalent distance between the tumor and the high vascular tie not statistically different (100 mm *vs* 99 mm; $P = 0.605$), translating in similar impressive long term survival[10].

RESULTS

The higher quality of surgical specimen translates in better long term oncologic outcome, with significant impact on local recurrence rate, disease free and overall survival: In the pioneering studies of West[46,9,10], Mesocolic plane of surgery and high tie ligation showed a non-stratified 15% survival advantage at 5 years when compared to *non-mesocolic planes* of resection; interestingly, the survival boost was even more remarkable in the subset analysis for stage Ⅲ patients, with an increased survival by 27% at 5 years.

These results were confirmed in subsequent studies comparing the different planes of resection, both in open[8-10,35,36,47] and laparoscopic surgery[40,48-55], reflecting a significant interest for the brilliant results of CME with CVL. Recently, two important studies further substantiated the effect of the correct plane of resection in colonic cancer: A systematic review on 5246 patients revealed a local recurrence rate, 5 years overall and disease free survival of 4.5%, 58.1% and 77.4% respectively[56]; and in 2015, a well structured population-based study by the Danish Colorectal Cancer Group[57] demonstrated a better disease-free survival for patients with stage Ⅰ-Ⅲ colonic cancer, suggesting that both laparoscopic and open CME with CVL may significantly improve outcome.

Unfortunately, these numerous studies (the most relevent reported in Table 1) have significant statistical power limitations, being predominately retrospective and non-homogeneous, so that at the moment a definitive high level of evidence cannot be drawn and thus no strong grade of recommendation may be assigned. This highlights the need for sufficiently powered randomized trials, to definitively address the issue and affirm with conclusive evidence that CME with CVL represents the gold standard in the surgical management of (right) colonic cancer.

CONCLUSION

The current evidence shows the equivalence in terms of tissue morphometry, quality of the surgical specimen and long term oncologic results between laparoscopic and open techniques[39,43,46,52,55-57], but with laparoscopic approach offering all the advantages of minimally invasive surgery, both in faster recovery and in less immunological stress response which could affect long term outcome[58-62].

In the multimodal management of right sided colonic cancer, laparoscopic CME with CVL is progressively gaining a pivotal role on the base of high quality surgical specimen, better local recurrence rate, better 5 years overall and disease-free survival when compared to less radical planes of surgery.

Laparoscopic CME with CVL should be regarded as the new frontier of a modern, *meso-resectional* oriented surgery, with all the advantages of minimally

invasive techniques, which allow for faster recovery and better immunological stress response: Higher quality of yielded surgical specimen, less complications when the laparoscopic procedure is *embedded* in an Enhanced Recovery After Surgery program[63-72] and better immuno-competence due to less surgical stress[58-62], may thus collectively contribute to better long term oncologic outcome.

Yet, in the absence of high level of evidence which precludes strong grade of recommendation, laparoscopic CME with CVL should be intensely investigated with highly powered, well structured prospective studies, so to define its role in the modern, multimodal management of right colonic cancer.

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REVIEW

Intestinal inflammation and the diet: Is food friend or foe?

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Abstract

Inflammatory bowel disease (IBD) is a chronic intestinal illness of autoimmune origin affecting millions across the globe. The most common subtypes include ulcerative colitis (UC) and Crohn's disease. While many medical treatments for IBD exist, none come without the risk of significant immunosuppression and in general do not have benign side effect profiles. Surgical intervention exists only as radical resection for medically refractory UC. There exists a dire need for novel treatments that target the inherent pathophysiologic disturbances of IBD, rather than global immune suppression. One avenue of investigation that could provide such an agent is the interaction between certain dietary elements and the aryl hydrocarbon receptor (AHR). The AHR is a cytosolic transcription factor with a rich history in environmental toxicant handling, however, recently a role has emerged for the AHR as a modulator of the gastrointestinal immune system. Studies have come to elucidate these effects to include the enhancement of T_h cell subset differentiation, interactions between enteric flora and the luminal wall, and modulation of inflammatory interleukin and cytokine signaling. This review highlights advancements in our understanding of AHR activity in the digestive tract and how this stimulation may be wrought by certain dietary "micro-nutriceuticals", namely indole-3-carbinol (I3C) and its derivatives. Greater clarity surrounding these dynamics could lead to a novel diet-derived agonist of the AHR which is not only non-toxic, but also efficacious in the amelioration of clinical IBD.

Key words: Inflammatory bowel diseases; Aryl hydrocarbon receptor; Mucosal immunity; Dietary phytochemicals; Autoimmune diseases

Core tip: Inflammatory bowel disease (IBD) is a chronic illness with a paucity of safe and effective treatments, either medically or surgically. The aryl hydrocarbon receptor represents a novel target for future treatments of IBD using dietary ligands of the receptor. Many studies have examined the interplay between the aryl hydrocarbon receptor and gastrointestinal mucosal immunity, though there remains a gap in the understanding of how dietary ligands can modulate

this activity. Our objective was to highlight elements of current literature focusing on aryl hydrocarbon receptor biology, IBD, and how their interplay can be activated with dietary "micronutriceuticals".

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INTRODUCTION

The incidence of inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) has been increasing worldwide; it is now estimated that between 1 and 1.3 million Americans are currently diagnosed with IBD[1,2]. This increased incidence is possibly due to currently unidentified environmental factors, which interact with an inherent genetic predisposition[3]. IBD is a family of chronic inflammatory conditions primarily involving the digestive tract, and often having additional extra-intestinal manifestations. The unique chronic inflammatory milieu maintained by IBD predisposes patients to non-adenomatous colorectal cancer as well as small bowel adenocarcinoma[4]. To date there is no accepted etiology or preventive measures for these conditions. Even more, there exists no cure aside from radical surgery for refractory ulcerative colitis[5].

The medical management of IBD currently stands at topical intestinal anti-inflammatories, systemic immunosuppression/immunomodulation, and novel biologic agents. The response rates, or rather the percentage of IBD patients experiencing true and deep remission using currently available treatment, is notoriously low. Only just recently have gut-specific monoclonal antibody inhibitors such as vedolizumab, which targets the integrin $\alpha4\beta7$ receptor, been approved for the treatment of IBD, possibly ushering in an age of targeted therapies[6]. However, many if not all of the current treatment modalities for IBD have significant side effect profiles, exorbitant cost, or both[7,8]. A prospective avenue of treatment for IBD that avoids many of the pitfalls of current therapy involves modulating mucosal inflammation using bioactive phytochemicals delivered by the diet. In fact, it has been reported that diets rich in fruits and vegetables are protective of IBD, which may indicate a role for future diet-derived treatments[9,10]. The ideal treatment would have influences on gut barrier permeability, innate GI inflammation, and mucosal immunity, all pathophysiological hallmarks of IBD.

One potential mediator of anti-inflammatory dietary compounds is the aryl hydrocarbon receptor (AHR). The AHR is a chaperoned cytosolic protein that has been found to influence transcription after binding to an exogenous ligand[11]. It is a member of the basic helix-loop-helix transcription factor family as well as the Per-Arnt-Sim protein homology that regulates environmental adaptation to ligand exposure[12,13]. Once bound, the AHR can shed its cytosolic chaperones, heterodimerize with the aryl hydrocarbon receptor nuclear translocator, bind to specific xenobiotic response elements within the genome, and induce downstream genes *via* transcriptional activation (Figure 1)[14,15]. The canonical function of the AHR exists as an environmentally responsive "sensor" which acts to detoxify its own ligands *via* upregulation of phase Ⅰ and phase Ⅱ enzymes, most notably the cytochrome P450 superfamily[16]. Its biology has been most famously attributed to the metabolism of dioxin, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)[17]. In addition to its roles in toxin handling, recently the AHR has been implicated in inflammatory pathways, tumorigenesis, and immune regulation within the intestines[18-20]. These downstream effects of AHR activity have been linked to manipulations of T-cell response, interleukin (IL) production, as well as altered cytokine function[21]. All of these phenomena have been found to contribute in some way to regulation of intestinal immunity, mucosal integrity, and alterations to the microvasculature of the intestine, which are all pathological disturbances inherent to IBD[22]. While it is known that AHR biology is linked to the development and progression of IBD, it is yet to be determined if the AHR can be manipulated in such a way to exert a preventative, protective, or even therapeutic role in IBD *via* dietary ligands[23].

The well-studied dietary component indole-3-carbinol (I3C) has been recognized as a precursor to a host of AHR ligands that are active in the gut. The compound glucobrassicin (precursor to I3C) is found in high concentrations in the Brassica family of vegetables which includes broccoli, cabbage, and Brussels sprouts (Figure 2)[24]. Mastication-induced enzymatic hydrolysis of glucobrassicin produces I3C in the mouth. I3C then dimerizes to 3,3'-diindolylmethane (DIM) in the presence of gastric HCl as well as indole [3,2-b] carbazole (ICZ) among others further down in the GI tract[25]. It is known that DIM is the molecule which exerts more robust effects on the AHR, not its parent I3C[24]. AHR activation has been found to modulate activity of intraepithelial lymphocytes, preserve lymphoid organs in the gut, and maintain mucosal homeostasis[26,27]. Moreover, DIM-supplemented diets have been shown to attenuate colonic inflammation as well as suppress colitis-associated tumorigenesis in mice[28]. This effect may be due to the ability of DIM to modulate various inflammatory cell actions in the gut lining[29]. What is known for certain is that dietary AHR ligands are able to induce the receptor within the gut epithelium as well as globally[30]. These recent advances in the understanding of the effects of AHR stimulation *via* dietary ligands may lead to diet-derived novel anti-inflammatory agents which combat the inherent disturbances of IBD.

This review highlights current knowledge on AHR

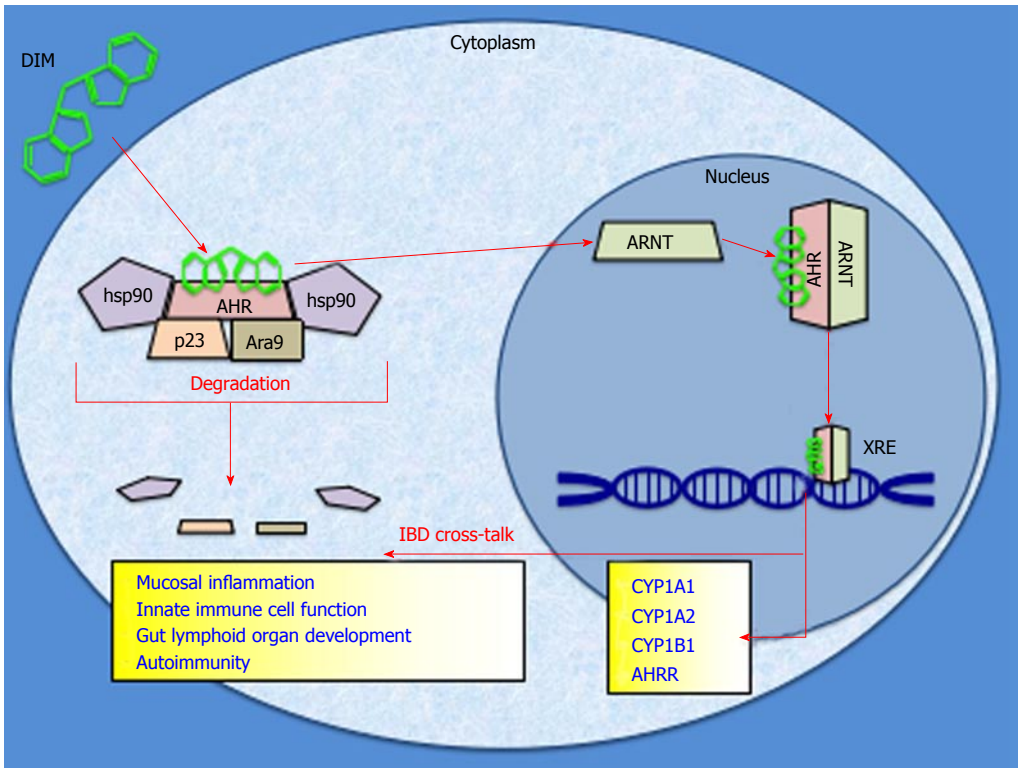

Figure 1 The aryl hydrocarbon receptor signaling pathway is depicted with 3,3'-diindolylmethane as a model agonist. Upon binding to a ligand, aryl hydrocarbon receptor (AHR) sheds its cytosolic chaperones and translocates to the nucleus to heterodimerize with aryl hydrocarbon receptor nuclear translocator (ARNT). This complex binds to the xenobiotic response element (XRE) within the genome and drives transcription of cytochrome P450 detoxifying enzymes. Proposed avenues of cross-talk with inflammatory bowel disease pathology are listed. IBD : Inflammatory bowel disease.

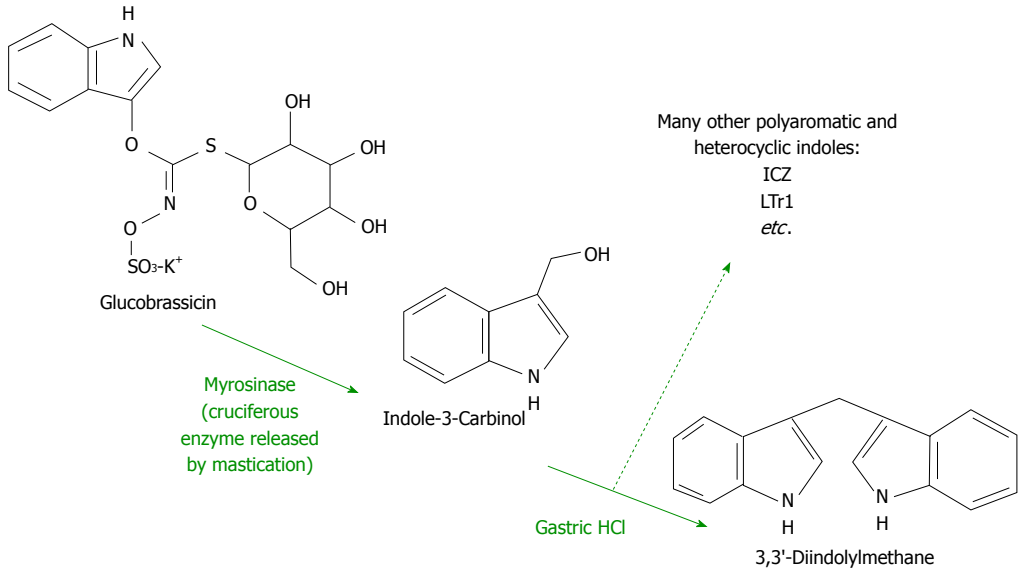

Figure 2 Presented is a simplified model for glucobrassicin digestion. I3C is freed from glucobrassicin by the mastication-released enzyme myrosinase. Gastric HCl drives dimerization of I3C to 3,3'-diindolylmethane, as well as other indole complexes that are released to the duodenum and distal digestive tract. I3C: Indole-3-Carbinol.

stimulation in the context of IBD, especially as it relates to dietary stimulation of the receptor. Continued study of the manipulation of the unique gastrointestinal inflammatory milieu associated with IBD could eventually lead to both novel therapeutics as well as diet-modifying strategies. Due to the apparent benign side effect profile of dietary AHR ligands, clinical application of this knowledge could reduce iatrogenic immunosuppressive morbidities associated with current IBD treatment as well as improve overall disease

control.

LITERATURE SEARCH

A systematic literature search was conducted using PubMed and Google Scholar for "aryl hydrocarbon receptor", "AHR", "IBD", "ulcerative colitis", "3,3'-diindolylmethane", "indole-3-carbinol", and "mucosal immunity". Searches containing relevant synonyms and combinations of the above terms were also utilized. Eighty-nine relevant references were identified and cited within this review. Included studies ranged from basic science investigations to clinical trials.

IN VITRO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The biology of the AHR is well studied in numerous *in vitro* models, however, recently the common understanding of the AHR solely acting as a toxicological sensor that upregulates detoxification enzymes has been challenged[31]. Interactions between the receptor and dioxin (TCDD) have always been the cornerstone of mechanistic and physiologic AHR studies, however it is now known that there is a wide compendium of exogenous chemicals that operate *via* the AHR[32-34]. In fact, it is micronutritional chemicals such as the indole family including I3C and DIM that have recently been identified as the bridge between AHR signaling and anti-inflammatory as well as chemoprotective effects in the gastrointestinal system[35]. These chemicals have been found to enhance mucosal integrity, maintain intraepithelial lymphocyte populations, as well as sensitize the GI tract to certain populations of enteric flora[36,37]. In contrast, TCDD treatment has been found to weaken mucosal immunity in the gut[38]. This would present a possible bifunctional role for the AHR and IBD. Further investigation of these actions is warranted to elucidate their role within the inherent disturbances of IBD. An important step in understanding the role of both the AHR and its dietary ligands is to examine their roles modulating inflammation *in vitro*.

Research surrounding the aryl hydrocarbon receptor and various aspects of immunity has recently exploded, especially concerning the effects of dietary ligands. First, it is important to note that not only has DIM been found to activate the AHR *in vitro*, but has also been found to elicit multiple chemoprotective responses in various intestinal cell lines[39-42]. In addition to its ability to upregulate the AHR in cells of the digestive tract, DIM treatment also modulates immune cell activity. For instance, DIM treatment suppresses the inflammatory response of murine macrophages *in vitro via* downregulation of TNF-α, IL-6, and IL-1β[43]. These effects and more were also found when murine dendritic cells were treated with I3C. This protocol prompted a downregulation of TNF-α, IL-6, and IL-1β as well as an upregulation of IL-10[44]. These are important findings as activated macrophages as well as these inflammatory cytokines, especially TNF-α, play key roles in the pathogenesis of IBD[45-49]. In fact, many of the most widely used biologic agents for the treatment of IBD are anti-TNF-α antibodies[50].

In addition to various cytokine and interleukin abnormalities, IBD has also been linked to various T-cell populations and their relative size and function in the GI tract[51]. Two distinct populations that have been linked to IBD disease activity are T-regulatory cells (T_{reg}) and T_h17 T-cells[52-54]. The action of T_{reg} cells has been found to be protective, while T_h17 cell activity has propagated inflammatory damage in IBD. It is well established that the aryl hydrocarbon receptor modulates various populations of immune cells, which has implications for the future treatment of IBD[55]. In fact, AHR stimulation *via* natural ligands has been linked specifically to upregulated T_{reg} cell activity and inhibition of T_h17 cell activity[27,55-57]. These effects have been further proven to be AHR-dependent[58]. Another immunomodulatory effect of *in vitro* AHR stimulation comes as a consequence of T_{reg} cell biology. AHR activity enhances T_{reg} differentiation and thus increases the population of immunoregulatory/anti-inflammatory cell populations that are responsive to IL-10[58]. This is not only important because, as mentioned earlier, DIM treatment of murine immune cells leads to the induction of IL-10 , but also because IL-10 has a firmly seated role in the pathophysiology of IBD. Mice null for IL-10 have been found to be deficient in various immunoregulatory functions in the GI tract[59]. Even more, in a small trial, patients with CD responded favorably to treatment with recombinant IL-10 producing microbes[60]. Further study of the interaction between dietary AHR ligands and immune cell function could lead to a better and more targeted understanding of their interplay.

There exists a large battery of cellular cascades and signaling pathways enhanced, inhibited, or modulated by the actions of dietary indoles such as I3C and DIM, though there remains a gap concerning a full understanding of their anti-inflammatory effects[61]. Further *in vitro* protocols focusing solely on the interaction between the AHR and certain "micronutriceuticals" like I3C and DIM could one day lead to a better understanding of their cellular effects in the context of IBD.

IN VIVO INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

The AHR has been extensively studied *in vivo*, mainly through the use of murine models null for the AHR to better understand its unique role in toxicology. Previous research has suggested the need to better understand the potential immunological function of AHR across various disciplines[62]. The AHR has been previously implicated as an important autoimmune target *in vivo* as it alters expression of the T_h17 cell subset and

associated cytokines in response to environmental toxins in the intestine[56,63]. Perhaps one of the most interesting avenues of research linking environmental exposures to altered immune response *via* the AHR can be found in the pathogenesis of IBD[21]. To best study the complex interaction of environmental factors and AHR expression in the context of immune function in the gut, many *in vivo* models have been developed to pick apart this inflammatory environment.

Due to the historical classification of AHR as the dioxin receptor, many models have been developed using TCDD treatment after induction of IBD. Dextran sulfate sodium (DSS) is a commonly employed agent to induce colitis in murine models, and multiple studies have shown that pre-treatment with low dose TCDD can prevent inflammation associated with colitis and/or reduce inflammation when administered after the onset of colitis in mice[57,64]. A similar study using trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice as a model for CD, showed that animals treated with TCDD recover quicker and experience less colonic damage than those that are untreated[43]. While these studies show promise for the role of AHR in IBD, dioxin is a carcinogen that is highly persistent in tissue, leading to efforts to identify novel AHR ligands with low toxicity for use *in vivo*.

As a non-toxic agonist of the AHR, β-naphthoflavone (βNF) has shown great potential in attenuating colitis through reducing the histological score in both wild-type and AHR null mice with varying severities of DSS-induced colitis[65]. Perhaps even more interesting is the use of an endogenous mammalian AHR ligand such as the non-toxic tryptophan byproduct 6-formylindolo(3,2-b)carbazole (FICZ), which has been shown to protect mice from DSS-, TNBS-, and T-cell transfer-induced colitis through reduced inflammatory cytokine levels and lack of IL-22 induction[18]. While these compounds attenuate colitis without the potential toxic side effects of TCDD, research into the use of dietary phytochemicals as AHR ligands is of even greater interest for the treatment of IBD[66]. One study showed that the AHR is induced by phytochemicals derived from plants of the Brassicaceae family, which includes broccoli, cabbage, kale, and others. It was found that this AHR activation is required for development of RORγt^{+}-expressing innate lymphoid cells (ILCs), as shown by increasing pools of these cells when mice are fed a diet supplemented with I3C, a product of glucobrassicin breakdown[26]. Another study established a role for I3C in controlling bacterial colonization of the gut, sustaining immune function, and protecting epithelial barrier organization as it pertains to colitis severity[27]. I3C remains a compound of great interest for the treatment of IBD, but the activity of I3C in the diet is most likely dependent on the activity of DIM, the dimer product of I3C hydrolysis by gastric acid. DIM would make up the majority of the indole load that reaches portions of the intestinal tract distal to the duodenum.

DIM has previously been shown to alleviate hepatic inflammation through shifting of diet-induced T_h17 dominance to T_{reg} dominance[67]. These data were further supported in studies where DIM was shown to attenuate experimental colitis as determined by pathological findings in mouse models, including evidence that DIM works through the AHR to decrease the T_h17 cell population while increasing the number of T_{reg} cells[29,68]. In DSS-induced colitis experiments, DIM has been shown to attenuate the disease by reducing the clinical severity of colitis, including prevention of colonic shortening and weight loss in addition to dramatically decreasing the number of tumors in AOM/DSS treated mice, which provide a common model of colitis-associated colorectal cancer[28].

In vivo models to study the AHR and IBD remain warranted, as there are numerous unidentified factors that affect progression of the disease. In particular, the interaction between immune cells and the gut microbiome is of growing interest to the research community. For example, AHR null mice succumb to infection by Citrobacter Rodentium because the absence of AHR signaling leads to a lack of RORγt+ ILCs that consequently do not produce enough IL-22[69]. Furthermore, the balance between ILCs and T_h17 cells regulated by AHR has been shown to control the composition of commensal flora[69]. In fact, the menaquinone precursor 1,4-dihydroxy-2-naphthoic acid, an AHR ligand produced by *Propionibacterium freudenreichii* has been shown to inhibit DSS-induced colitis in mice and is even commercially available in Japan as a dietary supplement that holds promise as an IBD treatment agent[70]. These findings are critical to the continued study of IBD, as interactions between dietary factors and various states of colonic dysbiosis have been shown to contribute to disease progression[71,72].

HUMAN AND CLINICAL INVESTIGATION OF THE AHR, DIETARY LIGANDS, AND IBD

While there is a wealth of data and analysis surrounding the aryl hydrocarbon receptor and DIM in both tissue culture and murine models, there are few studies in humans related to IBD, clinical or otherwise. Some correlations have been made however, and these have prepared the way for many potential future studies. Arsenescu *et al*[23] found that AHR activity is upregulated in colonic biopsy tissue in IBD patients when compared to healthy controls. Even more, this increased activity mirrored that of IL-8, a neutrophil chemotactic that is elevated in IBD patient tissues[23,73]. Conversely, it has also been reported that biopsies from patients with CD exhibit downregulated levels of AHR, which is thought to be due to T_h17 cell infiltration of inflamed tissue in CD[18]. This underscores the inherent bifunctionality of the AHR. Even though there are few studies which investigate human tissue, they do provide some exciting

evidence to a role for the AHR in human IBD.

There are not currently any clinical trials using DIM for any form of IBD. However, there are multiple chemopreventive and chemotherapeutic trials using both DIM and its parent I3C in the context of a variety of neoplasms. These trials aimed to treat, prevent, or modulate hormone response in breast cancer, vulvar epithelial neoplasia, cervical intraepithelial neoplasia, and recurrent respiratory papillomatosis[74-77]. Again, while these examples are outside the realm of IBD, they do serve to prove that a clinical trial using I3C and/or DIM is biologically feasible in humans. In addition, there have been multiple studies which have analyzed the pharmacodynamics of these compounds in humans, which provide groundwork to one day optimize dosing protocols for trials aimed at IBD[78-80]. One pharmacokinetic and safety investigation established that not only are I3C and DIM non-toxic at doses ranging from 200-800 mg daily, but also that in most of the participants tissue concentrations over 1 mmol/L were observed[81].

What all of this work has done is prove that both I3C and DIM have some form of biologic and therapeutic activity in humans. Whether or not this activity is the result of AHR stimulation remains to be seen. Moving forward, a clinical trial utilizing these phytochemicals to combat IBD is warranted. The concept of using natural chemicals to treat intestinal inflammation is not new. Curcumin, the biologically active derivative of the spice turmeric, has been found to modulate numerous inflammatory, oxidative, and tumorigenic pathways in various tissues, including the colorectum[82-85]. Numerous *in vitro* and *in vivo* studies have propelled curcumin into multiple IBD-related clinical trials. The first of these investigations was a very small pilot study which discovered that in IBD patients curcumin treatment lowered both erythrocyte sedimentation rates and CD Activity Index scores *vs* placebo[86]. More recently, Hanai *et al*[87] found in their RCT that curcumin performed well *vs* placebo for maintenance therapy of mild-moderate ulcerative colitis. While oral delivery proved to have therapeutic activity, curcumin enemas have also been employed in the treatment of distal colitis with similarly efficacious results[88]. In relevance to the paradigm of I3C/DIM acting *via* the aryl hydrocarbon receptor, curcumin as well as other dietary phytochemicals have been found to modulate AHR activity[89]. These trials of curcumin provide relevance to investigating the therapeutic potential of natural dietary chemicals such as I3C and DIM in the context of IBD.

CONCLUSION AND FUTURE DIRECTIONS

The complex and often dangerous treatment of IBD is a dilemma faced by gastroenterologists and colorectal surgeons alike. The intricate inflammatory milieu of IBD presents many avenues for potential targets to attenuate the inherent autoimmunity of the condition. In order to better understand the role that dietary ligands of the AHR play in attenuating IBD, potential avenues of study should focus on the aryl hydrocarbon receptor as it pertains to intestinal barrier function, immune regulation, and inflammation. To achieve this, portions of the IBD phenotype would be isolated and measured under AHR stimulation by a dietary agonist such as I3C or DIM. Also, the binding affinities of these compounds to the AHR in an array of gastrointestinal tissues must be established in order to localize the cell and tissue types where these agents will achieve the most robust response. Another important line of inquiry is to delineate the molecular cross-talk between AHR stimulation and the numerous other pathways previously identified as those that drive IBD. More globally, tissue-specific AHR activity should be investigated in order to ascertain off-target effects of treatment with a dietary AHR agonist. Finally, the most rigorous examination of these agents would be a randomized controlled trial of I3C or DIM for the treatment of IBD within the Phases set by the FDA. However, incorporation of dietary AHR ligands into human clinical studies demands a crystal clear picture put forth by exhaustive *in vitro* and *in vivo* murine models as to how these compounds exert their effects. Throughout these various investigations, it would remain important to delineate additional molecular pathways engaged by these dietary ligands in addition to the AHR in order to better understand their complete mechanisms of action.

Further investigation of how IBD-related cascades can be manipulated exogenously, perhaps *via* the AHR, could one day lead to diet-derived and well-tolerated regimens for those with ulcerative colitis and CD. That being said, it must be appreciated that the AHR is only one of many potential signaling cascades that may influence the IBD phenotype in humans. The characterization of a diet-derived agent, AHR agonist or not, that targets the hallmark imbalances in IBD without compromising host immune function would revolutionize current medical treatment modalities and save many from radical surgical intervention.

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REVIEW

Associating liver partition and portal vein ligation for staged hepatectomy: From technical evolution to oncological benefit

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Abstract

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel approach in liver surgery that allows for extensive resection of liver parenchyma by inducing a rapid hypertrophy of the future remnant liver. However, recent reports indicate that not all patients eligible for ALPPS will benefit from this procedure. Therefore, careful patient selection will be necessary to fully exploit possible benefits of ALPPS. Here, we provide a comprehensive overview of the technical evolution of ALPPS with a special emphasis on safety and oncologic efficacy. Furthermore, we review the contemporary literature regarding indication and benefits, but also limitations of ALPPS.

Key words: Liver tumor; Resection; Hepatectomy; Staged; Portal vein embolization; Future liver remnant; Liver hypertrophy; Liver failure; Morbidity; Mortality

Core tip: We provide a comprehensive overview of the technical evolution of Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) with a special emphasis on safety and oncologic efficacy. Furthermore, we review the contemporary literature regarding indication and benefits, but also limitations of ALPPS.

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INTRODUCTION

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), initially known as "*in situ* split", was first performed in September 2007, and until today, more than 600 procedures have been performed worldwide[1-4]. ALPPS has shown to have a promising efficacy regarding the induction of a rapid liver hypertrophy, thereby increasing the resectability of previously unresectable liver malignancy[5]. Furthermore, a sufficient volume increase can also be achieved by liver partition after unsuccessful portal vein embolization (PVE)[6,7].

Since the pioneering publication of Schnitzbauer *et al*[1] in 2012 with the first 25 cases in a multicentric study, considerable experiences have been obtained. A technical evolution of this novel procedure has been observed during the last four years. This was accompanied by a better understanding of the importance of patient selection, not only to minimize morbidity and mortality, but also to achieve the most oncological benefit[8].

This review was performed to report a current overview on the development of the ALPPS procedure. The review is based on personal experience from our institute as well as a detailed analysis of the international literature of the last four years.

LANDMARKS

The pioneer case and the first multicenter study

The pioneer case of ALPPS was performed in September 2007 by Dr. Schlitt at the University Hospital Regensburg, Germany in a young patient with hilar cholangiocarcinoma (CCA)[2]. During the exploration, the surgeon decided to perform a left hepaticojejunostomy to relief the cholestasis of the future liver remnant (FLR), which was considered too small for a one stage right trisectionectomy. To provide an access to the left bile duct, the liver was transected along the falciform ligament. The right portal vein was ligated to enhance the hypertrophy of the remnant liver. The patient recovered so well that a computer tomography (CT) was performed at the postoperative day (POD) 8, showing a 94% gain of the future remnant liver volume. Thus the second stage operation was successfully performed on POD 9.

This method was found to be reproducible and was soon adopted by many other surgeons around the world. In 2012, Dr. Schnitzbauer reviewed the first 25 cases of this novel concept of 2-staged hepatectomy in five German university hospitals between September 2007 and January 2011[1]. The indications were patients with either primary or secondary liver malignancy, who underwent a right trisectionectomy with a preoperative left lateral lobe to body weight ratio of less than 0.5%. After a median interval of 9 d (range, 5 to 28 d) from *in situ* splitting and right portal vein ligation (PVL), a CT volumetry was performed, indicating a median increase in volume of 74% (range: 21% to 192%). The procedure was then completed on the same or following day without drop-out. None of the patients developed irreversible liver failure after surgery. Sixteen patients (68%) experienced perioperative complications[1]. In-hospital mortality was 12%, the six-month median overall survival was 86%.

The above procedure was considered as a novel concept representing one of the most promising advances in oncological liver surgery by the editors of the Annals of Surgery[3]. The new strategy was found to elegantly address the most feared complication following major hepatectomy, postoperative liver failure (PHLF). The amount of hypertrophy induced by this procedure is unparalleled by any other techniques. Moreover, the rapid regenerative response offers additional significant advantages. For example, tumor progression is unlikely during this short period, and there are less adhesions during the second stage operation. Furthermore, this procedure thereby allows a faster recovery for the patient, with the possibility to resume chemotherapy earlier. The acronym "ALPPS" was proposed to describe this novel approach: "Associating Liver Partition and Portal vein ligation for Staged hepatectomy"[3].

ALPPS registry

The ALPPS registry was initiated by Dr. De Santibanes, Dr. Lang and Dr. Clavien in 2012 to achieve a more systematic exploration of this new surgical procedure[9]. It is an internet-based international registry for cases performed using the above method. The headquarter is located at the Department of Surgery, University Hospital Zurich, Switzerland. To establish the registry, an electronic case report form using the clinical trials software SECUTRIAL (Interactive System, Berlin, Germany) was presented to selected experts worldwide for approval (Scientific Committee of the ALPPS Registry). Any center willing to report patients in the registry is given access through the internet. The aim of the registry is to systematically and uniformly collect information from multiple centers worldwide[10]. Despite of a possible reporting bias, the registry enables surgeons to study a larger population to overcome shortcomings inherent to small case series reports. In 2014, the first report by the registry consisted of a total of 202 patients from 41 centers, provided complete data sets of procedures and 90 d survival status[10]. Till July 8th, 2015, 583 cases performed worldwide were enrolled into the registry.

The first consensus meeting on ALPPS

In February 2015, the first ALPPS consensus meeting was held by Dr. Oldhafer and Dr. van Gulik in Hamburg, Germany. Nearly all groups with vast experience in the ALPPS approach were invited to participate as faculty. The key points consisted of indications, preparations, techniques and outcomes. The two-day meeting provided the community a scientific base for future decision-making. The video and slides are available at the

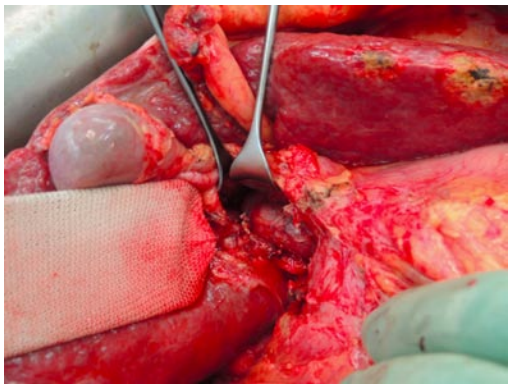

Figure 1 Exposure of the portal vein by lifting the common bile duct and right hepatic artery using a lid retractor. Here the right portal vein branches were transected.

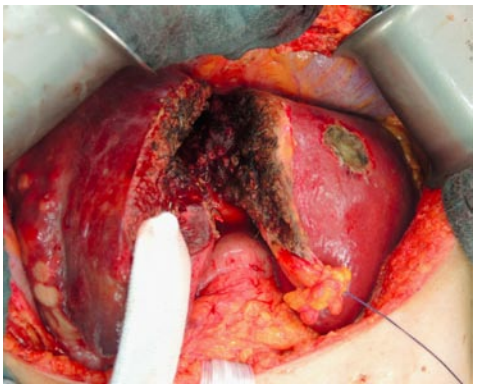

Figure 2 Liver parenchyma transection along the falciform ligament.

official website (www.alpps.com). The meeting not only summarized the development and the limitations of ALPPS, but also inspired the ideas and promoted the cooperation between international centers. The summary of the consensus meeting is yet waiting for publication.

EVOLUTION OF THE SURGICAL TECHNIQUE

Classical ALPPS

The first operation (right portal vein transection and in situ liver splitting): During the first operation, an exploration is carried out to exclude extrahepatic tumour dissemination. Resectability is determined if the remnant segments 2 and 3 have adequate inflow as well as outflow. Tumour involvement of segments 2 and 3 is no contraindication as long as it could be safely resected without tumour residual. The next step is the dissection of the hepatoduodenal ligament. A cholecystectomy is optional. In patients without tumour infiltration of the gall bladder, a cholecystectomy is usually carried out. After lifting the common bile duct and right hepatic artery by a lid retractor, the right portal vein and main portal vein is exposed (Figure 1). At this stage, the main right portal vein branch could be transected after suture ligation at the distal end and continuous suture, *e.g.*, with 5/0 Prolene at the proximal end. In patients with trifurcation of the portal vein with separate entry of the right anterior and posterior sectional branches, the anterior and posterior portal veins should be divided separately.

The umbilical portion of the left portal vein is exposed by dissecting the umbilical fissure. The portal branches of segment 4 are ligated and divided at its origin. The hepatic artery, the bile duct and the right hepatic vein are dissected and identified with rubber bands. Subsequently, transection of the liver parenchyma along the falciform ligament is performed (Figure 2). The falciform ligament could also be kept in the future remnant side for re-fixation of the left lateral lobe at the diaphragmatic dome if technically possible. Intraoperative ultrasound should be performed to confirm the absence of right portal flow at the end of the operation. Silicone sheeting or drainage could be applied to separate the two parts of the liver and the surrounding organs in order to prevent strong adhesion among the above mentioned structures. Closed drainage is placed in the liver hilum. An intraabdominal swab should be taken for microbiological analysis at the end of the operation.

Postoperative management after the first operation: The patient is usually transferred to the intermediate care unit and discharged to the normal ward according to the postoperative course. Prophylactic antibiotics are given as single shot intraoperatively. If any bacteria are isolated from the intraoperative swab, the antibiotics should be given until the second operation. In patients with stented bile duct, antibiotics and antimycotics are administered during the whole postoperative phase.

One week after the first operation, depending on the logistics, an abdominal CT scan (native phase) is performed for re-evaluation of the liver volume (Figure 3). When the future liver remnant/total liver volume ratio (FLR/TLV) is more than 30%, the second operation, *i.e.*, right trisectionectomy, could be carried out on the next available operation day. If the FLR/TLV is less than 30%, a repeat CT scan would be carried out in an interval of seven days, and the second operation being postponed accordingly.

The second operation (right trisectionectomy): After relaparotomy, the silicone sheeting or drainage is removed. An intraabdominal swab is taken for microbiological analysis for orientated antibiotic therapy if indicated. The hilar structures are easily identified by the rubber bands, and the right hepatic artery, right hepatic ducts (or the left hepatic duct when extrahepatic bile duct should be resected) and the right and middle hepatic veins are transected (Figure 4). Liver segment 1 could be preserved in patients with non-perihilar CCA without tumour involvement.

After removal of the transected liver, a lymphadenectomy could be conducted at this stage. Biliodi-

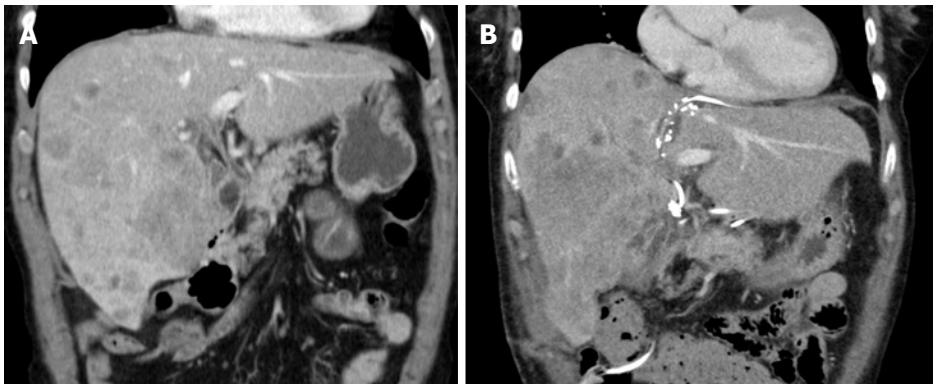

Figure 3 Computed tomography scan before associating liver partition and portal vein ligation for staged hepatectomy in a patient with intrahepatic cholangiocarcinoma and on day 10 after liver partition. A: The future liver remnant consisted of segment 2 and 3 with volume of 347 mL (23% of the standardized total liver volume); B: Showing the hypertrophy of the segment 2 and 3 with volume of 610 mL (41% of the standardized total liver volume).

gestive anastomosis is followed when resection of the extrahepatic bile duct is indicated in patients with perihilar CCA. The postoperative treatment after the second operation is the same as for the patients undergoing any major hepatectomy.

ALPPS variations

Improvement of patient safety by different approaches of *in situ* liver splitting: One of the major differences between traditional PVE and ALPPS in liver partition is that the latter, has a liver splitting along the transection line of the FLR. To simplify the first operation, three methods were developed to achieve liver partition without physically splitting the liver: Tourniquet compression, radiofrequency ablation (RFA) or microwave ablation.

The use of a tourniquet to ensure parenchymal compression and intrahepatic collateral occlusion along the future transection line was first described by Robles *et al*[11]. He used a 1 cm deep groove to place and tighten a 3 mm Vicryl tourniquet, after which ultrasound confirmed occlusion of the vessels between the two parts. This technique was termed Associating Liver Tourniquet and Portal Ligation for Stage Hepatectomy (ALTPS)[11]. In 22 patients undergoing ALTPS procedure, FLR at 7 d increased by a median of 61% (range: 33% to 189%).

Jiao *et al*[12] used in-line radio frequency (Habib Sealer, LH4X, Rita) to create a virtual liver partition in combination with portal vein ligation. The RFA produce a precise avascular area up to 1 cm wide. In the initial report of five patients, Radiofrequency-Assisted Liver Partition with Portal Vein Ligation could significantly increase the FLR by a median of 62.3% (range: 53.1% to 95.4%) after 21.8 ± 9.4 d.

Similar to RFA, Cillo *et al*[13] used microwave ablation on segment 4 in the first stage operation to complete the liver partition. The authors reported that this technique could minimize the risk of neoplastic left lobe invasion and limit portoportal shunts. They observed a 78% FLR growth, performing the second stage after 10 d.

All three techniques could be performed laparoscopically[13,14]. However, superiority of these procedures to the classic ALPPS approach regarding safety has not been confirmed apart from case reports.

Improvement of patient safety by partial ALPPS: To avoid bile leak from incidental transection of the segment 4 bile duct and to avoid segment 4 ischemia due to transection of the segment 4 artery or middle hepatic vein occlusion, non-total parenchymal transection was carried out systematically in the author's institute (Figure 5) and selectively in other institutes[15-17].

The group of De Santibanes identified total parenchymal transection as an independent predictor of postoperative complications during ALPPS. They found that most complications in patients with total parenchymal transection were surgical complications following the first stage. Avoiding total parenchymal transection might be related to the better outcomes in terms of liver-related complication in these patients[15]. The Zurich group observed in an experimental model that partial (75%-80%) transection of the liver triggered a similar degree of hypertrophy of the FLR compared to complete transection. On the basis of experimental observation and clinical implications, they switched from a complete to a well-defined partial transection (> 50% of the transection surface) in 2013[16]. In partial-ALPPS, a median hypertrophy of 60% was observed, compared to 61% after classic ALPPS approach, within a median time of 7 d. To facilitate communication among clinicians, Petrowsky *et al*[16] proposed to standardize the name of ALPPS with non-total parenchymal transection at stage 1 operation as "partial-ALPPS".

Improvement of patient safety by selecting different planes of liver splitting: Various modifications of ALPPS that alter the specific segments comprising the FLR have been described, including right hepatectomy ALPPS (segment 2-4 as FLR), left hepatectomy ALPPS (segment 5-8 as FLR), central hepatectomy ALPPS (segment 4, 5 and 8 as FLR)[18]. Liver partition in different extent of hepatectomy is aimed to increase the FLR, thereby avoiding post-hepatectomy liver failure.

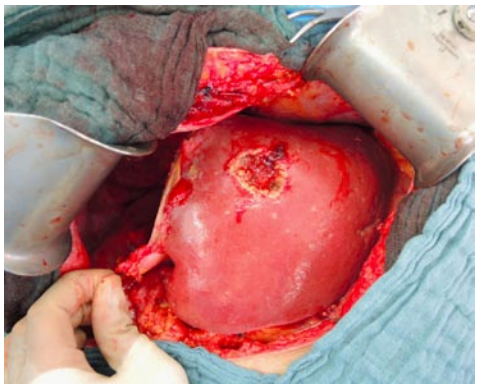

Figure 4 Completion of right trisectionectomy.

Figure 5 Partial associating liver partition and portal vein ligation for staged hepatectomy. The non-total liver parenchymal transection is indicated by the clips, left along the liver split area in a computed tomography scan performed on day 10 after the liver partition.

Recently, the concept of a monosegmental ALPPS has been addressed[19,20]. The authors proposed to name such procedures, leaving only a one-segmental FLR in the context of ALPPS, according to the remnant liver segment using third-order segment terms, for example "Segment 2 ALPPS", "Segment 3 ALPPS", "Segment 4 ALPPS" and "Segment 6 ALPPS". Among 333 patients, 12 underwent monosegment ALPPS hepatectomies in six centers, all for extensive bilobar colorectal liver metastases (CRLM). Four patients experienced liver failure, but all recovered. There was no mortality. Complications higher than Dindo-Clavien IIIa occurred in four patients with no long-term sequelae. The authors concluded that extreme liver resections for CRLM based on a single segment liver remnant are feasible and safe using the novel monosegmental ALPPS technique, a new surgical tool in the management of extensive CRLM[20].

Improvement of patient safety by imaging study and liver function test: The estimation of the postoperative liver function is mainly based on the remaining liver volume and liver function blood tests. Volumetric measurement of the intended FLR by CT or MRT is routinely carried out prior to the second stage operation. A FLR/TLV ratio exceeding 30% in patients with normal liver or higher than 40% in patients with parenchymal disease is preferred[8]. In the author's institute, a FLR to body weight ratio over 0.6% in patients with normal liver, or more than 0.8% in patients with preexisting parenchymal damage is used as a threshold, additionally to FLR/TLV ratio for performing the second stage operation. Otherwise, the operation is postponed for another week or even cancelled.

Tanaka *et al*[21] performed technetium-99 m galactosyl human serum albumin (99mTc-GSA) scintigraphy single-photon emission computed tomography (SPECT)/CT with 3-dimensional volume-rendering fused images preoperatively and at 7 d after the first surgical procedure. They found that the increase in functional FLR calculated at 7 d after the liver partition by ALPPS was similar to functional FLR at 3 wk after the liver partition by PVE alone (52.1% *vs* 59.2%). In the group of De Santibanes, hepatobiliary scintigraphy was performed in patients with borderline sufficient FLR volume after first stage operation, or when there were doubts regarding functional sufficiency. The regional FLR function was determined by quantifying 99mTc-dimethyl iminodiacetic acid uptake during 10 min (liver uptake phase) after intravenous injection[15]. They found this method to be helpful to decide the best timing of the second stage operation in four patients of this series. In those four patients with delayed hypertrophy, an increase of the FLR function over time was observed, although there was no significant volume increase. These findings suggested that in some patients, the recommended waiting time until second stage operation may be shorter than indicated by volumetric parameters alone.

Lau *et al*[22] described an intraoperative indocyanine green (ICG) clearance assessment to estimate the function of the future liver remnant. After complete parenchymal transection, Bulldog vascular clamps were applied to occlude the right hepatic artery and the portal vein, and ICG clearance was carried out. They found the plasma disappearance rate was 7.9%/min and with a 15 min residual (R15) amount of 30.6% during the first stage operation. During the second stage operation 14 d later, the plasma disappearance rate increased to 12.1%/min and an R15 of 16.3% was observed. They concluded that intraoperative ICG clearance allows for the direct assessment of the actual future liver remnant function. However, since no safe cut-off levels were suggested, future validation studies would be necessary.

Improvement of patient safety by other modifications: In the International ALPPS Registry, 35% of centers did not use any coverage on the raw surface after liver transection, 26% used a plastic sheet, 26% TachoSil, and 16% of centers still used a plastic bag (of a total 192 patients). The use of a plastic bag or plastic sheeting to cover the cut area and prevent adhesions is not an essential component of ALPPS[10,23]. In the author's institute, Penrose drainages are routinely used to separate the raw surface after liver transection as well as to avoid collections in case of a bile leak (Figure

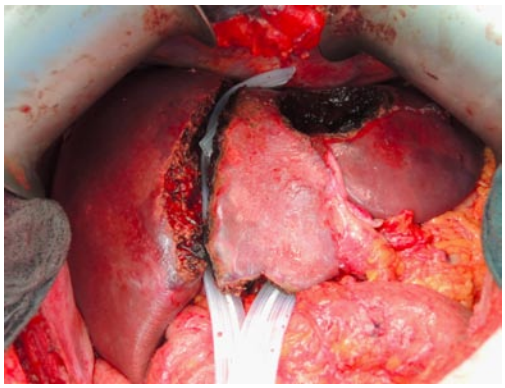

Figure 6 The future liver remnant was separated by two Penrose drains from the right liver lobe in a patient with bilobar colorectal liver metastases during the first stage operation. Three lesions at the left hemi-liver were resected.

6). However, the most important aspect to avoid bile leak and consecutive infection is not to perform *in situ* splitting in patients with dilated bile duct or cholangitis[24].

Improvement of surgical approach under oncological aspects: The classic approach of ALPPS includes full mobilization of the liver and dissection of the liver hilum[1]. Aloia *et al*[25] criticized that ALPPS was supposed to be an "all-touch" technique that would reduce the oncological efficacy to treat liver malignancy. This comment was addressed by two technique refinements: "anterior approach" and "hybrid ALPPS", to improve the efficacy of surgical oncology as well as to reduce the adhesion at the second stage of the operation[26,27]. An analysis of the registry data found that in 37% (66/175) of patients that underwent transection during the first stage of ALPPS, an anterior approach was applied However, caution has to been taken while applying the anterior approach due to the inability to achieve optimal vascular control during this technically complex procedure[23]. "Hybrid ALPPS" was developed in authors' institute to treat advanced gall bladder carcinoma in two patients[27]. *In situ* split of the left lateral liver lobe was combined with postoperative right-PVE as a hybrid procedure. The authors concluded that hybrid ALPPS provided rapid hypertrophy of the FLR for a right trisectionectomy in case of tumor infiltration of the RPV or biliary bifurcation, while allowing to adhere to the non-touch principles. A similar procedure was performed by Robles *et al*[28] by using a tourniquet-technique and sequential PVE to achieve liver partition in a patient with perihilar tumor burden.

Despite lacking sufficient data for a statistical analysis of disease-free or overall survival, non-touch technique is possible, and should therefore be applied for the resection of hepatic malignancy in ALPPS. Furthermore, hybrid ALPPS combining non-physical liver split and sequential PVE could be employed to reduce the rate of bile leak in patients with dilated bile duct.

Summary: Current results on safety and efficacy

Among the preliminary reports, ALPPS showed a high morbidity (59% to 68%) and mortality (12% to 12.8%)[1,29]. In the first report of the international ALPPS registry, 90 d mortality was 19/202 (9%). Severe complications including mortalities (Clavien-Dindo $\geqslant$ IIIb) occurred in 27% of patients[10]. In experienced centers, including the authors' institute, a much lower rate of major morbidity (13.6% to 14%) and mortality (0% to 6.6%) have been reported[15,17]. As is the case with many new techniques, there will be an inherent learning curve, and lower rates of morbidity and mortality will be observed, along with further technical improvements and standardization of the ALPPS procedure.

ALPPS has been found to result in faster FLR growth in comparison with PVE alone[30]. In a recent systemic review with a total of 295 patients, the FLR hypertrophy was 84%, with a confidence interval (CI) of 78%-91%[31]. This high efficacy in inducing FLR hypertrophy was confirmed universally by the published case series and the international ALPPS registry. Moreover, in contrast to a failure rate of 20%-30% after PVE due to inadequate hypertrophy or disease progression[32] (97%CI: 94%-99%) of all patients underwent stage one operation of ALPPS completed the procedure. Furthermore, histological complete resection (R0) was achieved in (91%CI: 87%-94%) of these patients[31].

BENEFITS OF ALPPS

To decrease the risk of grade C PHLF

Similar to PVE and 2-stage hepatectomy, the aim of ALPPS is to decrease the risk of grade C PHLF after major liver resection in otherwise too small FLR. Beside a more rapid FLR hypertrophy induced by ALPPS, this approach can also be used in cases of failed portal vein occlusion (PVO) or an anticipated extremely small FLR[33]. For an early prediction whether a patient will obtain a sufficient FLR, the concept of kinetic growth rate (KGR) or degree of hypertrophy has been introduced[34]. Growth rate was shown to be a predictor of PHLF. Patients with low KGRs are unlikely to benefit from PVO only and could thus be candidates for ALPPS. Another group of patients who might be especially suitable for ALPPS are those with "extremely low" FLRs, who, given the boundaries of growth achieved with PVO, are unlikely to reach a FLR volume deemed necessary for resection.

In the first report of the international ALPPS registry, a median KGR of 2% FLR or 30 mL FLR per day have been observed[10]. The second stage operations were performed at 10 d (interquartile ranges, 8 to 15) after the liver partition. Only 9% (16/202) of patients experienced liver failure according to the 50-50 criteria[35]. Within them PHLF was regarded as the main cause of mortality in 8 patients[10].

To provide more chance of R0 resection

Resection of a large tumor load in the liver may result in an excessive removal of hepatic parenchyma leading to PHLF and associated complications[36]. ALPPS not only allows for resection in patients with very small anticipated FLR that would not be possible with conventional techniques, but also enables surgeons to proceed with multi-staged resections in a short interval before a substantial tumor progression[17]. PVO is burdened with a considerable failure rate, and only about two thirds of patients will eventually be eligible for a subsequent curative resection due to tumor progression during the waiting interval between the two stages, or failure of the FLR to grow[37-39]. A retrospective multicenter study was carried out to compare the rate of complete tumor resection after ALPPS *vs* conventional two-stage approaches[5]. Eighty-three percent (40/48) of ALPPS patients achieved complete resection compared with 66% (55/83) in the PVO group. Seventeen percent (8/48) of ALPPS patients failed to achieve the primary endpoint due to mortality (n = 7) or incomplete resection (R1, n = 1). The author concluded that ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumours[5].

Evidences of oncological benefits compared to other two-stage liver resection when R0 achieved

Colorectal liver metastasis: Colorectal liver metastasis (CRLM) is the most common indication for ALPPS as indicated in the first report of the international ALPPS registry[10]. To compare the benefits of ALPPS to conventional 2-stage hepatectomy by PVO, evaluation of resection rate, postoperative mortality, as well as disease-free survival (DFS) or/and overall survival (OS) are necessary.

Resection rate, the resection rate for CRLM by traditional two-stage liver resection, either PVE or PVL, was reported to be 52%-80%[40-42]. Non-resectability was mainly due to progression of metastasis[40,41]. ALPPS avoided this type of drop-out by effectively inducing a sufficient liver hypertrophy within 6 to 15 d[33]. A retrospective study carried out by Tanaka *et al*[21] found that at first hepatectomy, Ki67 expression was evident in 28.2% ± 42.7% of tumor cells in the ALPPS group and 51.7% ± 35.6% in the conventional 2-stage group (P = 0.09). However, at second hepatectomy, expression of Ki67 was detected in 20.5% ± 24.7% and 54.5% ± 26.9% of patients in the ALPPS and in the conventional 2-stage group respectively (P = 0.01)[21]. Therefore, the reduced expression of Ki67 in tumors resected during the second stage in the ALPPS group may indicate an oncologic benefit from ALPPS, as the short period between the two interventions helps to avoid the risk of tumor progression. Of note, in a recent review on the treatment of CRLM, the resection rate by ALPPS was reported to be about 97.1%[33].

Postoperative mortality, PVO is a well-established, state of art procedure for patients with insufficient FLR whereas ALPPS is still among the phase of exploration. Therefore, a comparison of these two procedures should be done when the learning curve of ALPPS is overcome. According to the first report of the international registry data, mortality of ALPPS for CRLM is 8%, and 5.1% in CRLM- patients younger than 60 years of age[10]. In experienced centers, including the authors' institute, nil mortality after ALPPS for CRLM has been reported[17].

DFS/OS, the 1 and 2-year DFS for patients undergoing ALPPS for CRLM from the ALPPS registry is 59% and 41% respectively[10]. Overall survival is 86% at six months postoperatively, dropping to 59% at 2 years[10]. Similar to the high recurrence rate despite a survival advantage observed in patients with advanced CRLM (> 4 metastases) undergoing traditional resection[43-45], high recurrence rates have also been reported in patients undergoing ALPPS[5,33,46]. In some case series, the recurrence of CRLM after ALPPS was quite early. For example, in the 7 patients reported by Oldhafer *et al*[41] recurrence was observed after 3, 6, 7, 8, 11, 13 and 13 morespectively following ALPPS procedure[46]. However, to date there is no direct comparison of DFS in patients undergoing PVE or ALPPS. Of note, two RCTs investigating ALPPS *vs* conventional two-stage hepatectomies for CRLM were recently launched (clinicaltrials.gov-identifier NCT01775267 and NCT01842971).

To get the best benefit of ALPPS, Hernandez-Alejandro *et al*[17] proposed selecting the group of patients with biologically favorable CRLM. The inclusion criteria for ALPPS in their group were (1) no evidence of extrahepatic disease; (2) good functional capacity Eastern Cooperative Oncology Group performance status grade 0 or 1 and (3) complete or partial response to systemic chemotherapy after 6 cycles. In the 14 patients reported in this series, recurrence developed in 2 patients after a median follow-up of 9.4 mo. Overall survival at the time of follow-up was 100%[17].

Hepatocellular carcinoma: An aggressive surgical approach in patients with locally advanced hepatocellular carcinoma (HCC) has been reported to yield an acceptable long term outcome that is significantly better than that of patients with unresectable HCC treated with Sorafenib[47-49]. In this view, the ALPPS procedure could yield a better outcome and further expand the number of patients undergoing radical major liver resection for HCC in liver cirrhosis that were previously considered non-resectable, compared to non-surgical treatment[49].

Chan *et al*[50] reported the largest case series with 17 patients having HCC on the basis of chronic hepatitis B infection. Selection criteria included Child-Pugh A liver cirrhosis, indocyanine green retention rate < 20% at 15 min, FLR/sTLV (standardized total liver volume) < 40%, and platelet count $\geqslant 100 \times 10^9$/L. After a median of 6 d, a hypertrophy of the left FLR by 48.7% with a FLR/sTLV ratio of 38.5% (preoperative FLR/sTLV 24.2%) was noted. All patients proceeded to second-stage hepatectomy. Major surgical complications

Table 1 Recent published studies on associating liver partition and portal vein ligation for staged hepatectomy (only case series with more than 10 patients are listed)

Ref.	Date (yr)	Total cases (center involved)	Interval[1] (d)	FLR hypertrophy (median)	Completion stage 2	R0 resection	PHLF	Morbidity[2]	In-hospital mortality	Follow-up (median, months)	Recurrence	Overall survival
Schnitzbauer *et al*[1]	2012	25 (5)	9	74%	88%	96%	-	Overall: 64% ≥ III: 40%	12%	6	20%	86% at 6 m
Torres *et al*[29]	2013	39 (9)	14	83%	94.80%	100%	-	Overall: 59%	12.80%	-	-	-
Schadde *et al*[10]	2014	202 (56)	7	80%	98%	91%	-	≥ III: 40%	9%	9	40% at 12 m	73% at 12 m
Truant *et al*[4]	2015	62 (9)	8	48.60%	95.20%	-	25.8%	≥ III: 40.3%	12.90%	-	-	-
Robles *et al*[11]	2014	22 (1)	7	61%	100%	100%	22.7%	Overall: 64%	9%	6	5%	91% at 6 m
Nadalin *et al*[53]	2014	15 (1)	10	87.20%	100%	87%	-	Overall: 67%	28.70%	17	29%	67% at 17 m
Alvarez *et al*[15]	2015	30 (1)	6	89.70%	93%	93%	14%	Overall: 53% ≥ III: 43%	6.60%	17	22% at 12 m	67% at 12 m
Petrowsky *et al*[16]	2015	24 (1)	7	61%	100%	-	-	≥ IIIb: 33%	16.70%	-	-	-
Hernandez-Alejandro *et al*[17]	2015	14 (1)	7	93%	100%	86%	29%	Overall: 36% ≥ IIIb: 14%	0%	9	14%	100% at 9 m
Tanaka *et al*[21]	2015	11 (1)	7	54%	100%	100% (R0/R1)	18%	Overall: 46% ≥ III: 27%	9%	-	-	-
Chan *et al*[50]	2015	17 (1)	6	48.70%	100%	-	-	≥ III: 11.8%	5.90%	-	-	-

[1]Interval: Median days from the stage 1 to CT scan; [2]Morbidity: Clavien-Dindo classification was applied; FLR: Future liver remnant; PHLF: Post-hepatectomy liver failure according to 50-50 criteria (35).

(Clavien–Dindo grade Ⅲ or above) occurred in 11.8% of patients (n = 2), and in-hospital mortality rate was 5.9% (n = 1). No follow-up data were reported. Chan *et al*[50] concluded that ALPPS could also promote liver hypertrophy in patients with chronic liver diseases, with a similar safety profile compared to other established series. Another case series by Vennarecci *et al*[51] suggested that the ALPPS procedure could be very useful in a subgroup of patients with HCC and venous thrombosis. In their series, portal hypertension or liver cirrhosis more than Child-Pugh A was considered as a contraindication[49,52]. However, data regarding the long term outcome of ALPPS in patients with HCC are still very limited, and further reports on the use of the ALPPS in this setting are expected[49].

Perihilar cholangicarcinoma: Although the first case of ALPPS was successfully performed in a patient with hilar CCA, high rates of major postoperative complication and mortality were found in this population after ALPPS[10]. Li *et al*[24] first questioned the benefit of ALPPS in treatment of perihilar CCA. The authors found that patients undergoing ALPPS for perihilar CCA were at a high risk of intraabdominal infection and bacteraemia as the diseased liver and stented biliary system were not removed between the two operations. Two of three patients with hilar CCA received ERCP and a stent before referral. Both of them had postoperative intraabdominal bacterial infections, and eradication of bacteria failed. The deaths of those two patients account for the 22% mortality observed in the cohort of 9 ALPPS patients from this series. Thus, the authors considered the combination of a stented biliary system and cholestatic liver with low potential of regeneration as a contraindication for ALPPS. This opinion has been shared with the HPB community, in which caution has aroused against the use of ALPPS for hilar tumors[8,53].

Other indications: The other indications of ALPPS comprised of intrahepatic cholangiocarcinoma, gallbladder cancer, neuroendocrine tumors and other liver metastases. Because of the limited number of cases, no high quality evidence on the oncological benefit other than increased resectability is available[5,8,10].

Summary - current status of oncological benefit by patient selection

The ALPPS procedure was developed to decrease the morbidity and mortality related to PHLF, to avoid drop-out in patients undergoing conventional two-stage liver resection and to achieve histopathological complete tumor resections (R0) in otherwise non-resectable patients. Although contemporary reports have highlighted the importance of patient selection in avoiding perioperative morbidity and mortality, suitable indications for the ALPPS approach remain to be determined[17]. Till date, there is no clear evidence for the oncological benefit of ALPPS in treatment of CRLM over other procedures as long as R0 resection is achieved. For patients with hilar CCA, ALPPS should be considered with extreme caution due to the aforementioned safety issue. For other indications, there are no ongoing studies comparing ALPPS with non-surgical treatment in term of overall survival.

CONCLUSION

ALPPS is a pertinent alternative approach to the conventional two-stage liver resection after PVE or PVL. In selected cases, it could even increase the resectability of

previously unresectable liver malignancy by promising rapid hypertrophy of the FLR (Table 1). With the evolution of surgical technique, proper patient selection for ALPPS has been found to be the key element to achieve the best oncological results.

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REVIEW

Laparoscopic treatment of complicated colonic diverticular disease: A review

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Abstract

Up to 10% of acute colonic diverticulitis may necessitate a surgical intervention. Although associated with high morbidity and mortality rates, Hartmann's procedure (HP) has been considered for many years to be the gold standard for the treatment of generalized peritonitis. To reduce the burden of surgery in these situations and as driven by the accumulated experience in colorectal and minimally-invasive surgery, laparoscopy has been increasingly adopted in the management of abdominal emergencies. Multiple case series and retrospective comparative studies confirmed that with experienced hands, the laparoscopic approach provided better outcomes than the open surgery. This technique applies to all interventions related to complicated diverticular disease, such as HP, sigmoid resection with primary anastomosis (RPA) and reversal of HP. The laparoscopic approach also provided new therapeutic possibilities with the emergence of the laparoscopic lavage drainage (LLD), particularly interesting in the context of purulent peritonitis of diverticular origin. At this stage, however, most of our knowledge in these fields relies on studies of low-level evidence. More than ever, well-built large randomized controlled trials are necessary to answer present interrogations such as the exact place of LLD or the most appropriate sigmoid resection procedure (laparoscopic HP or RPA), as well as to confirm the advantages of laparoscopy in chronic complications of diverticulitis or HP reversal.

Key words: Diverticulitis; Laparoscopy; Emergent; Lavage; Drainage; Peritonitis; Purulent; Stercoral; Complicated; Perforation

Core tip: With the aim to improve surgery outcomes, laparoscopy has been increasingly performed in complicated diverticulitis. Despite the absence of solid proofs and under the condition of large expertise, it is an appropriate approach for the surgical management of both elective and emergent situations related to complicated diverticulitis. Moreover, the laparoscopic

lavage drainage represents a previously unknown modality of treatment of purulent peritonitis. Validation of these data by large-scale randomized controlled trials is mandatory to build future therapeutic algorithms on which general surgeons can rely in their daily practice.

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INTRODUCTION

Colonic diverticulosis is mainly an acquired disease with an age-dependent prevalence, ranging from 5% at 30 years to 60% at 80 years[1]. Acute diverticulitis occurs in 4%-25% of cases[2,3] of which 8%-35% present with perforated disease[4]. Generalized peritonitis from colonic diverticulitis (graded as Hinchey 3 and 4[5]) is a life-threatening situation requiring immediate surgical intervention[2,6,7]. Designated by Hartmann's procedure (HP), resection of the affected diverticular colon segment, closure of the rectal stump and formation of an end colostomy has been considered the treatment of choice for many years[8-13]. However, morbidity and mortality rates of 24% and 19% as well as high risk of permanent stoma[14-18] have pushed general surgeons to look for surgical alternatives with better outcomes.

In colorectal surgery, large-scale prospective studies have confirmed the superiority of laparoscopy over the open approach in terms of lowered postoperative morbidities, reduced postoperative pain, improved respiratory function and shortened hospital stay[19-22]. Based on that, laparoscopy has been considered as the preferred approach for the elective treatment of diverticular disease[1,23,24]. In 2006, however, the European Association of Endoscopic Surgeons[25] and the American Society of Colon and Rectal Surgeons[23] expressed their opposition to the routine usage of laparoscopy in the acute setting. Due to insufficient data confirming validity of the presumed advantages in emergent surgery, the laparoscopic approach was estimated not to be appropriate for the management of complicated perforated diverticulitis.

Since then, worldwide increasing experience in colorectal and minimally invasive surgery has broadened applicability of laparoscopy to abdominal emergencies, hypothesizing that the advantages observed in the elective setting can be translatable to acute situations[26]. Several recent studies claim the benefits of laparoscopy over the open approach when performed by experienced surgeons in selected patients with perforated diverticulitis[25,27-31].

Virtually all procedures for complicated diverticular disease have been achieved under laparoscopy. Since its first description almost twenty years ago[32], the laparoscopic reversal of HP has been progressively performed promising reduced morbidity and mortality[33,34]. Similarly, sigmoid resection and primary anastomosis (RPA) with or without derivating loop ileostomy (DI) has been repeatedly performed in diverticular peritonitis[35]. Furthermore, during the last ten years, we have been observing the emergence of the laparoscopic lavage drainage (LLD), a previously unknown technique for the management of purulent peritonitis[36,37].

In parallel, laparoscopy is being increasingly performed for elective surgeries related to complicated diverticulitis. The most common examples are the reversal of HP and the sigmoidectomy for chronic complications (such as fistula, inflammatory stenosis and phlegmon).

Nonetheless, despite worldwide application, laparoscopic surgery for complicated diverticulitis mostly relies on empirical experience. A precise consensus based on level 1 evidenced data has not yet been established to determine the exact status of laparoscopic techniques in this field.

This review aims to provide a critical appraisal of currently available data concerning the laparoscopic approach in both emergent and elective settings of complicated diverticulitis. We will focus on ongoing randomized controlled studies (RCTs) that are expected to provide clear practical recommendations for emerging techniques. Perspectives for future research will also be suggested to assist tomorrow's surgeons in their decision making when addressing these situations.

LITERATURE RESEARCH

A bibliographic search was performed in PubMed and Cochrane library for case series and comparative studies published from January 1995 to July 2015. RCTs were recorded from the official web site www.clinicaltrial.gov. The following medical subject heading (MeSH) terms were searched for titles and abstracts in the English or French languages: Diverticulitis; acute; emergent; laparoscopy; lavage; drainage; peritonitis; purulent; stercoral; fecal; complicated; perforation; Hinchey; Hartmann. The "related articles" function was used to enlarge the search. A manual search of the reference lists was also performed to identify additional relevant studies. The first two authors separately classified the selected articles into elective, emergent and future situations. Subsequently, relevant articles were discussed and discrepancies of findings were resolved with agreement of both authors. Overlapping publications were identified and only the most recent paper was selected for the review.

DISCUSSION

Emergent surgery

Laparoscopic surgery for failed medical treatment: Diverticulitis complicated by pericolic and/or

pelvis abscess (Hinchey 1 and 2) are most often managed conservatively with intravenous antibiotics more or less combined to percutaneous drainage[1,38,39]. In case of failure, an emergent surgery may be indicated for sepsis control and resection of the diseased colon. Available data are, however, limited to a single-institutional retrospective series[40] which has been recently updated[41]. When comparing outcomes of the laparoscopic approach (24 patients) to those of laparotomy (18 patients), laparoscopy was associated with a 4-fold decrease in overall complication rate, faster bowel movement, shorter hospital stay and comparable rate of RPA despite a longer operative time. In the laproscopy group, RPA could be achieved in all but one patient and conversion to open surgery occurred in 2 patients. In regard to these encouraging results and motivated by the scarcity of data on this specific aspect of colonic diverticular surgery, RCTs are needed to confirm the suggested benefits of laparoscopy in this group of patients.

LLD: First described in 1996[42,43], the procedure consists of a laparoscopic exploration of the abdominal cavity followed by lavage with heated saline serum and drainage of the diseased colon for the next several days. The need for extensive adhesiolysis in search of the colonic perforation remains controversial[44]. In a prospective multi-institutional study[45], 92 patients underwent laparoscopic peritoneal lavage for Hinchey 2 or 3 diverticulitis. All patients but two had complete clinical resolution. One patient required subsequent colonic resection whereas the other required percutaneous drainage for pelvic abscess. Mortality and morbidity rates were 3% and 4%, respectively. After a median follow-up period of 36 mo, only two patients were readmitted with acute diverticulitis successfully treated with antibiotics. The authors concluded that LLD can be a reasonable alternative to HP for Hinchey 3 perforated diverticulitis. Another prospective study[46] found that LLD offers the advantages of shorter operative time and hospital stay, reduced estimated blood loss and better postoperative outcomes compared with laparoscopic HP. Including all stages of complicated diverticulitis (mainly Hinchey 3), only 2.1% of patients undergoing LLD were converted to open HP, and 6.4% were reoperated for uncontrolled sepsis. Almost half of the patients who received LLD underwent subsequent sigmoid resection, but the reasons were not mentioned. Such favorable results (low morbidity and mortality rates, high chance of sepsis control, avoidance of stoma and bowel salvage) have been constantly reported in case series and systematic reviews[37,44,47-53]. Soon after and despite robust evidence, LLD was cited in national and international scientific committees' reports as a potential therapeutic option for purulent peritonitis of diverticular origin[1,54,55].

Preliminary results of the DILALA prospective randomized trial have been recently published after complete accrual[56]. Although the primary endpoint (the number of reinterventions) could not be assessed because of incomplete follow-up, this trial showed a higher than usual mortality rate of 7.7% after LLD. This result was comparable to that found in the open HP group. Both procedures provided comparable complication profiles, but LLD resulted in shorter operative time, shorter time in the recovery unit and shorter hospital stay. Recently, the enthusiasm toward LLD has been hindered by the results of the LOLA group within the Ladies trial confronting LLD to sigmoidectomy in Hinchey 3 diverticulitis[57]. This multicenter RCT has been prematurely terminated because of significantly increased in-hospital major morbidity or mortality in the lavage group compared with sigmoidectomy. Surgical reinterventions accounted for most of these adverse events. However, mortality rate was unaltered (9% in the LLD group *vs* 14% in the sigmoidectomy group), and sepsis was successfully controlled in 76% of cases (*vs* 90% in the sigmoidectomy group). In the long-term, there was no difference in the incidence of major morbidity or death between the two groups (37% *vs* 40% in the LLD and sigmoidectomy groups, respectively). LLD allowed salvage of the sigmoid in almost half of the cases and avoided stoma formation in three-quarters of the patients. In contrast to the resection procedure, LLD allows bowel salvage and avoids stoma but requires a multi-step careful surveillance and timely management. The authors conclude that peritoneal lavage cannot be favored over sigmoid resection as a routine intervention for purulent peritonitis of diverticular origin. Instead, it may be an alternative approach to sigmoidectomy with similar length of stay and long-term outcome in select patients. From this standpoint, in the Dutch Collaborative study group[58] as well as in another study[59], age older than 80 years, American Society of Anesthesiologists grade 3 or above, multiple comorbidities, immunosuppression, high C reactive protein and/or high Mannheim peritonitis index were associated with increased risk of failure after LDD. Currently, there are two ongoing RCTs comparing LLD to sigmoidectomy[60,61]. The results are eagerly awaited to provide further evidence about expected outcomes after LLD and to identify criteria for patients who would preferably benefit from each technique.

In contrast to the enthusiasm for LLD in purulent peritonitis, this approach is not commonly admitted for Hinchey 4 diverticulitis. The presence of a visible perforation in the colon has always represented the limit of application of the technique[42,62]. In his prospective study, Myers *et al*[45] stated that stercoral peritonitis constitutes an indication for conversion to open HP. Conversely, Liang *et al*[46] reported very encouraging results despite the inclusion of more than 10% of Hinchey 4 peritonitis in his prospective study. Many authors agree that LLD cannot be accepted unless perforation of the colon is formally ruled out[45,53]. Conversely, others propose suturing the colonic hole if stercoral peritonitis is not evident[59]. The diagnosis of stercoral peritonitis on explorative laparoscopy

excluded patients from both of the available randomized controlled trials[56,57]. This condition is presumed to significantly modify the results observed with purulent peritonitis. In fact, the high reintervention rate found in the Ladies trial is mostly attributed to the misdiagnosis of stercoral peritonitis. To optimize outcomes after peritoneal lavage, the authors pushed toward a meticulous search for colon perforation. In all cases, the adoption of LLD in emergency settings, abdominal exploration for generalized peritonitis, pelvic dissection in inflammatory conditions and possible suture of a diseased colon require that the surgeon have a minimum of colorectal and minimally invasive skills before he can propose this conservative approach[51,58].

Sigmoidectomy: Primary anastomosis and HP: Supported by considerable improvement in the perioperative care, RPA (without or without DI) has been proposed as an alternative to HP in emergent situations. A comparison of these two techniques has mostly enrolled patients undergoing open procedures before the widespread application of laparoscopy in emergent colorectal surgery. In fact, several comparative studies, systematic reviews and meta-analyses favored RPA over HP in respect to reduced mortality and morbidity rates, shorter cumulative operative time and hospital stay, more frequent stoma reversal and reduced cost[63-76]. Even without DI, RPA was shown to be preferable than HP for purulent peritonitis[70,72,77]. These studies, however, suffer from marked heterogeneity and selection bias with low-risk patients mainly undergoing RPA, whereas HP is offered to high-risk elderly patients[63,74]. A recent RCT showed that for Hinchey 3 and 4 diverticular disease, the main differences between RPA with DI and HP occur during the stage of stoma reversal[78]. When both stages (colonic resection and stoma reversal) were combined, the rates of overall complications, severe complications and mortality (13% in HP *vs* 9% in PA) were similar in both groups. In contrast, when the reversal procedure was considered alone, HP was associated with lower stoma reversal rate (58% *vs* 90%), more frequent severe complications (20% *vs* 0%), and longer operative time and hospital stay. The main flaw of this RCT would be the lack of information about the adopted approach (laparoscopic or open) for the reversal of the stoma. This issue is of paramount importance because laparoscopy has been proved to decrease the morbidity of HP reversal in several case series and systematic reviews[79-86]. The elevated rate of severe complications during stoma closure in the HP group may have been overemphasized by the open approach *per se*.

This evidence raises the question whether the laparoscopic HP may offer advantages over the open approach in terms of reduced morbidity and mortality in the acute setting of perforated diverticulitis. To improve the outcome after open HP, we have been among the first to show the feasibility of a laparoscopic two-staged strategy for complicated diverticular disease. Despite conversion in 19% of cases, this approach offered adequate control of sepsis with low rates of mortality (3%) and morbidity (23%)[33]. Similarly, in a small case series, Agaba *et al*[34] described favorable outcomes after laparoscopic HP for Hinchey 3 and 4 diverticulitis. Recently, a propensity-matched analysis of the ACS NSQIP database failed to show a decrease in postoperative morbidity and mortality when HP was performed under laparoscopy compared with the open approach. This study, however, suffers from substantial imperfections in methodology such as retrospective data acquisition and lack of analysis of pertinent variables that might substantially interfere with the results[26].

To clarify the role of laparoscopy in emergent sigmoidectomy, Mbadiwe *et al*[87] retrospectively analyzed the ACS NSQIP database. In a total of 11981 patients, a bivariate analysis showed that patients undergoing laparoscopy experienced lower rates of complications with both RPA (14% *vs* 26%, $P < 0.001$) and HP (30% *vs* 37%, $P = 0.02$). The laparoscopic approach was associated with decreased mortality rate for patients undergoing RPA (0.24% *vs* 0.79%, $P < 0.001$). The reduced complication rate after laparoscopic RPA was confirmed in the multivariate analysis[87].

To provide a high level of evidence in the present era of widespread use of laparoscopy for colorectal disease, a well-built RCT is highly desirable comparing laparoscopic RPA (with or without DI) with a two-step laparoscopic HP (sigmoid resection and stoma closure) in perforated complicated diverticulitis. Not only outcomes of both procedures will be clarified but also identification of precise criteria would define the subgroups of patients who will benefit more from each technique. Based on this perspective, the results of the ongoing DIVA section of the Ladies trial are keenly awaited to provide us with level 1 evidence about the preferable laparoscopic attitude in Hinchey 4 complicated diverticulitis[57].

Elective surgery

Based on solid proofs from a large-scale meta-analysis[88] and RCTs[89,90], international committees have adopted laparoscopy as the preferred approach for elective sigmoidectomy after acute diverticulitis[1,23,24]. Compared with an open procedure, the laparoscopic modality offers a significant decrease in major complications and morbidity, less blood loss, fewer analgesic requirements, shorter hospital stay and improved quality of life.

Conversely, in early experience, laparoscopy was contraindicated for the treatment of diverticular chronic complications (stricture, fistula and persistent phlegmon) because severe inflammation and distorted anatomy exposes the patient to high risks of bleeding and adjacent organ trauma (bladder, left ureter, female genital organs)[11,91]. With increasing experience, the laparoscopic approach has been progressively accepted as an alternative to open surgery but its routine usage in chronic complications remains controversial[92].

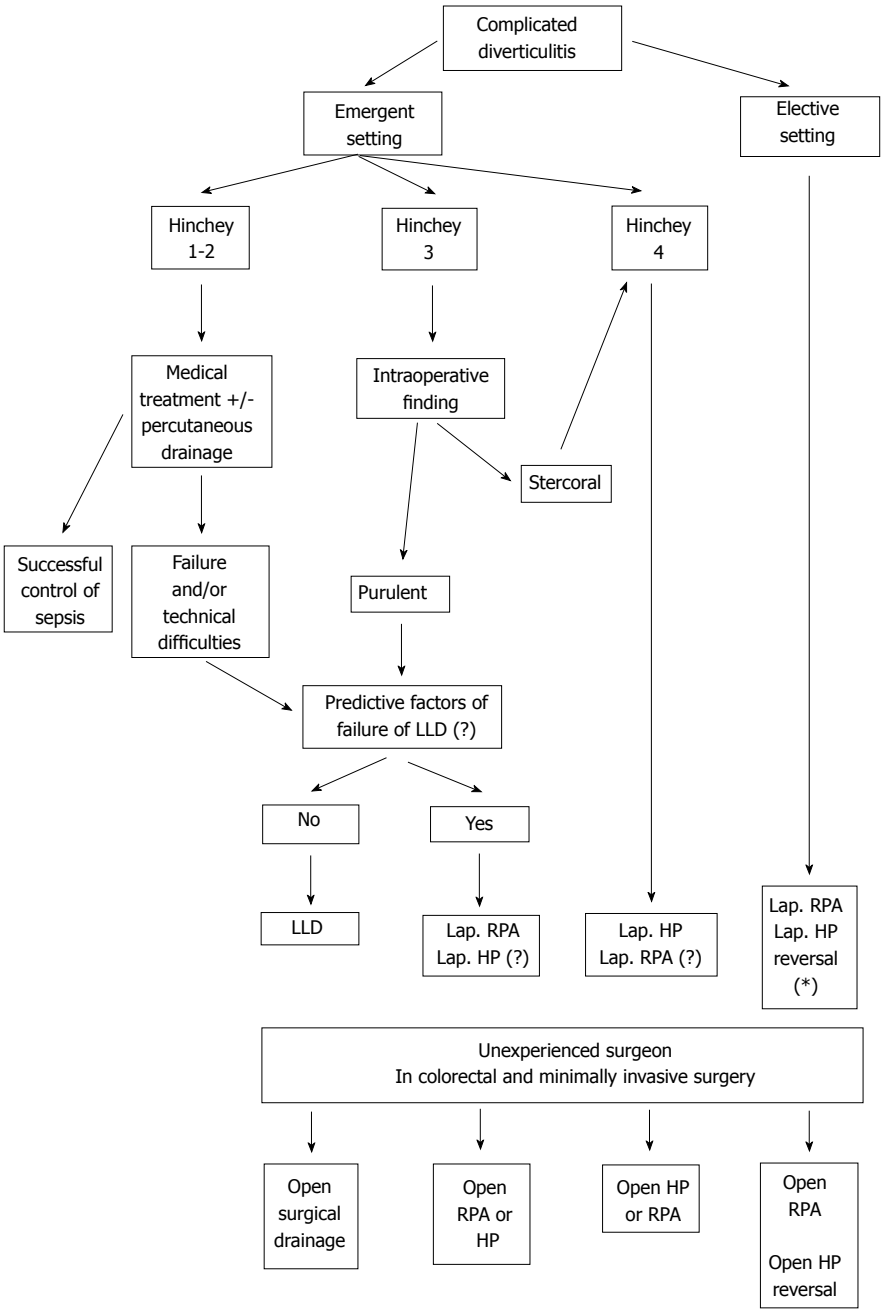

Figure 1 Algorithm for the laparoscopic management of complicated colonic diverticulitis. Lap: Laparoscopic; LLD: Laparoscopic lavage drainage; RPA: Resection with primary anastomosis; HP: Hartmann's procedure; (?): Data that need to be elucidated in RCTs, (*): Data that need confirmation in RCTs.

Because presently available data mostly rely on small retrospective series and case reports, several controversies cannot be fully elucidated. In a descriptive case series, Le Moine *et al*[93] suggested that chronic complicated diverticulitis increases the risk of conversion to laparotomy in elective laparoscopic sigmoidectomy. This effect has been recently disproved by two comparative studies[94,95] which stated that surgeons' expertise in minimally invasive and colorectal surgery is the principal determinant of morbidity and conversion rates in complicated cases. This evidence outlines that accumulating experience during the last ten years has inevitably challenged previously accepted knowledge.

Colonic fistula is the most reported late complications of diverticular disease, although available data is scarce and confined to retrospective case series. In recent systematic reviews[96,97], the laparoscopic approach was judged to be feasible and safe for the treatment of colovesical fistulae. However, due to a lack in methodology and/or a limited number of patients, the studies failed to show superiority of laparoscopy over the open approach. Furthermore, the conversion rate could not be determined and the predictive factors of its occurrence were not discussed[96]. This issue has been addressed in a previous case series including 31 patients conducted over 10 years. The overall conversion rate was approximately 30% but declined to 10% during the second half of the study period[98].

This finding is consistent with the statement of Abbass *et al*[99] that similar rates of conversion, morbidity and mortality can be expected with laparoscopy regardless of the presence of colonic fistula. Therefore, the current surgical management of colonic fistula relies on poor data derived from empirical experiences in open surgery. The most salient example is the adoption of a single-stage procedure as the preferred surgical option despite the absence of solid proofs confirming its superiority[98].

During this study, we noticed a striking lack of high quality papers dedicated to the issues of inflammatory phlegmon and stricture. Information on the most appropriate treatment in these situations is thus absent. If low incidence of such cases is the cause of this shortage, prospective enrollment of patients in large multi-institutional databases might be the solution to build precise therapeutic algorithms on which tomorrow's general surgeons can use for the treatment of their patients.

Finally, with the emergence of LLD as a conservative modality for complicated perforated diverticulitis, controversies have arisen about the need for systematic elective sigmoidectomy after the diseased organ has been saved. In a recent systematic review[44], rehospitalization was observed in 7% of patients who underwent LLD. More than half of them presented with a new episode of diverticulitis, 21% with generalized peritonitis, 10% with colovesical fistula and 7% with undetected colon cancer. At this stage of experience, the present data lack sufficient proof to know whether LLD can be regarded as a definitive treatment or a bridge to elective laparoscopic sigmoidectomy[100]. If LLD becomes widely admitted, well-built RCTs will be necessary to answer these questions and to determine the best candidates for bowel sparing.

CONCLUSION

In conclusion, accumulated empirical experience during the last two decades shows that laparoscopy is undeniably a promising adjunct in the management of complicated colonic diverticulitis. Analysis of presently available data also highlights the urge to build large-scale prospective RCTs in order to elucidate the exact benefits of laparoscopy and to define patients who are the best candidates for each approach. Like the ongoing trials NCT01019239 and NCT01047462, solid data are particularly awaited in order to clarify the exact place of LLD and to determine the most appropriate sigmoid resection procedure (laparoscopic HP or RPA) in Hinchey 3 and 4 peritonitis. The advantages provided by laparoscopy in chronic complications of diverticulitis and HP reversal also need to be confirmed. In the absence of precise recommendations, we suggest the following algorithm that may assist general surgeons in their decision-making when dealing with complicated colonic diverticulitis (Figure 1).

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MINIREVIEWS

Overview of robotic colorectal surgery: Current and future practical developments

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Abstract

Minimal access surgery has revolutionised colorectal surgery by offering reduced morbidity and mortality over open surgery, while maintaining oncological and functional outcomes with the disadvantage of additional practical challenges. Robotic surgery aids the surgeon in overcoming these challenges. Uptake of robotic assistance has been relatively slow, mainly because of the high initial and ongoing costs of equipment but also because of limited evidence of improved patient outcomes. Advances in robotic colorectal surgery will aim to widen the scope of minimal access surgery to allow larger and more complex surgery through smaller access and natural orifices and also to make the technology more economical, allowing wider dispersal and uptake of robotic technology. Advances in robotic endoscopy will yield self-advancing endoscopes and a widening role for capsule endoscopy including the development of motile and steerable capsules able to deliver localised drug therapy and insufflation as well as being recharged from an extracorporeal power source to allow great longevity. Ultimately robotic technology may advance to the point where many conventional surgical interventions are no longer required. With respect to nanotechnology, surgery may eventually become obsolete.

Key words: Colorectal surgery; Robotic surgery; Endoscopy; Robotics; Nanotechnology; Microtechnology; Rectal neoplasms; Colonic neoplasms

Core tip: Robotic assistance has the potential to revolutionise the way colorectal surgery is delivered. This overview summarises the current status of robotic colorectal surgery and considers the direction of developments in robotic and endoscopic surgery and future developments in micro- and nanotechnology.

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BACKGROUND

The objective of robotic surgery is allowing us to operate in challenging environments or to achieve levels of performance we would otherwise not be capable of. Surgeons interact with their environment by using their senses to gather information (perception), combining these inputs with their pre-existing knowledge and experience (processing) to change the environment (action). A robot may augment any or all of these aspects in order to improve the final outcome.

Over the last two decades colorectal surgery has dramatically changed due to the widespread implementation of laparoscopic surgery. Laparoscopic surgery offers comparable oncological outcomes[1], but with improved post-operative recovery[2]. The move towards minimal access surgery has, however, put challenges upon the surgeon's perceptive and action abilities with a resultant increased reliance on processing abilities required to make up for these deficits. Robotic assistance in minimal access surgery aims to make up for some of the practical shortcomings of laparoscopic surgery, providing assistance to the surgeon with improvements to perception, processing and action.

This aim of this review is to summarise the current benefits and shortcomings of robotics in colorectal surgery and endoscopy and to identify how the implementation of developing robotic technology may shape the future of colorectal surgery.

ESTABLISHED ROBOTIC COLORECTAL SURGERY

At present the Da Vinci Robot (DVR) (Intuitive Surgical) is the most widely used platform for robot assisted laparoscopic colorectal surgery. It consists of a high definition three-dimensional camera system allied to a patient "sidecart" that allows instruments to be delivered and controlled. The surgeon sits at a separate control module (Figure 1) that delivers three-dimensional images and allows remote control of the sidecart-mounted effectors.

The DVR addresses some of the limitations of conventional laparoscopic surgery by allowing dexterity in 7 planes of movement within a limited space, static ports, filtering of physiological tremor and variable motion scaling. The potential drawbacks of the system include lack of tactile feedback, prolonged operative time and financial cost, including initial outlay, consumables and servicing of equipment.

The attributes of the DVR make it suitable for assisting in precision surgery within confined spaces such as the pelvis and use of the DVR for radical prostatectomy is now widespread in the United Kingdom for this reason. Robotic prostatectomy is now seen as the primary treatment for localised prostate cancer, delivering equivalent oncological outcomes with decreased morbidity[3,4], but equivocal improvement in sexual function[5].

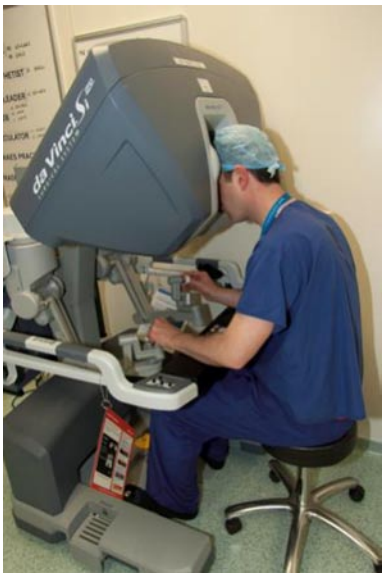

Figure 1 Surgeon interaction with the Da Vinci robot control module.

The practical challenges of pelvic surgery for prostate cancer are similar to those encountered in rectal surgery, particularly when performing total mesorectal excision (TME). It has been demonstrated that laparoscopic TME offers equivalent oncological outcome with faster recovery and less morbidity than open surgery[2,6]. However, it is technically demanding with higher conversion rates seen in the obese and during low rectal surgery[7].

Comparative studies have suggested an improved TME grade following robotic TME[8,9] and it is hypothesised that the improved precision of surgery enables the TME plane to be more accurately preserved, offering greater preservation of the pelvic autonomic nerves resulting in improved urinary and sexual function with some evidence of short-term benefit[10]. Rates of conversion are often used as a surrogate marker of operative difficulty and a systematic review of case-controlled studies identified that conversion rates may be lower in robotic assisted cases, although this was not statistically significant[11].

The Robotic *vs* Laparoscopic Resection for Rectal cancer trial is the first international, multi-centre randomised controlled trial to compare laparoscopic with robotic TME. The results of 471 participants have been presented at the European Society of Coloproctology, September 2015 and demonstrated no statistically significant difference in oncological clearance, patient outcome or conversion to open surgery between the two groups. These findings may impact the usage of the DVR in TME as it seems that the increased financial cost of robotic usage is not offset by improved surgical outcomes.

There are several centers performing robotic ventral mesh rectopexy. It has been argued that the increased dexterity of the instruments of the DVR facilitates dissection and more precise suturing of the mesh[12]. There are few studies that compare outcomes between laparoscopic and robotic ventral mesh rectopexy, however functional improvements with respect to obstructive defaecation symptoms have been noted in patients having robotic surgery[13].

The COST and COLOR trials demonstrated that laparoscopic surgery offers oncological and survival outcomes commensurate with open surgery in colonic tumors[14,15]. Decreased morbidity and length of hospital stay have also been shown[1,16,17]. The improved dexterity the robot offers has demonstrable benefit when performing intracorporeal anastomosis[18], but the benefits of robotic over laparoscopic colonic surgery however are less well established and no benefit of has been demonstrated when comparing laparoscopic to robotic right hemicolectomy[19]. Robotic left hemicolectomy can be used as training platform to practice mobilization of the left colon and splenic flexure as part of robotic anterior resection.

Currently there appears to be little evidence to support the use of DVR type robots in conventional multiport trans-abdominal surgery. The development of transanal endoscopic microsurgery (TEM) and single port laparoscopic surgery (SPLS) limits a surgeons dexterity still further and these fields may be particularly suited to robotic augmentation.

COLORECTAL ROBOTIC SURGERY UNDER DEVELOPMENT

Robotic surgical technology is expensive- initial outlay, maintenance and purchasing disposable equipment contributes to the financial expense that must be justified by reproducible cost effectiveness. This currently restricts robotic surgery to larger institutions that are able to absorb these costs and provide high utilisation in circumstances where financial gains can offset expenditure. Therefore developments in colorectal robotics over the next decade will concentrate on the widening application of robotics to other colorectal disciplines, such as endoscopy, single port surgery and transanal surgery and minimisation of cost.

Single port robotic laparoscopic surgery

SPLS offers improved cosmesis and less post-operative discomfort compared to that seen in multiport laparoscopic surgery[20]. SPLS restricts the triangulation and retraction easily achieved in multiport surgery. This can be managed utilising conventional straight instruments that are crossed intracorporeally or by using curved or articulating instruments such as the Autonomy Laproangle[20]. The technique is associated with equivalent oncological outcomes[21], but a systematic review of colorectal SPLS found conflicting evidence regarding demonstrable improvements in patient recovery and length of stay[22].

Figure 2 Robotic single port laparoscopic surgery module designed by Intuitive Surgical. ©[2015] Intuitive Surgical, Inc.

Robotic assisted SPLS systems offer superior triangulation, without the need for crossing instruments, while incorporating other robotic technology. The Da Vinci Si Surgical Robot (Intuitive Surgical) has obtained FDA approval. It incorporates remote centre technology that reduces interference between instruments in addition to a three dimensional camera, motion scaling and removal of tremor (Figure 2). Evidence has been published demonstrating the feasibility of robot assisted SPLS in right hemicolectomy[23] but to date no advantage of robot assisted over conventional SPLS has been demonstrated. Alternative robotic SPLS platforms are in the prototype stage, including the Single Port Orifice Robotic Technology robotic SPLS module (Titan Medical) which is predicted to cost a third of the Da Vinci system, although data on efficacy is awaited[24].

Robotic transanal surgery

TEM offers similar practical challenges to SPLS and has become established as an effective method of removing non-advanced distal rectal lesions and may be oncologically superior to conventional transanal excision[25]. Initially described in 2011, a SILS (Covidien) port was placed in the anus and the Da Vinci machine deployed as for SPLS[26]. The first cohort study of sixteen patients managed with robotic TEM reported that the procedure was technically feasible but did not offer comparative data with conventional TEM. Use of the robot added an additional €1000 per procedure in disposables alone[27].

Robotic transanal total mesorectal excision (RT-TME) is an alternative method of TME where the standard abdominal component of an anterior resection is completed laparoscopically before the DVR is introduced transanally to complete the TME in a retrograde fashion. This method facilitates distal rectal dissection in patients who are obese or who have narrow pelvises[28]. A study of twenty patients did not compare RT-TME to conventional TME but demonstrated the feasibility of the approach in distal rectal cancers[29].

Improving current laparoscopic technology

Modifying and augmenting existing laparoscopic surgical instrumentation to offer additional degrees of movement, tactile or haptic feedback may narrow the gulf between laparoscopic and robotic surgery with potentially significant cost savings. Movement of conventional laparoscopic instruments is restricted by the fulcrum of movement existing at the point of entry into the abdomen. The Radius Surgical System (RSS, Tuebingen Scientific) has been in circulation for over ten years and offers an additional fulcrum at the tip of the instrument to allow a greater degree of movement. As with the DVR, it offers 7 degrees of freedom for a significantly lower financial outlay although the extent of its distal joint articulation is reduced[30].

The RSS generally offers tools for suturing and manipulation, rather than dissection and there is no mechanism for removing surgeon tremor or changing the ratio of hand to instrument movement. Results suggest a shorter learning curve compared to the DVR[31] and it has been demonstrated that they can be used in sutured intracorporeal colorectal anastomosis with encouraging results[32]. The parallel development of reliable laparoscopic stapling devices has, however, generally obviated the need for an advanced suturing instrument, which may account for the lack of take up of the RSS system. The Autonomy Laparo-angle (CambridgeEndo) is a simpler system offering a range of graspers, scissors and needle holders that can articulate at a distal joint allowing a greater degree of movement not offered by conventional laparoscopic instruments. However, to date there is no published evidence of its use in colorectal surgery.

Robotic endoscopy

Developments in robotic endoscopy have focused on automatic endoscope propulsion and improved endoscopic instrumentation. Balloon endoscopy mimics the movement of an earthworm, using coordinated inflation and deflation of a series of balloon to advance the camera and it has been successful in small bowel enteroscopy[33]. Current research focuses on providing propulsion at the endoscopic tip to pull the scope through the colon, reducing discomfort and procedure duration. Development of legged locomotion allows efficient propulsion and a steering capability, but risks iatrogenic injury from the traction of the legs on the colonic surface. New generations of microscopic leg effectors aim to minimise injury while offering sufficient propulsive force for effective motion[34].

Capsule endoscopy utilises passive propulsion to traverse the GI tract and has proved successful in endoscopic practice, particularly in visualisation of the small bowel. The purely passive locomotion is also a drawback and does not allow retrograde motion to recheck areas of incomplete examination. Capsules with active control could be steered to closely examine certain areas, release medications and perform diagnostic or therapeutic interventions but they are limited by size as they must be swallowed. Size constraints currently preclude independently self-propelled capsules.

Vectoring using external magnets allows the capsule to remain as small as possible and was originally described using a hand-controlled external magnet[35]. To offer accurate and reproducible magnetic control requires a generated magnetic field utilising a series of magnets under computer control and offering very high positional accuracy at the cost of extensive magnetic equipment[36]. Early trials demonstrate that the technique is feasible but movement is restricted by collapsed bowel with no method of insufflation available and there are no reports from trials in human subjects[37].

Endoscopic mucosal resection is an established method of endoscopic piecemeal removal of sessile polyps or superficial cancers less than 20 mm in diameter that would otherwise require surgical excision[38]. Endoscopic submucosal resection (ESR) can be applied to larger lesions and aims to remove a greater depth of tissue in a single specimen. This allows more accurate histological examination and reduces the risk of recurrent disease[39]. Although initially developed for the management of upper gastrointestinal lesions, the procedure has shown great promise with respect to colonic lesions greater than two centimeters in diameter[40]. The procedure is technically challenging and relies on the application of tension to the target lesion to allow careful dissection, which is challenging with conventional endoscopic instruments.

A number of flexible multi-tasking platforms are available that consist of conventional endoscope video technology with an enhanced multichannel intervention system allowing two working instruments operated mechanically or robotically. The Master and Slave Transluminal Endoscopic Tool (MASTER) is a robotic endoscopic surgical system that introduces a two-channel endoscope with two slave robotic effectors possessing nine degrees of freedom. The system allows separation of the endoscopic control and instrument control to allow two operators to work together in tandem[41]. The MASTER was originally developed for Natural Orifice Transluminal Endoscopic Surgery (NOTES) but has been tested in ESR in animal models with success[42]. A trial of the MASTER system in ESR in human subjects was planned but results have not been published yet.

POTENTIAL FUTURE OF ROBOTIC COLORECTAL SURGERY

The ultimate aim of minimal access surgery is for surgery to be completed *via* natural orifices without any disruption to the normal functioning of the patient. Ultimately the development of nanotechnology may make this a reality but in the meantime the direction

of minimal access surgery is to further minimise access without compromising surgical outcome and to improve patient safety.

Advanced instrumentation

The Image-Sensing Navigated and Kinematically Enhanced (i-SNAKE) is an instrument delivered *via* a standard laparoscopic port. The distal end of the instrument possesses an articulated section carrying a camera, driven by a hybrid motor design, allowing a greater degree of flexion compared to cable actuators used in a conventional flexible endoscope[43]. In addition, there are two flexible surgical arms driven by cables that can carry a range of instruments and there is an additional channel that allows an instrument to be passed through the articulated section. The three arms are delivered *via* a 15 mm trocar and the arms are extended once safely within the peritoneal cavity.

Flexible robots such as this are required to operate in highly angulated positions while maintained sufficient control to allow careful dissection and to produce enough force to manipulate tissue. The i-SNAKE can retroflex completely, allowing tubal ligation from a vaginal NOTES approach[44]. The suitability of the platform for conducting intraluminal interventions such as ESR and Per-Oral Endoscopic Myotomy have been assessed[45] and it is would be anticipated that this technology could be used to augment SPLS and intraluminal colorectal interventions.

Haptic feedback

Haptic feedback describes the conveying of information from the robotic effector, now also functioning as a receptor, back to the surgeon. The aim is to provide "transparency", where the surgeon feels that they are contacting the patient directly, rather than *via* a robotic mechanism[46]. To achieve this level of feedback requires transmission of information regarding temperature, texture, force and vibration, and may not be technically feasible. Other industries make use of limited forms of haptic feedback, but surgery offers the unique challenges of size limitation, sterilisability and cost implications over existing technology. An economical approach would be to modify existing technology with feedback sensors and effectors[47], but this may make integration with complex technology such as the DVR challenging.

Colorectal surgery demands soft tissue differentiation, the careful manipulation of tissues and suturing, all of which benefit from haptic feedback. The TELELAP ALF-X (SOFAR) is a surgical robot that offers haptic feedback in a smaller package compared to the DVR[48]. The TELELAP ALF-X provides haptic feedback by exerting forces on the surgeon's hands- this requires a complex system of processors and actuators to achieve adequate fidelity and is therefore inherently complex. An alternative approach would be to relay haptic information to the surgeon by an auditory or visual representation of force feedback. Lab studies have demonstrated that color-coded visual display of stitch tension improves consistency in tension applied to ligatures[49,50].

To provide haptic feedback in the seven degrees of freedom that the DVR offers would be even more challenging. Given the wide uptake of the DVR it may be unlikely that institutions will invest in another robot simply to take advantage of haptic feedback when the surgeon feels it may be helpful. Therefore a successful haptic feedback system would most likely have to be integrated with the DVR, or operate in parallel with it.

A force-sensing adaptor for the Da Vinci Robot has been developed with some success in lab testing but there are no data from *in vivo* tests[51]. A wireless palpation probe is an alternative that could be used both in robotics and conventional laparoscopic surgery. This battery operated unit can be introduced *via* a port and used to measure indentation pressure and depth in order to characterise tissues. Initial porcine studies used the probe to serially palpate a porcine liver to produce a "stiffness map" that could be used to guide subsequent resection[52].

Tactility

Open surgery offers a uniquely tactile experience that is significantly dampened by minimally invasive surgery. Haptic feedback may offer some gross information on tissue resistance, but not the degree that the surgeon requires for accurate tissue differentiation. The technology to provide tactile transparency does not currently exist and may not do so for some time due to the technical complexity of detecting, processing and displaying such information.

Instruments for the detection of gross tactile information in minimal access surgery have been developed and tested in order to locate arteries and detect blood flow, in identifying the inferior mesenteric artery for example. The tools, such as TactArray (Pressure Profile Systems) carry multiple pressure sensitive receptors that may be applied to the tissues producing graphic representations of the tactile feedback detected[53]. An alternate approach would be to use intracorporeal Doppler ultrasonography as a proxy to assess the tissue instead or relying on tactile feedback. This has already been demonstrated in laparoscopic nephrectomy[54] but has not been utilised in colorectal surgery.

Capsule endoscopy

Diagnostic capsule endoscopy has proven itself as a diagnostic modality and is already in widespread use. Further development of this technology in the future will look to expand its diagnostic and therapeutic possibilities. Wireless capsule endoscopy is limited by the lack of a conventional insufflation system and the resultant lack of bowel distension limits diagnostic capability. Preliminary studies have demonstrated the feasibility of a wireless insufflation capsule utilising liquids or powders to produce gaseous insufflation[55]. There have been no published results from animal

studies but this demonstrates the widening functionality of capsule intervention.

As capsule endoscopes become more complex they will become limited by their power storage capacity. Complex luminal processes such as delivery of topical chemotherapy, brachytherapy or treatments for inflammatory bowel disease may require capsules to remain inside the body for a prolonged period of time. Therefore an alternate source of power may be necessary. Magnetic induction offers a method of transmitting power to a device within the body from an external charger over a prolonged period of time without causing deleterious effects[56].

Micro- and nanotechnology

Nanotechnology offers opportunities to investigate and intervene at the cellular level and may ultimately lead to a step change in the conduct of colorectal surgery over the next fifty to one hundred years. Currently machine actuators limit the minimum size of machines to a few milimetres- too large to be injected into the circulation for example, but alternative avenues for micro-interventions have been investigated.

Minimally invasive biopsy retrieval has been demonstrated using "micro-grippers". These tools possess minuscule biopsy tools that close in response to a change in temperature and are also composed of a ferromagnetic alloy. These tools were injected into the common bile duct during an endoscopic retrograde cholangiopancreatography in a live porcine model, allowed to sit for ten minutes to allow the grippers to close in response to change in temperature before being retrieved by a catheter with a magnetic tip[57]. The retrieved tissue was assessed and deemed suitable for cytological analysis. Potentially this technology could be adapted for use as a non-invasive diagnostic aid in colonic conditions such as inflammatory bowel disease.

Nanobot technology in medicine aims to deliver therapy at the cellular level and may have particular importance in the treatment of cancers. Mechanical actuators and processors are not viable at this scale and therefore the robots are genetically engineered bacteria that allow cellular-level interactions, containing ferromagnetic granules that allow steering and propulsion using magnetic fields. Microbot technology and its application in medicine are likely to radically change how we view therapeutics. The ranges of possible applications include targeted therapy, material removal, deployment of structures, such as stents and telemetry[56]. Although currently in its infancy, this aspect of robotic technology has the greatest potential to revolutionise how we manage colorectal pathology in the future.

CONCLUSION

The development of minimal access surgery has spurred the creation of robotic assistance in order to aid surgeons to overcome the shortcomings of this surgical technique. The breadth of robotic advancement considered in this review demonstrates that robotic colorectal surgery has advanced far beyond its original brief of surgeon assistance. The potential advancements within this field will allow utilisation of minimal access surgery in a wider range of increasingly technically challenging environments and could fundamentally change the way surgeons manage their patients.

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MINIREVIEWS

Chronic radiation proctopathy: A practical review of endoscopic treatment

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Abstract

Chronic radiation proctopathy (CRP) is a troublesome complication of pelvic radiotherapy. The most common presentation is rectal bleeding. CRP symptoms interfere with daily activities and decrease quality of life. Rectal bleeding management in patients with CRP represents a conundrum for practitioners. Medical therapy is ineffective in general and surgical approach has a high morbid-mortality. Endoscopy has a role in the diagnosis, staging and treatment of this disease. Currently available endoscopic modalities are formalin, potassium titanyl phosphate laser, neodymium:yttrium-aluminum-garnet laser, argon laser, bipolar electrocoagulation (BiCAP), heater probe, band ligation, cryotherapy, radiofrequency ablation and argon plasma coagulation (APC). Among these options, APC is the most promising.

Key words: Endoscopic treatment; Radiation proctopathy; Proctitis; Argon plasma coagulation; Cryotherapy; Radiofrequency ablation; Formalin; Laser; Bipolar probe; Pelvic radiotherapy

Core tip: The objective of this review is to critically analyze the available data and our experience with this disease, with suggestions for daily practice and further research. In our view, laser treatment is an obsolete technology and can be abandoned. The bipolar probe (BiCAP) is very well indicated for patients with implantable electronic devices. The best way to use formalin is still unknown. More studies with band ligation, cryotherapy and radiofrequency ablation are still needed. Argon plasma coagulation has emerged as the front-runner, due to its ease of use, affordability, better-defined settings, effectiveness and low risk of complications.

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INTRODUCTION

Chronic radiation proctopathy (CRP) is recognized as injury to the rectum and/or colon due to radiotherapy for the treatment of pelvic malignancies; it occurs when clinical symptoms persist or appear months to years after therapy (median 6-12 mo). The sigmoid colon may also be affected[1,2]. The term radiation proctitis is a misleading term since epithelial damage to the rectum due to radiation is associated with minimal or no inflammation[1,3]. Cancers of the cervix, prostate, rectum, bladder, testicles and uterus are commonly treated with pelvic irradiation. Among these, prostate malignance is the most frequent[1].

The incidence of CRP has yet to be ascertained due to the lack of prospective studies and variability in the definition and classification systems used for the condition[1,2]. However, it is estimated to range from 2% to 20%[3,4]. The method of radiation delivery is an important predictor of the risk for radiation proctopathy[2,5]. The rate of colorectal complications with brachytherapy is lower compared to external beam radiation[6]. The use of newer conformal radiation therapy techniques maximizes the dosage directed to the tumor while minimizing the dosage of radiation to the rectum[6,7]. CRP may be more frequent in patients with inflammatory bowel disease, diabetes, hypertension or peripheral vascular disease and in those who develop severe acute proctopathy[2].

CRP should be suspected in patients who develop symptoms such as diarrhea, urgency, tenesmus or bleeding, usually 6 mo or more after pelvic radiation exposure. Hematochezia occurs due to oozing from a friable, ischemic mucosa, and the rupture of radiation-induced telangiectasias and can lead to anemia and the need for blood transfusions[1-3,8]. Symptoms are non-specific and the diagnosis requires exclusion of other etiologies of colitis[3,4]. Diagnosis can be confirmed by colonoscopy or sigmoidoscopy[7]. Endoscopic findings of CRP are mucosal pallor, telangiectasias, spontaneous hemorrhage, edema and friability. Less frequent findings are ulcers, strictures and fistulas[9]. A scoring system has been developed for the endoscopic evaluation of radiation proctopathy severity, based on three factors: The presence of fresh blood, the telangiectasia distribution and the surface area involved[10]. Although biopsies are not diagnostic, they can rule out other causes of proctopathy such as inflammatory bowel disease or infection and can grade the mucosal damage[11,12].

TREATMENTS FOR CRP

In patients with CRP, the management should be based upon the severity and pattern of symptoms and experience within the treatment center[13].

Therapy for CRP includes medical, endoscopic and surgical therapies. Medical therapy includes: Use of non-steroidal anti-inflammatory drugs, sucralfate, short chain fatty acids, metronidazole, pentoxifylline, vitamins (A, C and E), and hyperbaric chamber treatment; all have been described with limited success. In a small study, vitamin A also showed some benefits on functional symptoms[14], although the effect of retinol on rectal bleeding was not evaluated[15]. Enemas of sucralfate are safe and well tolerated and have become the best medical therapeutic option[7,15,16].

The management of patients with symptomatic CRP remains essentially empirical because there are only a few randomized trials, in addition to the difficulty of grading symptoms, endoscopic severity and response to therapy. However, some concepts regarding the management of these patients have been suggested: Treatment for hematochezia is in general better if it involves a sclerosing agent or a topical cautery to obliterate telangiectatic mucosal vessels; non-steroidal anti-inflammatory drugs have a limited role in treatment; large rectal ulcers, strictures, fistulas, abscesses and intractable bleeding generally require surgical management[1,15]. However, surgical therapy has high morbidity and mortality rates[16].

ENDOSCOPIC TREATMENTS FOR CRP

The main objective of endoscopic therapies of CRP is to achieve control of blood loss, leading to improvements in quality of life by reducing the requirement for blood transfusions, iron replacement and hospital admissions, resolving anemia and hematochezia[10,16]. Endoscopic therapy using potassium titanyl phosphate (KTP) laser, argon laser, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, BiCAP, heater probe, endoscopic band ligation (EBL), cryotherapy, radiofrequency ablation (RFA) and argon plasma coagulation (APC) have been reported[15,16]. Formalin is a miscellaneous technique with aspects of medical and endoscopic approaches. However, Cullen *et al*[17] described instilling formalin into the rectum during flexible sigmoidoscopy, and it shall be included in the endoscopic treatment group. Endoscopic treatment can also be used for radiation-related strictures[7].

Formalin therapy

Formalin therapy for CRP is based on its use in patients with hemorrhagic cystitis[18]. Since Rubinstein's work, in 1986, reported the first successful CRP treatment using a rectal wash with formalin, many authors have published on the treatment of hemorrhagic CRP using this therapy[19]. Formalin functions as a local sclerosant and causes chemical cauterization of telangiectasias.

According to an email survey with members of the American Society of Colon Rectal Surgeons, formalin is the most popular method to treat CRP. Of the 327 respondents, 85% favored to formalin, while 42% used APC. Only 25% of practitioners reported using sucralfate (more than one modality could be chosen)[20].

Success rates vary from 27% up to 100%[16-23]. This

difference can be explained by the wide variability in application technique and concentration[21]. Formalin can be administered as an enema, irrigation in small aliquots, or soaked pledgets of cotton wool applied under rigid sigmoidoscopic, proctoscopic or flexible endoscope guidance[17,22]. Sedation may be needed, but because of pain due to the procedure, most authors reported the use of general anesthesia for this procedure. Formalin therapy can be repeated for two or three more applications until symptomatic improvement, especially with the cessation of rectal bleeding. Ulcers due to formalin application preclude repeating the procedure[18].

Patel *et al*[19], in a retrospective study, evaluated the combination of oral vitamin A with formalin application. The addition of vitamin A led to a significant decrease in the number of formalin sessions and a significantly shorter time for resolution. Supplementation with vitamin A also has a better success rate in controlling rectal bleeding than formalin alone (94% *vs* 64%).

There are also two small studies comparing formalin with APC. Yeoh *et al*[21] suggested that formalin and APC had similar success in managing hemorrhagic CRP. Nevertheless, Alfadhli *et al*[22] concluded that APC was significantly more effective (78.5% *vs* 27.2%, P = 0.017) and safer (P = 0.001) than formalin.

The advantages of formalin application include low cost, wide availability and good efficacy in general[23]. Despite this, high rates of complications have been reported, including chemical colitis, anorectal pain, anal and rectal strictures, rectal perforation, fissures, incontinence and diarrhea[16,18]. Further studies are needed to determine the optimal method of delivery.

Laser therapy

Lasers cause thermal destruction by tissue absorption of laser light and have been used to coagulate radiation proctopathy related vascular lesions in small retrospective series. The KTP laser, the Nd:YAG laser and the argon laser have been effectively used for CRP. A laser fiber is advanced into the working channel of a regular endoscope and is activated by the endoscopist, generating several laser pulses. The depth of thermal effect is dependent on the duration of pulses, power setting and light wavelength. Multiple sessions are generally required. Laser therapy usually decreases rectal bleeding, transfusion dependence and the frequency of hospitalization[24,25].

Complications secondary to deeper thermal injury, which include strictures, transmural necrosis, perforations and fistulas, occur in up to 15% of patients. Intervals between sessions of at least a few weeks and using the least amount of energy for ablation are recommended to avoid complications[26].

Chapuis *et al*[24] described the combination of formalin and Nd:YAG laser in 34 patients with CRP. The patients underwent an endoscopic Nd:YAG laser session and then were treated with formalin application. The authors reported that bleeding ceased in 25 patients (74%) with no major complications.

Compared with other ablative devices, lasers are unwieldy and far more expensive. Other considerations include availability, safety issues and limited portability[25]. The use of lasers in the treatment of CRP has declined[27].

Heater probe and BiCAP - contact therapy

BiCAP and heater probe and are contact methods for CRP treatment. The heater probes have Teflon-coated heating components at the extremity of a plastic catheters that deliver standardized energy over set times. The BiCAP probes have pair of electrodes (negative and positive) at its end through which current is passed using the tissue as a conduction surface[3,16]. No current is passed through the tissues to either a distant or local electrode; for this reason, the induced electromagnetic field is insignificant[28]. Both devices are directed in the setting of active bleeding[16]. In contrast to BiCAP, heater probe mucosal injury is based on direct heat application rather than electrical current. Both probes have an irrigation port[25].

The heater probe and BiCAP have advantages. They cause less tissue injury (in comparison to laser therapy), permit tangential application of cautery, and are both are relatively inexpensive and widely accessible[11]. They are also considered the best methods to use in patients with electronic devices, such as pacemakers and defibrillators[28]. The disadvantage of both methods is char formation on the tip of the probe, requiring catheter retrieval and repeated cleaning[7,11,16].

In a randomized prospective trial by Jensen *et al*[29], 21 patients with chronic recurrent hematochezia and anemia due to CRP were followed for 12 mo. Nine patients were treated with heater probe and 12 with BiCAP (power of 10-15 W). A median of four sessions was required. Severe bleeding episodes were significantly reduced after BiCAP (75% *vs* 33%) and heater probe (67% *vs* 11%) treatment without a statistically significant difference between the methods. The decreased rate of bleeding was accompanied by hematocrit improvement in both groups. There were no major complications.

A retrospective study evaluated 55 patients treated with three sessions of BICAP (power of 30 W) and sucralfate enemas. The authors concluded that BICAP was effective in stopping bleeding from telangiectasias, decreasing recurrence, hospital stay and blood requirements (especially in the group of more severe patients). Unfortunately, there were no comments about complications and follow-up in this study[30].

We recently published a prospective randomized trial comparing APC and BiCAP for rectal bleeding due to CRP. Fifteen patients were enrolled in each group. BiCAP was performed using a 7Fr Gold probe (Wilson-Cook, Winston-Salem, United States) and a high frequency generator (ERBE ICC 200; Electromedizin, Tubingen, Germany). The power setting was 50 W. Coagulation was achieved by applying light pressure with the

probe directly into each telangiectasia. Success was considered as the eradication of all abnormal vessel, and failure as the requirement for more than seven sessions or the need for other therapeutic modality. The complete eradication success rate was 93.3% for BiCAP after a mean of 2.9 sessions, *vs* 80% at 3.7 sessions for APC ($P > 0.05$). Ten of 15 (66.7%) patients had minor complications, mainly transitory anal and abdominal pain. One developed symptomatic stenosis (successfully managed with a fecal emollient). Five patients presented major or hemorrhagic complications (two patients had both minor and major complications). There were no statistical differences between the groups regarding complications when categorized as major ($P = 0.169$) or minor ($P = 0.068$). Nevertheless, the total rate of complications was significantly higher in the BiCAP group ($P = 0.003$, with power 97.4%). No other more severe adverse events, such as fistulas, extensive necrosis, bowel explosion or perforations were noticed in this study. The frequency of complications was evidently superior than those reported so far. Many potential factors can account for such a difference: Most prior studies have been retrospective and underestimated the real incidence of complications; in our study, BiCAP was used at a higher power setting; our patients had a meticulous follow-up; most of the complications were minor and all of them were managed on an outpatient basis. We concluded that APC and BiCAP are both effective for hemorrhagic CRP. There are probably no significant differences between the two methods. Even though, APC seemed to be safer than BiCAP in our study, further research with a larger sample size is necessary to assess complication rates and determines the best therapeutic choice[31].

Endoscopic band ligation

Endoscopic band ligation (EBL) was introduced in 1986 and is currently considered the endoscopic method of choice for the prevention of esophageal varices bleeding[32]. As far as we know, there is only one paper published on the use of EBL as a treatment for CRP[33]. The authors reported one patient who had been treated with APC sessions with no success. EBL was performed with a gastroscope and a standard multiband ligation kit. Three bands were placed in the first session and two during the second session (interval of 20 d between the first and second sessions). The procedure was well tolerated. A lower gastrointestinal endoscopy 45 d after the completion of treatment showed no evidence of ongoing CRP[33]. This was the first experience using this technique, and more data are needed to make further conclusions.

Cryotherapy

Cryospray ablation, similar to APC, is a non-contact therapeutic method by the application of liquid nitrogen or carbon dioxide gas at extremely cold temperatures[8,16]. Cryoablation has been used to treat esophageal early cancer and high-grade dysplasia[8]. Limited data exist on the efficacy of this technique for treating vascular lesions[25]. In a few studies, endoscopic cryoablation was performed in patients with CRP[34-38].

Cryotherapy is performed with a catheter passed through the working channel and its tip is positioned around 0.5 to 1.0 cm from the end of the scope. The spray is applied for 5 s directly onto the mucosa. The freeze/thaw cycle is repeated for a total of three series (total of 15 s) per involved area. A decompression tube with ports spanning the distal 35-40 cm is inserted over a Savary-like guide wire. Suction *via* the decompression tube is applied for the period of cryospray application to protect against over-insufflation[8,35]. Despite this care, one patient was reported with a cecal perforation caused by malfunction of the decompression tube. For this reason, the procedure was adapted to reduce treatment time and carry out full colonoscopy after the cryotherapy for bowel decompression[35]. Difficulties include the field of view with frosting of the lens, and management around the decompression tube. Using a friction-fit mucosectomy cap reduces the chance that the catheter will adhere to the surface and improves access to difficult areas[39].

The required number of sessions ranges from one to four. In one study, the endoscopic score considerably improved, as well as hematochezia and rectal pain. Symptomatic improvement was observed in 80% of patients[35].

The cryospray generators currently on the market are more cumbersome and less mobile than most APC and the radiofrequency units, and need maintaining a supply of liquid nitrogen, which lasts around 2 wk in the holding tank. Therefore, therapies for rare findings, mainly in a lower volume service, may be more difficult. One possible advantage of cryospray over the heat-generating ablative techniques is that colonic lavage is not required to reduce the probability of gas ignition. However, studies in animals showed that the depth of tissue destruction may be deeper with cryospray than that achieved by RFA, and it is unknown whether this could lead to fistulas, abscesses and strictures or whether cryospray is inherently less prone to such complications. Furthermore, the quickly expanding gas requires adequate venting, which may be difficult for proximal lesions in the sigmoid[16].

Studies using cryospray for CRP remain experimental and anecdotal. These initial case reports support the use of cryotherapy for the treatment of CRP. In spite of this, there has been no prospective study comparing cryotherapy with other methods such as APC, regarding the durability of results, safety and efficacy. Supplementary research is required to confirm the superiority or even utility of cryospray[16].

RFA

RFA is a newer endoscopic technique. The Halo RFA system uses two different types of probes with a closely spaced arrangement of electrodes, which thermally ablate tissue. The depth of injury (0.5-1 mm)

is dependent on the power, density and duration of contact. A generator connects to either a 360° Halo catheter or a 90° Halo catheter to provide circumferential or more focused ablation[40]. The FDA (United States Food and Drug Administration) approved the RFA for the treatment of Barrett's esophagus and for gastric hemostatic applications. RFA reaches large areas in a superficial way, suggesting that analogous benefits could be applied in the rectum and colon[41].

Recently, a number of studies have evaluated the safety and efficacy of RFA for CRP treatment[40-45]. RFA is generally performed on outpatients using a single use Halo90 electrode catheter (BARRx/Covidien, Sunnyvale, United States) that is passed through a standard gastroscope. A gastroscope is used instead of a colonoscope because Halo devices are designed for a gastroscope, and because retroflexion is easier using a gastroscope, especially with the RFA catheter attached. During the ablation procedure, the Halo90 catheter is mounted in the 6 o'clock position (as opposed to the 12 o'clock location usually used for the ablation of Barrett's esophagus). To promote hemostasis, the coagulum in treated areas is not scraped off. The endoscope and device are removed for cleaning every eight applications in order to preserve electrode surface effectiveness for subsequent areas treatment. Ablations are performed about 1 mm proximal to the dentate line (to prevent sensory injury to the anal mucosa) and restricted to a short length (less than 6 cm to the dentate line). The procedure is repeated as needed until complete rectal mucosa ablation is achieved. Based on prior studies, an energy density of 12-15 J/cm^2 at a power density of 40 W/cm^2 was selected, which showed no transmural damage at these settings[8,41,43].

Generally, the procedure is well tolerated with mild anorectal pain was reported in 12% of sessions. One of 39 patients presented with significant anorectal bleeding (endoscopic exam demonstrated arterial-like hemorrhage from a vessel in a shallow erosion at a place of excessive ablation) and was treated with a single hemostatic clip[41]. After one or two RFA sessions, hemostasis was achieved with a significant decrease in clinical symptoms and an increase in the hemoglobin concentration[8,41,43]. Thus, RFA seems to be safe and effective to treat CRP. The benefits of RFA include re-epithelialization with the prevention of rebleeding without stenosis and ulceration that may be more frequently observed in other thermal methods. The narrowly spaced bipolar array of the RFA catheter confines the radiofrequency energy penetration, restricting the RFA lesion to the superficial mucosa, in this manner avoiding deep tissue injury. In conclusion, RFA permits much broader areas of tissue to be treated at the same time compared to the point-by-point approach required with the bipolar or heater probes, or even with APC. Similar to APC, the equipment is transportable and can be utilized in different places. The BARRx units also deliver a consistent energy to the surface by using a well defined and a reproducible ramp-up of energy. This diminishes the likelihood of over-treatment and operator-dependence that may lead to ulcerations or perforations[16]. However, despite these theoretical advantages, some statements should be made before RFA is considered the treatment of choice for CRP. First of all, these studies were retrospective and conclusions are limited by the lack of a control group. They were also non-powered and even considering all published works, only a few dozen patients with CRP have been treated with RFA. Another important limitation is that no sigmoid or proximal rectal lesions were ablated, thus safety in those areas (with a thinner wall) remains uncertain. The cost of the RFA energy generator (applicable in only a few indications) and the price of the Halo catheter can be another drawback. Therefore, additional controlled studies are required to compare RFA to other therapeutic modalities for CRP.

APC

APC is a non-contact thermal method using ionized argon gas to deliver a monopolar high-frequency current, which efficiently coagulates tissue. APC is applied to tissue until a white coagulum appears, and then the endoscope and catheter are maneuvered in a vertical or circumferential linear pattern to coagulate additional tissue. The depth of tissue destruction is limited due to increased resistance and decreased current flow through coagulated tissue[39]. Once the tip makes contact with the target tissue, it works as a monopolar probe and it can cause deeper damage. And contact between the tissue and tip may also result in the infusion of extraluminal or submucosal gas. Due to repeated contact with the mucosa, a coagulum may also develop on the extremity of the catheter, which needs intermittent removal of the probe for manual cleaning[25].

The second-generation equipment (VIO/APC2) integrates numerous improvements over the first-generation device. The total effectiveness of the method was improved by 30% ± 50%, so lower power settings can be utilized to create the same thermal effects and, conversely, the same power settings may produce deeper and more extensive tissue injury than expected. Three different modes are now available on the apparatus: Forced, pulsed and precise. Forced mode provides continuous output and corresponds to the settings on the earlier system. Pulsed mode delivers an intermittent current with two alternative effects: Effect 1 pulses nearly every second with a higher energy output following each pulse, while effect 2 pulses around 16 times per second with a lower energy output *per pulse*. The latter may be preferred when superficial treatment of large surface areas is desired. Precise mode uses an integrated regulation system to control the flow. This results in a more superficial depth of damage compared to the other settings[39].

APC has been used to treat a wide spectrum of bleeding lesions in the gastrointestinal tract[25]. However, CRP is really a niche for APC[46]. An impressive

number of studies evaluated APC efficacy and safety for the treatment of CRP, with more than 500 patients enrolled[15,21,31,47-52]. Thus, APC is certainly the best-studied technique in the management of this disease. Nevertheless, until now, there has been no consensus regarding the best APC settings (gas flow rate and power). Power settings reported in the literature range from 25-80 W and flow from 0.6-2.5 L/min[8,15]. Gheorghe *et al*[53] compared two different power settings: 23 patients were treated with 60 W and 19 patients with 50 W. They concluded that there was no statistical significance concerning the efficacy and safety of APC application between the 60 W and 50 W power setting, although rectal stenosis was described only in patients treated with the higher power setting. Sato *et al*[52] using a porcine rectal wall *ex vivo*, found that the optimal setting was 40 W with 1.2 L/min gas flow and a two-s application, which was enough to treat submucosal vessels but did not affect the muscle layer.

More spread lesions commonly need repeated applications per session and several treatments. The mean number of sessions varies from 1 to 3.7 with a calculated overall cumulative mean of 2.13 sessions per patient (median: 2)[16,31]. APC session intervals range from every 2 d to every 8 wk[15,16]. APC improves rectal bleeding in 80%-90% of cases as well as symptoms of tenesmus, diarrhea and urgency in 60%-75% of cases[16]. Follow-up ranged from 2 to 60 mo[15]. Recurrences have been reported, which responded to additional rounds of APC therapy[16,31].

Ulcers after APC can be considered an effect of thermal injury to already damaged, compromised more fragile and tissue, with poorer healing. Ulcer incidence may be affected by the flow rate and power settings of the argon gas, way of application, interval between sessions, and number of sessions subsequent to ulcer development, which may delay ulcer healing due to repeated thermal damage. The fact that rectal ulcers are not clinically problematic denotes they should not be considered a complication or an absolute contraindication to APC, nor do they necessarily need any further endoscopic follow-up[16,54]. However, it is advisable that in the presence of a large ulcer (> 1.0 cm), treatment should be delayed.

The overall reported complication rate with APC has been variable[16], probably due to the lack of a standard technique, variation in the criteria for defining complications and different follow-up periods. The most common procedure-related complication is rectal or anal pain with or without tenesmus, which is most probable to occur following treatment near the dentate line, and habitually resolves spontaneously within a few days, with or without regular analgesics[16,31]. A method described by Coriat *et al*[55], using a transparent cap attached to colonoscope tip, improved visualization of the upper part of the anal canal and of low rectal lesions without retroflexion and a proper distance for safe and effective APC use. Vagal symptoms, cramping and abdominal bloating related to luminal distension have also been reported. One potential drawback of using APC is the risk of excessive bowel distention from the quick instillation of argon gas. It is recommended that, whenever available, a two-channel endoscope should be utilized so that the insufflated argon gas can be removed periodically, associated with a low flow rate[16].

Overall, the frequency of asymptomatic rectal strictures is 4.3%[16]. Although some eschew treating in a circumferential manner to avoid stricture formation, the results of Villavicencio *et al*[56] seem to indicate otherwise. It is likely that the long trawl back technique is more associated with rectal strictures than single-shot procedures with separated spots[57-59]. Ben-Soussan *et al*[59] reported three cases of colonic explosion in two poorly prepared patients. The pathophysiology of the explosion remains unclear but an accumulation of bowel gas (methane and hydrogen) at potentially explosive concentrations due to poor preparation could be the cause. Theoretically, intestinal gas production could also be influenced by the presence of fermentable products in the administered enema. In the Ben-Soussan study[59], the enema used (disodium phosphate and monosodium phosphate) did not contain any fermentable agent likely to increase gas production and facilitate colonic explosion. Thus, these authors concluded that rather than the type of preparation, the presence of stools above the telangiectasias constituted the main risk. In our previous study, we also used enema preparation before the APC session and did not encounter any colonic explosions[31]. As far as we know, no other explosions have been recently reported in the literature.

Bacterial translocation of endogenous microbial flora into the bloodstream may occur during any endoscopic procedure. We prospectively evaluated the frequency of bacteremia following APC during CRP treatment. A total of 21 patients were included and 30 APC sessions were performed. Bacteremia was found in two patients (6.67%). In one case, the isolated bacterium was *Staphylococcus hominis,* and regarded as a contaminant. Another patient had two different microorganisms (*Rhodotorula sp.* and *Streptococcus bovis).* None had infectious symptoms[50].

There are few comparative studies using APC. One of them compared two different power settings[53] and the other compared oral sucralfate with placebo following APC; the authors stated that additional sucralfate treatment did not influence clinical or endoscopic outcomes[49]. Only four studies have compared APC with other therapy for CRP. Two compared APC with formalin (vide formalin section)[21,22], one with hyperbaric oxygen[48] and our study assessed APC *vs* BiCAP (see contact method)[31]. The results of these preliminary studies show that APC is at least as effective and safer than other treatments. However, more comparative studies with larger series, especially between APC and the newest techniques (RFA and cryotherapy) are needed for definite conclusions.

DISCUSSION

CRP is a troublesome complication with an adverse effect on quality of life. The most common complaint is rectal bleeding. Most available data come from uncontrolled, undersized studies with short-term follow-up. Satisfactorily powered, randomized trials comparing different modalities are lacking, and an optimal management strategy has yet to be determined.

Vitamin A had some benefits on functional symptoms, but has not been studied regarding blood loss. Sucralfate enema seems to be the best medical therapy and is well tolerated and secure[15,16]. There is not enough data to support the use of other medical options in daily practice[1-3,8]. Surgical management is associated with high morbidity and mortality and should be considered a last resort. Fewer than 10% of patients eventually require surgery, which is usually for intractable bleeding, perforations, strictures and fistulas[6,7]. In this scenario, endoscopic treatment is becoming increasingly popular[31].

Besides the therapeutic aspects, endoscopy plays a role in diagnosis and grading and in ruling out another sources of bleeding, especially malignancy[3,4,11] Full colonoscopy is recommendable for all patients with rectal bleeding. Due to the risk of fistula formation, rectal biopsies should be performed judiciously. If necessary, they should be directed to the lateral and posterior walls to avoid irradiated areas[11].

Patients considered to be ideal candidates for endoscopic treatment are those with transfusion dependency, chronic hematochezia, refractory to medical management, no tumor recurrence, no other bleeding source, and no fistulas, ulcerations or strictures[18]. It is still controversial that patients with occasional hemorrhage without anemia should be treated endoscopically. We think that at least one endoscopic session during the first diagnostic colonoscopy is a reasonable approach. Presumably, it will resolve once and for all these milder cases[60]. Of course, this and subsequent treatments (if necessary) should be tailored to the patient's preferences.

Nowadays, we agree with other authors in advocating a four to 6 wk interval between sessions[46,59,61]. It is likely that the ischemic rectal mucosa needs this minimal amount of time to recover from thermal or chemical injury[1-3,8]. We agree with John Lee[46] that repeating endoscopy is not necessary in the absence of symptoms.

Good bowel preparation is crucial for endoscopic therapy. We currently recommend complete anterograde bowel preparation for all treatment sessions. Because enemas can cause trauma to a friable mucosa, and many patients with CRP have fecal incontinence[21], retrograde preparation may be more difficult and provide worse results. Because feces above the lesions are the main risk for bowel explosion[59], in cases of poor preparation, the procedure should be postponed or vigorous washing must be done. In the presence of significant oozing, adrenaline solution (1:10000) should be sprayed over the mucosal surface[31].

Like other invasive procedures, there is a debate about antibiotic, antiplatelet and anticoagulant prophylaxis with endoscopic therapy for CRP. The current American Society for Gastrointestinal Endoscopy guidelines do not mention the use of antibiotics in this patient condition (CRP) nor in this procedure (endoscopic ablation)[62]. Tam *et al*[57] suggested the use of antibiotics for immunocompromised patients before APC for CRP. Postgate *et al*[63] made this recommendation for all patients. However, in our study, the incidence of bacteremia after APC for CRP was low (6.67%), similar to the mean frequency of bacteremia associated with colonoscopy in the literature (4.4%). Therefore, APC for CRP may be considered a low-risk method regarding infectious complications, and does not demand the prophylactic administration of antibiotics[50]. Unfortunately, until now, no other study like ours has been done with other endoscopic techniques for CRP. Chruscielewska-Kiliszek *et al*[47] suggested that antiplatelet drugs can play a protective role against ulcer formation after APC. In our study, we found a negative impact of antiplatelet medication, with a statistically significant higher number of APC sessions being required to eradicate telangiectasias in patients using aspirin (P = 0.047) (unpublished data). Kaassis *et al*[61] also reported a higher number of treatments in patients using anticoagulants. In the Karamanolis *et al*[64]'s study recurrence was higher in those using an anticoagulant or aspirin (P = 0.02). The present European Society of Gastrointestinal Endoscopy guidelines recommend that clopidogrel or aspirin can be continued in patients undergoing APC for vascular lesions (recommendation grade C). In the lack of appropriate studies, no recommendation can be made for patients taking a combination of thienopyridines and aspirin[65].

Another issue is whether concomitant medical treatment improves the results of endoscopic treatment. Patel *el al*[19] demonstrated that adding vitamin A enhances the effectiveness of formalin application (see the section on formalin treatment). On the other hand, combined oral sucralfate for 4 wk with APC was not better than APC alone in improving the overall disease severity score (see APC section)[49]. Two possible reasons for the absence of an effect of sucralfate are the short-term period of use and the oral route. Kochhar *et al*[66] identified a good response with enemas with a 77% response in 4 wk and 92% response in 16 wk. Studies using oral vitamin A and sucralfate enemas (or both) for longer periods in association with different endoscopic modalities are welcome, especially in patients with intractable bleeding.

Intractable bleeding is traditionally managed surgically. Nonetheless, when surgery is needed, most studies have demonstrated poor outcomes (because a diversion rarely controls the bleeding completely), as well as high complication (15%-80%) and mortality (3%-9%) rates[6]. Therefore non-surgical strategies

are desirable. Some authors described the success of a second endoscopic modality when the first one had failed[22,33,56,67]. So a cross-over (two endoscopic methods) or a combined (medical plus endoscopic treatments - see above) schemes may avoid surgery in some patients.

A variety of endoscopic techniques for treating CRP were evaluated and discussed in this review. The choice of treatment should be based on the availability and experience of each center[13]. If there is more than one method at hand, some considerations can be made. Laser therapy is an obsolete technology and should be abandoned. Contact methods, especially BiCAP, are very well indicated for patients with pacemakers and other implantable devices. The best way to use formalin is still unknown. More studies with EBL, cryoablation and RFA are still needed. APC has emerged as the front-runner due to its ease of use, affordability, better-defined settings, efficacy and safety. Perhaps in the future, the results of the second generation APC device will improve further.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence?

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Abstract

AIM: To analyze outcomes in patients who underwent liver transplantation (LT) for hepatocellular carcinoma (HCC) and received autologous intraoperative blood salvage (IBS).

METHODS: Consecutive HCC patients who underwent LT were studied retrospectively and analyzed according to the use of IBS or not. Demographic and surgical data were collected from a departmental prospective main-

tained database. Statistical analyses were performed using the Fisher's exact test and the Wilcoxon rank sum test to examine covariate differences between patients who underwent IBS and those who did not. Univariate and multivariate Cox regression models were developed to evaluate recurrence and death, and survival probabilities were estimated using the Kaplan-Meier method and compared by the log-rank test.

RESULTS: Between 2002 and 2012, 158 consecutive patients who underwent LT in the same medical center and by the same surgical team were identified. Among these patients, 122 (77.2%) were in the IBS group and 36 (22.8%) in the non-IBS group. The overall survival (OS) and recurrence free survival (RFS) at 5 years were 59.7% and 83.3%, respectively. No differences in OS (P = 0.51) or RFS (P = 0.953) were detected between the IBS and non-IBS groups. On multivariate analysis for OS, degree of tumor differentiation remained as the only independent predictor. Regarding patients who received IBS, no differences were detected in OS or RFS (P = 0.055 and P = 0.512, respectively) according to the volume infused, even when outcomes at 90 d or longer were analyzed separately (P = 0.518 for both outcomes).

CONCLUSION: No differences in RFS or OS were detected according to IBS use. Trials addressing this question are justified and should be designed to detect small differences in long-term outcomes.

Key words: Cell saver; Cancer; Hepatocellular carcinoma; Liver transplantation; Recurrence

Core tip: This study addresses an alternative option for allogeneic blood transfusion during liver transplantation (LT) for hepatocellular carcinoma (HCC). The autologous blood salvage in LT, in our series, did not impact recurrence or death. This suggests that autologous blood transfusion should be considered an option avoiding the deleterious effects of allogeneic blood transfusion. Overall, we do believe that our data claim for trials looking for non-inferiority comparing the two modalities of blood transfusion in patients who underwent LT for HCC. We do believe that further studies are justified and should be designed to detect small differences in long-term outcomes.

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INTRODUCTION

Autologous intraoperative blood salvage (IBS) is used routinely in many surgical specialties to minimize the effects of intraoperative bleeding, avoiding the risks of allogeneic red blood cell (RBC) transfusion. A recent cochrane review showed a 40% reduction in the requirements for allogeneic blood transfusion with cell salvage[1]. IBS has been generally used in liver transplantation (LT), although it is not usually recommended in patients with hepatocellular carcinoma (HCC) since there is a putative risk of reinfusion of neoplastic cells. The IBS is an alternative to allogeneic blood transfusion but it remains a controversial technique in oncologic procedures since it could represent an uncertain risk of malignant cell reinfusion[2-5].

The circulation of viable neoplastic cells in the IBS device and their detection in the leukocyte depletion filter (LDF) have been proved, and LDF has been used as an effective method to clean the RBC component before infusing it back[5-9]. Although the rationale to use LDF to block neoplastic cells back by the IBS device has been investigated on experimental studies, the clinical relevance analysis over patients who underwent LT for HCC has been restricted to a single study[5]. In the latter case, no differences were observed in recurrence between patients who received IBS and those who did not. However, it was not possible to rule out the possibility that this result was a consequence of a small sample size.

The aim of this study was to evaluate if the use of IBS for HCC patients who underwent LT increases the risk of tumor recurrence. To our knowledge, this is the largest series addressing this question in this population.

MATERIALS AND METHODS

Subjects and data collection

Patients submitted to LT for HCC at Hospital das Clínicas of University of São Paulo Medical School (HCFMUSP) were analyzed from a prospectively maintained database containing demographic, clinical, operative, pathological, and follow-up data and studied retrospectively. Permission was obtained from the informed consent statement and institutional review board according to the institutional policy for protected health information.

All patients presented in this analysis were initially considered to meet the Milan criteria or UCSF criteria[10,11]. Patients who had detectable extra-hepatic disease during the pre- or intraoperative course and patients with a concurrent second neoplasm were not included. Patients who did not present HCC in the specimen were excluded with the exception of those previously treated with radiofrequency or chemoembolization. Pre-operative imaging modalities to evaluate the extent of intrahepatic disease and to exclude extra-hepatic metastatic sites included

computed tomography and/or magnetic resonance imaging of the chest, abdomen, and pelvis. Model of end-stage liver disease (MELD) scores were calculated using laboratory results collected prior to the LT. The MELD score was calculated using the standard UNOS formula: MELD = 3.78 × ln (bilirubin) + 11.2 × ln (INR) + 9.57 × ln (creatinine) + 6.43, where bilirubin and creatinine are in mg/dL units and INR is the international normalized ratio. The MELD score was analyzed separately as both continuous and categorical variables (*i.e.*, ⩾ 20 *vs* <20).

The estimated blood loss was not fully available and thus it was not described and analyzed. The intraoperative decision to transfuse either allogeneic or autologous blood was consensual between the surgeon and the anesthesiologist. It was based on hemodynamic status, blood loss, hemoglobin concentration and patient's comorbidities.

Follow-up time was calculated from the date of LT to the date of last clinical encounter captured by the HCFMUSP medical record system or the date of death. Recurrence-free survival (RFS) was calculated from the LT to the first detected recurrence or last follow-up without recurrence. Overall survival (OS) was calculated based on the survivorship status (deceased or alive) at last follow-up.

Blood salvage processing

The blood from the surgical field was collected using a Cell Saver auto-transfusion device (Fresenius C.A.T.S, Terumo Cardiovascular Systems, Germany) and anticoagulated with heparinized saline and stored. The RBC component of aspirated blood was centrifuged and washed with heparinized saline. The RBC concentrates were filtered through an LDF (FTS-RC202, Shuangweibio Corp., Nanjing, China). Processed RBCs were transfused back to the patient when appropriate.

Statistical analysis

Statistical analyses were performed using the Fisher's exact test and the Wilcoxon rank sum test to examine covariate differences between patients who underwent IBS and those who did not. Values are expressed as median (interquartile) or percentage, as appropriate. Survival probabilities were estimated using the Kaplan-Meier method and compared using the Log-Rank test. A Cox regression model was developed to determine factors independently associated with death. The use of IBS was included in the multivariate analysis regardless of its univariate significance. Other factors that were significantly associated with outcomes by univariate analysis (inclusion criterion, $P \leqslant 0.1$) were entered into a multivariate analysis to test for significance of IBS adjusting for possible confounders. For recurrence assessment, no Cox regression was used since the number of events per variable was not appropriated[12,13]. A P value < 0.05 was considered significant for univariate and multivariate analyses. All statistical analyses were conducted using STATA v 9.0 (Stata Corp, College Station, TX).

Table 1 Clinicopathological distribution according to the use of autologous intraoperative blood salvage for patients with hepatocellular carcinoma who underwent liver transplantation

	Total (%) *n* = 158	Intraoperative blood salvage		*P*
		Yes (%) *n* = 122 (77.2)	No (%) *n* = 36 (22.8)	
Age[1]	58 (51-62)	58 (51-62)	58 (51-62)	0.958
Male gender	122 (77.2)	95 (77.9)	27 (75)	0.821
BMI[1,2]	25.7 (23.6-27.8)	25.7 (23.6-27.8)	25.5 (23.5-2.3)	0.712
Pre-op AFP[3]	9.2 (3.7-35.4)	8.9 (3.5-3.6)	10.9 (6.7-33.7)	0.175
Cirrhosis[4]	135 (88.3)	100 (84.8)	35 (100)	0.014
Alcohol[4]	22 (14.4)	18 (15.3)	4 (11.4)	0.785
Hepatitis[4]				
B	20 (13.1)	12 (10.2)	8 (22.9)	0.082
C	97 (63.4)	73 (61.9)	24 (68.6)	0.551
Others[4]	8 (5.2)	8 (6.8)	0	0.199
Blood type				0.420
A	60 (37)	42 (34.4)	18 (50)	
B	21 (13.3)	17 (13.9)	4 (11.1)	
AB	14 (8.9)	11 (9)	3 (8.3)	
O	63 (39.9)	52 (42.6)	11 (30.6)	
Rhesus[5]	123 (86.6)	93 (86.1)	30 (88.3)	1.000
MELD[1]	10 (8-15)	10.5 (9-17)	9 (8-13.5)	0.058
Radiofrequency[4]	4 (2.6)	3 (2.6)	1 (2.8)	1.000
Chemoembolization[4]	69 (45.1)	53 (45.3)	16 (44.5)	1.000
Alcoholization[4]	7 (4.6)	5 (4.3)	2 (5.6)	0.668
Graft/body proportion[1,2]	1.75 (1.5-2.2)	1.8 (1.5-2.2)	1.7 (1.4– 2.2)	0.454
Number of lesions[1]	2 (1-3)	2 (1-3)	2 (1-3)	0.715
Largest lesion, mm[1]	25 (19-31)	25 (19-30)	25 (18-35)	0.384
Edmond-steiner degree (III and IV)[6]	88 (59.9)	67 (58.8)	21 (63.5)	0.689
Vascular invasion	53 (33.6)	44 (36.1)	9 (25)	0.236
Microsatellite lesions	26 (16.5)	19 (15.6)	7 (19.4)	0.612
Cholangiocarcinoma	6 (3.8)	6 (4.9)	0	0.338
Recurrence	14 (8.9)	10 (8.2)	4 (11.1)	0.525
Death	52 (32.9)	41 (33.6)	11 (30.6)	0.841

[1]Expressed as median (p25-p75); [2]N = 150; [3]N = 148; [4]N = 153; [5]N = 142; [6]N = 147. BMI: Body mass index; AFP: Alpha-feto protein; MELD: Model of end-stage liver disease.

RESULTS

Between January 2002 and September 2012, 158 consecutive patients who underwent potentially curative LT for HCC were included. One hundred and twenty-two (77.2%) patients in the IBS group and 36 (22.8%) patients in the non-IBS group were compared. Patients and clinicopathological presentation were compared between groups and are summarized in Table 1. Briefly, the demographic and clinicopathological characteristics were comparable between the two groups. The only significant difference was the presence of liver cirrhosis, which was more prevalent in the non-IBS group (100% *vs* 84.8%, $P = 0.014$).

Survival analysis

The median follow-up time for all patients was 27 mo; 25 mo for the group who received IBS and 32 mo for the group who did not ($P = 0.049$). The median follow-

Table 2 Univariate and multivariate analyses for predictors of overall survival

	Total	5-yr survival (%)	Median survival (mo)	Univariate analysis *P*	HR	95%CI	Multivariate analysis *P*
Overall	158	59.7	-	-			
Age (≥ 60 yr)	-	-	-	0.133			
Gender		-	-	0.097			
Male	122	61.5			0.88	0.45-1.74	0.714
Female	36	55.4	-				
BMI (≥ 28)				0.080			
Yes	37	48.2	46		1.55	0.81-2.98	0.186
No	113	63.6	-				
Pre-op AFP (≥ 100 ng/dL)				0.087			
Yes	19	51.8	-		1.50	0.68-3.32	0.316
No	129	60.8	-				
Cirrhosis	-	-	-	0.950			
Alcohol related				0.048			
Yes	22	86.4	-		0.30	0.09-1	0.051
No	131	55.5	-				
Hepatitis B infection	-	-	-	0.156			
Hepatitis C infection	-	-	-	0.130			
Others	-	-	-	0.281			
Blood type	-	-	-	0.470			
Rhesus	-	-	-	0.554			
Radiofrequency	-	-	-	0.821			
MELD (≥ 15)	-	-	-	0.721			
Chemo-embolization	-	-	-	0.877			
Tumor alcoholization	-	-	-	0.118			
Graft/body % (≥ 2)	-	-	-	0.163			
No. of lesions (> 3)	-	-	-	0.819			
Largest lesion (≥ 30 mm)	-	-	-	0.640			
Edmond-Steiner degree				0.013			
III-IV	88	48.9	51		2.19	1.07-4.47	0.031
0-II	59	74.4	-				
Vascular invasion	-	-	-	0.290			
Microsatellite lesions	-	-	-	0.283			
Cholangiocarcinoma	-	-	-	0.957			
IBS				0.510			
Yes	122	59.5	-		1.56	0.74-3.30	0.237
No	36	64.5	-				

BMI: Body mass index; AFP: Alpha-feto protein; IBS: Intraoperative blood salvage; MELD: Model of End-Stage Liver Disease. The number of patients included in multivariate model is 141.

up time for survivors was 38 mo; 37 mo for the group who received IBS and recurred and 41 mo for the group who did not (P = 0.017). The estimated 3- and 5-year OS rates were 68% and 59.7%, respectively. When OS was adjusted for the use of IBS or not, no difference was detected (P = 0.51), as depicted in the Figure 1A. The univariate and multivariate analyses for death were performed and are shown in Table 2. Briefly, no differences were detected according to MELD either as a continuous variable (recurrence, P = 0.633; death, P = 0.286) or as binominal, as demonstrated in Tables 2 and 3. Only elevated Edmond-Steiner degree of tumor differentiation (III-IV) remained significant for the risk of death, as shown in Table 2. The estimated 3- and 5-year RFS rates were 87.7% and 83.3%, respectively. When RFS was adjusted for the use of IBS or not, no difference was detected (P = 0.953; Figure 1B). The univariate analysis for recurrence is shown in Table 3. Briefly, elevated Edmond-Steiner degree of tumor differentiation (III-IV), pre-operative alpha-feto protein level equal to or higher than 100 ng/dL and presence of microsatellite lesions were independent predictors of recurrence, as demonstrated in Table 3.

Regarding the group of patients who received IBS (122 patients), the infusion volume was additionally analyzed as a continuous variable, and no differences were found in either recurrence (P = 0.512) or death (P = 0.055), as demonstrated in Figure 2A and B. Analyses of outcomes at 90 d or longer were performed and no differences in recurrence (P = 0.518) or death (P = 0.518) were detected (Figure 2C and D).

DISCUSSION

The IBS is largely accepted as an option for blood transfusion. However, the contra-indications are based on

Table 3 Univariate analysis for predictors of recurrence

	Total	5-yr survival (%)	Median survival (mo)	Univariate analysis *P*
Overall	158	83.3	-	-
Age (≥ 60 yr)	-	-	-	0.319
Male gender	-	-	-	0.410
BMI (≥ 28)	-	-	-	0.166
Pre-op AFP (≥ 100 mg/dL)				0.001
Yes	19	59.4	84.5	
No	129	85	-	
Cirrhosis	-	-	-	0.163
Alcohol related	-	-	-	0.207
Hepatitis B infection	-	-	-	0.911
Hepatitis C infection	-	-	-	0.568
Others	-	-	-	0.794
Blood type	-	-	-	0.912
Rhesus	-	-	-	0.494
MELD (≥ 15)	-	-	-	0.694
Radiofrequency	-	-	-	0.758
Chemoembolization	-	-	-	0.133
Tumor alcoholization	-	-	-	0.373
Graft/body % (≥ 2)	-	-	-	0.605
Number of lesions (> 3)	-	-	-	0.496
Largest lesion mm (≥ 30)	-	-	-	0.429
Edmond-Steiner degree				0.0162
III-IV	88	73	84.5	
0-II	59	94.3	-	
Vascular invasion				0.071
Yes	26	74.8	84.5	
No	132	86.3	-	
Microsatellite lesions				0.007
Yes	26	-	-	
No	132	86.5	-	
Cholangiocarcinoma	-	-	-	0.375
IBS				0.953
Yes	122	85	84.5	
No	36	78.8	-	

BMI: Body mass index; AFP: Alpha-feto protein; IBS: Intraoperative blood salvage; MELD: Model of End-Stage Liver Disease.

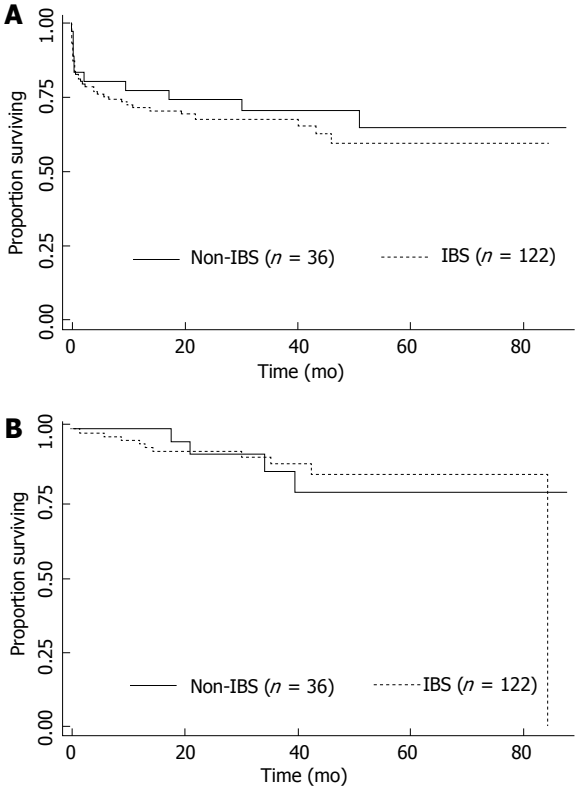

Figure 1 Kaplan-Meier estimates of survival from the date of liver transplantation according to the use of autologous intraoperative blood salvage. A: Overall survival (P = 0.51); B: Recurrence free survival (P = 0.953). IBS: Intraoperative blood salvage.

the use of contaminated blood as in chronic diseases like hepatitis or other viral infections, bile infection or colonization, and intra-operative contamination[4,8]. The same rationale is applied to avoid tumor dissemination in patients with liver cancer already identified. Although this apprehension has been justifying its practice, no clear relation between the use of IBS and cancer recurrence has already been proved. Operations with high blood loss including cancer surgery have been demanding IBS use, however retrospective series did not show any suggestive association between the increase of recurrence and IBS use[14].

Concerning HCC patients, IBS use was described in a few series for resection and LT. One series described no increase in recurrence with IBS, showing no differences in higher stages and even better results for patients who used IBS in early stage disease[15,16]. Two series of LT, respectively, with 31 and 40 patients in the IBS groups *vs* 16 and 96 patients as control group, were described[17,18]. Despite the theoretical risk of tumor cell dissemination, the recurrence rates were not increased by IBS use in both series[17,18].

The purpose of our study was to compare long-term outcomes for patients undergoing LT for HCC who received IBS or not. In our study population, the groups were comparable except for the remarkable presence of cirrhosis in the IBS group. As expected, patients with cirrhosis are technically challenging and the blood loss is usually elevated, more justifying IBS. With regard to oncologic outcomes, the use of IBS or not was not significantly associated with recurrence or death. The predictors associated with recurrence were presence of satellite lesions and elevated Edmond-Steiner tumor degree. This was also an independent predictor of death in the multivariate model. The principal finding of this study is that in a large patient population from a single institution there were no measurable differences in outcomes based on the IBS use for patients who underwent LT for HCC.

Regarding only the IBS group, differences in the volumes infused were associated with death but not with recurrence, as depicted in Figure 2. The volume infused changed when the time point of 90 d was used. In the earlier period, higher volumes were associated with death but not with recurrence. This performance translates the IBS volume as surrogate of estimated blood loss, which is an independent predictor of mortality and transfusion as well[19]. Patients in the earlier

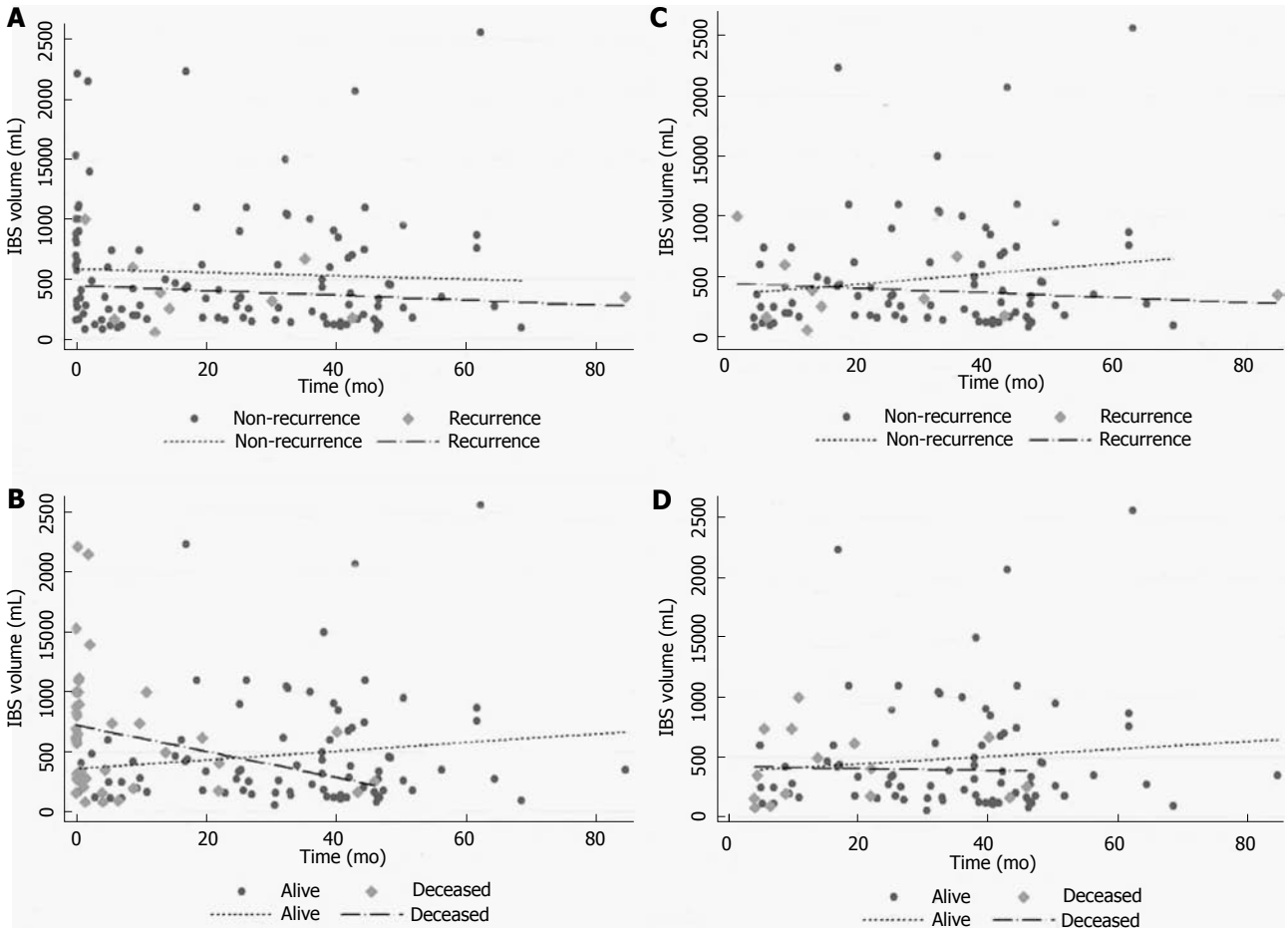

Figure 2 Scatter plots of the infusion volume of autologous intraoperative blood salvage over time. Overall distribution (total, *n* = 122) according to the time for recurrence (A: Recurrence, 10/91) and death (B: Death, 41/92). Distribution at 90 d and longer according to the time for recurrence (C: Recurrence, 9/91) and death (D: Death, 15/92). IBS: Intraoperative blood salvage.

period died in a short follow-up period and they could not have presented recurrence. With regard to longer follow-up (90 d or longer), the IBS volumes fit similarly for the distribution of recurrence or death. Long-term outcomes were not affected for the IBS volume in our series.

The limitations of the study are those associated with the immeasurable biases seen in all retrospective studies. We recognize that selection bias based on several nonobjective, undocumented criteria may have contributed to some of the differences between the two study groups. The estimated blood loss was not fully available and thus it was not described or analyzed.

The major finding of this analysis is the lack of any association between the use of IBS and oncologic outcomes. The results of this study should not be misinterpreted as an endorsement for the IBS use for all cancer patients. On the contrary, our data claim for more translational and clinical investigations of this issue. The operative hemorrhage in LT remains significant and blood transfusion is often demanded. The IBS should be applied as much as necessary, however the rationale of tumor cell reinfusion is a common concern[4,14,17,18,20-22]. Studies *in vitro* and retrospective series suggest that the use of LDF is effective enough to avoid tumor cell recirculation[5-7]. We believe that this finding is convincing and perhaps it is a reasonable explanation for no differences in recurrence or death in our series, since the LDF was used in all cases.

Moreover, a recent meta-analysis, including only non-randomized trials, showed an increase of risk for death and recurrence in patients with HCC who received allogeneic blood transfusion during hepatic resection[23]. Patients in the allogeneic group had a 16% more chance of recurrence at 5 years as well as a 60% more chance of all-case death in the same period. The reasons for the worse outcomes remain uncertain but it has been assumed that suppressive effects in the host immune system may have been responsible. The postulated mechanisms are allogeneic mononuclear cells; leucocytes-derived soluble mediators; and soluble HLA peptides circulating in allogeneic plasma inducing the host immune suppression[24]. These effects could be prevented by the autologous transfusion[24].

In summary, the present study shows that in a large consecutive series of patients undergoing LT for HCC in this single institution, there were no measurable differences in RFS or OS between patients who received IBS or not. With the lack of randomized clinical trials comparing the use of IBS for oncologic patients, its use could

be considered a reasonable option for individualized patients. Based on these data, a trial looking for no inferiority comparing the use of IBS and conventional blood transfusion for LT for HCC is justified and should be designed to detect small differences in outcomes.

COMMENTS

Background

Blood transfusion is usually necessary for liver transplantation (LT). Intra-operative blood salvage has generally been used in LT to avoid deleterious effect of allogeneic blood transfusion. However, autologous blood transfusion has not been recommended in patients with hepatocellular carcinoma (HCC) since there is a putative risk of reinfusion of neoplastic cells.

Research frontiers

Although there is a putative risk of reinfusion of cancer cells into circulation during surgery, there is no data yet demonstrating that it would really impact on oncologic outcomes. This study did not demonstrate impact on clinical and oncologic outcomes. However, since the data are retrospective, our finding claims for trials looking for no inferiority comparing the two modalities of blood transfusion in patients who underwent LT for HCC, to detect small differences in outcomes.

Application

This study addresses an alternative option for allogeneic blood transfusion during LT for HCC. The autologous blood salvage in LT, in this series, did not impact recurrence or death. This suggests that autologous blood transfusion should be considered an option avoiding the deleterious effects of allogeneic blood transfusion.

Innovations and breakthroughs

The use of intra-operative blood salvage would have immunological and economic impact during postoperative course. Circulating cancer cells were already demonstrated, however it also seems that leucocyte filters are safe enough to block those cells. Then, the use of auto-transfusion devices associated with leucocytes filters seems to be a potential resource to help patients who undergo LT for HCC

Terminology

IBS: Autologous intraoperative blood salvage; HCC: Hepatocellular carcinoma; LDF: Leukocyte depletion filter; LT: Liver transplantation; MELD: Model of End-Stage Liver Disease; OS: Overall survival; RFS: Recurrence free survival; RBC: Red blood cell.

Peer-review

Autologous IBS is generally used in liver transplantation to minimize the effect of intraoperative bleeding. However, the peripheral blood of HCC patients may be contaminated with cancer cells or cancer-inducing virus, which can lead to potential risks of recurrence. In this study, authors investigated the association between the intraoperative use of IBS and survival of HCC patients. According to the data of a postoperative follow-up cohort, they reported that the use of IBS cannot influence the survival of HCC patients. This is an interesting study and is useful for clinicians.

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CASE REPORT

Laparoscopic surgery for small-bowel obstruction caused by Meckel's diverticulum

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Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

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Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

A 26-year-old woman was referred to our hospital because of abdominal distention and vomiting. Contrast-enhanced computed tomography showed a blind loop of the bowel extending to near the uterus and a fibrotic band connecting the mesentery to the top of the bowel, suggestive of Meckel's diverticulum (MD) and a mesodiverticular band (MDB). After intestinal decompression, elective laparoscopic surgery was carried out. Using three 5-mm ports, MD was dissected from the surrounding adhesion and MDB was divided intracorporeally. And subsequent Meckel's diverticulectomy was performed. The presence of heterotopic gastric mucosa was confirmed histologically. The patient had an uneventful postoperative course and was discharged 5 d after the operation. She has remained healthy and symptom-free during 4 years of follow-up. This was considered to be an unusual case of preoperatively diagnosed and laparoscopically treated small-bowel obstruction due to MD in a young adult woman.

Key words: Surgery; Human; Meckel's diverticulum; Small-bowel obstruction; Laparoscopic surgery

Core tip: Meckel's diverticulum (MD) is a rare innate anomaly of the gastrointestinal tract caused by incomplete obliteration of the omphalomesenteric duct. It sometimes causes small bowel obstruction. However, as it symptoms are so non-specific, it may be difficult to make a correct diagnosis without exploratory laparotomy. This is a successful case of small-bowel obstruction caused by MD that was diagnosed preoperatively using multi-

dimensional contrast-enhanced computed tomography and treated by elective laparoscopic surgery.

Matsumoto T, Nagai M, Koike D, Nomura Y, Tanaka N. Laparoscopic surgery for small-bowel obstruction caused by Meckel's diverticulum. *World J Gastrointest Surg* 2016; 8(2): 169-172 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i2/169.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i2.169

INTRODUCTION

Meckel's diverticulum (MD) is one of the most common congenital anomaly of the gastrointestinal tract that results from an incomplete obliteration of the omphalomesenteric duct[1,2]. It has an incidence of 1%-2% among the general population, and most cases remain asymptomatic[2]. The rate of developing complicated MD is reported to be about 4% throughout lifetime[3], which comprises bleeding, inflammation or obstruction.

Intestinal obstruction may occur in cases where there is a volvulus or an internal hernia around a diverticulum, intussusception, or incarceration of the diverticulum in an inguinal (Littré) hernia[1]. However, as its symptoms, such as abdominal pain, distention, vomiting or constipation, are so non-specific, it may be difficult to make a correct diagnosis, and exploratory laparotomy is often required.

Here we report a case of small-bowel obstruction caused by MD that was diagnosed preoperatively using multi-dimensional contrast-enhanced computed tomography (CECT) and treated by elective laparoscopic surgery.

CASE REPORT

A 26-year-old woman was admitted to our hospital complaining of abdominal pain and recurrent vomiting. She had been hospitalized because of ovarian hyperstimulation syndrome 2 years previously, and had also suffered an episode of small-bowel obstruction 1 year prior to admission, which had been diagnosed as food impaction. She had no episode of hematochezia.

Physical examination demonstrated abdominal distention, with a soft abdomen and no tenderness or rebound pain. Her bowel sounds were hyperactive. Results of a hematologic examination were normal, and a urine pregnancy test gave a negative result.

Abdominal plain X-ray examination demonstrated a ladder-like series of distended small-bowel loops (Figure 1). Multi-dimensional CECT showed a blind-ending U-shaped loop of bowel in the pelvis and a fibrotic band connecting the mesentery to the blind end of the bowel, suggesting MD and a mesodiverticular band (MDB) (Figure 2). A change in the caliber of the ileum was evident adjacent to the band.

Figure 1 Abdominal plain X-ray examination demonstrated a ladder-like series of distended small-bowel loops.

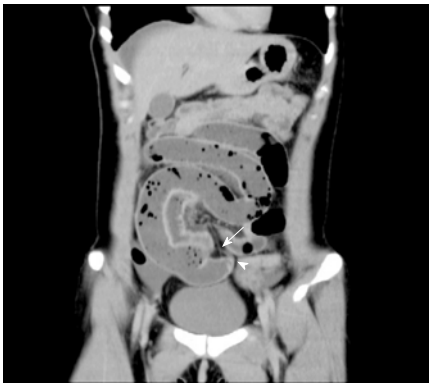

Figure 2 Contrast-enhanced computed tomography (coronal section image) showing a blind loop of the bowel extending near the uterus (arrowhead) and a fibrotic band connecting the mesentery to the top of the bowel (arrow) suggesting Meckel's diverticulum and a mesodiverticular band. The terminal ileum appeared to be conglutinated to the band and a change in caliber was ascertained.

We diagnosed the patient as having small-bowel obstruction, probably caused by adhesion to the MDB of MD, without any sign of vascular compromise.

A long tube was placed and her small intestine was successfully decompressed. After the tube had been removed, scintigraphy with 99mTc-Na-pertechnetate was performed, and this revealed uptake in the lower abdomen (Figure 3).

Although surgical treatment was proposed, the patient expressed a wish to temporarily leave hospital because of pressing business matters. She was therefore discharged after 1 wk of hospitalization.

Two months after discharge, we performed elective laparoscopic surgery using three 5-mm ports. MD was dissected from the surrounding adhesion and MDB was divided intracorporeally. Then subsequent Meckel's diverticulectomy was performed extracorporeally *via* a 2 cm mini-laparotomy. The postoperative course was uneventful and the patient was discharged on postoperative day 5, and she has since remained healthy and symptom-free during 4 years of follow-up.

Histological examination confirmed the presence of

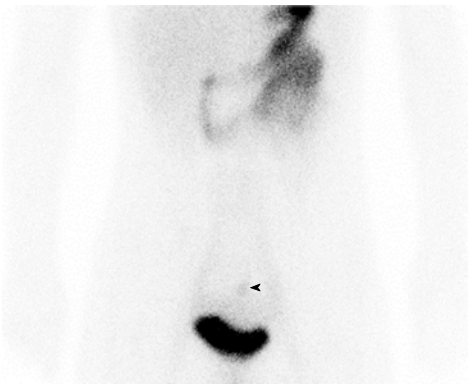

Figure 3 99mTc-Na-pertechnetate revealed uptake in the lower abdomen (arrowhead).

Figure 4 The resected Meckel's diverticulum and adjunctive small intestine. The cut mesodiverticular band is seen at the blind end of the diverticulum (arrowhead).

a MDB (Figure 3) and heterotopic gastric mucosa in the mucosa of the diverticulum (Figures 4 and 5).

DISCUSSION

MD is an innate anomaly of the gastrointestinal system caused by incomplete closure of the omphalomesenteric duct[1]. MD was so named in 1809 after its discoverer, the German anatomist Johann Friedrich Meckel. The presence of MD can be explained in terms of intrauterine evolution of the bowel. The omphalomesenteric duct is the embryonic communication between the yolk sac and the developing midgut. By the 10th week of embryogenesis, the omphalomesenteric duct becomes a thin fibrous band. However, incomplete atrophy of the omphalomesenteric duct may result in a variety of anomalies, they are, umbilicoileal fistula, omphalomesenteric duct cyst or MD[4].

The diverticulum originates from the antimesenteric border of the small bowel, within 40-100 cm of the ileocecal valve[4,5]. Blood is supplied *via* the vitelline artery, which is a branch of the ileocecal artery. The diverticulum is ordinarily lined by intestinal mucosa, but the heterotopic gastric mucosa or pancreatic tissue was frequently observed by the histological examination[4,5].

Reportedly, 25% of MD become symptomatic

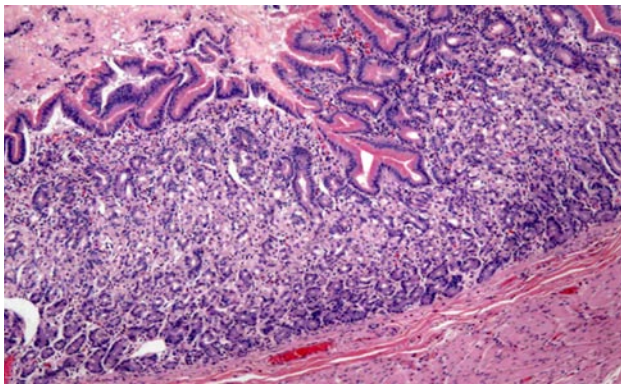

Figure 5 Histological features of the diverticulum. Heterotopic gastric mucosa was seen in the mucosa of the diverticulum (hematoxylin-eosin staining, × 100).

throughout the lifetime[4]. Bleeding, inflammation or obstruction are the main cause of complication[2]. Statistically, hemorrhage is the most common presentation in children aged 2 years or younger[6], whereas intestinal obstruction is the commonest presentation among adults[7]. Intestinal obstruction due to MD is the most common presentation in adults and the second most common in children[6,7].

The clinical symptoms are non-specific; patients may have abdominal pain and distension, vomiting or constipation. MD-related small-bowel obstruction occurs so infrequently that most articles have reported only small series or isolated cases. Moreover, many patients with MD have non-specific abdominal symptoms, often making a correct preoperative diagnosis difficult, especially in an emergency setting[8,9].

The present case illustrates that abdominal CECT has the potential to identify the MDB and MD as the cause of small-bowel obstruction. Multi-dimensional CECT, especially in the coronal view, may yield more information about the cause of the small-bowel obstruction and the presence of a MDB. CECT is less invasive and speedier than other examinations such as Tc scintigraphy, interventional radiology or a gastrointestinal series, and therefore is more preferable in an emergency setting, yielding information about the cause of the small-bowel obstruction, such as internal hernia or other intestinal mass. CECT can also reveal the presence of strangulation. In the present case, we were able to confirm by CECT that there was no sign of vascular compromise, enabling us to start intestinal decompression in preparation for elective laparoscopic surgery.

Laparoscopic surgery for MD has been widely used recently. However, as it is not clear whether laparoscopic surgery is preferable to laparotomy in the setting of small-bowel obstruction[10], we performed intestinal decompression first. MD can be resected either extracorporeally or intracorporeally[9,11]. Although some reports have indicated intracorporeral laparoscopic diverticulectomy, we selected laparoscopy-assisted diverticulectomy *via* a small incision in the lower abdomen to allow palpation of the MD, thus helping

to rule out any mass or thickening of the base, and allowing a more complete assessment for the presence of any ectopic gastric mucosa[12].

In conclusion, we successfully treated MD causing small bowel obstruction by laparoscopic surgery. Multi-dimensional CECT may yield to detect both the etiology of small-bowel obstruction and the presence of strangulation in such unusual settings.

COMMENTS

Case characteristics

A 26-year-old woman with past history of small bowel obstruction presented with abdominal pain and recurrent vomiting.

Clinical diagnosis

Physical examination demonstrated abdominal distention, with a soft abdomen and no tenderness or rebound pain. Her bowel sounds were hyperactive.

Differential diagnosis

Small bowel obstruction due to food impaction, sue to internal hernia, or due to intestinal tumor.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Multi-dimensional contrast enhanced computed tomography showed a blind-ending U-shaped loop of bowel in the pelvis and a fibrotic band connecting the mesentery to the blind end of the bowel, suggesting Meckel's diverticulum (MD) and a mesodiverticular band (MDB).

Pathological diagnosis

MDB and heterotopic gastric mucosa in the mucosa of the MD.

Treatment

Long tube decompression and subsequent laparoscopic diverticulectomy.

Related reports

MD occurs with an incidence of 1%-2% among the general population, and most cases remain asymptomatic. Complications result most commonly from bleeding, inflammation, or obstruction.

Term expression

The MDB is an embryologic remnant of the vitelline circulation which carries the arterial supply to the Meckel's diverticulum. In the event of an error of involution, a patent or nonpatent arterial band persists and extends from the mesentery to the apex of the anti-mesenteric diverticulum.

Experiences and lessons

This is a successful case of small-bowel obstruction caused by MD that was diagnosed preoperatively using multi-dimensional contrast-enhanced computed tomography and treated by elective laparoscopic surgery.

Peer-review

This is an interesting report on a rare etiologic factor of bowel obstruction in young adults.

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CASE REPORT

Pneumatosis intestinalis with obstructing intussusception: A case report and literature review

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Yujiro Itazaki, Hironori Tsujimoto, Nozomi Ito, Hiroyuki Horiguchi, Shinsuke Nomura, Kyohei Kanematsu, Shuichi Hiraki, Suefumi Aosasa, Junji Yamamoto, Kazuo Hase, Department of Surgery, National Defense Medical College, Saitama 359-8513, Japan

Author contributions: Itazaki Y, Tsujimoto H and Hiraki S designed the research; Ito N, Horiguchi H, Nomura S, Kanematsu K and Aosasa S performed the research; Itazaki Y, Tsujimoto H, Yamamoto J and Hase K wrote the paper; all authors had substantial contributions to conception, design, and reviewing the manuscript; all authors have approved the manuscript and agree with submission to the journal.

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Conflict-of-interest statement: All authors certify that they have no commercial associations that might pose a conflict of interest in connection with submitted article.

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Abstract

Pneumatosis intestinalis (PI) often represents a benign condition that should not be considered as an argument for surgery. We report a patient with PI and obstructing intussusception who underwent urgent colectomy and review the literatures regarding PI with intussusception. A 20-year-old man presented at our hospital with a 3-d intermittent lower abdominal pain history. He underwent steroid therapy for membranoproliferative glomerulonephritis for 4 years. Computed tomography revealed ascending colon intussusception with air within the wall. Intraoperative colonoscopy revealed numerous soft polypoid masses with normal overlying mucosa and right hemicolectomy was performed. Histological examination of colonic wall sections revealed large cysts in the submucosal layer. The pathological diagnosis was PI. Nine cases of intussusception associated with primary PI have been reported. Although primary PI often represents a benign condition that should not be considered as an argument for surgery, if the case involves intussusception and obstruction, emergent laparotomy should be considered.

Key words: Pneumatosis intestinalis; Intussusception; Urgent surgery; Immunosuppressive drug; Ischemia of the intestine

Core tip: We report a patient with pneumatosis

intestinalis (PI) and obstructing intussusception who underwent urgent colectomy and review the literatures regarding PI with intussusception. A 20-year-old man presented at our hospital with abdominal pain, and has undergone steroid therapy for 4 years. Computed tomography revealed ascending colon intussusception with air within the wall, and colectomy was performed. Histological examination of colonic wall sections revealed large cysts in the submucosal layer. Nine cases of intussusception associated with primary PI have been reported. Although primary PI often represents a benign condition, if the case involves intussusception and obstruction, emergent laparotomy should be considered.

Itazaki Y, Tsujimoto H, Ito N, Horiguchi H, Nomura S, Kanematsu K, Hiraki S, Aosasa S, Yamamoto J, Hase K. Pneumatosis intestinalis with obstructing intussusception: A case report and literature review. *World J Gastrointest Surg* 2016; 8(2): 173-178 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i2/173.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i2.173

INTRODUCTION

Pneumatosis intestinalis (PI) is a rare condition characterized by the presence of gas within the wall of the gastrointestinal tract. This condition can result from a wide variety of pathologies, including chronic obstructive lung disease, collagen diseases, necrotizing enterocolitis in premature infants, intestinal infections, ischemic bowel disorders, and immunosuppressive drug therapy[1]. PI often represents a benign condition that should not be considered as an argument for surgery[2]; however, immediate surgery may be required in some life-threatening circumstances such as the presence of bowel obstruction, perforation, or ischemia[3].

Here we describe a case of PI in the ascending colon with obstructing intussusception for which urgent surgery was performed, and review the available published literature on PI with intussusception. Written informed consent was obtained from the patient.

Search strategy

The literature search strategy for this study was based on published systematic review guidelines[4]. Literature databases such as PubMed MEDLINE (National Library of Medicine) were searched from 1980 to 2015 using the following medical subject headings: "PI (or Pneumatosis cystoides intestinalis)" and "intussusception" or "PI (or Pneumatosis cystoides intestinalis)" and "invagination". In addition, references within the retrieved articles were reviewed. We identified 24 manuscripts using this search strategy and selected 8 case reports for this review. Nineteen articles were excluded because their content was not applicable to this review and 7 articles were excluded because they were not written in English.

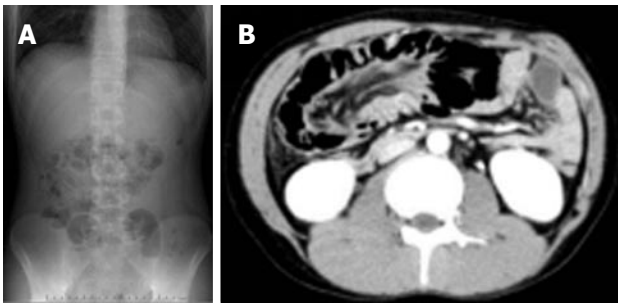

Figure 1 Abdominal radiograph. It showing multiple distended loops of small bowel with fluids and multiple air pockets (A) and computed tomography showing multiple gas-filled cysts, a streaky collection of air in the bowel wall, and an intussusception of the colon (B).

Figure 2 Intraoperative findings showed intussusception of the ascending colon with palpable soft polypoid masses.

CASE REPORT

A 20-year-old man presented our hospital with a 3-d history of intermittent lower abdominal pain. He had been on steroid therapy (methylprednisolone 25 mg/d) for membranoproliferative glomerulonephritis for 4 years. A physical examination revealed tenderness in the lower right quadrant of the abdomen. His body temperature was 37.7 ℃ and pulse was 81 beats per minute. All serum levels tested were within the normal range, with the exception of serum total bilirubin (1.5 mg/dL; normal range, 0.3-1.2 mg/dL). White blood cells (WBCs) (21000/μL), hemoglobin concentration (17.1 g/dL), and the C-reactive protein concentration (0.5 mg/dL) were also elevated, indicating acute inflammation and dehydration, with a level of base excess of 2.4 mmol/L. Abdominal X-ray showed multiple air-filled lucencies in the right upper quadrant and multiple distended loops of small bowel with fluid (Figure 1A). Computed tomography (CT) revealed intussusception of the ascending colon with air within the wall (Figure 1B). We performed an urgent laparotomy under the diagnosis of acute abdomen with obstructing intussusception. The colo-colic intussusception that was caudal to the polypoid lesion easily resolved using Hutchinson's maneuver and soft polypoid masses were palpable from the cecum to the ascending colon (Figure 2). Intraoperative colonoscopy revealed the presence of numerous soft polypoid

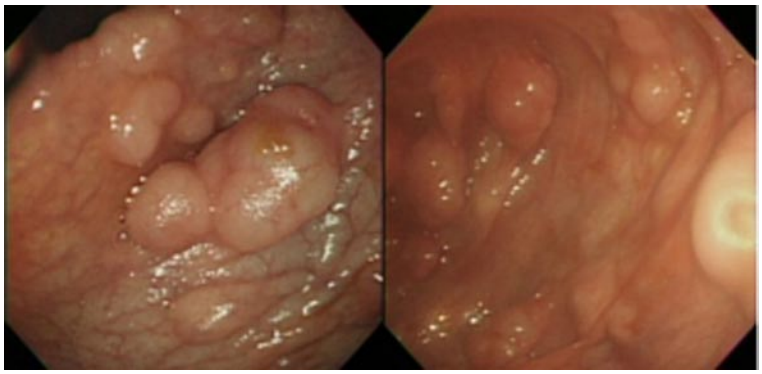

Figure 3 Intraoperative colonoscopy showed numerous soft polypoid masses with normal overlying mucosa located between the ascending colon and middle part of transverse colon.

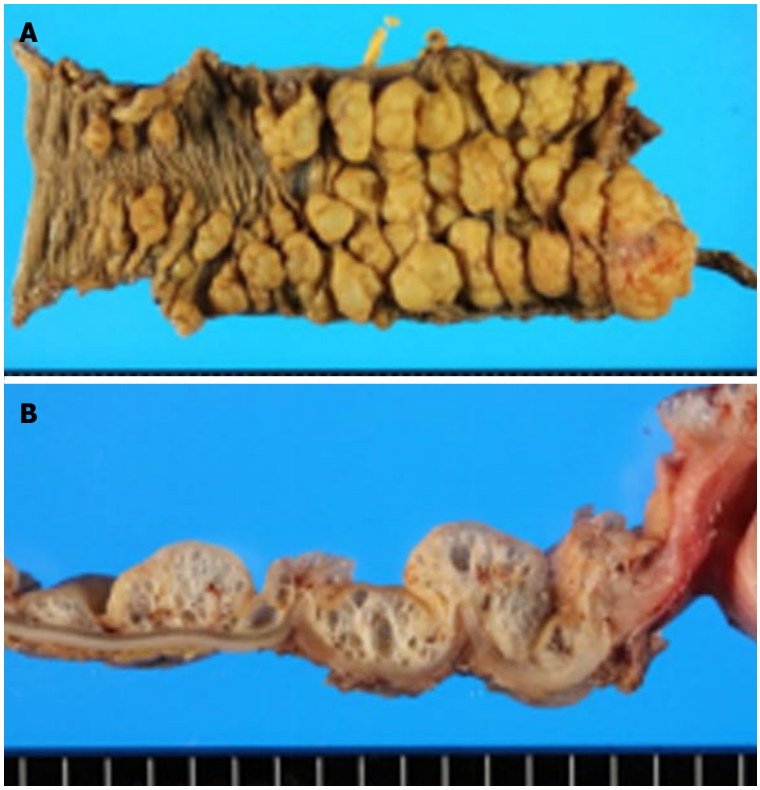

Figure 4 The resected specimen revealed polypoid lesions with normal mucosa and cystic structures (A), submucosal cysts had a spongy consistency (B).

masses with normal overlying mucosa (Figure 3). A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out, and to help make a final pathological diagnosis. A gross examination showed that the mucosa of the resected colon appeared normal with no evidence of ulceration or ulcer-related lesions, but instead a number of soft, yellowish cystic masses (Figures 4). A histological examination of sections of the colonic wall revealed large cysts in the submucosal layer (Figure 5A). The cysts were empty, but were surrounded by a distinct fibrous wall and were lined by macrophages that frequently coalesced to form multinucleated giant cells (Figure 5B). Based on these findings, the patient was diagnosed with pneumatosis cystoides intestinalis. The postoperative course was uneventful and the patient was discharged on postoperative day 9. No recurrence was noted on radiographic imaging performed on postoperative 14 mo.

DISCUSSION

Classically, PI can be subdivided into 2 distinct groups: primary PI, representing 15% of cases, and secondary PI, representing 85% of cases[5]. Secondary PI, where the gas accumulates as linear collections and reflects a pathological condition, has been attributed to endoscopic procedures, immunological disturbances, bowel mucosal disruptions, and intra-abdominal pathologies. In contrast to secondary PI, primary PI is characterized by intramural gas that is cystic and benign in nature and does not always require urgent laparotomy[6]. Although PI may occur in association with acquired immunodeficiency[7], transplant status[8], cancer treatment[9,10], scleroderma[11], cystic fibrosis[12], systemic lupus[13], inflammatory bowel disease[2], intestinal ischemia[14], colitis[15], or trauma[16], the exact etiology of both primary and secondary PI remains unknown.

There is currently no consensus on the appropriate

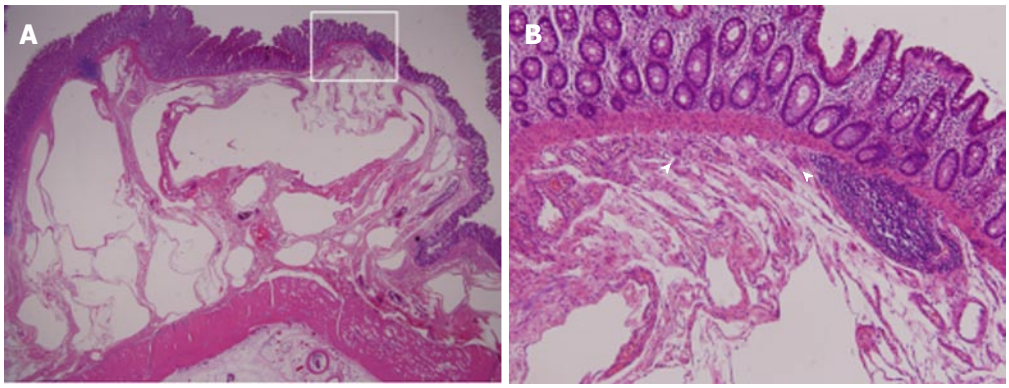

Figure 5 Histopathological examination revealed cystic air-filled spaces within the submucosa, which were partially lined by clusters of foreign-body macrophages (arrow heads) (hematoxylin-eosin stain; A: × 40, B: × 400).

Table 1 Reported cases that had intussusception associated with primary pneumatosis intestinalis

Ref.	Year	Sex	Immunosuppressive drug	Ischemia	PVG	Site	Treatment	Indication of surgery	Co-morbidity
Nagata *et al*[20]	23 yr	Male	No	No	No	A/C	CS→Surgery	Abdominal pain	None
Emanuel *et al*[21]	48 yr	Male	NR	NR	NR	D/C	Surgery	Obstruction	Hybrid perineurioma-schwannoma
Sugita *et al*[22]	5 yr	Female	Yes	No	Yes	A/C	BE	-	CML
Stern *et al*[23]	32 yr	Male	No	No	No	A/C	BE	-	None
Morrison *et al*[24]	3 mo	NR	Yes	Yes	NR	T/C	BE→Surgery	could not resolved intussusception	Peter's anomaly
Dubinsky *et al*[25]	1 yr	Male	Yes	NR	NR	A/C	Surgery	Obstruction	Crohn's disease
Navarro *et al*[26]	13 yr	Male	No	No	NR	T/C	BE→Surgery	Obstruction	None
Ahrar *et al*[27]	29 yr	Male	No	No	NR	A/C	BE→Surgery	NR	None
Our case	20 yr	Male	Yes	No	No	A/C	Surgery	Obstruction	MPGN

NR: Not referred; PVG: Portal venous gas; A/C: Ascending colon; D/C: Descending colon; T/C: Transverse colon; CS: Colonoscopy; BE: Barium enema; CML: Chronic myelogenous leukemia; MPGN: Membranoproliferative glomerulonephritis.

management of PI, although many mechanical, bacterial, and pulmonary hypotheses have been proposed regarding PI etiopathogenesis, and its management can be challenging for surgeons[17]. Many studies have investigated the use of risk factors as predictors of a compromised bowel and the probable need for surgery, such as patient age and the presence of hypotension, peritonitis, renal failure, or serum lactate levels[18]. Other studies have attempted to create algorithms for PI management that, while helpful, are also tedious and may be difficult to apply clinically in circumstances where the patient requires rapid evaluation[19]. In this case, we performed urgent laparotomy because he had intestinal obstruction due to intussusception and several inflammatory symptoms.

Although the course of primary PI may be benign or may not frequently result in a need for urgent surgery, laparotomy should be considered in cases with intestinal obstruction due to intussusception. To our knowledge, 9 reported cases, including the present case, had intussusception associated with primary PI (Table 1)[20-27]. The mean patient age was 19.0 ± 16.0 years (range 0-48 years), which is younger than has been reported previously[19]. It is notable that more than 44% of these patients received an immunosuppressive drug, and few patients appeared to have intestinal ischemia. All patients had the intussusception in the colon, particularly on its right side. Five out of 9 patients had co-morbidities, most of which required an immunosuppressive drug. With the exception of the article placed as reference number 22, no other articles referred to the presence of portal venous gas, which often indicates ischemic bowel disease. Only 2 cases experienced successful reduction of the intussusception with barium enema[22,23], although long-term outcomes were not reported. Among the 4 cases with initial successful reduction of the intussusception by colonoscopy or barium enema, all of these patients eventually needed surgery: One case had persistent abdominal pain after solution of intussusception; in one case, the intussusception could not be completely resolved; one case had bowel obstruction; and for one case the indication of surgery was not clearly stated. For the present case, we performed an urgent laparotomy because of bowel obstruction with intussusception of the ascending colon. Right hemicolectomy for this case was performed because of the possibility of there being another polyposis disease present and because relapse

of the intussusception could not be ruled out.

In conclusion, although primary PI often represents a benign condition that should not be considered as an argument for surgery, emergent laparotomy should be considered for cases with intussusception, obstruction, and unsuccessful resolution of intussusception by colonoscopy or barium enema.

COMMENTS

Case characteristics

A 20-year-old man presented our hospital with a 3-d history of intermittent lower abdominal pain.

Clinical diagnosis

The authors performed an urgent laparotomy under the diagnosis of acute abdomen with obstructing intussusception.

Differential diagnosis

A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out.

Laboratory diagnosis

All serum levels tested were within the normal range, with the exception of serum total bilirubin (1.5 mg/dL; normal range, 0.3-1.2 mg/dL). White blood cells (WBCs) (21000/μL), hemoglobin concentration (17.1 g/dL), and the C-reactive protein concentration (0.5 mg/dL) were also elevated.

Imaging diagnosis

Computed tomography revealed intussusception of the ascending colon with air within the wall.

Pathological diagnosis

A gross examination showed that the mucosa of the resected colon appeared normal with no evidence of ulceration or ulcer-related lesions, but instead a number of soft, yellowish cystic masses, suggesting that to be pneumatosis cystoides intestinalis.

Treatment

A right hemicolectomy was performed because other polyposis diseases or intussusception relapse could not be ruled out, and to help make a final pathological diagnosis.

Related reports

To our knowledge, 9 reported cases, including the present case, had intussusception associated with primary pneumatosis cystoides intestinalis.

Experiences and lessons

Although primary pneumatosis intestinalis (PI) often represents a benign condition that should not be considered as an argument for surgery, emergent laparotomy should be considered for cases with intussusception, obstruction, and unsuccessful resolution of intussusception by colonoscopy or barium enema.

Peer-review

This is an interesting article summarising a case of PI and intususception with a review of the cases in the literature.

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