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Endoscopic Fundoplication: Real or Fantasy?

Alejandro Nieponice · Blair A. Jobe

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Keywords Endoscopic fundoplication · GERD · Antireflux surgery · Proton pump inhibitor

Overview

Since the introduction of proton pump inhibitors (PPI) as a highly effective antireflux medical therapy, there has been an ongoing controversy regarding the indication spectrum for a surgical fundoplication. Although laparoscopic Nissen fundoplication has gained widespread acceptance and become the gold standard surgical procedure[1,2], many clinicians are still reluctant to refer patients for surgery and they look at this option only as an alternative when PPI treatment fails. Often times, these are the patients who are least suited for a surgical fundoplication.

The source of provider reticence to patient referral for laparoscopic fundoplication is multi-factorial and relates primarily to fundoplication-related side effects, concerns over repair durability and difficulties encountered in widely disseminating a standardized surgical approach that results in calculable success[3]. It is from within this milieu that the drivers for a non-invasive, incisionless anatomic repair were born: Patients desire to be cured of volume reflux in addition to heartburn as the potential consequences of long-term PPI therapy come to light; industry would like to access the extremely large market of patients with medically dependent reflux; surgeons and gastroenterologists would like to have a transoral incisionless method by which to provide an anatomic repair that rivals medical therapy and places them on the "cutting edge" of technology. While insurance carriers are ever searching for ways to reduce medical costs, they are very cautious after the first iteration of endolumenal antireflux procedure and require concrete evidence of efficacy prior to authorizing payment for these novel procedures.

The "ideal" approach to the transoral incisionless anatomic reconstruction of a defective esophagogastric junction (EGJ) would have the benefits of being easy to learn, perform, and reproduce with low morbidity, durably eliminate all symptoms of GERD (heartburn and regurgitation), and have none of the side effects of surgical fundoplication. The hope of the stakeholders is that with this idyllic device, the threshold for patient referral within the vast population of PPI-dependant patients who may

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A. Nieponice
McGowan Institute for Regenerative Medicine,
University of Pittsburgh,
Pittsburgh, PA, USA

B. A. Jobe
Department of Cardiothoracic Surgery, University of Pittsburgh,
Pittsburgh, PA, USA

B. A. Jobe (✉)
Division of Thoracic and Foregut Surgery,
University of Pittsburgh Medical Center,
Shadyside Medical Center, Suite 715, 5200 Centre Avenue,
Pittsburgh, PA 15232, USA
e-mail: jobeba@upmc.edu

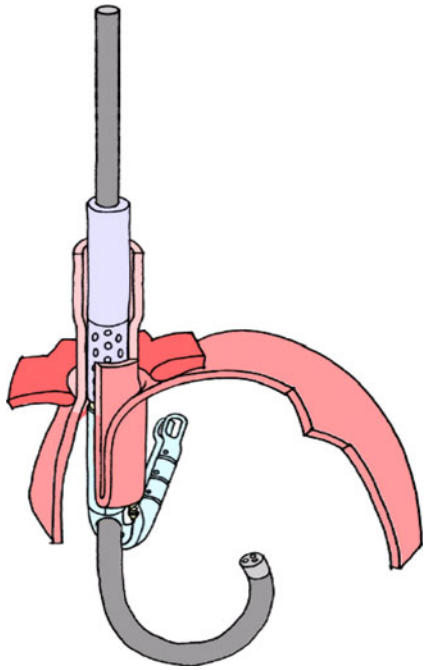

Fig. 1 The esophagogastric junction is retracted and the gastric fundus is plicated to the esophagus under endoscopic visualization

have imperfect reflux control will be lowered. To date, such a procedure remains elusive. The first-generation devices demonstrated variable efficacy in achieving short-term symptomatic improvement, with very little objective evidence of effective reflux control[4–7]. Although there has been evidence of symptomatic improvement and liberation from medical therapy in highly selected patient populations, no intraluminal technique has achieved the dramatic improvement in objective measures comparable to laparoscopic fundoplication. As a result of this initial effort, there are currently only two commercially available devices available on the market: Radiofrequency ablation of the lower esophageal sphincter and endolumenal fundoplication. This paper will focus on endoluminal fundoplication.

Transoral Incisionless Fundoplication

The experience with EsophyX™ transoral incisionless fundoplication (TIF) commenced in 2007 for the treatment of symptomatic GERD in patients requiring and responding to antireflux medication. As opposed to previous approaches, the TIF procedure relies on full-thickness plication around the majority of the circumference of the EGJ, and is purported to enable reduction of a hiatal hernia of up to 2 cm. The device has an inner helix that engages the tissue and enables traction and pleating so that the distal esophagus is "submerged" into the proximal stomach creating a gastroesophageal plication (Fig. 1); conceptually, the end result is reconstruction of the acute angle of His, restoration of intra-abdominal esophageal length and a Hill classification grade I valve. One of the most interesting theoretical aspects of TIF when compared to previous devices is that it facilitates modifications in technique that may prove to be critical in procedure development and ultimately, clinical outcome. The ideal surgical technique is one that can be individualized based on factors such as preoperative esophageal motility status, anatomy, and disease severity. This is the case with laparoscopic antireflux surgery and should serve as the benchmark for transoral therapy.

The TIF procedure, which was evaluated in a European multicenter company -initiated study of 86 patients, places polypropylene H-shaped fasteners, at the level of the EGJ, allowing serosa-to-serosa contact and effectively creating a gastro-gastric fundoplication[8] (Fig. 2a). In terms of safety, two patients suffered esophageal perforation during device insertion, and one patient had hemorrhage requiring transfusion. At 12 months post-procedure, distal esophageal pH had been normalized in only 37% of patients, while 49% of subjects were completely liberated from all forms of medical therapy. Despite these objective findings, a significant improvement in GERD-related quality of life was evident in 73% of subjects. Two-year follow-up of a

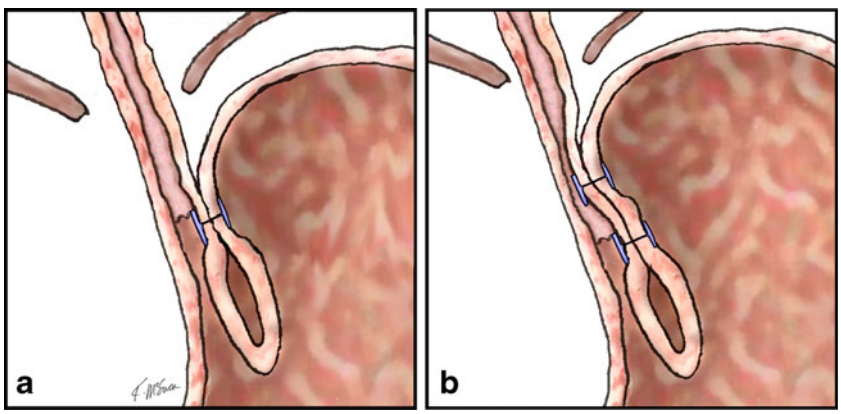

Fig. 2 Fastener placement for the two methods of transoral incisionless fundoplication. **a** TIF 1.0 and **b** TIF 2.0

cohort of 19 patients treated with TIF reported that this procedure was effective in eliminating heartburn in 93% of patients and daily PPI use in 71% of patients[9]. There were no long-term complications reported at this follow-up interval, however six patients were not included in the final analysis. Despite these results, there is a very wide range of reported outcomes. For example, within the published literature, reported rates of liberation from anti-secretory medication range from 25% to 83% at 6 months to 2-years follow-up[8–13].

A modification of the TIF procedure places H-fasteners 3–5 cm proximal to the EGJ (Fig. 2b). This approach results in accentuation of the acute angle of His and creates a nipple valve through the "wrapping" of the distal esophagus into the proximal stomach. In a canine model with 2-week post-procedure follow-up, this approach was shown to be safe, feasible, and well-tolerated[14] (Fig. 3). When compared with the initial approach, this method of TIF significantly improved DeMeester score, lower esophageal sphincter pressure and length, and preserved sphincter receptive relaxation with swallowing.

Personal Experience

The University of Pittsburgh and Australian (Adelaide and Victoria) experience has been less favorable than that reported by others. In our combined experience of 19 patients, over 50% have had recurrent symptoms and subsequently required conversion to Nissen fundoplication within 1-year of the TIF procedure (these data were presented, in part at the 51st Annual Meeting of the Society for Surgery of the Alimentary Tract). The primary mechanism of failure was likely related to tension and subsequent "pull-through" of the "H" fastener through the esophageal wall.

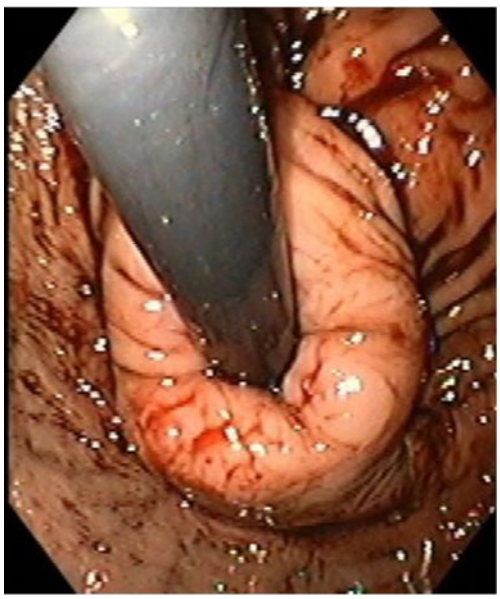

Fig. 3 Endoscopic valve appearance of transoral incisionless fundoplication 2.0 in a canine model

Conclusions

As with the majority of the transoral antireflux procedures, the preponderance of objective follow-up data associated with TIF has been underwhelming. It is difficult to tease out the impact of placebo effect associated with the degree of symptom resolution. Because of our collective track record with endolumenal antireflux procedures, the onus is now upon us to deliver controlled and preferably cross-over data which demonstrate efficacy with this novel device. Winston Churchill said that "success consists of going from failure to failure without loss of enthusiasm." It is critical that in our enthusiasm to establish endolumenal antireflux surgery as a reality, we learn from our mistakes and adhere to the principles of surgery which have withstood the test of time.

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Endoscopic Mucosal Resection of Barrett's Esophagus and Early Esophageal Cancer

Jeffrey H. Peters · Thomas A. Watson

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The introduction of endoscopic techniques capable of removing 2- to 3-cm pieces of mucosa and submucosa has been one of the most significant advances in the treatment of esophageal and gastric neoplasia over the past decade. Endoscopic mucosal resection (EMR) was initially developed in Japan by Inoue and others for treatment of superficial squamous cell carcinomas of the esophagus.[1] It was adopted slowly in the USA and Europe, and its use continues to evolve. The most common application in Western populations is for excisional biopsy of small (less than 2 cm) mucosal irregularities or nodules in patients with Barrett's esophagus (BE), high-grade dysplasia (HGD), and intramucosal adenocarcinoma. Data to date support endoscopic resection (ER) as the treatment of choice for focal mucosal esophageal adenocarcinoma and as an important adjunct to radiofrequency (RF) ablation in dysplastic Barrett's epithelium.

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J. H. Peters (✉) · T. A. Watson
Division of Thoracic and Foregut Surgery, Department of Surgery,
University of Rochester,
601 Elmwood Ave,
Rochester, NY 14642, USA
e-mail: Jeffrey_peters@urmc.rochester.edu

Endoscopic mucosal resection has two potential benefits. First, it serves as a larger and deeper biopsy specimen, allowing more precise determination of the depth of tumor penetration than any other method currently available. Most specimens contain significant portions of the submucosa allowing differentiation of mucosal from submucosal tumors. Second, it can be performed with curative intent for tumors at low risk for metastatic spread to regional lymph nodes or distant sites and can be combined with mucosal ablation to facilitate complete removal of esophageal metaplastic or dysplastic epithelium.

Although EMR can be and has been used to ablate large circumferential areas of esophageal mucosa, it is most commonly and best used when guided by a visible "cue." These can vary from an obvious nodule, tumor, or ulceration to an identifiable short tongue or island of columnar mucosa. In fact, stepwise improvements in endoscopic imaging including high definition, magnification, and narrow band imaging have markedly improved the ability to identify focal lesions, increasing the potential for EMR as initial or definitive therapy.

In the setting of invasive adenocarcinoma, the depth of tumor penetration, as assessed at the time of pathologic evaluation of the resected specimen, is critical in determining the potential for nodal spread. Multiple series from the surgical literature have evaluated outcomes after esophagectomy with regional lymphadenectomy for esophageal adenocarcinoma and have correlated the incidence of nodal metastasis with the depth of tumor invasion. Tumors limited to the mucosa appear to have a limited potential for nodal disease, approximating 2–5%. For adenocarcinomas penetrating the muscularis mucosa and involving the submucosa, the incidence of nodal metastasis appears to increase to the 20–30% range. Some series, however, would suggest that tumors invading into the superficial submucosa (SM1) have a

low incidence of nodal metastasis, similar to disease limited to the mucosa, while deeper submucosal lesions (SM2–3) portend a worse prognosis. The data supporting this contention, however, are far too premature to allow definitive conclusions to be drawn. In addition, EMR may not excise the entire submucosa, making determinations of relative submucosal depth of penetration difficult. Tumors involving the muscularis propria have an even higher chance of associated nodal spread, in the range of 45–80%.

Current data support ER as appropriate therapy with curative intent only for tumors limited to the mucosa. If the resected specimen demonstrates submucosal penetration, esophagectomy with regional lymphadenectomy is indicated. In the setting of HGD or intramucosal carcinoma (IMCA) which is often multifocal, ER should be used in conjunction with endoscopic ablation with the goal of eliminating the metaplastic epithelium.

Technique The widely utilized terminology "endoscopic mucosal resection" is somewhat of a misnomer in that the resection plane is within the submucosa, often down to its interface with the muscularis propria.

Several techniques have been described for performing ER. All share the basic principle of isolation of a defined segment of esophageal mucosa and excision using a snare cautery device. Differences relate to the use of submucosal injection of saline (with or without dilute epinephrine) to separate the esophageal mucosa from the underlying muscle layer and the manner in which the lesion is isolated for snare application.

The simplest variant of ER is snare resection alone, with or without submucosal injection. This technique is best applied to pedunculated lesions of the esophageal mucosa and uncommonly applicable.

The most common method utilizes a small cylindrical "cap" fitted to the end of the endoscope in which the target lesion is isolated for resection by applying endoscopic suction bringing the lesion into the cap. Outlining the area of interest via small cautery marks using an endoscopic cautery probe or snare is often helpful, as is injection of 10–15 cc of saline with dilute epinephrine (10–20 mL injectate, 1:100,000 solution) beneath the lesion. The latter separates the mucosa/submucosa from the underlying muscularis propria. The target lesion is then aspirated into a specially designed cap (Olympus EMR-001, Olympus America, Center Valley, PA) attached to the end of the endoscope ("cap-assisted" ER). The cap is equipped with an inner groove that allows seating of a standard cautery snare. Once the mucosa is within the cap, the snare can be tightened around the base of the lesion, and cautery can be applied, amputating the specimen in the submucosal plane. Prior to application of cautery, the lesion should be gently "tugged" to give the operator a sense of mobility away from the muscularis and to prevent inadvertent full-thickness injury to the esophageal wall. The resected specimen typically remains within the cap and can be extracted as the endoscope is withdrawn. This procedure can be completed with a single passage of the endoscope.

A similar, and perhaps the most widely performed, method utilizes a cap and band system originally designed for variceal ligation. Various single-use multiband systems (Duette Multiband Mucosectomy System, Cook Medical, Bloomington, IN; Bard Six-Shooter, Bard Interventional Products, Billerica, MA) are commercially available. This technique involves "sucking" the mucosa into the cap (often without prior submucosal injection) and applying a rubber band to the base of the elevated mucosa, creating a pseudopolyp ("suck and ligate" ER). The lesion is then excised either above or below the band using snare electrocautery. The excised specimen can be retrieved using an endoscopic retrieval net or polypectomy grasper. The advantages of this technique compared to the cap-fitted snare are that submucosal injection is not necessary and that the snare does not need to be seated in the cap, a tedious process that may be time consuming and difficult to master. Disadvantages include the need to reintroduce the endoscope after banding to position the snare and the need to retrieve the free-floating specimen.

Specimen handling and subsequent pathologic assessment are key components of any ER procedure. The specimen can be tacked to a small piece of corkboard to preserve the margins and to allow measurement of specimen diameter. The importance of an experienced pathologist cannot be overemphasized. If an expert in esophageal pathology is not available at the endoscopist's institution, consideration should be given to having the specimen sent to a center of excellence for review, particularly that a high degree of interobserver variability exists in the grading of dysplasia and early esophageal neoplasia, and the subtleties of pathologic evaluation may impact the subsequent course of treatment.

Risks Bleeding and esophageal perforation are the most significant risks. Neither is common. Limited data suggest they occur in less than 1% of patients. Most bleeding is self-limited and will resolve with observation. More brisk bleeding can be controlled with injection of dilute epinephrine, electrocautery, or application of endoscopic clips. Perforations require significant judgment and skill to treat in the most efficacious manner without excessive morbidity. Esophageal strictures can occur, particularly when 50% or more of the circumference is resected at a single setting. They are generally managed with serial dilations.

Both deep and lateral margins should be pathologically assessed, as ER of a discrete lesion risks leaving a positive

deep or lateral resection margin. While the significance of positive margins remains poorly studied, most would suggest that a deep margin involved with cancer is an indication for additional definitive therapy such as esophagectomy or combined chemoradiation. The importance of positive lateral margins is less clear particularly since it can be addressed via further ER or radiofrequency mucosal ablation. A tumor invading beyond the muscularis mucosa into the submucosa carries a significant risk of metastatic nodal spread and also should be addressed with a more definitive approach. Whether there is a "low-risk" population of patients with superficial submucosal invasion that can be safely treated with ER remains an area of study.

Endoscopic resections, particularly for larger regions of disease, may be piecemeal in fashion. Large areas of dysplasia/neoplasia can be approached with multiple resections in one or more sessions. In such cases, the target lesions may be removed in fragments, and margins may be impossible to determine on pathologic assessment.

Outcomes The largest experience with ER for early esophageal adenocarcinoma was reported in 2007 by Ell et al. from Wiesbaden, Germany.[2] A group of 100 patients were selected from a cohort of 667 referred with suspected intraepithelial neoplasia. A total of 144 resections (1.47 per patient) were performed without major complications. Most tumors (69%) occurred in the setting of short-segment BE. Endoscopic resection was combined with either argon plasma coagulation for short-segment BE or photodynamic therapy for long-segment BE in 49 patients. Only one third of resections were proven histologically to be R0 at the lateral margins, though no resection specimen was found to have a positive deep margin. Complete local remission, defined as an R0 resection plus one normal follow-up endoscopy or an R1 or Rx (indeterminate) lateral resection margin plus two consecutive negative follow-up endoscopies, was achieved in 99 out of the 100 patients with a maximum of three resections at a mean of 1.9 months. Metachronous or recurrent disease occurred in 11% of patients during an average follow-up of 36.7 months. Recurrences were re-treated with endoscopic resection which was successful in all cases. The calculated 5-year survival was 98%, with no cancer-related deaths during the follow-up period.

A follow-up report to the Wiesbaden experience was published in 2008.[3] The study population increased to 349 patients with a mean follow-up of 63.6 months. Metachronous lesions were noted in 21.5%, and esophagectomy for failed endoscopic control of neoplasia was necessary in 3.7%. Risk factors for recurrent disease were identified including piecemeal resections, long-segment BE, lack of ablative therapy after ER, and multifocal neoplasia.

Achieving these outcomes required an intensive surveillance protocol. Follow-up endoscopies were performed at 1, 2, 3, 6, 9, and 12 months after treatment and then at 6-month intervals for 5 years. Every second visit included an endoscopic ultrasound, computed tomography, and abdominal ultrasound. Annual checkups after 5 years included high-resolution endoscopy with biopsies, as indicated. The intensity of the follow-up can be difficult for both the patient and the endoscopic center, and forms one of the major disadvantages of endoscopic therapy. Whether such close follow-up is required and the minimum essential elements for optimal outcomes remain unknown.

ER in Combination with Radiofrequency Ablation for Early Carcinoma A recent report from the Netherlands assessed outcomes of combined ER and radiofrequency ablation in 44 patients with dysplastic Barrett's esophagus or early esophageal adenocarcinoma.[4] Thirty-one patients underwent ER as initial therapy, 16 with early adenocarcinoma, 12 with HGD, and 3 with low-grade dysplasia (LGD). Following ER, prior to the first RF ablation, histology revealed HGD in 32, LGD in 10, and no dysplasia in 2. Complete histologic eradication of all dysplasia, as well as complete endoscopic and histologic clearance of BE, was achieved in 98% after a median of one circumferential ablation session, two focal ablation sessions, and rescue ER in three patients. Complications of ER occurred in five patients: four mild bleeding episodes managed with endoscopic techniques and one esophageal perforation treated with endoscopic clips and placement of a covered esophageal stent. Four patients (9%) developed dysphagia after ablation, which improved after a median of three endoscopic dilatations; all had undergone widespread ER. At a median follow-up of 21 months, no dysplasia had recurred.

These data underscore the feasibility of ER combined with RF ablation in patients referred with HGD or IMCA and treated at a specialty center. Given these circumstances, the outcomes at 5 years are excellent, with cure rates approximating those obtained via esophagectomy.

The applicability of these techniques to the overall population of patients referred with esophageal neoplasia remains to be defined, as does whether similar results can be obtained in the general community by non-specialty physicians and centers. The presence of occult malignancies, particularly those involving the submucosa with possible nodal metastases, must be considered. Further, the biology that led to the development of dysplasia and cancer remains, making it increasingly clear that eradication of all metaplastic epithelium is the ultimate goal and that

the importance of close follow-up cannot be overemphasized. While the advantages of a less-invasive approach to treatment of HGD/IMCA are intuitive, less obvious is the anxiety that comes with the slow and/or incomplete eradication of neoplasia, the need for serial endoscopic interventions, and surveillance over a prolonged time period. As such, surgical resection remains a very viable option, particularly for the young with a long life expectancy in which the possibility of new tumors arising beyond 5 years must be considered.

Endoscopic resection has emerged as a valuable tool in the treatment of early esophageal neoplasia. As with all new procedures, the treating physician should fully understand the strengths and limitations of the technique in order to apply it in appropriate circumstances. Patient selection is critical, and the exact indications for ER will continue to be elucidated as the available data mature. An expert team of endoscopists knowledgeable in assessment and treatment of esophageal disease, experienced esophageal surgeons, and dedicated pathologists is desirable. Given the commitment of resources and personnel necessary for optimal assessment and management, patients with such neoplasms are currently best treated in a specialty center.

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Transmediastinal Endoscopic Intervention

Denise W. Gee · David W. Rattner

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Natural orifice translumenal endoscopic surgery (NOTES) procedures were originally conceived for use in the abdominal cavity. Growing interest, however, has focused on thoracic and mediastinal NOTES applications. Today, access to the chest with conventional thoracoscopic and mediastinoscopic approaches has become routine for staging of oncologic disease, biopsy of pathologic tissues, and lung resection, among others. Unfortunately, even these minimally invasive techniques can result in significant pain and prolonged recovery. While diagnostic and therapeutic endoscopic procedures involving the thoracic cavity are common in clinical practice, transesophageal access has been confined to endoscopic ultrasound (EUS)-guided FNA. The transesophageal NOTES approach evolved as a potential means to reduce postoperative and chronic pain from conventional thoracoscopic techniques. A transesophageal NOTES approach could permit access to the mediastinal and thoracic cavities with less pain and scarring than with conventional thoracoscopic or transcervical mediastinoscopic approaches, while providing greater capabilities for therapeutic intervention than EUS. Initial results showed feasibility of this approach in swine models. NOTES thoracic procedures would eliminate skin incisions, spare deep dissection of the pretracheal fascia, and could prevent cutaneous surgical site infections. This approach could also be applicable in small patients (infants and children), in patients with limited extension of the neck (cervical arthritis), and could be performed in patients with a tracheostomy when conventional mediastinoscopy is contraindicated.

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D. W. Gee (✉) · D. W. Rattner
15 Parkman St. WACC 460,
Boston, MA 02114, USA
e-mail: dgee@partners.org

Transesophageal Access Techniques

As with the transgastric approach, techniques continue to be developed that permit safe and controlled transesophageal access to the mediastinum and thorax. Using EUS to identify an appropriate esophageal entry site, Fritscher-Ravens et al. created an esophageal incision using a needle-knife and exited directly into the mediastinum.[1] EUS permitted identification and avoidance of large vessels and positioning near the heart for planned procedures. The use of EUS was later abandoned due to lack of necessity and a standard gastroscope only was used along with a needle-knife to create a 2-cm full thickness incision in the esophageal wall. The defect was then closed with T-tags.

Sumiyama et al. reported a new technique called submucosal endoscopy with a mucosal flap safety valve.[2] In this approach, saline injection into the esophageal wall was used to confirm entry into the submucosa and then high-pressure gas insufflation was used to perform a submucosal dissection. A biliary catheter was then inserted into the submucosal layer and a 10-cm long submucosal tunnel created. Subsequently, an endoscopic mucosal resection (EMR) cap device (Olympus Optical Co, Ltd, Tokyo, Japan) was used to create a defect in the muscularis propria and the mediastinum was entered after removal of the EMR cap from the endoscope. The goal of this technique is to offset closure of the exit site defect from the mucosal entry site using the overlying mucosal flap.

A similar approach was taken by Willingham et al. who demonstrated mediastinal access via a submucosal tunneling approach.[3] The technique uses a needle-knife, prototype flexible carbon dioxide laser fiber (OmniGuide Inc., Cambridge, MA, USA) or Duette multiband mucosectomy device (Cook Medical, Inc) to incise the esophageal mucosal layer. In this method, a long submucosal tunnel of at least 10-cm is created using air and blunt dissection under direct vision with closed biopsy forceps. The tunnel is extended to the gastroesophageal junction. Unlike Sumiyama et al., a needle-knife was used to directly incise the muscular layer and provide a portal to the mediastinum.

Each of these techniques provides relatively safe and efficient access to the mediastinum. In the three studies combined, only one major complication occurred—a tension pneumothorax.[1–3]

Clinical Applications

Despite the relatively rapid evolution of NOTES into human trials, transesophageal NOTES procedures have been slower to gain attention. In clinical practice, transesophageal access in humans remains limited to the sampling of lymph nodes with EUS. Studies in swine suggest that the new frontier of transesophageal access to perform minimally invasive procedures is feasible. Gee et al.[4] published a study looking at the feasibility of transesophageal mediastinoscopy and thoracoscopy in a swine model. These results reported excellent visualization of mediastinal structures. Following entry into the mediastinum, a small incision in the pleura was made to enter the chest cavity. Thoracic structures were then easily identified. In this study, all animals survived, thrived, and had no clinical evidence of mediastinitis or thoracic contamination. EUS has also been used to identify small mediastinal lymph nodes that could be targeted for sampling and complete removal. In cases where fine needle aspirates do not provide sufficient information, the preserved lymph node architecture with this technique could provide a more definitive pathologic sample.

The use of transesophageal access to perform diagnostic and therapeutic intervention in the mediastinum and chest seems to be a growing possibility. To date, interventions in swine models have included lymph node biopsies and lymphadenectomy, pericardial fenestration, myocardial saline injections, pleural biopsy, the creation of a pericardial window, and thoracic sympathectomy, among others.[1, 4]

Esophageal Closure

Safe esophageal closure remains a challenge in transesophageal NOTES procedures. Currently, described closure methods include the use of suturing or T-tag devices which can be time consuming and risk organ injury due to their blind deployment. Endoclips have also been used, but these are often difficult to deploy in the narrow esophagus and do not provide full thickness closure of the muscular esophageal wall. The submucosal tunneling technique creates a flap-valve that offsets the proximal mucosal incision from the distal incision through the esophageal muscle layers. Upon withdrawal of the endoscope, the tunnel collapses. This technique has served as sufficient closure in many studies. Nevertheless, there is always a concern that esophageal contents may leak through the tunnel, contaminating the mediastinum and thorax in the early postoperative period.

Esophageal stent placement is an effective method for the treatment of nonmalignant perforations of the esophagus. Non-randomized human studies of stent placement for esophageal leaks and perforations demonstrate rapid leak occlusion, prevention of mediastinal and thoracic contamination, and implementation of earlier nutrition. Esophageal stenting as well as the use of sealants may prove useful and produce better outcomes than current techniques.

Barriers to Clinical Practice

Esophageal closure technique, the risk of esophageal leak, and infections including mediastinitis, pneumonia, and bacteremia are major concerns when attempting to access the chest cavity with a transesophageal route. Large studies investigating infectious complications have not been reported and are challenging to complete due to limitations of the animal model. Human trials in patients undergoing endoscopy during Roux en Y gastric bypass investigating transgastric instrumentation of the peritoneal cavity show clinically insignificant contamination of the peritoneal cavity. Furthermore, years of experience with alimentary tract surgery show that whereas bacterial contamination of the peritoneal cavity occurs in nearly all bowel procedures, intra-peritoneal abscess formation is unusual in the absence of anastomotic leak or pre-exisiting peritonitis.

Other adverse events including bleeding and pneumothorax are well-known complications of human thoracoscopic procedures. These complications have also been observed in swine NOTES thoracic studies. Conventional interventions such as needle decompression or chest tubes can be performed, though no investigative team has reported the need for chest tube placement in animal studies. Since control of bleeding is challenging, it will be important to perform studies that look at hemostatic methods in the chest. Vessels within the chest, including intercostal arteries and veins, can be difficult to access due to surrounding bony structures (i.e., ribs, vertebral bodies).

In a systematic review of all published experimental animal thoracic NOTES procedures, mortality was found to be 5% and morbidity 19%.[5] The review included two studies where thoracic procedures were accomplished with a transvesicular, transdiaphragmatic, or transgastric approach, while the remaining five studies were transesophageal. The morbidity and mortality in the combined studies represent one of the major challenges in creating a new, minimally invasive technique and underscores the need for technological improvements to move transesophageal NOTES to human clinical applications.

Future Directions

The major challenges of thoracic NOTES procedures include determining the optimal access method to the desired area of the mediastinum or thorax and, most importantly, safe closure of the esophagus. These concerns have limited thoracic NOTES experiments to the animal model. A closure device and/or technique permitting full-thickness closure of the esophageal wall without the development of stricture or leakage requires further development. Continued instrument development will also be needed to improve hemostatic ability when bleeding complications occur or when transesophageal surgical resections are performed.

Moving forward, there is a need for studying the hemodynamic and physiologic consequences of these transesophageal interventions. Studies have been performed on the effects of carbon dioxide insufflation during video-assisted thoracoscopic procedures. Future studies will need to examine the consequences of controlled endoscopic insufflation with room air versus the use of carbon dioxide regulated insufflation and other potential consequences of an esophageal entry site. In addition, future work must focus on potential infectious complications and how to best prevent these occurrences. Finally, larger, randomized studies must be performed to compare NOTES procedure times and outcomes to standard thoracoscopic interventions.

Perhaps most exciting is the potential for cardiac applications of the NOTES technique. Atrial fibrillation is the most common arrhythmia in the USA and current endovascular catheter-based techniques of pulmonary vein ablation have many limitations. Transesophageal NOTES can provide access to the posterior mediastinal compartment and allow direct visualization of the pulmonary veins. This might be a potentially faster and less morbid approach to pulmonary vein ablation than other surgical or catheter-based procedures. The benefits of NOTES would be maintained with a minimal scar, decreased postoperative pain, and quick postoperative recovery.

Summary

Transesophageal NOTES is a promising technique that offers a less-invasive means of accessing the mediastinum and pleural cavities. The continued relationship between surgeons, gastroenterologists, and the biomedical engineering community will be critical for device development that will permit better endoscopic control and precision during planned NOTES procedures. Technological advances and improved closure methods are still required to make transesophageal NOTES a truly viable approach in humans, but preliminary studies suggest that this technique has great potential to.

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Indications and Techniques of Transanal Endoscopic Microsurgery (TEMS)

Yanjie Qi · David Stoddard · John R. T. Monson

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Abstract Transanal endoscopic microsurgery (TEMS) has recently reemerged as a valuable technique for the management of rectal neoplasms — both benign and malignant. Since the original description of this technique in the early 1980s, TEMS has emerged as the approach of choice for most benign rectal tumors because of the excellent views provided and superior dissection techniques possible when compared to traditional transanal excision. Many published reports demonstrate that the lowest rates of recurrence are associated with TEMS probably because of full-thickness excision with negative margins. Increasingly, TEMS is being applied to primary rectal cancer when used alone as a full-thickness excision alone or in combination with additional therapies, depending on tumor stage. There is now a significant evidence base to suggest that this approach should be considered as part of a multidisciplinary approach to rectal cancer. This paper describes indications and techniques for this technology.

Keywords Indications · TEMS · Rectal cancer · Surgery

Introduction

Since its introduction in 1983,[1] transanal endoscopic microsurgery (TEMS) has established itself as a safe and successful approach to transanal excision of rectal neoplasms. TEMS involves the use of specialized equipment including an operating proctoscope, insufflation, and stereoscopic magnification that allow for improved visualization and a more precise excision of lesions throughout the rectum. It expands the surgical range of transanal resection to mid- and upper-rectum lesions that had previously required more invasive abdominal low anterior resections.

Despite its technological advantages and lower surgical risks, TEMS should not be used indiscriminately for all rectal lesions. Careful preoperative evaluation and patient selection remain to be important surgical tenets and paramount for optimal outcomes. Research and experience over the past two decades have identified that a range of benign and malignant lesions are successfully treated by TEMS resection.

Y. Qi · D. Stoddard · J. R. T. Monson (✉)
Division of Colorectal Surgery, University of Rochester Medical Center,
601 Elmwood Avenue, Box SURG,
Rochester, NY 14642, USA
e-mail: John_Monson@urmc.rochester.edu

Indications

Because TEMS allows for access to the entire rectum, any rectal lesion could theoretically be removed. Resection is for the most part not limited by feasibility but the optimization of outcome. For benign diseases, any lesion that can be safely excised is appropriate. For malignant lesions, consideration must be given to resection with optimal margins and aims of cure.

Benign Disease

Buess et al. [2] initially described TEMS in treatment of benign rectal adenomas. It was originally developed to tackle large rectal polyps unresectable by traditional endoscopic approaches and to spare patients from high-risk abdominal surgery. TEMS is especially effective for

large and flat lesions located between 5 and 15 cm from the anal verge. Lesions, such as villous adenomas, that tend to grow to a large size, expanding several centimeters down the length of the rectum as well circumferentially around the lumen, are notoriously difficult to resect with either colonoscopic snares or traditional transanal excision. TEMS offers a number of advantages in this setting including accurate identification of the margins of mucosal abnormality in the distended rectum which in turn leads to reduced risk or margin positivity. The high-quality magnified image allows for a more precise dissection technique both for full-thickness and partial-thickness excisions. Better imaging and access also facilitate control of hemostasis. In experienced hands, polyps above the peritoneal reflection of the rectum (>15 cm), polyps of >8-cm diameter, and polyps occupying >50% of the circumference have been shown to be amenable to TEMS resection.[3]

Recent experiences have shown that TEMS can be applied to a variety of anorectal diseases. Other benign rectal and extrarectal masses can also be excised such as carcinoids, some retrorectal cysts, and masses within the anovaginal septum, although experience in these rarer indications is very limited. Problematic high rectovaginal fistulas can be repaired with mucosal advancement flaps with TEMS.[4] TEMS has also been effectively used to treat anastomotic strictures, rectal prolapse, high extrasphincteric fistulas and for transrectal drainage of pelvic collections.

Malignant Disease

Local excision of rectal cancer must include consideration for the risk of lymph node involvement, incidence of local recurrence, operative mortality, and risk of anorectal dysfunction. It is important to identify early disease with low chances of metastasis, which may benefit from the lower operative risks of TEMS. In the last few years, multiple studies have been published showing efficacy of TEMS in the treatment of early rectal cancer.[5–7] Transanal ultrasound or magnetic resonance imaging (MRI) should be performed to identify T stage and lymph node status. All patients with lymphadenopathy should be directed to more radical resection, because endoscopic resection cannot evaluate and treat regional lymph nodes. T1 lesions have been proven to be ideal candidates for TEMS, since local recurrence rates are low and the benefits of reduced morbidity are substantial. T2 lesions can also be resected with TEMS, but the evidence strongly indicates that such patients require additional therapy—usually chemoradiotherapy—if acceptable outcomes are to be achieved. In addition to T stage, tumor diameter and lymphovascular invasion will also increase the risk of recurrence.[8]

All malignant tumors require full-thickness excision. For large tumors, primary repair after TEMS excision may result in loss of rectal volume and anastomotic strictures. For proximal lesions on the anterior and lateral wall, full-thickness resection may lead to entrance into the peritoneal cavity particularly in female patients where the level of the peritoneal reflection is variable. This is not a contraindication to TEMS, but it can make the procedure more challenging. Despite obvious concerns, a recent study has shown that entrance into the peritoneal cavity is not associated with operative complications or oncological compromise.[9]

T3 lesions are not appropriate for TEMS—as a curative procedure—except for high-risk patients who may not survive a low anterior resection.

Equipment

TEMS is possible thanks to a highly specialized complement of equipment which include a 40-mm-diameter rectoscope, available in 12- and 20-cm lengths, beveled along the inferior aspect to allow for good operative exposure. The rectoscope has a removable airtight faceplate with four ports for instrument access. The stereoscope is a 10-mm optical instrument with a 50° downward viewing angle, a 75° field of view, and two eyepieces for stereoscopic, three-dimensional vision. Because of the downward viewing angle of the stereoscope, TEMS instruments are designed with downward-angled tips to facilitate access to the operative field. The rectoscope is fixed to the table by means of a double-ball jointed Martin arm. The Martin arm allows for the rectoscope to be precisely placed for optimal exposure. It is adjustable to any angle and locks to position during surgery. The rectoscope is attached to a dedicated insufflator that provides continuous carbon dioxide insufflation and is capable of maintaining constant pressure (typically between 15 and 20 cm H_20) and rectal distention even during irrigation and suction.[10]

Operative Description

Prior to TEMS, rectal cleansing is essential and is best achieved by phosphate enema—one the night before and one the day of surgery. General anesthesia is most often used in TEMS. Initial rigid sigmoidoscopy is performed to localize the lesion and ensure the feasibility of resection. The patient is positioned such that the lesion is located at the 6 o'clock orientation (i.e., prone for anterior lesions and split-leg lithotomy for posterior

lesions). The rectoscope is introduced with accompanying obturator to the level of the tumor and fixed to the table by means of the Martin arm. The surgical margin around the lesion is first marked out by electrocautery—this is essential for accurate identification of resection margins. The aim is for a 5-mm margin of normal mucosa for benign lesions and a 10-mm margin for known or suspected cancer. Mucosectomy, partial-thickness, or full-thickness excision of the lesion is then undertaken by means of needle electrocautery or bipolar diathermy. Except for resections that enter into the peritoneal cavity, full-thickness excision does not require repair of the defect. The area of resection heals relatively quickly without strictures. If primary repair is necessary, 3-0 PDS is placed in a running fashion and secured by suture beads. After excision of the specimen, the operative site is checked for hemostasis and the rectoscope withdrawn. The specimen is secured on a cork-board with pins to preserve anatomical orientation, placed in formalin, and sent for pathological examination of surgical margins.[10]

Postoperative Course

Patients typically recover rapidly from TEMS quickly and start a standard diet the same day. Most are discharged within 24 h postoperatively. Postoperative complications are rare and include perforation, bleeding, fistula formation, wound breakdown, and temporary minor urgency or incontinence. Follow-up should include clinical exam, rigid sigmoidoscopy, and carcinoembryonic antigen levels for malignant lesions. Patients may also need a colonoscopy and MRI for surveillance.

Conclusion

TEMS has proven to be a safe and effective approach to treat large rectal polyps and early rectal malignancy. It is a unique surgical technique that has potential for wide application in the USA. However, like all surgical approaches, it is limited both by appropriate patient selection and operator experience. For safe implementation, it is important to understand its clinical indications and acquire familiarity with its specialized equipment.

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Laparoscopic-Facilitated Colonic Endoscopic Mucosal Resection and Endoscopic Submucosal Resection of Adenomas: Techniques to Avoid Segmental Colectomy

Richard L. Whelan

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Keywords Endoscopic mucosal resection · Endoscopic submucosal dissection · Polypectomy

A significant percentage of the colorectal neoplasms referred to colon and rectal surgeons for consideration for a segmental colectomy are benign sessile adenomas deemed "not amenable to colonoscopic removal" by the referring gastroenterologist. Up until the last decade, the treatment options for these lesions have been: (1) repeat colonoscopy, reassessment, and possible attempt at colonoscopic removal in the endoscopy suite, (2) formal transabdominal segmental colectomy, (3) transabdominal wedge-type colon wall excision, or (4) observation alone. Most surgeons, when faced with this situation, will perform a "cancer type" segmental colectomy because of the well-known possibility that the supposedly benign polyp may harbor an invasive cancer. Unfortunately, in a certain percentage, after doing such a resection, most often a right hemicolectomy, when the specimen is opened the surgeon is underwhelmed by the polyp in question. Most endoscopists worldwide are fearful of sessile polyps 2 cm or larger, especially those that are located in the cecum or right colon, since these latter polyps are far from the anus and because the wall of the right colon is thin and prone to perforation. Despite these challenges, over the past 30–40 years, endoscopists have developed endoscopic methods for dealing with larger benign sessile colonic polyps that allow colectomy to be avoided for many lesions that would otherwise be dealt with via segmental colectomy.[1]

Although initially introduced and developed for gastric biopsy, endoscopic mucosal resection (EMR) methods were later utilized to fully remove large gastric benign lesions, in piecemeal fashion. Later still, EMR methods were used as definitive treatment of superficial cancers invading into the superficial submucosa. As an offshoot of EMR, endoscopic submucosal dissection (ESD) methods were developed and introduced as a means of doing en bloc resection of large mucosal lesions, which permits a more thorough and useful pathologic evaluation in regard to completeness of resection and depth of invasion. In the past 20 years, EMR and ESD methods have been utilized for colorectal polyps. Again, the majority of the pioneers in this field were Japanese gastroenterologists.[2] Because the colon wall is considerably thinner than the gastric wall, the enthusiasm for EMR in the colon is not as great as for the stomach due to fear of perforation. Thus, for large colonic polyps, ESD methods, although more difficult, may be safer and more logical. The literature attests to the fact that, in expert hands, polyps 4–6 cm in size can be safely excised in one piece via ESD. Despite these ESD successes, even the experts advise

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R. L. Whelan
St. Luke's Roosevelt Hospital Center,
New York, NY, USA

R. L. Whelan (✉)
St. Luke's Roosevelt Hospital Center Chief of Division, Colon & Rectum Surgery,
425 West 59th Street, Suite 7B,
New York, NY 10019, USA
e-mail: rwhelan@chpnet.org

caution in regard to cecal and right colon polyps, again because the colonic wall is thinnest in this segment. American gastroenterologists are also reluctant to attempt polypectomy on sizable right colon sessile adenomas; thus, colon and rectal as well as general surgeons are referred these neoplasms for definitive treatment.

Although the prevailing operation carried out in these circumstances, a formal right hemicolectomy, fully removes the lesion, for the great majority of lesions, which are benign, it is not necessary from an oncologic viewpoint. Several surgeons, most notably Morris Franklin and Jeffrey Milsom, in an effort to avoid segmental colectomy, suggested the use of laparoscopic methods to facilitate colonoscopic polypectomy in the operating room setting. Laparoscopic instruments can be used to externally compress, push, and maneuver the colon lesion into a position that facilitates colonoscopic removal. Furthermore, after polypectomy, it is possible to laparoscopically inspect the external colonic wall for a leak or injury and to repair the wall if a perforation is found. Also, should endoscopic removal prove impossible, a wedge resection of the colon wall or a standard colectomy can be accomplished laparoscopically, thus assuring complete polyp removal during this combined procedure. Thus far, standard colonoscopic tools (monopolar snare, biopsy forceps, etc.) have been utilized during the laparoscopic-facilitated colonoscopic polypectomies. It seems logical to add EMR and ESD methods to the armentarium of the endoscopic surgeon. A brief description of EMR and ESD follows.

Submucosal Lift

A critical prerequisite to EMR and ESD is injection of saline or another solution via a sclerotherapy needle into the submucosal space between the mucosal polyp and underlying muscularis propria. The purpose of the submucosal injection is to increase the distance between the polyp and the deeper layers of the bowel wall, thus decreasing the chances of full thickness perforation during polypectomy. A colonoscopic injection needle device (as is used for sclerotherapy) is used to inject the submucosa (23–25 gauge). A variety of solutions can be injected including: saline, saline and epinephrine (1:100,00–1:200,000 strength), 50% dextrose, hyaluronate, and hydroxypropylmethylcellulose.[3] The ideal solution is absorbed slowly from the submucosal space which increases the duration of the "lift." The author currently uses saline and epinephrine which has a duration of about 3 min. Periodically, the submucosal injection must be repeated to reestablish the lift. As more of the submucosa is exposed, the duration of the lift shortens because the solution can easily leak out.

EMR

Numerous EMR methods have been described; the common goal of these approaches is to entrap and excise a portion of a sessile polyp using an endoscopic snare. Thus, except for small lesions, EMR methods mandate piecemeal excision. The EMR "strip biopsy" method entraps a part of the polyp by pressing an open snare against the sessile polyp while suctioning gas from the colon and simultaneously closing the snare. A variation of this method is the so-called lift and cut method which utilizes a double-channel therapeutic endoscope. A biopsy forceps, after being passed through an open snare (inserted via the second working channel), is used to grasp and lift the polyp. The snare is then closed around the elevated part of the polyp and the entrapped tissue excised.

Cap EMR utilizes a transparent plastic cap which is attached to and extends 1 cm or so from the endoscope's tip. The cap has a groove close to its end into which a wire snare is preloaded. Once situated over the desired area of the polyp, the scope tip is turned toward the polyp and suction is applied. This draws a portion of the polyp into the cap and through the open snare which is subsequently closed. Monopolar electric current or high-frequency electric current (HFEC) is then applied and the ensnared part of the polyp excised. The EMR ligation method utilizes a flexible endoscopic bander, such as is used for esophageal banding, which is affixed to the endoscope tip. Similar to cap EMR, a portion of the polyp is suctioned into the banding cap after which a band is released onto the entrapped mucosa. This creates a pseudopolyp which is then excised with a snare. Whichever EMR method is used, it must be repeated until the entire polyp has been destroyed. The multiple specimens are then retrieved and sent to pathology for evaluation.

ESD

As mentioned, the goal of ESD methods is to excise the polyp en bloc with a margin of normal mucosa. This requires first that the mucosa around the polyp be scored or incised and the submucosal plane entered. Next, dissection in the submucosal plane beneath the polyp is necessary in order to detach the mucosal lesion. Some type of "knife" is needed to cut the tissue. A standard polypectomy snare with just 2–4 mm of the snare extended from the sheath can be used as a knife to cut the tissue. Unfortunately, the tip of the snare and the plastic sheath tend to bend, which makes it a less than ideal dissection tool. Thankfully, a variety of endoscopic wire knifes are available including: (1) straight needle knife (with exposed tip), (2) hook needle knife (with exposed but bent tip), (3) insulated tip needle knife (with ceramic ball or triangle-shaped insulation at tip), and (4)

"flex knife" (thick wire with small loop at its tip) which is more flexible than the needle knives.[4] Although standard monopolar cautery current can be used with these instruments, it is advised that HFEC be used, if possible. There are several different HFEC devices on the market (ERBE unit Vio-300D, Olympus PSD-30). Many experts advise that an "Endo Cut" (mostly cutting current which produces less tissue damage but also more bleeding) setting be used to score the mucosa and that a "forced coagulation" mode be utilized for the submucosal dissection (more tissue damage but less bleeding).

ESD presents numerous challenges and obstacles that are not encountered with EMR or standard snare excision. ESD is more like a surgical procedure than a typical endoscopic polypectomy in that successful resection of the polyp requires retraction of the polyp, the establishment of the correct dissection plane within the submucosal layer, and the full dissection of that plane beneath the polyp. Retraction is a real challenge. The use of gravity to retract the partially excised polyp is an excellent strategy. In the outpatient endoscopy suite under IV sedation, it is possible to alter the patients' position. Unfortunately, during laparoscopy under general anesthesia, it is not possible to place the patient in the decubitus or prone position. Alternatively, to obtain retraction, the edge of a clear plastic cap affixed to the endoscope that extends 1–1.5 cm from the scope tip can be used to push the mobilized part of the polyp into the lumen, thus exposing the submucosal plane.

Another strategy is to utilize a double-channel scope; in theory, a biopsy forceps can be used in one channel to lift or retract the edge of the polyp (after the initial scoring has been done) and expose the dissection plane after which the needle knife, passed via the second channel, is used to cut the tissue. The problem with this method, using currently available double-channel scopes, is that to retract the polyp edge, the scope tip must be reflected up and into the lumen which means the operator cannot see the area to be dissected, namely the submucosal/muscularis propria junction. There is a prototype scope called an "R" Scope, made by Olympus, which has two working channels that allow deflection of the instrument tips (one deflects upward and the other transversely). This scope permits the polyp edge to be retracted into the lumen without moving the scope tip in the same direction, thus, allowing the operator to see the dissection plane and to cut the tissue via a knife in the second channel. This is an elegant solution to the retraction issue which is central to successful completion of ESD.

Coordinating the movement of the endoscope tip and needle knife to cut and dissect is very difficult. In order to move the needle knife as desired, it is necessary that the endoscopist have both hands free to control the deflection wheels. This means that a dedicated assistant is needed to hold the scope shaft near the anus and to control the amount of torque applied. A second skilled assistant is needed to control the needle knife tip (to retract or extend it) or the sclerotherapy needle. A third person (usually the circulating nurse) is also needed to keep the solutions for submucosal injection and irrigation ready and to open endoscopic instruments as needed. The endoscopist must determine, before actually cutting the tissue, which combination of vertical and horizontal tip movement will move the knife tip in the desired direction. This often requires simultaneous movement of the two deflection wheels in opposite directions while the scope is held in position. Because it is necessary to make a circular score around the lesion, this process can take up quite a bit of time.

Combined Laparoscopy and EMR/ESD

Currently, EMR and ESD are carried out alone in endoscopy suites. If a perforation is noted, an attempt may be made to close the hole with endoscopic clips. If a large perforation is made or if the clips are not adequate, then surgery is necessary to deal with the problem. There is inevitably a delay before surgery is carried out, which is not ideal. It is because the risk for perforation on the right side of the colon is high that most ESD experts shy away from cecal and right colon polyps. The simultaneous use of laparoscopic and advanced endoscopic methods in the operating room setting allows a surgical endoscopist to rationally employ ESD methods for large right-sided polyps. The laparoscopy allows for: (1) lysis of adhesions that may impede endoscopic access, (2) the external manipulation of the colon and polyp-bearing segment, (3) inspection of the colon wall after endoscopic polypectomy, (4) "wedge" full-thickness partial circumferential bowel wall excision to either deal with a perforation or to accomplish the polypectomy if endoscopic attempts fail, and (5) a standard segmental colectomy if necessary. From the perspective of the patient, this approach will definitively take care of the polyp in question, via one of the above methods, at a single procedure. This is likely to be more attractive to a patient than the prospect of multiple endoscopic procedures in the outpatient endoscopy suite during which the polyp is removed piecemeal. However, doing ESD and EMR in the operating room poses numerous challenges as well.

Additional staff are needed, some with a different skill set than the standard circulating nurse or surgical resident (or assisting surgeon). To begin with, it is necessary to gather in the operating room the necessary ESD/EMR equipment. A partial list follows: (1) colonoscope/endoscope (some experts advise having two available: double-channel colonoscope and a thinner diameter upper endoscope onto which the transparent caps useful for dissection can be

fitted), (2) CO_2 endoscopic insufflation device, (3) endoscopic sclerotherapy needles, (4) India ink or indigo carmine for tattooing and marking, (5) several needle knives, (6) EMR/ESD endoscope cap, (7) endoscopic clips (4–6), (8) specimen retrieval net, (9) standard polypectomy snare, (10) standard biopsy forceps, (11) HFEC generator (vs. standard monopolar cautery machine), (12) cable that runs from HFEC/cautery machine to the needle knife or snare, (13) submucosal lift solution and multiple 10-cc syringes, and (14) 50–60-cc syringes and saline for endoscopic irrigation. Staff wise, having an additional circulator or RN with endoscopic experience in the room is strongly recommended. This critical person makes sure that all the necessary equipment is ready and that the various tools that may be required are nearby and ready to go. Also, another person (resident, medical student, or assistant) is needed to hold the colonoscope shaft close to the anus in order to free up the right hand of the endoscopic surgeon. These procedures are labor-intensive and have a considerable learning curve; thorough preparation and planning are necessary. Furthermore, these procedures are lengthy. In addition to the staffing and equipment challenges, there is the distinct possibility that after performing ESD for several hours, it will prove necessary to abandon the endoscopic polypectomy to perform, instead, a wedge resection or segmental colectomy.

In terms of approach, it is advised that the procedure be started by establishing pneumoperitoneum and inserting several 5-mm laparoscopic ports after which the abdomen and the colon segment in question are inspected. Adhesions may need to be lysed to expose the polyp-bearing segment. The surgeon may also choose to partially or fully mobilize the segment in question (cecum and proximal right colon for example). Once this is done, the pneumoperitoneum is released and the colonoscopy carried out. Once the polyp is found, it is the authors practice to mark the margins of the planned polypectomy with submucosal injections of India ink. This will help orient the endoscopist during both endoscopic and laparoscopic wedge partial-thickness resection. Next, an attempt is made to "lift" the polyp via submucosal injection of saline and epinephrine (or whatever solution is to be used). If this is possible, then the procedure is begun as per the above description. If the polyp or a portion of the polyp will not lift, then there is concern that the lesion may be invading into the muscularis propria. In this case, the endoscopic polypectomy approach should be abandoned and a standard segmental colectomy carried out. If ESD is employed but not completed, for whatever reason, then the next step would be to carry out a laparoscopic partial circumference wedge resection of the colon wall. If, after completing ESD, a perforation(s) is noted, the options open to the surgeon are: (1) repair with endoscopic clips, (2) laparoscopic suture imbrication of the perforation or polypectomy site, (3) wedge partial circumference wedge resection of the colon wall (stapler).

The Future

One of the central challenges facing NOTES surgeons is the need for a reliable method to endoscopically close full-thickness bowel perforations. Numerous methods and devices are in development and are being tested. Once perfected, the availability of full-thickness endoscopic suturing devices should make it possible to endoscopically perform wedge full-thickness colon wall resections. This would eliminate the need for transabdominal surgery for most benign neoplasms. Eventually, these full-thickness resections would be performed as ambulatory procedures, which should reduce the overall costs. Further, patients will benefit much from the avoidance of formal surgery for benign colonic neoplasms. ESD and EMR methods are likely the forerunner of endoscopic full- thickness wedge resection. Surgeons and endoscopists must be adept at ESD if they are to participate in the development and employment of the advanced tools and methods in development.

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SSAT/SAGES JOINT SYMPOSIUM

TEM as a Platform for NOTES

John H Marks

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Transanal Endoscopic Microsurgery (TEM) offers the only established experience to date in endoluminal surgery. Dr. Monson has already presented many of the traditional utilizations of TEM surgery for the treatment of polyps and select cancers. In this paper, we will explore many of Transanal Endoscopic Microsurgery's advantages and opportunities as a platform for endoluminal surgery.

The first Natural Orifice Transluminal Endoscopic Surgery (NOTES) procedure was performed in 2003 and consisted of a transgastric appendectomy with tubal ligation by doctors Rao and Reddy in Hyderabad, India.[1] This set off a great deal of activity both within the surgical community and with our partners in the medical device industry. The first transvaginal cholecystectomy was performed in the USA by Dr. Marc Bessler at Columbia Hospital on March 20, 2007.[2] The procedure was done with a hybrid laparoscopy platform using three small ports to assist in the operation. This is an important matter to note as this has been a constant challenge with the NOTES approach as originally conceptualized. The original NOTES approach comprised a flexible endoscope coming through another organ in order to carry out a procedure.

Surgical evolution is sometimes progressive and sometimes traumatic. The advent of laparoscopic surgery in the late 1980s and early 1990s involved primarily a change in access in order to perform an operation. Rather than making a large incision in the abdominal wall in order to carry out an operation, small ports were utilized. The procedure itself, for the most part, remained the same. This approach made infinite sense, at its greatest adoption, in the performance of cholecystectomy. In this operation, the intra-abdominal trauma is relatively small, taking just the cystic duct and cystic artery and removing the gallbladder from the gallbladder fossa. The conventional subcostal incision made to perform the operation represented a tremendous amount of trauma, and the benefit to the patient was readily apparent.

In talking about surgical evolution from laparoscopy to NOTES, we are looking at a very different paradigm. The issues become fourfold: access to the target organ, the procedure performed, visualization, and retraction. These are all quite different using a NOTES approach. As originally conceived, this includes gaining access through another healthy organ and performing a procedure perhaps in a different fashion with the challenge of retraction, using flexible instrumentation having inadequate strength, in order to hold the tissue and provide proper visualization.

The issue of access for NOTES surgery demands additional attention. Azurin reported a 0.8% umbilical trocar site herniation rate following laparoscopic cholecystectomy in 1,300 patients. This is a laudable figure which

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J. H. Marks
Colorectal Surgery, Main Line Health System,
Wynnewood, PA, USA

J. H. Marks
Lankenau Institute for Medical Research,
Wynnewood, PA, USA

J. H. Marks (✉)
Lankenau Hospital,
100 Lancaster Avenue, MOB West #330,
Wynnewood, PA 19096, USA
e-mail: marksj@mlhs.org

appears quite low as compared to my experience in residency. But, even if accepted as is, it begs the question of whether we as surgeons would be willing to disrupt a healthy organ in order to gain access to a diseased one. Had those same 1,300 patients been operated on in a NOTES fashion, and if a similar breakdown of the access closure of 0.8% was encountered, one would be looking at 10–13 gastric perforations or colonic perforations if one was approaching the gallbladder transgastrically or transrectally. Would we be willing to tolerate 10–13 colostomies in this group of patients? Would these patients tolerate being bowel prepped in order to undergo a cholecystectomy in a NOTES fashion?

With this as a background, I offer TEM as the ultimate approach in minimally invasive endoluminal surgery and as a potential platform for NOTES. The logic of NOTES is quite clear. When there is no abdominal incision, the patients are almost entirely devoid of pain. We have seen this for two decades in TEM surgery. Utilizing a transcolonic route in order to perform colorectal surgery makes infinite sense. One is making a defect in a target organ, not in a healthy bystander. Furthermore, entry into the peritoneal cavity during a TEM resection has been encountered and performed with safe closure dating back to the 1990s. Dr. Swanström's group beat me to this point in their publication in *Gastrointestinal Endoscopy* in November of 2008 describing porcine and cadaveric surgeries using TEM instrumentation and flexible endoscopes.[3] They were able to perform liver biopsy, sigmoid resection, and hepatic wedge resection in this fashion. The strong appeal of this approach has to do with the stability of the working platform that is achieved with a Martin arm attachment to the table (Fig. 1). The strong instrument shafts allow direct dissection of heavier organs and a strong visual–spatial orientation which is often difficult to maintain with the flexible scope. Additionally, the extraction of larger specimens is easily performed. The challenges that we encounter in using TEM and NOTES as an alternative to colorectal procedures have to do with the large amount of mobilization which is often necessary for colorectal surgery and the disease processes that are being operated upon. Benign disease consists of polyps and inflammatory conditions such as diverticulitis and colitis. Polyps are generally handled as if there might be a malignant component to them, and therefore, an adequate lymphadenectomy needs to be performed. Inflammatory conditions carry with them the difficulty of dissection in an inflamed area which is often both hypervascular and densely adherent making any type of dissection challenging. In 2007 in the USA, there were 240,000 colectomies performed, 140,000 of which were for colorectal cancer. Cancer represents additional challenges in terms of exploration, staging, and lymphadenectomy.

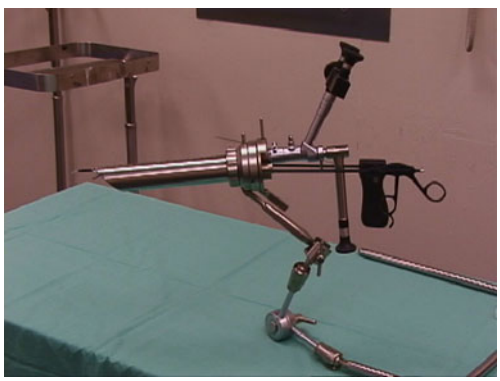

Fig. 1 TEM working platform

We have been performing radical TEM surgery for treatment of cancers receiving neoadjuvant chemoradiation and being downstaged to ypT2N0 cancers. We are reliant upon the reaction of the index cancer to be an indicator of the tumor response microscopically in any lymph nodes. The operation is started endoluminally by a marking around the lesion circumferentially using the electrocautery to yield a 1-cm margin. This highlights an important facet of operating endoluminally via the NOTES approach. It is essential to have established landmarks in your target organ as visualization sometimes becomes difficult once there is even a small amount of smoke or blood in the field. The rigid TEM equipment, however, does allow for full-thickness transection and lymphadenectomy down to the puborectalis or presacral space in the same plane as one operates in performing a total mesorectal excision. Using this approach, we are able to excise large segments of bowel, up to 12 cm in length. This can either be a hemicircumferential or a sleeve resection. We generally view this as both the last step of staging and the first step of treatment. If there is full-thickness invasion with T3 pathology, radical surgery is recommended. If the tumor is ypT2 or less, this represents a therapeutic approach requiring close clinical follow-up. To date, I have personally treated 261 patients with TEM, 41% of whom have had invasive cancer and 77% of whom have had neoadjuvant therapy. We recently presented a case-matched study of 30 TEM patients to 43 TME patients with T2 carcinoma with chemoradiation, showing a 3.3% local recurrence rate with TEM, which is not statistically different than 2.3% local recurrence rate with TME.[4] This is currently in print. This holds an exciting option for the select usage of this approach to cancers with neoadjuvant therapy in the future. While this represents exciting results from individual experiences, they need to be corroborated in larger, multi-institutional experiences.

Many of the challenges of closing the bowel with the NOTES procedure are highlighted with TEM. Stay sutures need to be placed circumferentially in four quadrants in order to perform the anastomosis, and to date, there are no flexible instrumentations that allow this to be done reliably.

The long solid shafts of the TEM equipment allow for this type of work to be done. This remains a very significant barrier to be crossed in the NOTES forum. Furthermore, when dealing rectally with lesions after neoadjuvant therapy, on occasion, a diverting stoma is utilized. While this is quite acceptable and customary in dealing with rectal cancer, clearly this would not be an acceptable outcome for someone having another organ operated upon.

This author's opinion is that the ultimate utilization of NOTES will be in a very different format than what has been proposed to date. A combined NOTES laparoscopic TEM approach makes a great deal of sense, where some of the upper mobilization will be done laparoscopically and some of the lower pelvic work will be done using TEM equipment. I have had experience doing this faced with difficult problems to avoid complete conversion or permanent colostomy. The beauty of this approach is that it allows for excellent visualization endoluminally in the most difficult part to see from above, which is the very low rectum, and excellent visualization higher-up in the area that is difficult to visualize with the TEM equipment. Lastly, there is the ability to handle larger blood vessels with these straight instruments quite readily in a fashion that is not available with flexible endoscopy. To date, I have performed 42 of these "incisionless" procedures where the cancers have been delivered from below. This represents an exciting option as we move forward.

Lastly, as Dr. Whelan has presented on endoscopic mucosal resection, some of the new devices that are becoming available, such as the Olympus R Scope which is a prototype form that has dual-channel adjustable working ports, are going to allow different things to be carried out with flexible instruments.

As a growth of experience occurs worldwide in doing all sorts of NOTES surgery as well as transluminal surgery, new applications will arise in parallel with new instrumentation. The path to the future will certainly utilize more forms of endoluminal surgery. There are a multitude of challenges oncologically, technically, and functionally that need to be overcome in order for us to apply this more broadly. Furthermore, the applicability of something that is more technically challenging in a field such as colorectal surgery where less than 20% of the operations are being done laparoscopically causes pause. Clearly, the logic of approaching colorectal disease endoluminally through the colon has a tremendous advantage over some other organ sites. TEM, or variations of TEM, offers an exciting possibility to advance in this field.

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ORIGINAL ARTICLE

Prevention of Leaks in Esophageal Surgery

Fernando Mier · Brant K. Oelschlager

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Keywords Esophagectomy · Esophageal leak · Esophageal cancer

Esophagogastric anastomosis leaks continue to be a significant source of morbidity and mortality after esophageal surgery. There are many variables that may be implicated in the development of this complication, and it is important to understand these factors for the surgeon to prevent their occurrence. The patient factors, such as the patient's age, comorbidities, nutritional status, and the use of steroids or neoadjuvant therapy, play an important role by impairing esophageal or conduit healing. Technical variables such as conduit preparation and type, anastomosis location, and technique are also implicated. Surgeons must control and manage these risk factors and variables perioperatively in order to improve their outcomes.

Patient Factors

Comorbidities

Several factors such as advanced age and the use of steroids, among others, have been associated with impaired tissue healing, nevertheless none has been proven to increase leaks in esophageal surgery. One study has shown that patients with comorbid conditions are more prone to develop leaks,[1] yet individual patient risk factors have not been proven to significantly increase them, though this may be due to a lack of statistical power in most esophageal surgical studies.

Nutrition

Nutrition is one of the most important modifiable risk factors implicated in wound healing; therefore, any factor that disturbs the patient's nutrition will likely increase their risk for developing leak. Often, patients undergoing an esophagectomy are unable to maintain adequate oral intake. Such a malnourished patient, with a preoperative serum albumin of less than 3 g/dL, or a weight loss greater than 10% of their total body weight, would be predicted to have an increased risk of developing an anastomotic leak. In this case, consideration of preoperative enteral or parenteral nutrition prior to surgery should be given. We recommend the liberal use of removable esophageal stents to increase oral intake, although feeding jejunostomy, nasoenteric tube feedings, or TPN are also acceptable methods of preoperative nutrition. The use of a percutaneous gastrostomy tube, although not contraindicated,[2] should be avoided if possible if the stomach is to be used as the conduit of choice, as the gastrostomy may compromise the integrity of the conduit and complicate the operation.

Neoadjuvant Therapy

The use neoadjuvant therapy such as chemotherapy and/or radiotherapy may theoretically compromise the esophageal or gastric conduit tissue integrity and may also contribute to the patient's weight loss and malnutrition. As such, this may consequently increase the risk of developing a leak.

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F. Mier · B. K. Oelschlager (✉)
Department of Surgery, University of Washington,
1959 NE Pacific St., Box 356410, Seattle, WA 98195, USA
e-mail: brant@u.washington.edu

Although no single trial has been able to demonstrate such an effect, a meta-analysis of 11 randomized controlled trials (RCT) that compared neoadjuvant therapy and surgery to surgery alone for resectable esophageal cancer showed that neoadjuvant therapy may contribute to a small increase in the risk for developing an anastomotic leak (OR 1.08 [95% CI 0.45–2.60]).[3]

Technical Factors

Care of the Conduit

The preparation of the esophageal conduit and completion of esophageal anastomosis are two of the most challenging steps in esophageal surgery. Taking good care during these steps can decrease the risk of graft ischemia and hence decrease the rate of anastomotic complications. A meticulous preparation of the conduit should be performed, by verifying its blood supply, perfusion, tension, and orientation.

Conduit ischemia is a factor that increases the rate of anastomosis leaks; therefore, verifying the blood supply and the perfusion of the graft is of extreme importance. If the stomach is the conduit of choice, then the surgeon must make sure that the right gastroepiploic artery is intact, because this will be the primary blood supply of the remaining stomach being used to replace the esophagus.[2] Also, a proper orientation of the conduit will guarantee an adequate perfusion. In order to verify the graft's perfusion the use of intraoperative techniques such as a laser Doppler flowmeter, oxymetry, spectrophotometer, photoplethysmography, or radioisotopes have been used, though none has shown such an advantage as to be recommended for widespread clinical use.

Laparoscopic ischemic conditioning of the stomach has been used as a method to improve conduit perfusion at the time of the anastomosis; although not yet proven, enhancing conduit perfusion with this technique may decrease the likelihood of developing a leak. This has been done by simply ligating the left gastric vessels during a staging procedure prior to the esophagectomy,[3] or by using a more complex laparoscopic technique as explained by Hölscher et al.[5] In the latter the stomach is freed by dissecting the short gastric vessels, while preserving the right gastroepiploic arcade, followed by a Kocher maneuver, then the left gastric vessels are dissected, preserving the right gastric artery, and finally, a staple line along the lesser curvature of the stomach is placed in the direction of the gastric fundus, as would be done to prepare the gastric tube. Five days after the laparoscopic procedure, the esophagectomy and anastomosis are performed. With this approach only 6% of the patients experienced minor leaks.[4]

During the esophagectomy the surgeon must decrease the tension and pressure on the conduit throughout the posterior mediastinum in order to ensure the integrity of the anastomosis. This can be done by performing a meticulous dissection of the hiatus, the posterior mediastinum, and thoracic outlet, in order to facilitate the gastric pull-up through the posterior mediastinum. A Kocher maneuver is also recommended to decrease conduit tension. If the colon is being used as the conduit, some authors suggest that a preoperative visceral angiogram might help visualize and identify the graft's principal arterial and venous supply.[2]

Conduit Type and Anastomosis Site

Three types of organs can be used as the conduit to replace the esophagus: the stomach, the colon, and the jejunum. The stomach is used most commonly because of its simplicity and its proximity to the esophagus. However, there are some controversy in regards to which organ should be used as esophageal substitute in order to prevent anastomotic complications. In a series of 760 resections, Moorehead et al. reported only a 1% incidence of conduit necrosis when the stomach was used, versus a 13.3% incidence of conduit necrosis when the colon was used as a substitute.[6] However, in another series of 363 patients, the authors reported an increased prevalence of anastomosis leaks when the stomach was used as the conduit compared to the colon, 14.3% versus 6.1% ($p=0.013$), respectively.[1] In our experience there is no clear difference between these types of conduit, therefore patient-specific and technical factors play an important role.

The site of the anastomosis clearly influences the leak rate, and as a result, whether the anastomosis should be performed in the neck or in the thorax is still controversial. There is a higher rate of leaks in the neck (5–15%) than in the thorax (0–3%); however, the leak morbidity is significantly lower in the neck when compared to the thorax (as thorax leaks are more often associated with severe sepsis and mediastinitis). Despite these differences, there is no difference in overall leak mortality between these two sites. Regardless of the anastomosis site, with the technical advances and in the hands of experienced surgeons the rate, morbidity and mortality of leaks are decreasing.

Tubes and Drains

Nasogastric (NG) tubes are commonly placed during the operation and are kept after the operation in order to decrease gastric distention, which may compromise the integrity of the anastomosis. Whether this decreases the leak rate has not been proven. Daryaei et al. assessed the leak rate in 30 patients undergoing esophagectomy with

gastric pull-up with or without a postoperative NG tube. They found a significantly higher rate of leaks in the group of patients with an NG tube (27%) when compared to the group without an NG tube (0%).[7] On the contrary, another RCT compared the use of two different types of nasogastric drainage (single and double lumen NG tubes) with no nasogastric drainage, and their effect on tracheal acid aspiration following esophagectomy. There were no leaks present in either of the groups; however, the group with NG tube placement had significantly less tracheal aspiration and pulmonary complications, which improved the postoperative outcome.[8]

External drains have been widely used in all types of surgery, and their use remains controversial. In the only RCT, the use of cervical external drains after esophagectomy was evaluated in 40 patients; no leaks were present in the two groups.[9] Some argue that even if drains do not prevent leaks, the presence of a drain may facilitate management if one occurs.

Anastomotic Technique

In our experience we have found that a linear stapled esophagogastric anastomosis as described by Orringer has better results in preventing leaks, when compared to the traditional hand-sewn anastomosis. This is supported by three authors that compared their outcomes and leak rates after esophagectomy using linear stapled anastomosis or hand-sewn anastomosis, with all favoring the former.[10–12] There are very few good comparative studies on the best technique; moreover, it is quite difficult to separate the technique from the skill and experience of the surgeon. As a result, it must be recognized that high volume centers and experienced esophageal surgeons have better outcomes and fewer rates of anastomotic complications.

Conclusions

There are many factors that likely play into development of a leak in esophageal surgery, only some of which are within the control of the surgeon. Proper patient preparation and attention to their risk (such as malnutrition), detailed surgical planning, ensuring the integrity of the conduit, and meticulous surgical technique will likely lead to lower leak rates and better outcomes.

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ORIGINAL ARTICLE

Diagnosis and Management of Anastomotic Leaks after Esophagectomy

Donald E. Low

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Abstract
Introduction Complications following esophagectomy significantly affect outcomes, including perioperative mortality, costs, and survival. Anastomotic leak remains one of the most serious complications, and early recognition and appropriate initial treatment are essential.
Methods Mortality associated with esophageal leaks is decreasing, due in part to the increased use of CT scans and endoscopy for diagnosis. Endoscopic and interventional radiology techniques are being increasingly applied, but appropriate patient selection is important. Removable esophageal stents can be utilized successfully in a significant proportion of patients with limited anastomotic defects.
Results and Conclusion It is critically important to differentiate between leaks and conduit necrosis. Endoscopic examination is the best method for making this assessment. Surgeons should become familiar with the expanding options for endoscopic assessment and treatment of esophageal anastomotic leaks.

Keywords Anastomotic leak · Esophagectomy complications · Esophageal stent

Background

Esophageal resection remains a routine component of treatment for all physiologically appropriate patients with stage I–III esophageal malignancy and is required in certain benign conditions such as end-stage achalasia. The incidence of esophageal cancer in the USA is increasing, as is the overall number of esophageal resections.

There is currently no generally accepted classification system defining the clinical significance of anastomotic leaks. Classification systems have been suggested by Bardini and Csendes;[1] however, no system has seen routine application. The incidence of esophageal leaks in large series range from 3% to 21% and the incidence of leaks does not appear to be affected by neoadjuvant chemoradiotherapy. Mortality associated with esophageal anastomotic leaks in major series has been reported between 0% and 35%.[2] Technical complications, the most common being anastomotic leak, have been shown to significantly affect length of stay, associated medical complications, and survival.[3]

Diagnosis

Clinical factors most often heralding an anastomotic leak or disruption can be divided into nonspecific findings such as tachycardia, dysrhythmia, unexplained leukocytosis and respiratory failure, and specific issues such as erythema and swelling of associated neck and chest incisions, and a change in drain output. It is estimated that up to 55% of leaks are clinically silent initially. We have developed an algorithm which provides a framework for a consistent approach to investigation and management of esophageal anastomotic leaks. See Fig. 1.

This paper was originally presented as part of the SSAT/ISDS Joint Symposium, Prevention, Evaluation, and Treatment of Leaks After Gastrointestinal Surgery: Esophagus, at the SSAT 50th Annual Meeting, June 2009 in Chicago, IL, USA. The other article presented in the symposium was Oelschlager BK, Prevention of Leaks in Esophageal Surgery.

D. E. Low (✉)
Virginia Mason Medical Center,
1100 Ninth Ave, PO Box 900, Seattle, WA 98111–0900, USA
e-mail: Donald.Low@vmmc.org

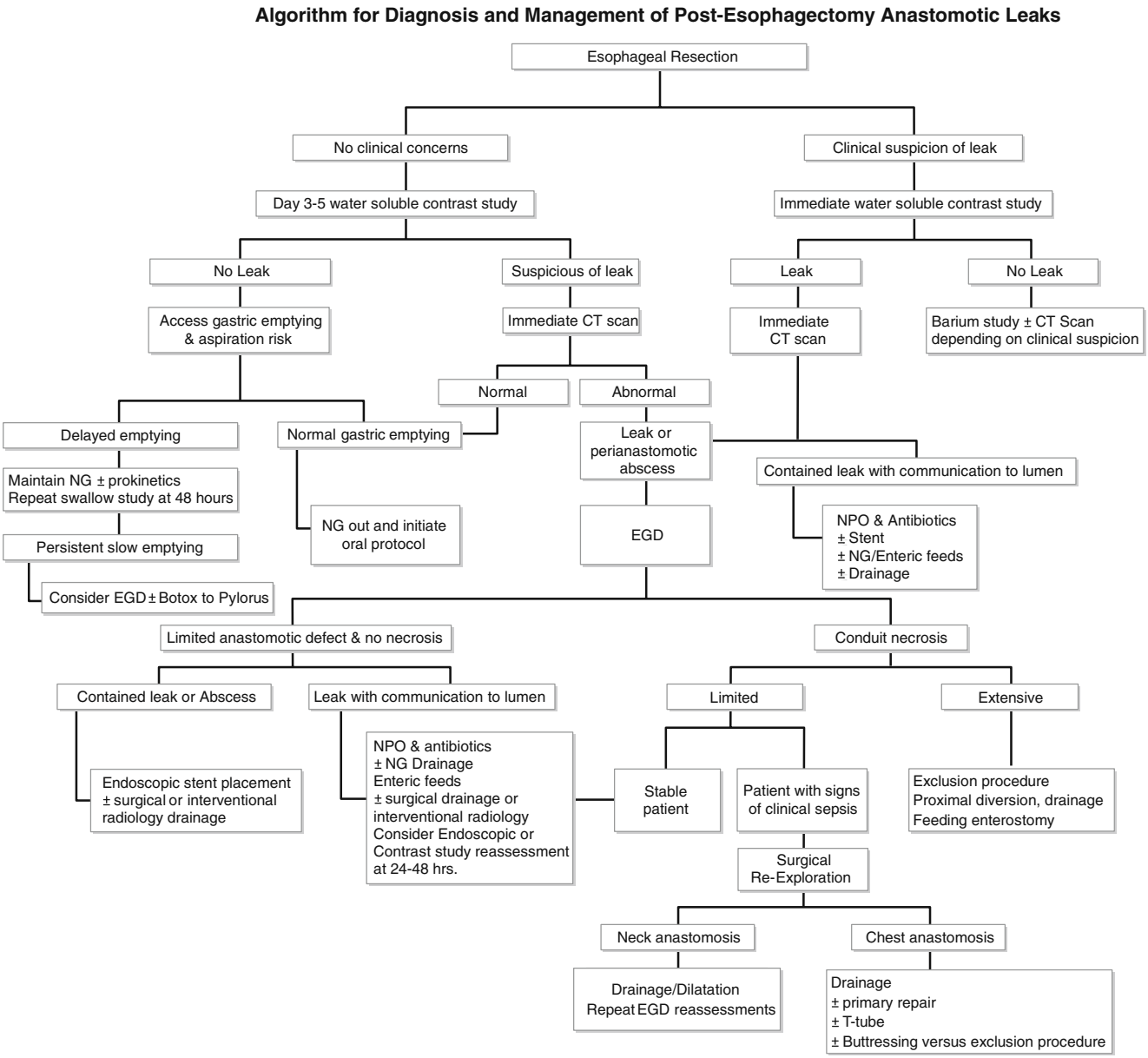

Fig. 1 Algorithm for diagnosis and management of post-esophagectomy anastomotic leaks

Diagnostic Studies

Contrast Studies Water-soluble contrast studies remain the most common, routine diagnostic test done following esophageal resection. Although esophageal anastomotic leaks have been reported between days 1 and 30, the most common timing for leaks is between days 4 and 8. There is little agreement regarding the appropriate protocol for contrast studies. We advocate having a member of the surgical team present to provide specific information about the resection and reconstruction. The patient is positioned upright, takes several sips of water prior to the water-soluble contrast, followed by barium. Due to the fact that many anastomoses are not done strictly end-to-end, we have advocated adding a "reflux study" which involves placing the patient head-down after swallowing contrast material to allow reflux into the apex of a gastric conduit.

Contrast studies are often misleading, with normal water-soluble contrast assessments being reported in the presence of ultimate esophageal leak or disruption in 5–48% of cases. This has led many to forgo these examinations and reserve contrast studies for patients with worrisome clinical signs. Another issue regarding water-soluble contrast agents is the risk of aspiration of the hyperosmolar contrast, (such as Gastro-

grafin), which is reported in up to 6.5% of patients and can lead to aspiration pneumonia and, in some cases, respiratory failure. In patients who have difficulty swallowing sips of water prior to their contrast study, or who have a recurrent laryngeal nerve injury, we routinely recommend switching to non-ionic contrast media (e.g., Isovue 300, Bracco Diagnostics Inc., Princeton, NJ) which is safer if aspiration occurs.

Barium has been demonstrated to improve the accuracy of post-operative contrast studies by a factor of 50%, with the high-density barium being most accurate. When a leak is identified, barium can produce difficulties in subsequent CT scan assessment. However, extravasated barium does not produce mediastinal fibrosis or inflammation which has been a concern in the past.

We also utilize these studies to assess gastric emptying and as a routine assessment of aspiration risk, which can provide a guide for prolonging NG tube drainage, modifying the initiation of oral protocols or initiating a consultation with speech pathology or considering a post-operative injection of Botox into the pylorus.

CT Scan Assessment CT scans have been used as primary but more typically follow-up assessment for leaks after standard contrast studies. A CT scan, done immediately following a standard contrast study, can identify extraluminal contrast missed on the initial fluoroscopic exam. However, it is difficult to confirm the significance of small pockets of fluid and air in the mediastinum on CT exams done in the first week following surgery.

Upper Endoscopy Historically, surgeons have been reluctant to utilize endoscopic examination in patients immediately following esophageal resection. We currently have a low threshold for utilizing endoscopy to rule out conduit necrosis and identify the presence and location of leaks and staple-line disruptions not clearly outlined on contrast studies. Successful endoscopic treatment in the absence of necrosis has been reported even when 50–70% of the anastomosis is involved.[4] Endoscopy can be combined with anastomotic dilation when required and can facilitate immediate treatment, such as the insertion of an esophageal stent when a localized leak has been identified.

Treatment

Observation It is currently estimated that approximately 73% of detected leaks directly result in modification of post-operative plans or specific changes in treatment. However, in clinically stable patients who are found to have an isolated peri-anastomotic cavity or tract and who are clinically stable, some can be kept on normal recovery protocols and monitored closely for clinical changes or swallowing difficulties.

Non-Surgical Treatment There has been a trend towards treating an increasing number of controlled leaks or contained anastomotic disruptions non-operatively in clinically stable patients. Non-surgical therapy has historically involved maintaining the patient nil by mouth, broad spectrum antibiotics, and anti-fungals, endoscopic or radiologically guided dilation or drainage when required, and a decision regarding maintaining or reinstituting transnasal drainage (NG tube) of the conduit. There are now multiple series of published reports demonstrating the ability to use endoscopically placed removable expandable stents in selected patients with esophageal leaks.[5] These stents have demonstrated a high success rate of obliterating the anastomotic defect and facilitating early resumption of oral nutrition. Various reports have documented control of the leak in 70–100% of instances, with stent migration reported in 20–40% of cases. There are indications that the incidence of strictures following anastomotic leak are decreased when temporary stents have been used. The placement of these stents must usually be associated with establishing adequate drainage of any contaminated space associated with the leak. Stent removal is typically done endoscopically 2–10 weeks following insertion. Stents should not be placed in patients with major disruptions of the conduit staple line or significant segmental gastric necrosis.

Other options available for non-surgical therapy include transnasal drainage of perianastomotic cavities, application of endoscopic clips or fibrin glue, and the injection of Botox into the pylorus to facilitate gastric emptying in conjunction with other non-surgical methods.

Surgery Surgical approaches can involve a simple reexploration of neck incisions, drainage and subsequent dilation. In large leaks, a thoracoscopic approach can improve drainage and facilitate decorticating trapped lung. Open thoracic procedures will be required in selected cases to improve drainage, wash and debride the mediastinum with primary closure alone or repair the leak over a T tube. The buttressing of large anastomotic or staple line defects with omentum or muscle flaps has been used with success.

Conduit necrosis requires an immediate surgical response. Segmental necrosis can selectively be managed with drainage and buttressing with follow-up endoscopy within 48 h. However, extensive conduit necrosis requires exclusion procedures involving drainage, proximal diversion of the esophagus, debridement of the conduit and redelivery of the healthy portion of the conduit into the

abdominal cavity and the placement of gastric or jejunal feeding tubes. Reconstruction is done at a later date, often using colon and a retrosternal route.

Summary

Previous reports have documented an inverse direct relationship between volume of esophageal resections in a single institution and mortality. Without question, one of the most important factors associated with mortality is the clinical expertise of the surgical team with respect to the early recognition and appropriate initial application of diagnostic and therapeutic interventions in patients with anastomotic leaks and disruptions.

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ORIGINAL ARTICLE

Evaluation and Treatment of Biliary Leaks after Gastrointestinal Surgery

Gary C. Vitale · Brian R. Davis

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Abstract
Introduction Since the introduction of laparoscopic cholecystectomy more than two decades ago, the incidence of bile duct injury has remained greater than that established during the era of open cholecystectomy.
Discussion This article reviews the common causes of bile duct injury during laparoscopic cholecystectomy and makes recommendations that should help prevent these serious injuries from occurring.
Conclusions The incidence of bile duct injury during laparoscopic cholecystectomy, although greater than during open cholecystectomy, can be minimized using specific operative strategies and dissection principles.

Keywords ERCP · PTC · Bile duct injury · Bile duct stenting · Percutaneous drainage

Biliary leaks carry a high morbidity and mortality, but significant advances have been made in the treatment of this complication allowing minimally invasive approaches that reduce the overall consequences to patients. Early detection and aggressive biliary drainage remain primary therapeutic modalities, while endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) have supplanted reconstructive bypass procedures in many tertiary referral centers. This review examines the detection and treatment options for this common and often highly morbid complication.

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G. C. Vitale (✉)
Department of Surgery, University of Louisville,
School of Medicine,
Louisville, KY 40292, USA
e-mail: garyvitale@gmail.com

B. R. Davis
Department of Surgery, Texas Tech University
Health Sciences Center,
El Paso, TX 79905, USA

Bile leaks can have multiple different presentations and should be suspected in patients with abdominal pain and fevers in the first post-operative week. They may present with peritonitis, sepsis, or external biliary fistulae. An elevated serum bilirubin level may indicate a large bile leak or biloma. Post-operative initial evaluation can be done with CT or US to look for free fluid or a biloma. Hepatobiliary iminodiacetic acid scans can be useful to differentiate a hematoma from a bile leak. Fistulagrams can be used when drains are present. ERCP is the procedure of choice for both the diagnosis and treatment of bile leaks. MRCP can also be used in some series where the anatomy is not amenable to ERCP.

Cystic duct stump leaks and duct of Luschka leaks are the first and second most common causes of bile leaks post-cholecystectomy. Bile leaks may be exacerbated by scarring at the ampulla or retained common bile duct stones. Leaks are rarely detected at completion of the initial operation. The incidence of biliary leak is higher with laparoscopic than with open cholecystectomy. Intraoperative cholangiography can aid in the identification of bile leaks and bile duct injury, but this has not decreased their overall occurrence.

Sandha et al.[4] created a grading system for post-cholecystectomy bile leaks diagnosed by ERCP. Low-grade leaks were described as identification of a leak after opacification of intrahepatic radicals and high grade as leakage that was detected before radical opacification. Low-grade leaks were treated with sphincterotomy alone, while high-grade leaks mandated biliary stenting, with resolution

occurring in 91% of low-grade leaks and 100% of high-grade leaks. Sphincterotomy alone for the treatment of bile leaks has been found to be less effective than stenting it, but reduces the overall number of ERCPs. Nasobiliary drainage has been used as an alternative to bile duct stenting, resulting in an overall decreased number of ERCP interventions as well. A biliary sphincterotomy should be performed routinely for bile leaks because it reduces the incidence of pancreatitis following placement of large-bore stents.

Distal bile duct obstruction from a stone or stenosis will precipitate leaks and keep the leak open until it is rectified. Sphincterotomy with removal of a stone or stenting of a stenotic lesion will relieve obstruction and allow fistulae to close. Refractory leaks may require surgery. Kahaleh et al.[2] has treated refractory cystic duct leaks with temporary self-expanding covered metallic stents, reporting a 94% success rate.

PTC can be critical in identifying anatomy in major bile duct injuries with leaks. PTC can be therapeutic in cases of distal leaks caused by iatrogenic injury or necrotizing pancreatitis. ERCP and PTC can identify bile duct injuries with tissue destruction or loss due to duct excision or placement of multiple clips with necrosis. These injuries are not amenable to endoscopic therapy and require surgical repair. Chaudhary et al.[1] reported a series of six patients with necrotizing pancreatitis eroding into the biliary tract with bile leak. Treatment included pancreatic debridement, cholecystectomy, and proximal biliary drainage by PTC.

Vitale et al.[6] describes endoscopic management of bile duct injuries following laparoscopic cholecystectomy. Injuries involving biliary strictures with or without concomitant bile leak were treated with 11–14 months of balloon dilation and biliary stenting, with stent changes at 3-month intervals. The mean duration of stenting was 12 months with a mean follow up of 30 months following stent removal. In this series, 78% of patients experienced resolution of bile duct injury after the initial treatment interval. Of the remainder, 22% had a recurrent stricture, of which 13% responded to repeat stenting and 9% required hepaticojejunostomy.

As the second most common cause of bile leaks, the duct of Luschka is an accessory bile duct which originates in the right hepatic lobe, runs through the gallbladder fossa, and has variable drainage into the right or common hepatic duct. It has an estimated anatomic incidence in 20–50% of the population. Strasberg et al.[5] reviewed 270 iatrogenic common bile duct injuries noting that 15% were duct of Luschka leaks. Duct of Luschka leaks can be effectively treated with a biliary sphincterotomy and common bile duct stenting.

Bile leaks also have an incidence of 4.8–7.6% after hepatic resections, resulting in a mortality rate as high as 40–50% secondary to lack of residual hepatic function and liver failure. Pace et al.[3] notes a mortality rate of 37.5% associated with reoperation for bile leaks following hepatic resection. Multiple studies ranging from 10 to 77 patients have noted a 90–100% resolution rate for biliary leaks post-hepatic resection treated with sphincterotomy and stenting. The University of Louisville experience (unpublished data) examines bile leaks after hepatic surgery in a 30 patient series, where 24 patients (80%) required percutaneous drainage and 9 (30%) had ERCP with bile leaks identified in 66%. At ERCP, sphincterotomy was done in 89%, and stent placement in 100%. Only 5 patients out of the 30 (16%) required reoperation, while 28/30 (90%) patients experienced resolution of the bile leak at mean of 37.5 days. ERCP has also proven valuable for biliary leaks following hepatic trauma, with small case series of between 5 and 11 patients reporting complete leak resolution after bile duct stenting.

Bile leaks also present significant morbidity following liver transplantation. The incidence of biliary leak is less than 10% in cadaveric liver transplants but rises to 15–40% in split-liver living donor transplant patients. Survival rates of liver recipient patients with bile leaks at 1 and 5 years were 76% and 65% versus 89% and 85% for those without leaks, respectively.

Biliary leaks continue to carry a high morbidity despite advances in surgical therapy. Treatment utilizing ERCP is critically important in delineating the anatomy of the biliary system post-operatively, as well as providing a high success rate in the management of these leaks non-operatively. Cases with difficult anatomic access can be treated effectively with PTC as well, using similar techniques to ERCP. Overall, with early detection and aggressive biliary drainage therapy, the consequences of post-operative bile leaks can be significantly reduced.

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ORIGINAL ARTICLE

Prevention, Evaluation, and Treatment of Leaks after Gastrointestinal Surgery

Prevention of Leaks After Pancreatic Surgery

Keith D. Lillemoe

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Abstract Pancreatic fistula remains a frequent and serious complication following pancreatic surgery. The incidence ranges from 10–20% in most series, with pancreatic texture being the most common predictor of the complication. There is little level 1 evidence to support any potential measures to reduce the incidence of pancreatic fistula.

Keywords Pancreatic surgery · Pancreatic fistula · Pancreaticoduodenectomy

Pancreatic surgery for decades was considered high risk, in part due to the high reported perioperative mortality following pancreaticoduodenectomy (PD) prior to the 1980s. Since that time, dramatic reductions have been observed with most clinical series from major centers reporting 30-day mortality rates less than 5%. Despite these improvements, the incidence of postoperative complications remains high after PD, approaching 40–50%. Leakage of the pancreatic anastomosis remains the "Achilles heel" of the procedure and is reported in 10–20% of cases even in experienced centers. Pancreatic leak remains a major cause of serious, even life threatening, complications including bleeding and sepsis and, in its mildest forms, adds to postoperative length of stay and hospital cost. In addition to PD, there are a number of other pancreatic resectional procedures that are associated with a pancreatic leak, although not all are associated with a pancreatic anastomosis. These include distal pancreatectomy, central pancreatectomy, and enucleation of pancreatic tumors. In many of these, the incidence of pancreatic fistula is even higher than with PD.

There are a number of risk factors associated with pancreatic leak following PD. These include patient factors such as age, gender, comorbidities, jaundice, and prior biliary stenting. Technical factors related to the procedure include anastomotic technique, the use of pancreatic stents and peri-anastomotic drains, operative time, and intra-operative blood loss. Finally, and thought by many to be the most important, are factors related to the pancreas, such as pancreatic texture, pancreatic pathology, and duct size.

A number of series have analyzed the incidence of pancreatic fistula following PD in an attempt to identify the most important risk factors. A series from the Johns Hopkins Hospital analyzed 1,891 patients undergoing PD between 1981 and 2000.[1] The overall incidence of pancreatic fistula was 11.4%. In univariate analysis, gender, coronary artery disease, diabetes mellitus, operative times, blood loss, radical lymphadenectomy, gland texture, and specimen pathology correlated with fistula rates. In a multivariate model, however, only gland texture and coronary disease was statistically predictive. A soft gland was associated with 22.6% fistula rate, a 20.4-fold increase in fistula rate over patients with a medium or firm gland.

A series from Memorial Sloan-Kettering reviewed outcomes from 908 patients undergoing any form of pancreatic resection. The pancreatic fistula rate in the series was 17%. The risk of leak was increased in men and non-pancreatic cancers. The leak rate following PD (18%) was not

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K. D. Lillemoe (✉)
Department of Surgery, Massachusetts General Hospital,
55 Fruit St., WHT506,
Boston, MA, USA
e-mail: klillemoe@partners.org

significantly higher than for distal pancreatectomy (13%). The incidence of a culture-positive postoperative collection/drainage, however, was significantly higher following PD (74% vs. 31%).

Finally, a multicenter report for Europe reviewed the results of 302 cases of distal pancreatectomy. The incidence of pancreatic fistula was 12%. Univariate and multivariate analysis indicated that age over 50, closure of the pancreatic stump with a stapling device, and an operating time greater than 480 min were associated with a higher incidence of pancreatic fistula. Multi-visceral resection and splenectomy also increased the pancreatic fistula rate on univariate analysis.

The importance of pancreatic leak following pancreatic surgery is reflected by the large number of prospective randomized trials (RCT) that have been conducted to address this problem. The majority of these studies have attempted to lower the rate of pancreatic leak following PD and have included administration of pharmacologic agents as well as technical approaches to the procedure.

Several RCT have evaluated the role of octreotide in preventing pancreatic fistula after pancreatic surgery with mixed results. A handful of European trials appeared to show a benefit to octreotide, while two single-center RCTs performed in the USA, showed no benefit. As expected, with these conflicting data, the question has been addressed by meta-analysis technique. The first such meta-analysis published by Poon and colleagues, showed an overall reduction of pancreatic fistula following any type of pancreatectomy with the use of octreotide; however, no significant benefit on overall complication and mortality rates was observed. But when only PD was considered, the overall risk for pancreatic fistula was not affected by the use of octreotide. Finally, a recent meta-analysis including eight studies showed that the use of either somatostatin or its analogues did not show significant benefit in reducing the incidence of pancreatic fistula, total pancreatic specific postoperative complications, delayed gastric emptying, total complications, mortality, or length of hospital stay following PD.[2]

Fibrin glue sealant has been used to reinforce the pancreatic-enteric anastomosis, but two RCTs did not show any significant reduction of pancreatic fistula rate with this technique.

Various techniques to manage the pancreatic remnant have also been studied by both retrospective and prospective ramdomized trials. The classic reconstruction after PD has been either an end-to-side duct to mucosa anastomosis or an end-to-end or end-to-side invagination (dunking) anastomosis. However, a number of retrospective studies and non-randomized trials have suggested that pancreaticogastrostomy, in which the pancreatic remnant is anastomosed to the posterior wall of the stomach, may have a lower rate of anastomotic break down than pancreaticojejunostomy. However, three prospective RCTs[3] have failed to show a difference in either pancreatic fistula or overall complication rates between the two methods, leading one to conclude that pancreaticogastrostomy and pancreaticojejunostomy are equivalent techniques of reconstruction.[3]

Another modification in pancreatic enteric anastomosis is the use of a transanastomotic stent for internal or external drainage of the pancreatic secretions. A prospective RCT found that using a short internal stent did not reduce the overall frequency or severity of pancreatic fistula after PD. Furthermore, subgroup analysis in patients who had a soft pancreas did not show any protective effect of an internal stent. However, a single institution RCT from Hong Kong demonstrated that the use of a long external diverting stent in patients undergoing end-to-side duct to mucosa anastomosis did reduce the incidence of pancreatic fistula from 20% to 6.7% and significantly shortened the length of hospital stay to 17 days from 23 days.[4] The incidence of clinical pancreatic fistula associated with fever, leukocytosis, sepsis, and the need for percutaneous drainage of an amylase-rich fluid collection or reoperation was significantly reduced with the use of external stent.

Many non-randomized series have suggested that the duct-to-mucosa technique offers advantages over the invagination technique. A recent dual institution RCT surprisingly showed that the incidence of pancreatic fistula in the duct-to-mucosa cohort was significantly greater (24%) than the incidence in the invagination cohort (12%).[5] There were no significant differences in overall complications, mortality, and rate of reoperation in the study. However, there was a significant increase in major complications in the duct to mucosa group as well as the need for interventional procedures. The median postoperative length of stay was identical between the two groups.

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ORIGINAL ARTICLE

Prevention, Evaluation, and Treatment of Leaks after Pancreatic Surgery

Jeffrey B. Matthews

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Abstract Despite overall improvement in outcomes after pancreatic surgery, the problem of leak continues to challenge surgical specialists. Failure to adequately address this complication can lead to sepsis, hemorrhage, organ failure, and death. Prompt recognition and early intervention are essential. Once fistula output and intra-abdominal infection have been adequately controlled often by percutaneous techniques, successful resolution without the need for re-operation is usually possible.

Keywords Pancreas · Pancreatic surgery · Postoperative complications · Pancreatic cancer · Pancreatitis · Anastomosis

In decades past, a postoperative leak after pancreatic surgery was a dreaded complication that often spelled disaster. In current practice, pancreatic leaks are usually less ominous events, and the great majority will resolve successfully with non-operative therapy. However, even in experienced centers, mortality after pancreatic leakage remains high at 5–10%,[1,2] and leaks are the risk factor most closely associated with perioperative death.[3]

The incidence of pancreatic leak depends upon its definition. Leak has been variably defined by arbitrary threshold values for volume, duration, and amylase levels of operative or percutaneous drainage effluent.[3] It may be difficult to differentiate a pancreatic leak from other complications such as intra-abdominal abscess or biliary and gastric/duodenal anastomotic disruption.[1] The International Study Group on Pancreatic Fistula (ISGPF) introduced a classification system in order to standardize reporting of results, assigning patients into three groups based upon the clinical significance of the leak.[4] According to the ISGPF system, a grade A fistula is transient and asymptomatic, recognized only by elevated amylase in drain effluent. Grade B fistulae are symptomatic, requiring evaluation and specific but straightforward therapies such as antibiotics, nutritional support, or percutaneous drainage. Grade C fistulae are more severe, requiring major intervention such as re-operation to address life-threatening sepsis or organ dysfunction. Although the ISGPF system has been widely adopted, its practical relevance may be limited. Grade A fistulae are of little consequence and can probably be avoided altogether by abandoning routine drain placement after pancreatic surgery. The distinction between a grade B and C fistula, both of which are clinically relevant, may be somewhat artificial.[2]

Early clues of possible pancreatic leak include unexplained fever, leukocytosis, prolonged ileus or delayed gastric emptying, a change in the character of drain effluent, or other subtle deviations from the expected postoperative course. Initial treatment includes assurance of adequate intravascular volume repletion and withholding of oral intake. Routine measurement of drain amylase content may reveal the presence of a grade A leak, and

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J. B. Matthews (✉)
Department of Surgery, The University of Chicago,
Surgeon-in-Chief, The University of Chicago Medical Center,
5841 S. Maryland Ave.,
Chicago, IL 60637, USA
e-mail: jmatthews@uchicago.edu

because in this situation, the patient is otherwise well, no additional intervention may be necessary. In the presence of signs of systemic infection, broad-spectrum antibiotics should be initiated, and an early priority should be the establishment of a controlled fistula. A contrast-enhanced CT is the preferred approach to identify undrained fluid collections. It may be difficult to distinguish an infected fluid collection from unopacified bowel, even with oral and intravenous contrast. Most postoperative intra-abdominal fluid collections in this setting are accessible via radiologically guided percutaneous drainage techniques.[5] The presence of an operatively placed surgical drain does not guarantee complete control of intra-abdominal sepsis. In fact, in one series, additional percutaneous drain placement was necessary in 75% of patients who developed leak or abscess, despite the presence of an operative drain.[1]

In the minority of cases, re-operation may be required either due to inaccessibility of an infected fluid collection to percutaneous drainage or due to clinical instability associated with uncontrolled sepsis. The risk of worsening an anastomotic disruption or creating an inadvertent enterotomy at re-operation is significant in the early postoperative period. Except in unusual circumstances, anastomotic revision or completion pancreatectomy should be avoided. Goals should be limited to washout of peritoneal contamination and establishment of adequate surgical drainage. Primary reclosure of the abdominal wound may be difficult to achieve. Early re-operation carries substantial risk of mortality and should be avoided if reasonable non-operative alternatives exist.

Protection of the skin against the corrosive action of pancreatic fistula effluent is important. Leaks associated with pancreatic-enteric anastomosis, such as after pancreaticoduodenectomy, are more likely to be contaminated and contain activated digestive enzymes and deconjugated bile salts. Leaks that occur following distal pancreatectomy or enucleation of small tumors are often sterile and less problematic. Clinically silent leaks after distal pancreatectomy may form small walled-off collections that may be mistaken for recurrent cystic neoplasm or pseudocyst on routine follow-up imaging studies. Occasionally, postoperative pancreatic leak may present as part of a complex abdominal wound infection, with fluid necessitation through an underlying fascial defect. Fistula drainage through the abdominal incision can pose significant difficulties; ideally, percutaneous drain placement should be achieved so that infected, activated pancreatic secretions can be diverted from the wound. Negative pressure applied by vacuum-assisted wound closure devices may be useful in this setting.

Depending upon fistula output and the presence of symptoms of delayed gastric emptying or adynamic ileus, nutritional support either via parenteral or enteral routes should be initiated. Early resumption of oral intake is often possible provided that fistula output does not markedly increase food-induced secretin and cholecystokinin stimulatory responses after pancreaticoduodenectomy are usually blunted.

After initial control of the pancreatic leak and associated infection, patience becomes the watchword of subsequent management. Low-output fistulae (less than ~150 ml per day) can usually be treated in the outpatient setting provided that the patient's general condition has otherwise sufficiently improved. After normal oral diet has resumed and daily drain output has decreased to ~30 ml (typically in about 2–3 weeks), drains can be withdrawn.[2] High-volume fistulae, particularly those associated with more serious initial systemic infection or wound complications, often require prolonged hospitalization for nutritional support, antibiotic therapy, nursing care, and physiotherapy. High fistula output may exceed the oral intake capacity of a debilitated postoperative patient. The somatostatin analogue octreotide may simplify management of high-output fistula, although the cost effectiveness of this treatment is debatable and there is no evidence that the rate of fistula closure is meaningfully reduced. Follow-up imaging studies of complex intra-abdominal fluid collections should be obtained, particularly if there are signs of incomplete resolution of infection. On occasion, persistent fistula may eventually require elective re-operation. Fistulojejunostomy, in which internal enteric drainage to a fibrous fistulous tract is created, may be an attractive alternative to anastomotic revision or further pancreatic resection.

In summary, despite overall improvement in outcomes after pancreatic surgery, the problem of leak continues to challenge surgical specialists. Failure to adequately address this complication can lead to sepsis, hemorrhage, organ failure, and death. Prompt recognition and early intervention are essential. Once fistula output and intra-abdominal infection have been adequately controlled, often by percutaneous techniques, successful resolution without the need for re-operation is usually possible.

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ORIGINAL ARTICLE

Trends in Diagnosis and Surgical Management of Patients with Perforated Peptic Ulcer

Kenneth Thorsen · Tom B. Glomsaker · Andreas von Meer · Kjetil Søreide · Jon Arne Søreide

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Abstract
Introduction While the laparoscopic treatment of perforated peptic ulcers (PPU) has been shown to be feasible and safe, its implementation into routine clinical practice has been slow. Only a few studies have evaluated its overall utility. The aim of this study was to investigate changes in surgical management of PPU and associated outcomes.
Material and Methods The study was a retrospective, single institution, population-based review of all patients undergoing surgery for PPU between 2003 and 2009. Patient demographics, diagnostic evaluation, management, and outcomes were evaluated.
Results Included were 114 patients with a median age of 67 years (range, 20–100). Women comprised 59% and were older ($p<0.001$), had more comorbidities ($p=0.002$), and had a higher Boey risk score ($p=0.036$) compared to men. Perforation location was gastric/pyloric in 72% and duodenal in 28% of patients. Pneumoperitoneum was diagnosed by plain abdominal x-ray in 30 of 41 patients (75%) and by abdominal computerized tomography (CT) in 76 of 77 patients (98%; $p<0.001$). Laparoscopic treatment was initiated in 48 patients (42%) and completed in 36 patients (75% of attempted cases). Laparoscopic treatment rate increased from 7% to 46% during the study period ($p=0.02$). Median operation time was shorter in patients treated via laparotomy (70 min) compared to laparoscopy (82 min) and those converted from laparoscopy to laparotomy (105 min; $p=0.017$). Postoperative complications occurred in 56 patients (49%). Overall 30-day postoperative mortality was 16%. No statistically significant differences were found in morbidity and mortality between open versus laparoscopic repair.
Conclusion This study demonstrates an increased use of CT as the primary diagnostic tool for PPU and of laparoscopic repair in its surgical treatment. These changes in management are not associated with altered outcomes.

Keywords Peptic ulcer · Perforation · Diagnosis · Surgery · Laparoscopy

K. Thorsen · T. B. Glomsaker · K. Søreide · J. A. Søreide (✉)
Division of Gastroenterologic Surgery, Department of Surgery, Stavanger University Hospital, 4068 Stavanger, Norway
e-mail: jon.soreide@kir.uib.no

A. von Meer
Department of Radiology, Stavanger University Hospital, Stavanger, Norway

K. Søreide · J. A. Søreide
Department of Surgical Sciences, University of Bergen, Bergen, Norway

Introduction

In spite of improved understanding of the multifactorial etiology of peptic ulcer disease (PUD),[1–3] life-threatening complications including acute hemorrhage or perforation occur in a considerable proportion of patients. The mortality rate ranges from 10–40% among patients with perforation,[4–6] and immediate surgery is the treatment of choice in most patients with suspected perforated peptic ulcer (PPU).[4]

Laparoscopic surgical management of PPU was first reported by Nathanson[7] and coworkers in 1990 and has gained increasing attention in recent decades. Preliminary early reports,[8–10] including randomized controlled trials,[11] data provided from a recent meta-analysis,[12] and

other publications,[13,14] have strengthened the scientific evidence supporting this approach. While laparoscopy is regarded as feasible and safe, it is hindered from integration into routine practice by the lack of surgeons capable of this technique on a 24-h basis in all hospitals caring for patients with PPU. A recent report from Denmark reported that only 6% of patients with PPU were treated laparoscopically.[15]

The aim of this audit was to evaluate the surgical management and outcome of consecutive patients diagnosed with PPU during a time period when the laparoscopic treatment of PPU was introduced and available in a busy surgical department covering a defined population in Norway.

Materials and Methods

All consecutive patients diagnosed with perforated gastric ulcer (GU) or duodenal ulcer (DU) between January 2003 and December 2009 were identified from the hospital's prospective administrative electronic database using pertinent ICD-9 and ICD-10 codes (K25.1, K25.2, K25.5, K25.6, and K26.1, K26.2, K26.5, K26.6). Additional searches were performed using appropriate surgical procedure codes (JDA60 Gastroraphy, JDA61 Laparoscopic gastroraphy, JDH70 Duodenoraphy, and JDH71 Laparoscopic duodenoraphy) to enable a complete identification of all patients. Our hospital is the only hospital in the region which has a population of 320,000.

Included in the study were patients with perforated GU or DU who underwent surgical treatment. Patients treated medically/conservatively were excluded, as were patients diagnosed at autopsy. Demographics and clinical data were obtained from hospital records, surgical notes, and other sources as needed.

American Society of Anesthesiologists (ASA) classification, as judged and recorded by the responsible anesthetist at surgery, was retrieved from perioperative forms. Each patient was retrospectively classified according to the Boey score[16] based on available information on the three criteria: (a) shock at admission (systolic blood pressure <90 mmHg), (b) severe medical illness (ASA III–V), and (c) delayed presentation (duration of symptoms >24 h). For this scoring system, the patient is given one point for each positive criterion, with possible scores of 0–3. Severity of complications was retrospectively classified according to the Dindo–Clavien criteria.[17]

A unique personal 11-digit identification number of all citizens in our country enabled complete follow-up data with regard to survival. Data without case-sensitive personal identification were recorded in an appropriately designed database.

Study Ethics

The study was as approved as a quality control assurance according to general guidelines provided by the Regional Ethics Committee.

Statistical Analysis

PASW Statistics 18.0 for Mac (SPSS Inc., Chicago, IL) was used for statistical analysis. A nonparametric distribution was assumed, and descriptive analysis was performed using Chi-square or Fisher's exact test where appropriate for dichotomous data, and Kruskal–Wallis or Mann–Whitney U test for continuous data, where applicable. A p value <0.05 was considered statistically significant.

Results

Between 2003 and 2009, 114 consecutive patients (67 females (59%) and 47 males (41%)) were surgically treated for PPU at our hospital. The calculated average annual incidence of surgically treated patients with PUP was 5/100,000.

Table 1 reports patient characteristics. While a significantly higher proportion of females ($p=0.002$) was diagnosed with additional diseases and comorbidity, the ASA classification was similar for both genders (Table 1). Concomitant diseases included 49 patients (43%) with cardiovascular disease, 20 (18%) with a current or previous diagnosis of cancer, 17 (15%) with chronic pulmonary disease, and 15 (13%) with an autoimmune disorder. In addition, 52 patients (46%) had either other concomitant diseases not specifically classified or a combination of several diagnoses.

Risk Factors

Fifty-nine patients (52%) smoked daily. Ongoing medical treatment was recorded in a significant proportion of patients, including aspirin in 26 patients (23%), nonsteroidal anti-inflammatory drugs in 23 (20%), and systemic steroids in 9 (8%).

Thirty patients (26%) had a Boey score of 2 or 3, indicating increased risk of unfavorable outcome. The Boey score profile was significantly lower in females compared to males ($p=0.036$). At admission, clinical evidence of peritonitis was present in 76 patients (66%), with no differences according to gender.

Diagnosis and Preoperative Imaging

As shown in Fig. 1, plain abdominal imaging was more or less replaced by abdominal computerized tomography (CT) as the imaging modality of choice during the study period. Forty-

Table 1 Patient characteristics

Variable	Males 47 (41%)	Females 67 (59%)	Total 114 (100%)	*p* value
Age, years (median, range)	61 (20–90)	73 (29–100)	67 (20–100)	<0.001
Age >60 years	26 (55%)	52 (78%)	78 (68%)	0.012
Comorbidity[a]	32 (68%)	61 (91%)	93 (82%)	0.002
Smoking	25 (78%)	34 (56%)	59 (52%)	0.8
ASA				
1	–	–	–	0.6
2	–	2 (3%)	2 (2%)	
3	31 (66%)	40 (60%)	71 (62%)	
4	15 (32%)	22 (33%)	37 (33%)	
5	1 (2%)	3 (5%)	4 (3%)	
Boey score				
0	17 (36%)	9 (13%)	26 (23%)	0.036
1	20 (43%)	38 (57%)	58 (51%)	
2	9 (19%)	16 (24%)	25 (22%)	
3	1 (2%)	4 (6%)	5 (4%)	
Surgery completed laparoscopically	11 (34%)	25 (37%)	36 (32%)	0.2
Complications[b]	21 (45%)	34 (51%)	55 (48%)	0.5
Mortality[c]	5 (11%)	13 (19%)	18 (16%)	0.2
LOS, days (median, IQR)	7 (6–19)	8.5 (5–16)	8 (6–17)	0.7

ASA American Society of Anesthesiology score, *LOS* length of stay, *IQR* interquartile range

[a] Defined as current concomitant diseases recorded at hospital admission

[b] Defined according to the Dindo–Clavien criteria[17]

[c] Defined as death within 30 days

one patients (36%) underwent plain abdominal x-ray, and pneumoperitoneum was diagnosed in 30 (75%) of these patients. Diagnosis and surgery were delayed in six patients with initial negative plain abdominal x-ray. Abdominal CT, usually low dosage, was done in 60 patients (68%), with pneumoperitoneum diagnosed in 59 (99%). In 91 patients (80%) with pneumperitoneum diagnosed radiographically, visceral perforation was already suspected based on history and clinical examination. On the other hand, 23 patients (20%) had pneumoperitoneum diagnosed without clinical suspicion of visceral perforation.

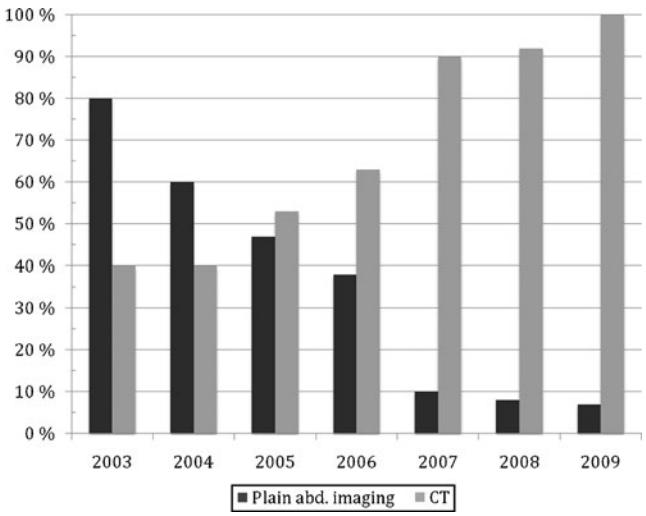

Fig. 1 Changes in preoperative abdominal imaging during the study period

Perforations

Perforations were localized to the prepyloric region in 46 patients (40%), duodenum in 32 (28%), pylorus in 15 (13%), and antrum in 6 (5%). In the remaining 15 patients (14%), perforation was either in the corpus of the stomach or not otherwise specified. No differences between genders were observed. In 16 patients (14%), a combination of ulcer bleeding and perforation was encountered.

Surgery

A gastro- or duodenoraphy was performed in 106 patients (93%), including tegmentation in 93 (82%). Pre- and postoperative antibiotics were given to 98 (86%) and 101 (89%) patients, respectively.

Laparoscopy was initiated in 48 patients (42%), and the surgical treatment (i.e., raphy) was completed laparoscopically in 36 (75%) of these patients; thus, 32% of the total

114 patients were treated laparoscopically. In three patients, a Billroth I or a Billroth II resection was done, of whom one patient was eventually surgically treated for a second PPU. As the study period progressed, the use of laparoscopy increased significantly (p=0.002; Fig. 2).

Operative Time

Median time from hospital admission to surgery was 6.2 h (interquartile range (IQR), 4.4–16.1). Median operation time was 80 min (IQR, 60–106), and median length of postoperative stay (LOS) was 8 days (IQR, 6–17).

Morbidity and Mortality

The 30-day postoperative mortality was 16% (18 patients) and was associated with high comorbidity (i.e., ASA score ≥3) and older age. Death of a patient is classified as grade V, according to the Dindo–Clavien criteria.[17] Cause of death was not confirmed by autopsy in every case, but sepsis, usually in combination with multiorgan failure, was the most frequent cause (at least seven (50%) of deaths). Other causes included myocardial infarction and renal and respiratory failures. No significant association between postoperative mortality and surgical approach was found (Table 2).

Shock and/or syncope at admission were more commonly encountered in patients with a duodenal perforation (7/32; 22%) as compared to those with other ulcer localization (13/82; 16%), but this difference was not statistically significant. Postoperative complications were recorded in 55 patients (49%). Most of these patients had more than one complication, which included respiratory failure in 29 (25%) patients, postoperative intra-abdominal infection in 18 (16%) patients, cardiovascular events in 17 (15%) patients, renal failure in 14 (12%) patients, postoperative suture leakage in 10 (9%) patients, wound infection in 6 (5%) patients, postoperative bleeding in 2 (2%) patients, and various other complications in 10 (9%) of the patients. In addition, 16 patients (14%) received treatment for suggested clinical sepsis. While the Dindo–Clavien grade I–II complications are treated without any physical interventions, the grade III complications require surgical, endoscopic, or radiological intervention. Grade IV complications are life-threatening, including single or multiorgan dysfunction.[17] Among the 56 patients recorded with complications, 8 (14%) patients had grade II, 10 patients (18%) had grade III, 20 patients (36%) had grade IV, and the 18 patients (32%) who died were classified as grade V.

In 13 patients (11%), re-admittance to the hospital within 3 weeks after discharge was encountered. Causes for re-admittance were pneumonia (n=3), subphrenic abscess (n=1), wound infection (n=2), and deterioration of concomitant diseases (n=7) including lung cancer, brain cancer, non-Hodgkin lymphoma, and cardiovascular disease.

We compared patients' characteristics and outcomes according to type of surgical approach (Table 2). Age and gender distributions were similar, as were ASA and Boey scores (Table 2). No significant differences were observed with regard to preoperative delay and ulcer localization. The median duration of operation was shorter in the laparotomy group compared to the groups treated laparoscopically or the group of converted operations (p=0.017). There was a nonsignificant difference with regard to postoperative complications, with more complications encountered in the laparotomy group (p=0.057). However, the proportions of complications categorized according to

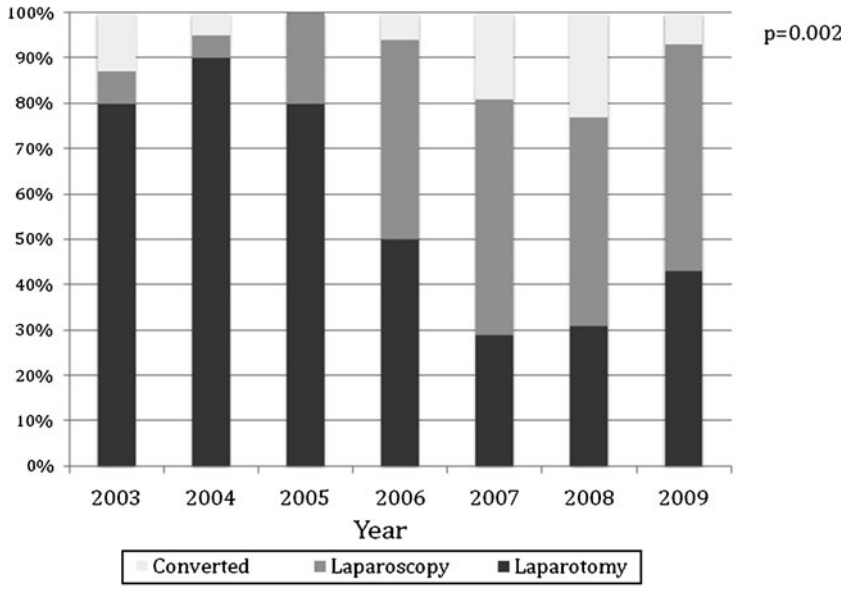

Fig. 2 Distribution of surgical approaches during the study period

Table 2 Characteristics and outcomes according to surgical approach (n=114)

Variable	Laparotomy 66 (58%)	Laparoscopy 36 (32%)	Converted 12 (11%)	p value
Females	37 (56%)	25 (69%)	5 (42%)	0.18[a]
Median age [years] (range)	71 (20–100)	62 (29–95)	65 (40–87)	0.16[b]
ASA score				
I	0	0	0	0.69[a]
II	1 (1%)	1 (3%)	0	
III	38 (58%)	26 (72%)	7 (58%)	
IV	25 (38%)	8 (22%)	4 (33%)	
V	2 (3%)	1 (3%)	1 (9%)	
Boey score				
0	12 (18%)	10 (28%)	4 (33%)	0.33[a]
1	33 (50%)	21 (58%)	4 (33%)	
2	17 (26%)	4 (11%)	4 (33%)	
3	4 (6%)	1 (3%)	0	
Preoperative delay [h] (median, range)	6.6 (1.4–116)	5.8 (1.8–113)	6.0 (3.3–50)	0.5[b]
Localization of perforation				
Gastric	34 (52%)	17 (47%)	7 (58%)	0.72[a]
Pyloric	6 (9%)	7 (19%)	2(17%)	
Duodenal	19 (29%)	11 (31%)	2 (17%)	
Not specified	7 (11%)	1 (3%)	1 (8%)	
Median operative duration[min] (range)	70 (39–291)	82 (37–160)	105 (60–155)	0.017[b]
Postoperative complications	38 (66%)	12 (36%)	5 (12%)	0.057[a]
Complications according to Dindo–Clavien[17] score				
Grade I	0	0	0	0.30[a]
Grade II	7 (11%)	1 (3%)	0	
Grade III	5 (8%)	4 (11%)	1 (8%)	
Grade IV	13 (20%)	6 (17%)	3 (25%)	
Grade V	14 (21%)	3 (8%)	1 (8%)	
Postoperative mortality (≤30 day)	14 (21%)	3 (8%)	1 (8%)	0.18[a]

[a] Chi-square test

[b] Kruskal–Wallis test

the Dindo–Clavien criteria[17] had a similar distribution within each group.

Discussion

Surgical treatment for perforated ulcer has changed during the last three decades, and duodenoraphy or gastroraphy with omentoplasty have more or less replaced gastric resection as emergency operations.[18,19] Furthermore, a decrease in surgical trauma with the use of laparotomy for these often fragile patients is suggested to be of importance. However, others propose a laparoscopic approach is beneficial for low-risk patients in particular.[13]

While early studies were hampered by various shortcomings, including patient selection bias, study design, and low statistical power, a recent Cochrane report concludes that results from laparoscopic surgery are not clinically different from those of open surgery.[14] Nevertheless, implementation of the laparoscopic approach for the treatment of patients with PPU has evolved rather slowly and is still not available around the clock in many surgical departments.[15] This surgical emergency is commonly treated at local hospitals. Given the rather low number of cases, as indicated by our observed annual incidence of 5 per 100,000, it is difficult for all surgeons to gain the necessary technical experience.

This population-based study on consecutive patients confirms that perforation still remains a serious complication of peptic ulcer disease. However, the observed 30-day postoperative mortality of 16% is lower than the 25% mortality reported recently from Denmark,[15] and the complication rate of 48% is comparable to other reports. Nevertheless, these data should be interpreted in the light of the advanced age and the general comorbidity of this population requiring surgical treatment for a potentially life-threatening condition.

The observed postoperative mortality of 8% in the laparoscopically treated patients is in concordance with recent reports.[15,20–23] Of note is the high proportion of patients, between 45% and 50%, treated laparoscopically during the last 4 years of the study period. This is in contrast to recent figures reported from another Scandinavian population, which showed that only 6% patients were treated laparoscopically, and only half of the departments responsible for acute abdominal surgery offered laparoscopic repair of perforated peptic ulceration.[15] In spite of a significantly larger proportion of laparoscopic completed procedures during the second half of the study period, our average conversion rate of 25% decreased to 12% during the last 3 years of the study period, which corresponds well with recent papers.[12,13,24,25]

Several risk factors, as mirrored by the Boey score,[16] are of importance for interpretation of our results. Of note, these risk factors are, in most patients, determined during the pre-hospital time period from symptom onset to hospital admittance. Yet, an effective diagnostic work-up that could prompt urgent surgical treatment is of importance. Thus, appropriate clinical decision making should not be delayed by suboptimal imaging. This study also showed that plain abdominal imaging harbors a substantial risk for false negative results. Accordingly, when imaging is used, low-dosage CT should be preferred in this clinical situation.[26,27]

Similar to previous reports, there is a significant proportion of elderly patients with high comorbidity.[6,20,28,29] The importance of an urgent diagnosis and appropriate surgical treatment in this fragile group of patients has been emphasized by others.[28,30] The preoperative in-hospital waiting times experienced by most of our patients are in line with other authors.[6]

Although applied in a few single patients with PPU before 2004, since 2005, we have intended to use a laparoscopic approach for surgical treatment of patients with PPU when this technique was available among the responsible surgeons.[13,14,23,31] Thus, we observed a significantly higher proportion of patients treated laparoscopically during the last part of the study period. Other studies have found less postoperative pain, shorter hospital stay, fewer septic events, and reduced wound infection with laparoscopy.[32]

Similar to the recent report by Møller et al.,[30] we observed a higher median age and significantly more comorbidities in females. This may partly be explained by a higher proportion of elderly females in our population, with high comorbidity closely relating to older age.

Gastric ulcer perforations, frequently associated with smoking in patients <75 years of age, were most commonly encountered, as previously reported by Svanes and coworkers.[6]

Conclusions

Data from the present study indicate that laparoscopic surgical treatment of patients with peptic ulcer perforation can be implemented and completed safely in a large proportion of patients with this life-threatening condition, given that the responsible surgical team has the appropriate technical expertise. Observations made in this study do not allow firm conclusions as to which patients should be selected for open versus laparoscopic treatment. The laparoscopic treatment of these patients may offer advantages in line with mini-invasive procedures for other conditions. It remains to be shown if promising figures reported from controlled trials can be achieved in the general surgical practice.

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ORIGINAL ARTICLE

Prognostic Significance of HLA Class I Expressing in Gastric Carcinoma Defined by Monoclonal Anti-Pan HLA Class I Antibody, EMR8-5

Hae-Wan Lee · Soo Kee Min · Young-Su Ju · Joohon Sung · Man Sup Lim · Dae Hyun Yang · Bong Hwa Lee

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Abstract
Introduction Downregulation or loss of HLA class I molecules has been demonstrated in human cancers. The aim of this study was to assess the clinical significance of HLA class I expression in gastric cancer.
Methods Gastric cancer tissues from 189 patients were examined for expression of HLA class I heavy chain antigens by immunohistochemical staining with EMR8-5. The expression level of HLA class I of tumor cells is categorized by combining an estimate the percentage of immunoreactive cell with an estimate of the staining intensity. The relationship between HLA class I expression and clinicopathologic parameters, patient survival, and tumor recurrence were analyzed.
Results HLA class I was downregulated in 85 (45.0%) of the gastric carcinomas. Staining revealed 104 (55.0%) tumors with strongly positive expression of HLA class I antigens, 76 (40.2%) tumors with weakly positive expression, and 9 (4.8%) tumors with negative expression. The expression of HLA class I antigen did not correlate with any other clinicopathologic parameters. Moreover, HLA class I expression was neither a risk factor for tumor recurrence nor survival.
Conclusion The downregulation of HLA class I expression is not associated with patient prognosis.

H.-W. Lee (✉)
Department of Surgery,
Hallym University Hangang Sacred Heart Hospital,
94-200, Yeongdeungpo-dong, Yeongdeungpo-gu,
Seoul 150-719, South Korea
e-mail: leehw@hallym.or.kr

S. K. Min
Department of Pathology,
Hallym University Sacred Heart Hospital,
896 Pyungchon-dong, Dongan-gu, Anyang-si, Kyungki-do,
431–070, Seoul, South Korea

Y.-S. Ju
Department of Occupation and Environmental Medicine,
Hallym University Sacred Heart Hospital,
896 Pyungchon-dong, Dongan-gu, Anyang-si, Kyungki-do,
431-070, Seoul, South Korea

J. Sung
Department of Epidemiology,
Seoul National University School of Public Health,
599 Gwanak-no, Gwanak-gu,
Seoul 151-742, South Korea

M. S. Lim · B. H. Lee
Department of Surgery, Hallym University Sacred Heart Hospital,
896 Pyungchon-dong, Dongan-gu, Anyang-si, Kyungki-do,
431–070, Seoul, South Korea

D. H. Yang
Department of Surgery, Hallym University,
Kangnam Sacred Heart Hospital,
948-1, Daerim-dong, Yeongdeungpo-gu,
Seoul 150-950, South Korea

Keywords Gastric cancer · Human leukocyte antigen class I · Immunohistochemistry

Introduction

The malignant transformation of cells is frequently associated with altered human leukocyte antigen (HLA) class I expression. It has been known that alteration of HLA class I expression provides one of the effective mechanisms by which tumors can escape from immune recognition by cytotoxic T cell.[1] Loss or downregulation of HLA class I molecules occurs frequently in many cancers, and these abnormalities may affect the clinical course and the outcome of treatment.

HLA class I antigens comprise the classical HLA-A, -B, and -C antigens and non-classical HLA-E, -F, and -G antigens. They are transmembrane glycoproteins comprising polymorphic 45-kDa heavy chain and a non-polymorphic 12-kDa β_2-microglobulin light chain. HLA class I-A, -B, and –C loci on chromosome 6p21 encode the heavy chain, whereas β_2-microglobulin on chromosome 15q22-23 encodes the light chain.[2,3] These antigens are expressed on the surface of most nucleated cells in the human body.

HLA class I molecules have a bidirectional regulatory role for cytotoxic T lymphocytes and natural killer (NK) cells. Cytotoxic T cell recognized a complex of HLA-A, -B, or -C heavy chain, β2-microglobulin, and peptide via their specific T-cell receptor. In contrast, NK cells recognized HLA class I molecules via different inhibitory receptors of the killer immunoglobulin-like receptor and C-type-rectin receptor families.[4] NK cells also are likely to play an important role in the host defenses because they kill viral-infected or tumor cells but spare normal cell. The molecular mechanism that explains why NK cell do not kill indiscriminately has recently been elucidated. It is due to several specialized receptors those recognize MHC class I molecules expressed on normal cells. The lack of expression of one or more class I alleles leads to NK-mediated target cell lysis.[5] Therefore loss of HLA class I may make the tumors more susceptible to NK killing and result in better prognostic outcome.

The prognostic value of downregulation of HLA class I expression has not been established, and previous investigations conducted on this topic have yielded contradictory results. Some have reported that HLA class I antigen expression was associated with a favorable prognosis in a variety of carcinoma,[6–12] whereas others have suggested that loss of HLA class I molecules was indicator of good prognosis.[13,14] Most of those studies have analyzed small numbers of tumors or short clinical follow-up. Few studies have examined the prognostic significance of HLA class I expression in gastric carcinoma.

The aim of this study was to assess the prognostic value of HLA class I expression. Here, we determine the expression level of HLA class I by immunohistochemical staining with monoclonal anti-pan HLA class I antibody EMR8-5 first, described the correlation between downregulation of HLA class I expression and clinicopathologic characteristics, and finally elucidated whether downregulation of HLA class I expression can predict clinical outcome in patients with gastric cancer.

Material and Methods

Patients

One hundred and eighty-nine patients, who were submitted to surgery for gastric carcinoma at the Department of Surgery of Hallym University Sacred Heart Hospital between January 2003 and December 2004, were enrolled in this study. Patient characteristics including age and sex, were collected and information on histologic type, lymphovascular invasion, and pTNM (pathologic Tumor–Node–Metastasis) stage was also retrieved from medical records. Tumor stage was characterized according to the sixth TNM classification.

The mean age was 58.6 years (range, 25–85 years). The study includes 134 men and 55 women, and involved 85 early and 104 advanced gastric cancers. The cases were composed of 106 (56.1%) cases of pathologic stage I, 30 (15.9%) of stage II, 37 (19.6%) of stage III, and 16 (8.5%) of stage IV. Patient clinical outcomes were followed form data of surgery until date of death or July 31, 2010, which resulted in follow-up period that ranged from 2 to 63 months (mean, 38 months). No patients received preoperative chemotherapy, and patients with stage II, III, or IV disease received postoperative chemotherapy using fluorouracil-based regimen. No patient underwent radiotherapy. This study was approved by the Institutional Review Board of the Hallym University Sacred Heart Hospital, and informed consent was obtained from all individuals.

Immunohistochemistry

HLA class I expression was investigated by immunohistochemical staining with monoclonal anti-pan HLA class I antibody EMR8-5 (Abcam, Cambridge, UK). This monoclonal antibody reacts with the heavy chains of human HLA class I-A, -B, and -C. Human-tonsil sections were used as positive controls for HLA class I. Negative controls had the primary antibody replaced by buffer. Immunohistochemical reactions were performed on paraffin tissue sections using an automated immunomhistochemical stainer

(Ventana BenchMark XT, Ventana Medical Systems, Inc., Tucson, AZ, USA), according to the manufacturer's protocol. Detection was done using the Ventana I VIEW DAB Detection Kit (Ventana Medical Systems). Briefly, 4-μm-tissue sections were deparaffinized using EZ Prep solution. CC1 standard (pH 8.4 buffer contained Tris/Borate/EDTA) was used for antigen retrieval for 60 min at 99°C. I VIEW inhibitor (3% H_2O_2, endogenous peroxidase) was blocked for 4 min at 37°C. Slides were incubated with primary antibody (1:100, HLA class I, Abcam, Cambridge, UK) for 32 min at 42°C and a secondary antibody of I VIEW biotinylated Ig for 8 min at 37°C. Slides were incubated in I VIEW Streptavidin HRP for 8 min at 37°C and then DAB+H_2O_2 substrate for 8 min followed by hematoxylin and bluing reagent counterstain at 37°C. Reaction buffer (pH 7.6 Tris buffer) was used as washing solution.

Evaluation of Positivity of HLA Class I in Gastric Cancer

All specimens were reviewed using light microscope in at least five areas at ×200 magnification by investigators who were blinded to clinicopathological data. The expression level of HLA class I of tumor cells is categorized by combining an estimate the percentage of immunoreactive cell with an estimate of the staining intensity.[7] Expression was defined as negative when stained cells comprised <20% (Fig. 1a), weakly positive when tumor cells for which the membrane was strongly and homogenously stained at the same level as stromal lymphocytes comprised 20–80% of tumor cells (Fig. 1b), or tumor cells with the membrane stained more weakly than stromal lymphocytes comprised >20% (Fig. 1c), strongly positive when tumor cells for which the membrane was strongly and homogenously stained at the same level as stromal lymphocytes comprised >80% of tumor cells (Fig. 1d). A case with negative or weakly positive staining was judged to be downregulation.

Statistical Analysis

The significance of correlations between the expression level of HLA class I of tumor cells and clinicopathologic parameters was determined using the chi-square test (or Fisher's exact test when appropriate). Survival rates were calculated using the Kaplan–Meier method. Difference in recurrence and survival rates between patients subgroup were analyzed using the log-rank test. Univariate and multivariate analyses were made using Cox proportional hazards models. All statistical analyses were conducted using SAS (EG version; SAS Institute, Cary, NC, USA). Statistical significance was established at $p<0.05$.

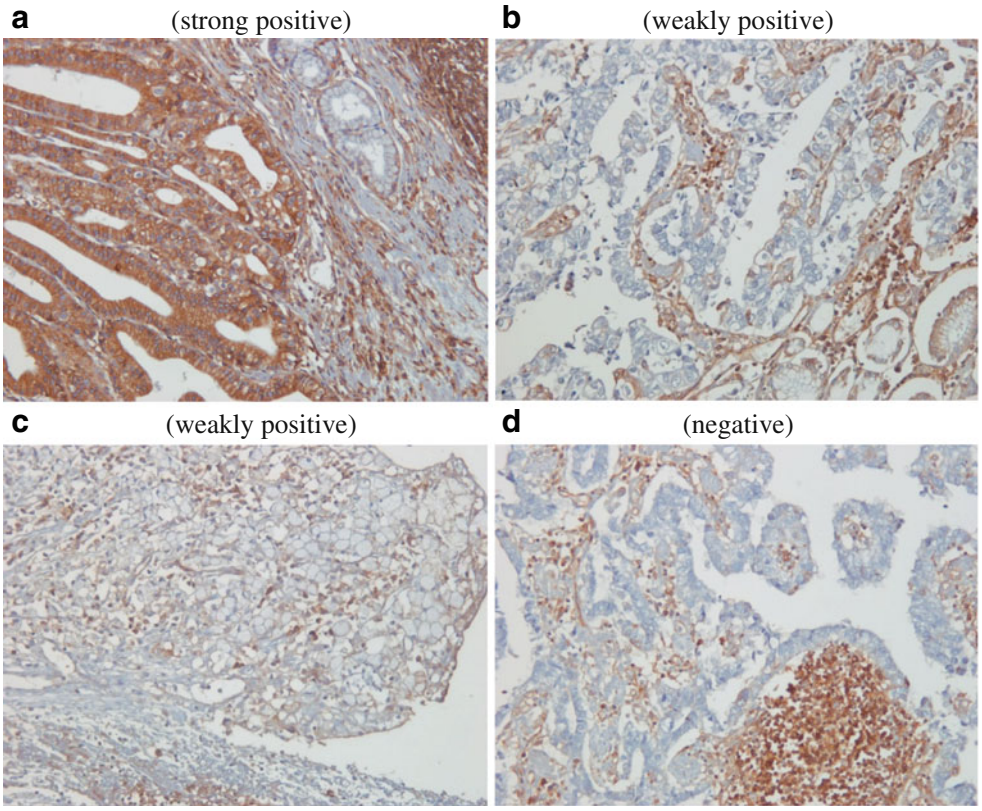

Fig. 1 Expression of HLA class I molecule detected by immunohistochemistry in gastric cancer (EMR8-5 antibody, original magnification: ×200). **a** *strong positive*, the expression of HLA class I heavy chain was observed in the cell membrane and some cytoplasm of cancer cells and tumor-infiltrated lymphocytes. **b** *weakly positive*, some cancer cells were stained by EMR8-5 antibody, and others were not stained. **c** *weakly positive*, staining is seen in cytoplasm but not in cell membrane of cancer cells. **d** *negative*, lack of staining of cancer cells, but the presence of strong stained lymphocytes

Results

Staining revealed 104 (55.0%) tumors with strongly positive expression of HLA class I antigens, 76 (40.2%) tumors with weakly positive expression, and 9 (4.8%) tumors with negative expression. In other words, HLA class I was downregulated in 85 (45.0%) of the gastric carcinomas.

The relationship between HLA class I expression and clinicopathologic characteristics is summarized in Table 1. However, the expression of HLA class I antigen did not correlate with any other clinicopathologic parameters, such as gender, age, depth of invasion, lymph node involvement, stage, expression of p53 expression, and expression of Ki67.

To determine the role of HLA class I expression, we analyzed the overall survival and disease-free survival of

Table 1 Clinicopathologic characteristics of gastric cancer patients according to HLA class I expression in gastric cancer

Clinicopathologic parameters	HLA class I expression		*p* value
	Strongly positive *n*=104	Weakly positive to negative *n*=85	
Gender			0.932
Male	74	60	
Female	30	25	
Age			0.279
<60	42	41	
≥60	62	44	
Tumor invasion			0.408
T1	43	42	
T2	37	25	
T3	22	24	
T4	2	4	
Nodal involvement			0.696
No	57	49	
Yes	47	36	
Lymph node metastasis			0.886
N0	57	49	
N1	24	21	
N2	16	11	
N3	7	4	
Stage			0.798
1	56	50	
2	16	14	
3	23	14	
4	9	7	
Lympho-vascular invasion			0.082
No	73	69	
Yes	31	16	
Histology			0.686
Well	21	18	
Moderate	25	16	
Poor	58	51	
p53 expression			0.916
No	51	41	
Yes	47	39	
Ki67 expression			0.218
Low	43	44	
Moderate	19	15	
High	36	20	

patients using Kaplan–Meier analysis with log-rank test. The 5-year survivals were 76.0% and 72.9% in the HLA class I positive and downregulated arms, respectively. Although the 5-year survival of patients with strongly positive HLA class I was slightly higher than those of patients with downregulation, there is no significant difference (Table 2). When stratified by pathological stage, no correlation was found between HLA class I expression and survival of patients with pathologic stage. The 5-year disease-free survival rates were 70.7% and 60.2% in the HLA class I positive and downregulated arms, respectively. Although the 5-year disease-free survival rate of patients with downregulated HLA class I was lower than those of patients with strongly positive expression, there is no significant difference (Table 3). When stratified by pathological stage, no correlation was found between HLA class I expression and disease-free survival of patients with pathologic stage.

Moreover, univariate analysis using Cox's proportional hazards model revealed that HLA class I expression was neither risk factor for tumor recurrence nor survival (Table 4). In multivariate analysis, tumor invasion and lymph node metastasis were independent prognostic factors [relative risk (RR): 1.477, p=0.038 and RR: 1.392, p= 0.046]. Lymph node metastasis was an independent risk factor for tumor recurrence (RR: 2.395, p<0.0001; Table 5).

Discussion

In this study, we described the relationship of HLA class I expression with various clinicopathologic characteristics and clinical outcome of patients with gastric cancer. It is well known that downregulation or loss of HLA class I molecules has been demonstrated in human cancers. They are caused by distinct mechanisms, which include defects in β_2-microglobulin synthesis, loss of gene encoding HLA antigen heavy chain, mutations which inhibit the HLA class I transcription or translation, defects in the regulatory mechanisms controlling HLA antigen expression and/or abnormalities in antigen processing.[15–17]

The incidence of HLA class I downregulation in our series of gastric carcinoma was approximately 45.0%. In several studies, the ratio has been reported to vary widely, from 32% to 75%.[18–20] The unsettled ratio of HLA downregulation was caused by several factors, such as different antibodies, or preparation of section. The authors evaluated expression of HLA class I using EMR8-5 (monoclonal anti-pan HLA class I antibody), which reacts with the heavy chains of human HLA class I A, -B, and -C. For validity in HLA class I immunohistochemistry, the staining of stromal lymphocytes was recognized as internal positive control, and membrane staining of tumor cells was assessed.[21]

Evasion of anti-tumor immunity has been thought to be critical to progress for cancers. HLA class I complex in cell membrane plays a major role in interactions with CD8+ T cells.[1] Actually, many studies has been reported that HLA class I antigen expression was associated with a favorable prognosis in a variety of carcinoma, including those arising from the larynx,[6] lung,[7] kidney,[8] bladder,[9] bone,[10] esophagus,[11] and rectum.[12] On the other hand, Madjd et al. report that total loss of MHC class I was an independent indicator of good prognosis in breast cancer.[13] Furthermore, Menon et al. reported that downregulation of HLA-A expression

Table 2 Survival rate of patients according to HLA class I expression in gastric cancer

Stage (n)	Overall survival rate					Mean survival time	S.E.	p value
	1 year	2 years	3 years	4 years	5 years			
Stage 1								0.5699
Strongly positive (51)	0.9216	0.9216	0.9020	0.8024	0.8024	60.0279	2.6674	
Downregulated (48)	0.9583	0.9583	0.9167	0.8542	0.8333	63.0877	2.3402	
Stage 2								0.8241
Strongly positive (15)	1.0000	1.0000	1.0000	0.9333	0.8000	61.7265	1.8430	
Downregulated (10)	0.9000	0.9000	0.9000	0.8000	0.8000	43.5713	5.0161	
Stage 3, 4								0.9077
Strongly positive (38)	0.7632	0.7105	0.6579	0.5789	0.5789	47.9844	4.6231	
Downregulated (27)	1.0000	0.8148	0.7037	0.5185	0.5185	38.6889	2.5336	
Total								0.9795
Strongly positive (104)	0.8750	0.8550	0.8269	0.7700	0.7596	58.1758	2.2059	
Downregulated (85)	0.9647	0.9059	0.8471	0.7412	0.7294	59.3637	2.1304	

by log-rank test

Table 3 Recurrence-free survival rate of patients according to HLA class I expression in gastric cancer

Stage (*n*)	Recurrence- free survival rate					Mean survival time	S.E.	*p* value
	1 year	2 years	3 years	4 years	5 years			
Stage 1								0.2320
Strongly positive (48)	1.0000	1.0000	1.0000	1.0000	1.0000	74.1191	–	
Downregulated (46)	0.9778	0.9514	0.9185	0.9185	0.8003	49.6446	1.6930	
Stage 2								0.7591
Strongly positive (15)	1.0000	1.0000	0.8333	0.7407	0.5556	33.2621	3.6936	
Downregulated (10)	0.7619	0.7619	0.7619	0.7619	0.7619	8.6443	0.6522	
Stage 3, 4								0.4711
Strongly positive (38)	0.7703	0.5500	0.5500	0.5156	0.4687	33.2621	3.6936	
Downregulated (27)	0.8400	0.4025	0.4025	0.3063	0.3063	29.3095	3.6409	
Total								0.7684
Strongly positive (101)	0.9143	0.8294	0.8013	0.77684	0.7071	59.6754	0.7566	
Downregulated (83)	0.9100	0.7799	0.7622	0.7032	0.6019	42.6328	1.9915	

by log-rank test

correlated with a better prognosis in colorectal cancer patients.[14] Several studies have failed to show any correlation between HLA class I expression and prognosis of patient.[22,23]

Few studies have examined the prognostic significance of HLA class I expression in gastric cancer. Ishigami et al. reported that the HLA class I positive group in gastric cancer had a significantly shallower depth of invasion, less nodal involvement, and better differentiated histology than the HLA class I negative group.[18] In contrast, Ueda et al. reported that positive expression of HLA-A, or -B/C was characterized by deeper cancer invasion and higher incidence of lymph node metastasis in gastric cancer.[19] Shen et al. did not find any relationship between the expression of HLA I antigen and TMN stage.[20] In present study, HLA class I expression did not correlate with any other clinicopathologic parameters, such as gender, age, depth of invasion, lymph node involvement, stage, p53 expression, and expression of Ki67. Moreover, no correlation was observed between HLA class I expression and oval survival or disease-free survival of patients.

These results were unexpected. Many scientists estimate that loss of HLA class I expression could lead to escape from T-cell recognition and a higher probability of disease recurrence. But on the other hand, HLA class I expression is associated with proapoptotic bax gene and inversely correlated with expression of the antiapoptotic bcl-2 genes.[24] Downregulation of HLA class I may be associated with inhibition of apoptosis. The recently coined term, immunoediting, applies to those immune-induced tumor alterations that make the tumor acceptable to the immune system, which includes any alteration, adaptation, or change that occurs in the tumor in response to the immune response. It is well known that there is a complex and often paradoxical role of the immune system in cancer in which immune cells are cast in a protagonist versus antagonist role. On one hand, immunity may protect against cancer and on the other, it appears to be pathologic.[25]

Table 4 Univariate analysis using Cox proportional hazards model for patients' prognosis and risk factors for recurrence

	RR	95% CI	*p* value
Prognostic factors[a]			
Tumor invasion	1.861	1.393–2.485	<0.0001
Lymph node metastasis	1.738	1.355–2.229	<0.0001
HLA class I expression	1.007	0.584–1.738	0.9795
Risk factor for recurrence			
Tumor invasion	2.268	1.655–3.107	<0.0001
Lymph node metastasis	2.563	1.940–3.387	<0.0001
HLA class I expression	1.093	0.605–1.977	0.7678

[a] Clinicopathologic factors affecting overall survival

Table 5 Multivariate analysis using Cox proportional hazards model for patients' prognosis and risk factors for recurrence

	RR	95% CI	*p* value
Prognostic factors[a]			
Tumor invasion	1.477	1.022–2.137	0.0381
Lymph node metastasis	1.392	1.006–1.926	0.0462
HLA class I expression	1.332	0.332–4.629	0.6520
Risk factor for recurrence			
Lymph node metastasis	2.395	1.794–3.197	<0.0001

[a] Clinicopathologic factors affecting overall survival

Many previous studies on HLA class I expression in cancer have produced controversial results, which could be explained as follows. First, a few studies have investigated the HLA class I expression using antibody. Therefore, previous studies involved heterogeneous tumors regarding histologic types, pTMN stage, and treatment modality including chemotherapy.[6–14,18–23] Second, virtually, these studies were involved highly heterogeneous populations. The distribution of HLA alleles and the linkage disequilibrium among alleles from diverse HLA gene differ in various ethnic populations.[26,27] In addition, relatively small populations were included in several studies. Third, the different antibody, immunostaining method, and scoring system may have contributed to discrepancies. Fourth, the cut-off points used to classify downregulation and positive groups vary substantially.

As mentioned above, allele and haplotype frequencies of HLA loci differ among various human populations. Each ethnic group was characterized by the presence of unique genetic linkage throughout the HLA region. The monoclonal antibody against HLA class I molecules, EMR8-5, reacts with extracellular domains of HLA-A*2402, A*0101, A*1101, A*0201, A*0207, B*0702, B*0801, B*1501, B*3501, B*4001, B*4002, B*4006, B*4403, Cw*0102, Cw*0801, Cw*1202, and Cw*1502 (http://www.abcam.com/HLA-class-1-ABC-abtibody-EMR8-5-ab70328.html). This monoclonal antibody may be suitable to search for HLA class I antigen in Japanese population.[10] Although allele distribution in Korean shows similarities with almost common alleles in Japanese, some alleles show significant difference in frequencies from Japanese.[28,29] Moreover, different HLA alleles may be contribute to development and progression of gastric cancer in the diverse ethnic groups.[27]

Conclusions

Generally, HLA class I abnormalities occur at high frequency in gastric cancer. The underlying molecular mechanisms of such loss of HLA class I expression are diverse, which could occur at each different step of the HLA class I antigen processing machinery. These abnormalities might be due to a reduced host anti-tumor immune response based on the resistance of tumor cells to T cell-mediated lysis. Unfortunately the selective loss of expression of HLA class I was not associated with patient prognosis in the present study. It might be caused by complex and often paradoxical role of the immune system in cancer. To validate the prognostic value of expression of HLA class I, prospective large-scale studies with appropriate inclusion criteria of patients have to be performed.

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ORIGINAL ARTICLE

Improvement in Insulin Sensitivity and B-Cell Function Following Ileal Interposition with Sleeve Gastrectomy in Type 2 Diabetic Patients: Potential Mechanisms

Aureo Ludovico De Paula · Alessandro R. Stival · Alfredo Halpern · Carolina C. L. DePaula · Andrea Mari · Elza Muscelli · Sergio Vencio · Ele Ferrannini

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Abstract
Introduction Bariatric surgery in morbidly obese type 2 diabetic (T2DM) patients is associated with high rates of diabetes remission. We investigated the mechanisms of the anti-diabetic effect of the laparoscopic ileal interposition with sleeve gastrectomy (LII-SG) in normal weight (NW), overweight (OW) and obese (OB) T2DM patients.
Methods Ninety-four patients (aged 54±8 years) with long-standing (median 10 years), treated diabetes (median HbA_{1c}= 8.6%), who were NW (15), OW (64) or OB (15) based on BMI, underwent LII-SG. Insulin sensitivity and parameters of ß-cell function were measured from an Oral Glycaemic Tolerance Test pre- and post-operatively.
Results At a median of 13.4 months post-operatively, weight loss averaged 9.4±1.3, 16.8±0.8 and 23.2±1.7 kg in NW, OW and OB subjects, respectively ($p<0.0001$). Insulin sensitivity was fully restored (395 [108] vs 208 [99] ml min^{-1} m^{-2}), fasting insulin secretion rate decreased (68 [52] vs 146 [120] pmol min^{-1} m^{-2}) and total insulin output increased (52 [26] vs 39 [28] nmol m^{-2}, all $p\leq0.001$). ß-cell glucose sensitivity doubled (37 [33] vs 18 [24] mol min^{-1} m^{-2} mM^{-1}, $p<0.0001$). The only parameter predicting remission of diabetes was a lower baseline insulin sensitivity ($p=0.005$).
Conclusions LII-SG induced changes on T2DM by mechanisms in part distinct from weight loss, principally involving restoration of insulin sensitivity and improvement of ß-cell function.

Keywords Diabetes · Ileal interposition · Sleeve gastrectomy · Insulin sensitivity · Insulin secretion · β-cell function · Metabolic surgery

A. L. De Paula (✉) · A. R. Stival
Department of Surgery, Hospital de Especialidades,
Av. 136, no. 961, 14 andar, Setor Marista,
74.093-250, Goiânia, Goiás, Brazil
e-mail: adepaula@uol.com.br

E. Muscelli · E. Ferrannini
Department of Internal Medicine, University of Pisa,
Pisa, Italy

A. Halpern
Department of Endocrinology, University of São Paulo,
São Paulo, Brazil

A. Mari
National Research Council Institute of Biochemical Engineering,
Padova, Italy

C. C. L. DePaula · S. Vencio
Catholic University of Goias,
Goiânia, Goiás, Brazil

Introduction

A recent systematic analysis of 621 studies in the English literature including over 135,000 morbidly obese patients undergoing bariatric surgery reported resolution of type 2 diabetes (defined as discontinuation of all diabetes-related medications and blood glucose levels within the normal range) in 78% of cases.[1] Furthermore, in a retrospective cohort of 7,925 bariatric patients, deaths attributed to diabetes were reduced by a remarkable 92%.[2] Finally, in ~85,000 morbidly obese patients, early (≤30 days) and late (>30 days to 2 years) mortality rates for bariatric surgery have trended downward (0.28% and 0.35%, respectively).[3] Thus, in the very obese patient with type 2 diabetes (i.e., with a body mass index [BMI] ≥35 kg/m^2),

bariatric surgery appears to be a treatment modality that is both highly effective and increasingly attractive. On the other hand, the most frequent kind of type 2 diabetes, i.e., the hyperglycaemia surfacing after the fourth decade of life in moderately obese subjects, is a progressive disease, and resolution, whether spontaneous or by treatment, is rare.[4] This difference in outcome is irrefutable and unaccounted for. One potential explanation is that the hyperglycaemia of morbid obesity has a different pathogenesis from the hyperglycaemia of the moderately obese or normal weight diabetic. Another possibility is that bariatric surgery per se interferes with glucose metabolism in ways that none of the other anti-diabetic treatments does. As recently reviewed, the available evidence, if limited and heterogeneous, suggests that at least some of the anti-diabetic effect of bariatric surgery may be independent of the induced weight loss.[5]

While generally causing weight loss, the various bariatric operations differ from one another in the volume of the remaining proximal stomach, the degree of induced malabsorption and the gut rearrangement; thus, bariatric surgery can be mainly restrictive, mainly malabsorptive, or mixed.[6,7] The experience using different types of surgery in diabetic patients with a BMI <35 kg/m^2 is limited. Dixon and co-workers reported a 73% diabetes remission after laparoscopic gastric banding in 30 patients with BMI ranging 30–40 kg/m^2, which was related to the weight loss (~20 kg).[8] We have previously described the clinical impact in diabetic patients with a BMI 23–35 kg/m^2 of the laparoscopic ileal interposition combined with a sleeve gastrectomy or a diverted sleeve gastrectomy.[9] The concepts behind this technique are to provide an early exposure of ingested nutrients to the interposed ileum in order to determine an early stimulation of the entero-insular axis and other mechanisms.[10] To test the hypothesis that the anti-diabetic effect of ileal interposition with sleeve gastrectomy may be in part independent of the induced weight loss, we used data obtained in a group of type 2 diabetes patients in the BMI range 21–35 kg/m^2 who received detailed metabolic studies at baseline and at a median of 14 months following this operation.

Patients and Methods

Study Population This study included 94 patients (61 men and 33 women) with type 2 diabetes (diagnosed according to the revised ADA criteria[11]) and a BMI <35 kg/m^2 undergoing surgery between October 2005 and February 2008. All subjects had had diabetes for at least 3 years, but none had prior major upper abdominal surgery. No patient was pregnant or had malignant or debilitating diseases, severe disease of lung, heart or kidneys as well as eating disorders such as bulimia or binge eating. Antidiabetic therapy was metformin alone in 16 patients, sulfonylureas alone in 10, associations of metformin and sulfonylureas in 37, insulin (in association with oral therapy in 24, alone in seven patients). Only one patient was on thiazolidinediones. The insulin dose ranged from 18 to 90 U, with an average value of 39±19 U/day. Some patients were receiving only bedtime injection, others were on long-acting insulin plus regular insulin before one or more meals. For the purpose of our analysis, patients were classified as normal weight (NW), overweight (OW) or obese (OB) based on their BMI (<25, 25–30 and 30–35 kg/m^2, respectively; Table 1).

All subjects underwent laparoscopic ileal interposition up into the jejunum associated with a sleeve gastrectomy (JII-SG, n=46) or up into the duodenum also associated with a sleeve gastrectomy (DII-SG, n=48). There were no specific criteria for the indication of the two operations. Patients were invited to repeat the metabolic study, which was performed a median of 13.4 months (range 2–33) after surgery. All subjects gave written informed consent to the study, and the protocol was approved by the Local Ethics Committee of the hospital.

Protocol After an overnight fast, patients received a standard (75 g) oral glucose load (OGTT). After obtaining baseline samples, venous blood was sampled at 30, 60 and 120 min after glucose ingestion for plasma glucose, insulin and C-peptide measurements. Antidiabetic therapy (insulin or oral agents) was stopped 72 h before the OGTT; however, when deemed necessary by the diabetologist, ultra-rapid insulin was given until the night before the study.

Surgical Procedure The surgical procedures were performed by laparoscopy. The JII-SG started with division of the jejunum 20 cm below the Treitz ligament using a linear stapler. An ileal segment of 170 cm was removed 30 cm proximally to the ileocecal valve and interposed peristaltically into the jejunum. The anastomoses were performed functionally side by side. The intestinal measurements were performed with traction along the anti-mesenteric border using a 10-cm atraumatic gasper. The sleeve gastrectomy was performed after devascularization of the greater curvature using the ultrasonic scalpel, beginning in the proximal portion of the antrum, 2 cm above the distal end of the anterior vagus nerve. The objective was to preserve the antrum and to perform a limited sleeve gastrectomy. A 60-Fr bougie orogastric calibration tube was placed by the anesthesiologist along the lesser curvature toward the pylorus. The gastric resection was performed starting at the level of the incisura angularis and proceeded up to the angle of His using a

Table 1 Anthropometric and metabolic characteristics of the study subjects

	Normal weight	Overweight	Obese	*p* Value[a]
n (M/F)	15 (7/8)	64 (41/23)	15 (13/2)	ns
Age (years)	59±7	53±7*	52±10*	0.01
Diabetes duration (years)	10.0 [4.3]	10.0 [8.0]	7.0 [7.5]*	ns
HbA_{1c} (%)	8.7±1.8	8.6±1.9	8.6±1.5	ns
Treatment (OHA/I) (%)	(47/53)	(56/42)	(80/20)	ns
Body weight (kg)	64±1	80±9*	95±11*,**	<0.0001
BMI (kg/m^2)	23.1±0.8	28.3±1.3*	32.9±1.9*,**	<0.0001
Fasting glucose (mg/dl)	180±75.6	192.6±72	212.4±90	ns
2-hour glucose (mg/dl)	374.4±63	351±90	360±77.4	ns
Total cholesterol (mg/dl)	202.8±31.2	202±41.3	218.4±101.4	ns
HDL-cholesterol (mg/dl)	43.3±5.8	46.8±5.4	40.9±12.5**	0.05
LDL-cholesterol (mg/dl)	101.4±35.9	111.9±36.3	84.6±28.9**	ns
Triglycerides (mg/dl)	233.2±156.6	237.6±165.5	239.4±169.1	ns

OHA oral hypoglycemic agents, *I* insulin, *BMI* body mass index

[a] One-way ANOVA

*$p \leq 0.05$ vs normal weight group by Bonferroni–Dunn, **$p \leq 0.05$ vs overweight by Bonferroni–Dunn

linear 45- or 60-mm stapler. A 3–0 polypropylene running invaginating suture covered the staple line. When performing the DII-SG version, once the sleeve gastrectomy was concluded, the devascularisation was continued to the duodenum for 3 to 4 cm beyond the pylorus. The duodenum was transected using a 60-mm linear stapler and the staple line suture covered by a running invaginating suture. The gastric pouch and proximal duodenum then were transposed to the lower abdomen through the mesocolon. The ileal segment was interposed peristaltically to the proximal duodenum. A point in the duodenum 50 cm below the ligament of Treitz was measured and anastomosed to the distal part of the interposed ileum.

Analytical Procedures Plasma glucose was measured by the glucose oxidase technique (Advia Chemistry System, Advia 1650, Siemens, Los Angeles, CA). Plasma insulin and C-peptide were measured by a chemiluminescence immunometric assay with two binding sites of solid phase, with intra- and inter-assay variation coefficients of 5.5% and 6.7% for insulin and 6.2% and 8.0% for C-peptide (Immulite 2000, Siemens; Los Angeles, CA). Glycosylated haemoglobin (HbA_{1c}) was assayed by HPLC (Bio Rad D-10, Hercules, CA). All patients were screened for GAD antibodies (RIE, RSR limited, UK).

Calculations

Insulin sensitivity was calculated using the oral glucose-derived insulin sensitivity index (OGIS), which provides a validated estimate of the glucose clearance (in millilitre per minute per square meter of body surface area) during the insulin-stimulated conditions of the euglycaemic hyperinsulinaemic clamp.[12,13] Areas under time–concentration curves were calculated by the trapezoidal rule.

Insulin secretion ß-cell function was resolved from the OGTT using a mathematical model that describes the relationship between insulin secretion and glucose concentration, which has been illustrated in detail previously.[14] The model expresses insulin secretion (in picomole per minute per square meter of body surface area) as the sum of two components. The first component represents the dependence of insulin secretion on absolute glucose concentration at any time point during the OGTT and is characterised by a dose–response function relating the two variables. The characteristic parameter of the dose–response, i.e., the mean slope within the observed glucose range, is denoted as *ß-cell glucose sensitivity* by analogy with insulin sensitivity (slope of the dose–response of insulin-mediated glucose uptake vs insulin concentrations). Thus, glucose sensitivity as used here is not meant to measure the multiple cellular phenomena responsible for glucose sensing (or stimulus/secretion coupling) but only as a metric for the in vivo output of all glucose sensing pathways. In the mathematical model, the dose–response is modulated by a potentiation factor, which accounts for the fact that during an acute stimulation insulin secretion is higher on the descending phase of hyperglycaemia than at the same glucose concentration on the ascending phase. The second insulin secretion component, denoted as *rate sensitivity*, represents the dependence of insulin secretion on the rate of change of glucose concentration.

The model parameters were estimated from glucose and C-peptide concentration by regularised least squares, as previously described.[15]

Statistical Analysis Data are given as mean ± SD or as median and [interquartile range] for non-normally distributed variables. Group comparisons were carried out by one-way Anova or Kruskal–Wallis testing, for normally and non-normally distributed variables, respectively. Post hoc group differences were analysed by the Bonferroni–Dunn test. Paired group values were compared by the paired *t* test or the Wilcoxon signed rank test. Associations were tested by Spearman's rho. Kaplan–Meier plots were used to compare diabetes survival curves by means of the log-rank τ^2 statistic. Cox proportional hazards models were used to estimate hazard ratios (HR) and associated 95% confidence intervals (C.I.). All analyses were performed using JMP version 3.1 (SAS Institute Inc., Cary, NC).

Results

At Baseline Obese and OW patients were slightly younger than NW patients; Diabetes duration, severity of diabetes (as judged from the HbA_{1c} and plasma glucose levels) and anti-diabetic treatment did not differ across BMI class and gender (Table 1). The early and late complications (mostly related to the gastrointestinal tract) were 6.3%, and there were no deaths.

As a group, our patients presented a pattern of metabolic defects (Table 2) characterised by insulin resistance, a profound reduction in ß-cell glucose sensitivity and an increased rate of insulin secretion in the fasting state.

Follow-Up

Table 2 demonstrates the changes in metabolic parameters before and after surgery. Post-operatively, both fasting and postglucose plasma glucose concentrations were significantly lower in NW, OW and OB groups, while the plasma insulin and C-peptide responses were generally heightened (Fig. 1). None of these parameters differed by gender. Fasting insulin secretion rate was reduced, particularly in OB subjects, while total insulin output increased, especially in NW and OW patients. Moreover, total insulin output increased progressively through increased levels of glucose concentration (Fig. 2). Marked improvements also occurred in rate sensitivity and potentiation (Fig. 3). ß-cell glucose sensitivity doubled similarly in NW, OW and OB patients, as shown in Fig. 4. Likewise, insulin sensitivity nearly doubled after surgery, without significant differences

Table 2 Metabolic parameters before and after surgery

	Study	Normal weight	Overweight	Obese	*p* Value
Fasting glucose (mg/dl)	Pre	180±75.6	192.6±72	212.4±90	ns
	Post	129.6±28.8*	111.6±34.2*	115.2±27*	ns
2-hour glucose (mg/dl)	Pre	374.4±63	351±90	360±77.4	ns
	Post	196.2±99*	169.2±75.6*	167.4±43.2*	ns
Fasting insulin (pmol/l)	Pre	57±48	87±86	125±123	ns
	Post	20±11*	18±12*	21±11*	ns
Insulin sensitivity ($ml \cdot min^{-1} \cdot m^{-2}$)	Pre	214 [136]	208 [86]	201 [111]	ns
	Post	370 [106]*	408 [113]*	390 [107]*	ns
Fasting ISR ($pmol \cdot min^{-1} \cdot m^{-2}$)	Pre	120 [73]	145 [138]	156 [90]	ns
	Post	74 [60]	62 [52]*	87 [51]*	<0.04
Total insulin output ($nmol \cdot m^{-2}$)	Pre	32 [28]	40 [26]	47 [46]	ns
	Post	54 [23]*	52 [24]*	48 [61]	ns
Glucose sensitivity ($pmol \cdot min^{-1} \cdot m^{-2} \cdot mM^{-1}$)	Pre	16 [21]	19 [20]	15 [47]	ns
	Post	36 [39]*	36 [29]*	46 [40]	ns
Rate sensitivity ($nmol \cdot m^{-2} \cdot mM^{-1}$)	Pre	14 [386]	165 [511]	24 [347]	ns
	Post	285 [377]	452 [448]*	494 [596]*	ns
Potentiation factor	Pre	1.00 [0.24]	0.97 [0.22]	0.97 [0.25]	ns
	Post	1.05 [0.62]	1.15 [0.65]*	1.29 [0.67]	ns

p value by Kruskal–Wallis test between groups

ns not significant

*$p \leq 0.05$ vs pre-surgery by Wilcoxon signed rank test

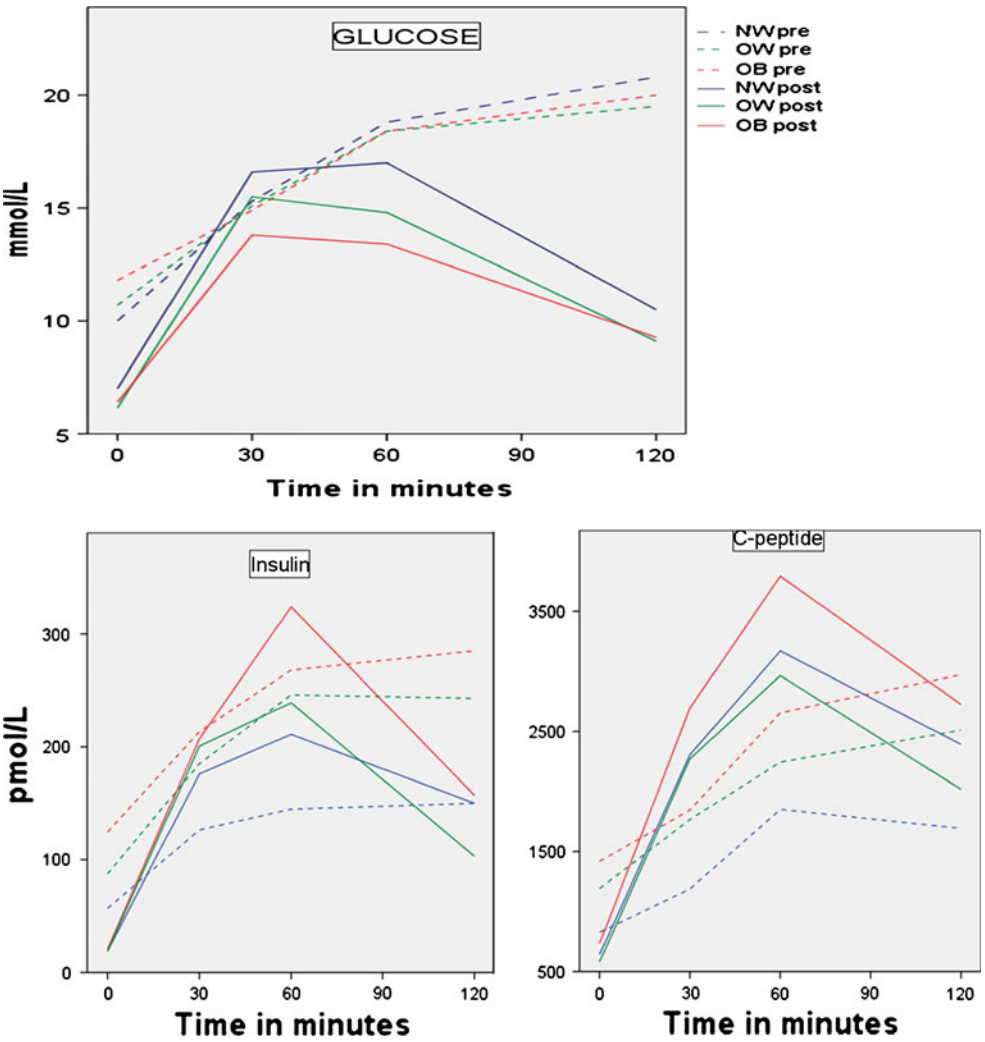

Fig. 1 Plasma glucose, insulin and C-peptide concentrations during a standard OGTT

between groups (Fig. 5). The change in insulin sensitivity was only weakly related to the amount of weight lost (rho= 0.16, p=0.13).

Surgery induced a progressively greater weight loss across obesity groups, averaging 9.4±1.3, 16.8±0.8 and 23.2±1.7 kg in NW, OW and OB subjects (p<0.0001), such that at the follow-up visit, only one patient was still obese, 15 were overweight, one was underweight and all the others were normal weight (Fig. 6). In contrast, HbA_{1c} was reduced to a similar extent in all three groups, by a median of 2.0%, or −25% of baseline (Fig. 7). At a median of 13.4 months (range 2–33) after surgery, anti-diabetic treatment was discontinued in 77 patients, one patient continued on reduced doses of insulin, 13 on one and three on two oral hypoglycaemic agents.

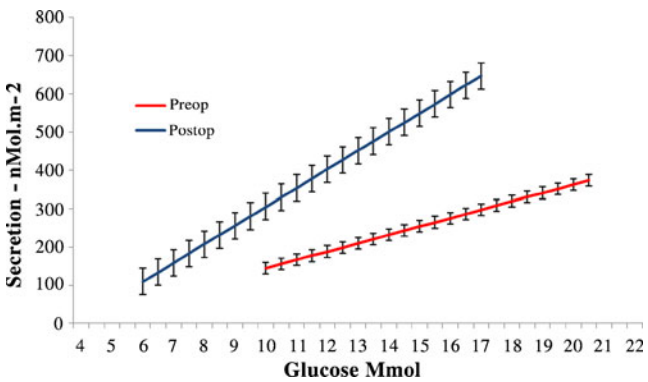

Fig. 2 Total insulin output

By defining optimal glycaemic control as HbA_{1c} <6.5% with no anti-diabetic treatment, 82% of patients reached this target after surgery, equally in the NW, OW and OB and equally in women and men. In these patients, in whom the surgery-induced changes in HbA_{1c}, fasting and 2-h glucose levels were significantly lower than in patients who remained diabetic, age was younger, and there was a tendency for diabetes duration to be shorter and HbA_{1c} to be higher. Neither baseline BMI nor weight loss was a significant predictor of diabetes resolution, Fig. 8a. Likewise, gender and anti-diabetic treatment did not predict this outcome. The only baseline metabolic parameter distinguishing patients with or without remission of diabetes, HbA1c<

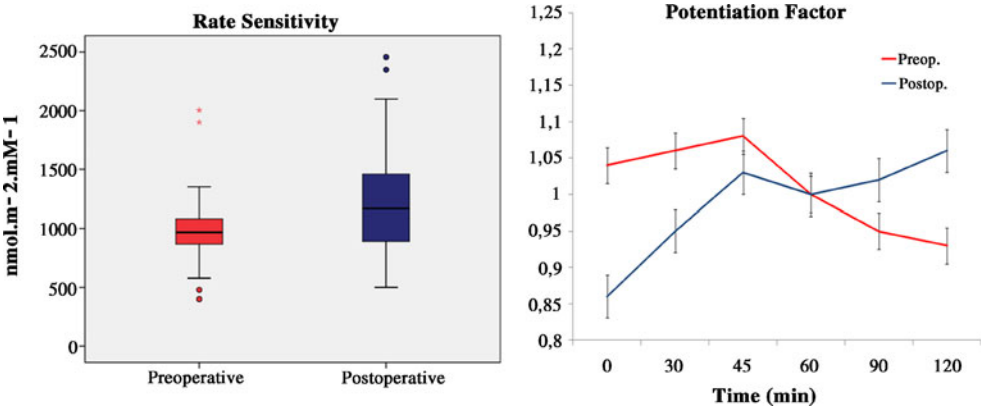

Fig. 3 Pre- and post-operative rate sensitivity and potentiation factor

6%, was the lower insulin sensitivity. The Kaplan–Meier plots of diabetes persistence by tertile of baseline insulin sensitivity confirms that diabetes remission was significantly (p=0.005) better in the patients with the worse baseline insulin sensitivity even after adjusting for age, gender, degree of obesity, previous therapy or duration of diabetes (Fig. 8b). Cox proportional hazards modelling showed that patients in the lower tertile of insulin sensitivity had ~4-fold higher probability of becoming non-diabetic at follow-up as compared to patients in the top tertile (HR=3.83, C.I. 1.56–9.48, p=0.004). This result was not changed by controlling for any baseline variables, including sex, BMI and HbA_{1c} or anti-diabetic treatment. By restricting the analysis to the 52 patients who were evaluated at 1 year (±2 months), the results (by logistic regression) were essentially superimposable on those of the entire cohort.

In a subgroup of 12 patients (aged 55±6 years, BMI of 26.8±3.0 kg/m^2, HbA_{1c} of 8.5±1.9%, fasting glucose of 180±59.4 mg/dl) in whom the metabolic study was performed 90 days and again 1 year after surgery, a marked glycaemic improvement was already observed at the earlier time (HbA_{1c}=6.4±0.8%, fasting plasma glucose=115.2±32.4 mg/dl, both p<0.0001 vs preoperatively), when weight loss averaged 12±1 kg. At this time, insulin sensitivity was much improved (351 [103] vs 202 [87] ml min^{-1} m^{-2}, p<0.0001), while ß-cell glucose sensitivity was unchanged (34 [23] vs 37 [34] pmol min^{-1} m^{-2} mM^{-1}, p=ns). At 1 year after the operation, these metabolic parameters showed further improvement.

Patients undergoing the DII-SG did not differ in their baseline characteristics from those undergoing the JII-SG other than for a younger age (51±8 vs 56±7 years, p< 0.004). At follow-up, diabetes remission had occurred in a higher percentage of the DII-SG than non-diverted patients. By Cox analysis, however, this difference fell short of statistical significance when accounting for the age difference (χ^2=1.64, p=0.20).

Discussion

The patients included in the present study had moderate to severe type 2 diabetes as judged by disease duration and on-treatment values of HbA_{1c} and glucose levels. Their metabolic features included marked insulin resistance and severe ß-cell glucose insensitivity. The main clinical outcome was that hyperglycaemia improved substantially, with 82% of the patients achieving target glycaemic control (HbA_{1c}<6.5%)—a figure similar to those reported with the use of gastric banding, Roux-en-Y gastric bypass (RYBP), bilio-pancreatic diversion (BPD) or sleeve gastrectomy in morbidly obese diabetic patients.[16–18] Unlike with other

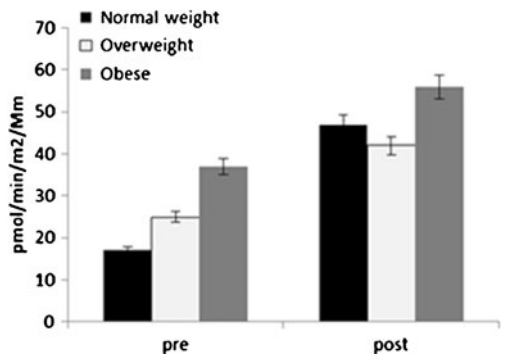

Fig. 4 Pre- and post-operative beta-cell glucose sensitivity

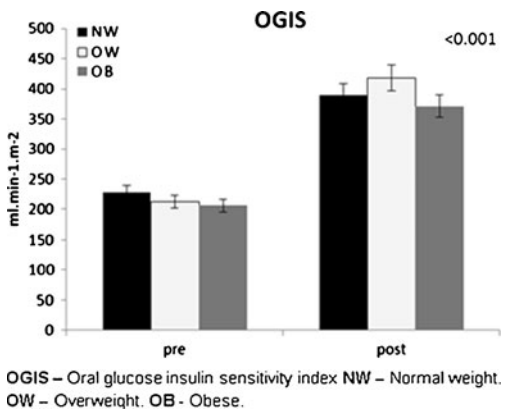

Fig. 5 Pre- and post-operative insulin sensitivity (OGIS)

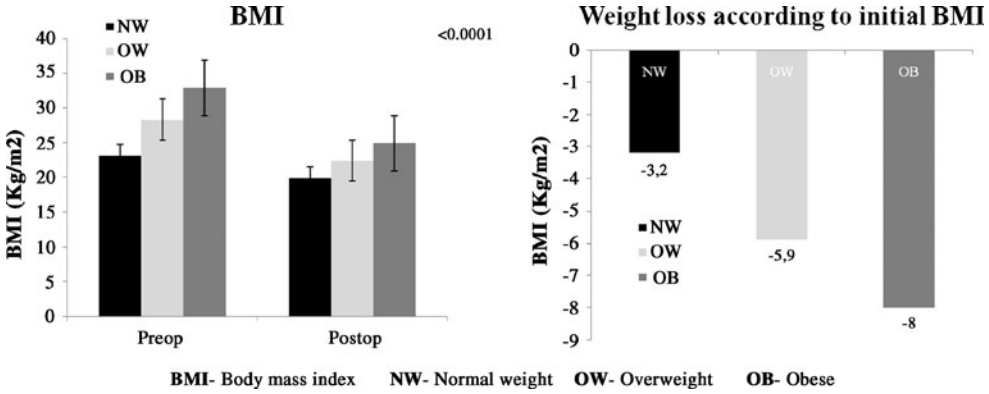

Fig. 6 Post-surgery changes in BMI in normal weight, overweight and obese patients with type 2 diabetes

types of bariatric surgery, this improvement did not appear to be related to the initial BMI nor did it correlate with the achieved BMI (or the corresponding weight loss). Furthermore, we systematically searched for other phenotypic characteristics (gender, age, duration of diabetes, HbA_{1c}, anti-diabetic treatment) that might predict the outcome but could find none that was significantly associated with either diabetes remission or an HbA_{1c} under 6.5%. Clearly, a larger database is necessary to identify clinical predictors, though insulin sensitivity and ß-cell glucose sensitivity did emerge as a significant antecedent. Nevertheless, the current data do suggest that ileal interposition with sleeve gastrectomy may impact on the glycaemic control of diabetic patients also by a direct mechanism in addition to weight loss.

With regard to the underlying pathophysiology, both the insulin resistance and ß-cell dysfunction underwent striking improvements after surgery, as it is expected of any intervention that induces marked amelioration in glucose tolerance.[19] As a group, our patients presented a pattern of metabolic defects almost identical on that previously reported in a cohort of 105 type 2 diabetic patients with a similar clinical phenotype: insulin resistance, a profound (~80%) reduction in ß-cell glucose sensitivity and an increased rate of insulin secretion in the fasting state when compared with NW subjects with normal glucose tolerance.[20] In these post-diabetic individuals, insulin sensitivity had risen to 395 [108] ml min^{-1} m^{-2}, a value that is similar on that (446 [74] ml min^{-1} m^{-2}) obtained in 426 normal weight (BMI<25 kg/m^2) volunteers with normal glucose tolerance and a negative family history of type 2 diabetes.[21] In other words, in post-diabetic patients, insulin sensitivity was normalised. In contrast, ß-cell glucose sensitivity, although much improved after surgery, remained lower than in the historical controls (123 [89] pmol min^{-1} m^{-2} mM^{-1}). Likewise, it is important to emphasize that within the normal glucose tolerance range, it was previously demonstrated[20] that ß-cell glucose sensitivity was already declined by 50–70%. On the other hand, this may also be reflected in the glucose tolerance curve, which shows that post-diabetic subjects had similar fasting and 2-h plasma glucose concentrations but much higher glucose excursions at intermediate OGTT times than spontaneously NGT subjects. Thus, at this moment of the follow-up in post-diabetic subjects, ß-cell function remains compromised; therefore, signals risk for diabetes relapse. In fact, it has been previously demonstrated that depressed ß-cell glucose sensitivity is a strong predictor of subsequent deterioration of glucose tolerance even in subjects with an initially normal glucose tolerance.[22] By this paradigm, in post-diabetic subjects such as those studied here, weight regain might remove the protection offered by the normal insulin sensitivity and, in the presence of an incompetent ß-cell response, might precipitate glucose intolerance. It should be observed that a degree of acceleration of gastric emptying following sleeve gastrectomy, or a paradoxal increase in glucagon levels, could contribute

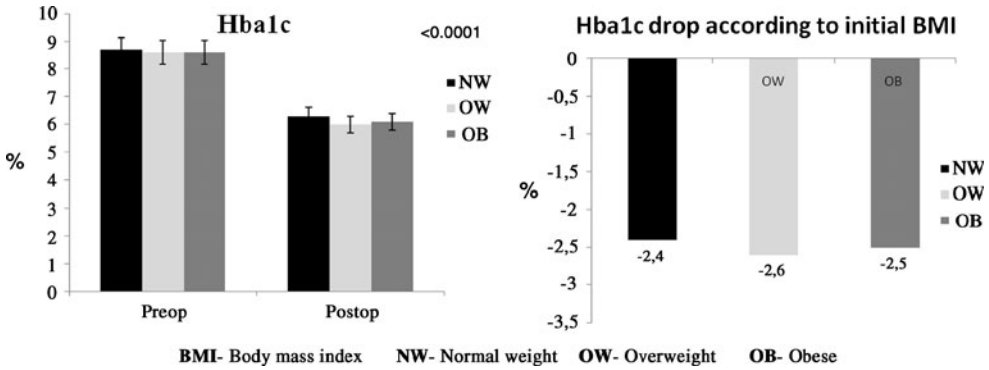

Fig. 7 Pre- and post-operative haemoglobin A1c changes according to BMI

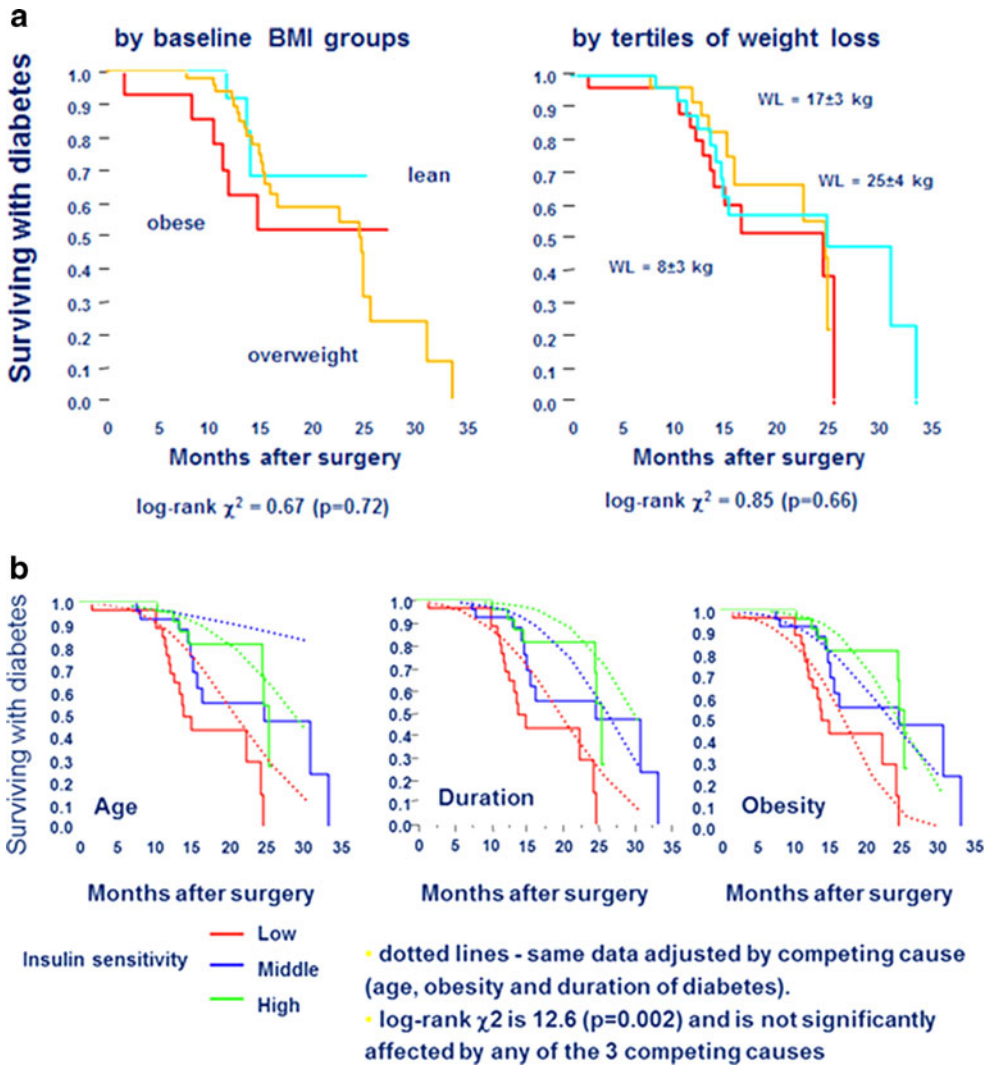

Fig. 8 **a** Kaplan–Meier plots of the proportion of patients surviving with diabetes by baseline BMI (*top panel*, log-rank τ^2= 0.67, p=0.72); **b** Kaplan–Meier plots of the proportion of patients surviving with diabetes by tertile of baseline insulin sensitivity (*bottom panel*, log-rank τ^2=12.6, p=0.002)

to the high peaks of postglucose glycaemia. Although not clinically demonstrated, the other possibility is that the ileal interposition concept could lead to long-term development of nesidioblastosis and pathologic hypoglycaemia. In other words, some of these patients, by the same mechanism that improves ß-cell function, would overshoot "normal" in terms of glucose handling and develop significant problems with hypoglycaemia.

Like RYBP and BPD for morbidly obese diabetic patients, ileal interposition with sleeve gastrectomy in non-morbidly obese subjects can achieve rates and degrees of glycaemic improvement that are normally difficult to obtain with non-surgical interventions.[4] In our cohort, this effect was seen in normal weight, overweight and obese patients alike and was mostly explained by large increases in insulin sensitivity, but ß-cell function was only partially restored and may have resulted from removal of glucose toxicity rather than from a specific effect of surgery.[23] While true diabetes resolution may occur rapidly (as seen in the group of patients studied 3 months after surgery), with time, more patients may enter the non-diabetic range but diabetes may recur in others. Only a longer, appropriately controlled and powered trial will provide the data upon which to assess the true longterm value of this kind of surgery for the treatment of type 2 diabetes. The current results also suggest, but do not prove conclusively, that stable NGT—or cure of diabetes—as the outcome may be more difficult to achieve in normal-weight patients undergoing surgery, possibly because these patients carry a stronger genetic imprint for ß-cell dysfunction or have lost more of their ß-cell function when they first develop diabetes and thus had less reserve to fall back on.

The cellular mechanisms underlying the surgery-induced increase in insulin sensitivity and ß-cell function remain speculative. We have previously demonstrated the impact of the ileal interposition with sleeve gastrectomy in several gastrointestinal hormones, with emphasis on the postoperative changes of ghrelin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide, PYY and glucagon.[24] Surgical restriction of the stomach

may decrease circulating concentrations of ghrelin—a hormone secreted by endocrine cells in the fundus. When infused into healthy volunteers in pharmacological amounts, ghrelin induces acute insulin resistance,[25] but the effect of physiological increases on insulin sensitivity is unknown. Changes in other gastrointestinal hormones have been analysed for those procedures that alter food transit. GLP-1 potentiates glucose-dependent insulin release[26]; GLP-1 responses are impaired in association with both type 2 diabetes and obesity[27] and increases early after II-SG, RYBP and BPD but apparently not diet.[28,29] Thus, heightened GLP-1 responses may contribute to the post-surgical improvement in ß-cell function. However, infusion of GLP-1 to pharmacological levels fails to stimulate insulin-mediated glucose disposal in healthy volunteers.[30]

In the current study, the duodenal variant of the operation appeared to make a small difference in the outcome and pathophysiological changes. In a prospective randomized controlled trial comparing these two versions of ileal interposition with sleeve gastrectomy, the duodenal ileal interposition provided better results, with normalization of HbA1c (≤6%) in 81.3% of the patients at a mean follow-up of 25.6 months.[31] On the other hand, ileal interposition alone reproduced recent findings in streptozotocin-diabetic rats, in which interposition of 10 cm of ileum into the jejunum was associated with a marked and prompt improvement in glycaemia without weight loss.[32]

In conclusion, ileal interposition with sleeve gastrectomy impacts on type 2 diabetes through different mechanisms, principally involving restoration of insulin sensitivity.

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ORIGINAL ARTICLE

Factors Associated with Operative Recurrence Early After Resection for Crohn's Disease

Wisam Khoury · Scott A. Strong · Victor W. Fazio · Ravi P. Kiran

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Abstract
Introduction Some Crohn's disease (CD) patients develop rapid disease recurrence requiring reoperation. Identification of factors associated with early operative recurrence of CD may help risk-stratify patients and prevent recurrence.
Methods Prospectively collected data of CD patients undergoing bowel resection for CD with unequivocal evidence of recurrence at reoperation were retrieved. Patients with earlier recurrence (less than median time of recurrence of study cohort) were compared with those who developed later recurrence (greater than median time of recurrence) for patient and disease characteristics and risk factors for recurrence. A multivariate logistic regression model was performed to identify factors associated with earlier operative recurrence.
Results Sixty-nine patients (45 female, 24 male) met the inclusion criteria. Median time to reoperation was 38 months (range, 3.3–236 months). One hundred six reoperations in the 69 patients were for abscess/fistula/perforation (n=45), stricture/stenosis (n=41), inflammation (n=17), bleeding (n=2), and dysplasia (n=1). Factors associated with early rather than late reoperation included behavior of disease (stricturing, odds ratio (OR) 12.1; confidence interval (CI), 1.8–80.9; penetrating OR, 9.9; CI, 1.4–67.9 rather than nonstricturing nonpenetrating) and the development of postoperative complications at previous surgery (OR, 12.1; CI, 1.2–126.6).
Conclusion Earlier recurrence of CD requiring reoperation is associated with specific disease and potentially modifiable operation-related factors such as postoperative complications, i.e., anastomotic leak or intraabdominal abscess. Strategies to reduce recurrence in such patients include the identification of factors that may reduce postoperative complications.

Keywords Crohn's disease · Recurrence · Early reoperation · Risk factors

Introduction

Treatment of Crohn's disease (CD) is primarily medical, with surgery being reserved for failure of medical therapy or complications of the disease. Previous studies[1] suggest that patients with CD on average require an operation every 10 years. Some patients however present with rapid recurrence requiring reoperation. A previous study from this institution evaluated the effect of margins of resection on long-term outcomes and determined that a wide resection margin is not predictive of delayed recurrence.[2] However, after surgical resection symptomatic recurrent disease develops in approximately 34–41% of these patients within 3 years of operation.[3,4] Endoscopic follow-up suggests that recurrent disease occurs in the neoterminal ileum in 80% of patients 1 year post-ileocecectomy.[5] The pattern of recurrence is characteristic for the individual patient,[6] and it is postulated that the trigger for development of recurrent lesions may be a luminal factor.[7,8] Rapid recurrence after surgical resection occurs in some patients and can be frustrating for the patient and clinician alike. Little data are currently available regarding the factors associated with early recurrence that requires operative intervention in patients who undergo initial resection for CD. The aim of

W. Khoury · S. A. Strong · V. W. Fazio · R. P. Kiran (✉)
Department of Colorectal Surgery, Cleveland Clinic Foundation,
9500 Euclid Avenue,
Cleveland, OH 44195, USA
e-mail: kiranp@ccf.org

this study is to evaluate factors associated with the development of early recurrence requiring resection after initial resection of involved bowel for CD patients.

Patients and Methods

All CD patients who underwent laparotomy with bowel resection for CD and were subsequently reoperated, between 1998 and 2008, were identified from an institutional review board-approved prospectively maintained Crohn's disease database. Only patients with pathologic confirmation of CD in the resection specimen at initial surgery and evidence of recurrence of CD at reoperation were included. In six patients who did not undergo resection at reoperation, there was unequivocal evidence of CD recurrence based on clinical, radiologic and operative findings. In all of the remaining patients, confirmation of CD recurrence was based on pathologic confirmation of the specimen resected at the reoperation. Patients who underwent combined resection and strictureplasty at initial operation were considered to have an operative recurrence if the recurrence occurred at sites other than the strictureplasty site. Since patients who undergo bowel sparing procedures such as stricturoplasty, by definition, have disease left in the small bowel, disease will likely be identified in these patients when they undergo the second surgery soon after the first operation (early recurrence group). In order to avoid this potential confounder, we decided to include patients who had bowel resection at the first operation and hence deemed to be negative for disease after that surgery. Thus, any disease noted at second operation even in those undergoing the second surgery early would be due to disease recurrence and not residual disease. Patients who underwent their first operation at an outside hospital, or had their first operation performed prior to 1998, were included if the relevant data were available.

Information relating to patient demographics, family history of inflammatory bowel disease (IBD), smoking history, duration, site, extent, and behavior [using the Vienna classification:[9] nonstricturing nonpenetrating (B1), stricturing (B2), and penetrating (B3)] of disease at the time of primary operation, type of primary surgery, and postoperative complications was collected. Extent of disease was evaluated using the number of sites involved and location of disease in the upper gastrointestinal tract (esophagus gastric and duodenum), jejunum, ileum, colon, and rectum. Perianal disease was documented and evaluated separately. Time duration to the first reoperation and the indication for reoperation were determined. In addition, behavior and site of disease at the time of reoperation, type of reoperation, and medical treatment between operations were evaluated. When patients underwent stoma closure, perianal procedures, and early laparotomy for complications related to the index surgery, (e.g., anastomotic leak, bleeding, evisceration, intraabdominal abscess), or lysis of adhesions at the second operation, these procedures were not considered as recurrent surgery for CD.

The median time to first operative recurrence for the patients was determined. The patients were then classified into two groups: patients with earlier operative recurrence (less than median time of recurrence) and patients with later operative recurrence (greater than median time of recurrence). When patients developed more than one recurrence, they were classified as having an early or late recurrence based on the time to first operative recurrence to avoid potential problems that may arise with the analysis and interpretation of findings due to some such patients falling into both the groups if they developed an early recurrence after one surgery but late recurrence after another.

The two groups were compared for differences in patient and disease characteristics, treatment, and risk factors for recurrence. Risk factors associated with early and late operative recurrence were determined.

Statistical Analysis

Categorical variables were summarized as frequency (percentage), and quantitative variables as mean ± standard deviation and minimum, 25th percentile, median, 75th percentile, and maximum. Associations with categorical variables were analyzed by Fisher's exact test or chi-square test, and associations with quantitative and ordinal variables were analyzed by logistic regression. Odds ratios (OR) of extended time period are reported for continuous variables relative to an increase in the variable by the number of units. OR of extended time period are reported for categorical variables with two values as the odds of the second group relative to the first. A multivariate logistic regression model was performed including only factors that were significant on univariable analysis to identify factors associated with early operative recurrence.

Results

Between the years 1998 and 2008, 113 patients underwent two or more operations for CD; 69 patients (45 female and 24 male) met the study inclusion criteria. Median time to reoperation was 38 months, with 34 patients undergoing early reoperations (median, 21.6 months; interquartile range (IQR), 8.8–30.2 months) and 35 patients undergoing late reoperation (median, 74.2 months; IQR, 57.1–145.5 months). The 69 patients underwent 106 reoperations

for abscess, fistula, or perforation (n=45), stricture or stenosis (n=41), inflammation (unresponsive disease, n=17), bleeding (n=2), and dysplasia (n=1). Ten patients had both early and late recurrences. Based on the recurrence after their first surgery, two of them were included in the early and eight in the late recurrence group.

Patient demographics, disease duration, number of involved sites, site of disease (i.e., small bowel versus large bowel versus combined disease involvement), associated perianal disease, and smoking history were comparable between the early and late recurrence groups (Table 1). A family history of IBD was more common in patients with late operative recurrence (Table 1).

The indications for surgery and types of the initial and repeat operations are listed in Table 2. A greater proportion of patients in the early recurrence group had index surgery for fistula, while more patients in the late recurrence group were operated for inflammation at first operation. A similar trend was seen during the second operation. More patients in the late reoperation group had their repeat surgery for fistula, abscess, or perforation as compared to the indications for surgery for the same group at the previous surgery. Thus, disease behavior (Table 3) changed for some patients at the time of second surgery. In the early reoperation group, more patients presented with advanced disease, (i.e., B2, B3) at previous operation, while a greater number of the late reoperation group of patients had their previous operation indicated for inflammatory disease, (i.e., B1).

In both groups, a disease progression was noticed from the time of initial surgery to the time of reoperation. In the early reoperation group, 5.9% patients had B1 disease, 50.0% B2, and 44.1% B3 at the initial surgery in contrast to 2.9% B1, 32.3% B2, 64.8% B3 at repeat surgery. In the late reoperation group, 36.7% had B1, 40.0% B2, and 23.3% B3 at initial surgery, and 8.5% B1, 34.2% B2, and 57.3% B3 at repeat surgery (Table 3). In addition, a significantly greater number of patients in the late recurrence group were previously misdiagnosed with ulcerative colitis (Table 3). A comparable number of patients in both groups received medical treatment prior to the repeat surgery (Table 3).

Factors associated with early rather than late reoperation after the previous operation included behavior of disease

Table 1 Demographics and disease characteristics of the patients who developed early and late operative recurrence of Crohn's disease

	Late recurrence (n=35) (50.7%)	Early recurrence (n=34) (49.3%)	P value
Age_median (IQR) (years)	35 (29.8–42.3)	36.9 (25.3–50.1)	0.98
Gender			0.73
Female	23 (65.7%)	21 (61.8%)	
Male	12 (34.3%)	13 (38.2%)	
Time period between operations median (IQR) (months)	74.2 (57.1–145.5)	21.6 (8.8–30.2)	<0.001
Duration of disease (years)	10.7 (3.8–17.3)	10.4 (5.6–15.6)	0.93
Number of intestinal sites involved			0.75
1	20.6%	27.3%	
2	38.2%	27.3%	
3	38.2%	36.4%	
4	2.9%	6.1%	
5	0%	3%	
Bowel involved by disease			0.16
Small bowel	10 (28.5%)	12 (35.3%)	
Large bowel	14 (40%)	6 (17.6%)	
Small and large bowel	9 (25.7%)	12 (35.3%)	
Upper gastrointestinal tract	2 (5.8%)	4 (11.8%)	
Family history of IBD	12 (34.3%)	4 (11.8%)	0.033
Family history of Crohn's disease	6 (17.1%)	2 (5.9%)	0.15
Perianal disease	12 (34.3%)	10 (29.4%)	0.66
Smoking status			0.77
Current[a]	41.2%	37.5%	
Never smoked	35.3%	43.8%	
Past	23.5%	18.8%	

IQR interquartile range, *IBD* inflammatory bowel disease

[a] Prior to second operation

Table 2 Indications and type of operation at primary and repeat operations

	Late recurrence (n=35)	Early recurrence (n=34)	P value
Indication for first operation			0.036
Fistula	3 (8.6%)	13 (38.2%)	
Abscess	2 (5.7%)	1 (2.9%)	
Perforation	1 (2.9%)	0	
Stricture	10 (28.5%)	11 (32.3%)	
Persistent inflammation	18 (51.4%)	8 (23.5%)	
Bleeding	0	1 (2.9%)	
Dysplasia	1 (2.9%)	0	
Type of first surgery			0.216
Small bowel resection	6	9	
Ileocecectomy/ileocolectomy	11	16	
Proctocolectomy	8	3	
Total abdominal/subtotal colectomy	8	3	
Segmental colectomy	2	2	
Proctectomy		1	
Indications for reoperation			0.031
Fistula	7 (20%)	14 (41.2%)	
Abscess	1 (2.9%)	1 (2.9%)	
Perforation	0	4 (11.8%)	
Stricture	19 (54.2%)	8 (23.6%)	
Unresponsive inflammation	6 (17.1%)	6 (17.6%)	
Bleeding	2 (5.8%)	0	
Dysplasia	0	1 (2.9%)	
Type of reoperation			0.287
Small bowel resection	10	11	
Ileocecectomy/ileocolectomy	15	12	
Proctocolectomy	2	0	
Total abdominal/subtotal colectomy	0	4	
Segmental colectomy	1	2	
Proctectomy	5	3	
Fistula takedown	2	1	
Stricturoplasty	0	1	

[stricturing, OR, 12.1; confidence interval (CI), 1.8–80.9 and penetrating, OR, 9.9; CI, 1.4–67.9 rather than nonstricturing nonpenetrating] and the development of postoperative complications at previous surgery [OR, 12.1; CI, 1.2–126.6] (Fig. 1). Moreover, 88% of the patients who experienced major postoperative complications at the previous surgery experienced early recurrence. Complications included anastomotic leak in two patients and intraabdominal abscess in seven patients. Six of these nine patients (eight early and one late reoperation) were classified as B3 disease at the time of surgery. Early reoperations for CD in the eight patients were for fistula in four, stricture in three, and inflammation in one patient.

A family history of inflammatory bowel disease was associated with an increased late rather than early operative recurrence [OR, 4.77; CI, 1–23.4] (Fig. 1).

Discussion

Symptomatic recurrence of CD is reported to occur in 34–41% of patients within 3 years after surgical resection,[3,4] and endoscopic recurrence is seen in the neoterminal ileum in 79% of patients 1–3 years post-ileocecectomy.[5] Further, 50% of CD patients are expected to require a second operation within 10 years.[1] Although the pattern and timing of recurrence cannot be accurately predicted, they are likely to be characteristic for an individual patient.[6] Several risk factors have been reported to increase recurrence requiring surgery; however, factors associated with an early or late recurrence have not been well determined. One study suggested that 45% of patients who have had previous surgery will need reoperation for recurrent disease within 3 years.[4] Common indications for recurrent surgery included abscess, fistula, and bowel obstruction.[4] The

Table 3 Factors at second surgery: disease behavior, postoperative complications, and medical treatment prior to reoperation

	Late recurrence (n=35) (50.7%)	Early recurrence (n=34) (49.3%)	P value
Crohn's behavior at previous surgery			0.007
B1: nonstricturing, nonpenetrating	36.7%	5.9%	
B2: stricturing	40.0%	50%	
B3: penetrating	23.3%	44.1%	
Crohn's behavior			0.57
B1: nonstricturing, nonpenetrating	8.5%	2.9%	
B2: stricturing	34.2%	32.3%	
B3: penetrating	57.3%	64.8%	
Previous diagnosis of ulcerative colitis	14 (40%)	6 (17.6%)	0.045
Complications at previous operation	1 (2.9%)	8 (23.5%)	0.013
Abscess	0	7	
Anastomotic leak	1	1	
Preoperative medical treatment	88%	86.2%	1

authors reported that the repeat procedures were usually more aggressive, and that outcomes for patients undergoing reoperation were worse than those of the primary surgery.[4] The aim of the current study is to evaluate risk factors associated with recurrence that dictate early reoperation, as compared to factors associated with late recurrence of CD.

In order to answer this question, all patients who had two or more abdominal operations for CD were identified, and those who had operations for stoma closure and perioperative complications only were excluded. Patients who did not undergo resection of the diseased bowel during their primary operation (i.e., stricturoplasty, fistula repair) were excluded due to potential problems with assessing whether any disease noted at second surgery for those with an early recurrence was due to a true recurrence or residual disease left in the small bowel. However, if the recurrence occurred at a location different from the strictureplasty or fistula repair site, the patients were included in this study. Time to

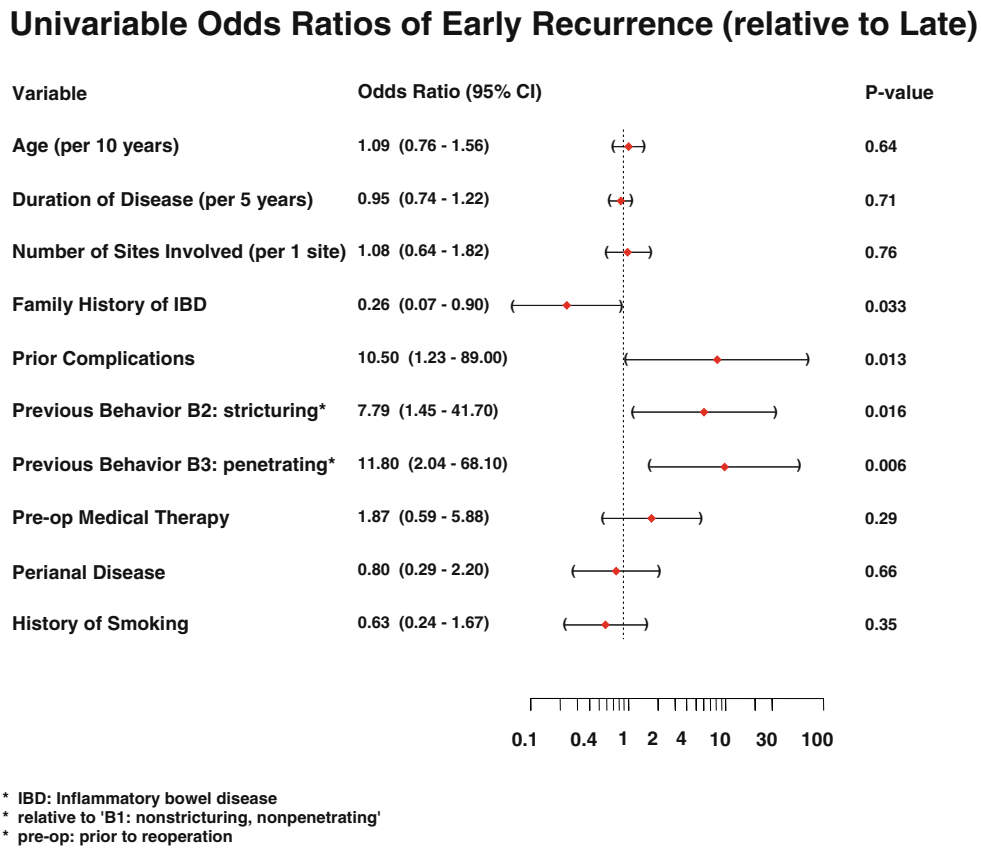

Fig. 1 Risk factors for early and late operative recurrence of Crohn's disease

operative recurrence was defined as the time period from the first abdominal operation to the next operation for patients for whom these data were available. Characteristics at first operative recurrence were evaluated since subsequent recurrences are expected at shorter time intervals[4,10] and usually represent disease progression.

Indications for repeat surgery as well as for early reoperations in the CD patients were consistent with a previous study,[4] which reported early repeat abdominal surgery within 3 years for abscess or fistula in 49%, obstruction in 41%, and other indications in 10% of the patients.[4] In our patients who required early reoperation, indications included fistula, abscess, or perforation in 55.9%, stricture in 23.6%, persistent inflammation in 17.6%, and dysplasia in 2.9% of the patients. Disease severity is known to be a risk factor for recurrence, with fistulizing disease more likely to recur. Accordingly, a high proportion of patients in the early recurrence group had fistula as an indication for primary surgery. This finding further highlights the significance of disease severity as a risk factor for early recurrence. Since we have modeled the likelihood of early recurrence given the disease will be recurrent, our dataset only includes patients with disease recurrence. This may be responsible for the high proportion of patients with penetrating disease seen in this series.

As discussed, the majority of patients who needed repeat surgery, in our study, had advanced disease behavior (i.e., structuring disease, penetrating disease), which contradicts previous reports.[1,11,12] Other studies have suggested that multiple recurrences should be considered as risk factor for future recurrence and an indicator of aggressive disease.[13-15] In our study, subsequent recurrences were also associated with disease progression. Patients who had early recurrence also had more severe disease at initial surgery, with more having fistula as indication for surgery and disease classified as B2 and B3 by the Vienna classification when compared with the late recurrence group.

Patients with advanced disease may be at increased risk for postoperative complications as well as development of recurrent disease.[12] On the other hand, postoperative complications have been reported to predict CD recurrence.[16] An issue to thus consider is whether the healing process and long-term outcome of an anastomotic leak or intraabdominal abscess (and consequently the occurrence of a fistula in some cases) in CD patients are influenced by the disease pathophysiology.[1] In the present study, these postoperative abdominal complications were associated with increased risk for early operative recurrence. We, however, included only patients who underwent resection of the macroscopically involved segments of bowel at the primary operation. As such, we expected that the healing process was not directly affected by the disease.

Whether a family history of CD or IBD increases the risk of operative as well as symptomatic recurrence is still controversial.[17-19] Family history of IBD in the present study was found to affect the operative recurrence time. Although the incidence of a family history of CD was similar between the two groups, a family history of IBD was associated with late rather than early operative recurrence. These findings further point to a milder phenotypic manifestation for the late recurrence group, this possibility is further strengthened by the fact that a greater proportion of patients in the late recurrence group were initially misdiagnosed with UC.

In summary, when considering all of these factors, the presence of a more aggressive phenotype and the development of postoperative complications at index surgery were associated with early recurrence. Previous studies[1,6,7,9,20,21] have shown that several risk factors, such as young age, female gender, smoking history, perianal disease, extent of disease, number of sites involved, and inadequate medical therapy, may increase the risk of operative recurrence. However, these were not associated with the timing of recurrence in our study.

One of the limitations of this study is the absence of data pertaining to the adequacy of medical treatment prior to the repeat surgery since this is expected to affect the operative recurrence time.[20] Details pertaining to the use of suppressive medication were available and comparable in both the early and late operative groups prior to the repeated operation. A further potential weakness of the study may be related to the small number of patients in the subgroups that may have precluded the derivation of a P value that was significant.

In conclusion, severity of disease and the occurrence of postoperative complications at the first surgery are associated with an earlier recurrence of CD indicating repeat surgery. Strategies to reduce recurrence in such patients including the consideration of suppressive therapy and the identification of modifiable factors that may reduce postoperative complications need careful consideration.

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ORIGINAL ARTICLE

Mosapride Citrate Improves Postoperative Ileus of Patients with Colectomy

Yoshitaka Toyomasu · Erito Mochiki · Hiroki Morita · Atsushi Ogawa · Mitsuhiro Yanai · Tetsuro Ohno · Takaaki Fujii · Soichi Tsutsumi · Takayuki Asao · Hiroyuki Kuwano

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Abstract
Background and Aims Postoperative ileus is a transient bowel dysmotility that occurs following many types of operations and is a common complication of gastrointestinal surgery. Mosapride citrate is an agonist of the 5-hydroxytryptamine 4 receptor and accelerates upper gut motility. No study has evaluated its effect on gastrointestinal motility after surgery. The aim of this study was to investigate whether mosapride citrate reduces the duration of postoperative ileus.
Methods Thirty patients with colon cancer who underwent colectomy were divided into two groups: the mosapride group and the control group. The mosapride group received mosapride 15 mg by mouth with a minimal amount of water three times a day, starting on postoperative day 1. The control group received only a minimal amount of water on the same schedule. Patients were allowed to resume oral feeding on postoperative day 4. Postoperative time to first flatus and defecation were evaluated, and the amount of food intake was observed. Gastrointestinal motility was recorded on postoperative day 8.
Results The appearance ratio of interdigestive migrating contractions and the motility index at the antrum and duodenum were significantly higher in the mosapride group than in the control group. The time to first flatus and defecation were significantly shorter in the mosapride group than in the control group. The amount of food intake on postoperative days 6 and 7 was significantly larger in the mosapride group than in the control group.
Conclusion Mosapride citrate reduces the duration of postoperative ileus and may improve outcomes after gastrointestinal surgery.

Keywords Gastrointestinal motility · Transducer · Interdigestive migrating motor contractions

Abbreviations
IMC Interdigestive migrating motor contractions
MI Motility index

Y. Toyomasu (✉) · E. Mochiki · H. Morita · A. Ogawa · M. Yanai · T. Ohno · T. Fujii · S. Tsutsumi · T. Asao · H. Kuwano
Department of General Surgical Science (Surgery I), Graduate School of Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
e-mail: toyomasu@med.gunma-u.ac.jp

Introduction

Postoperative ileus occurs after all abdominal operations and is characterized by impaired intestinal motility and transit, absence of the passage of flatus, diminished bowel sounds, abdominal distension, and intestinal dilatation. It may cause pain, nausea, and vomiting in the immediate postoperative period and delay the resumption of normal oral feeding.

Mosapride citrate is a selective 5-hydroxytryptamine 4 (5-HT4) receptor agonist that is effective on the upper gastrointestinal tract.[1] It has been reported to be effective on the lower gastrointestinal tract as well.[2–5] Sakurai-Yamashita et al. demonstrated that the localization of the 5-HT4 receptor in the guinea pig colon is similar to that in the

Table 1 Values are expressed as mean±SEM

	Mosapride (n=15)	Control (n=15)	P value
Age (years)	60.0±10.7	66.1±8.3	0.11
Sex (male/female)	9/6	10/5	0.64
Height (cm)	162.3±8.6	162.5±9.4	0.95
Weight (kg)	58.9±10.9	65.5±7.8	0.18
Location of tumor (left/right)	8/7	8/7	–
Operation time (min)	153.7±48.1	170.0±34.7	0.42
Blood loss (ml)	70.0±44.0	88.9±67.9	0.48

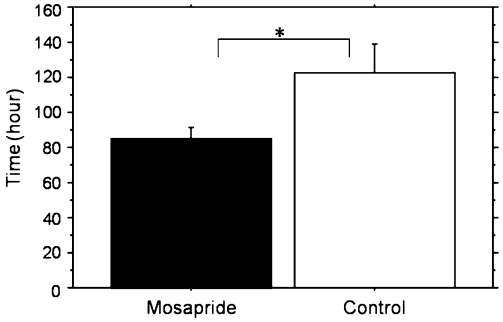

Fig. 2 Time to the appearance of first defecation after surgery in the mosapride group and the control group. *P<0.05

human colon.[6] Recently, it was reported that mosapride enhances rectorectal and rectoanal reflexes in guinea pigs.[7]

Thus, we hypothesized that mosapride may accelerate the motility of the upper and lower gut via stimulation of the 5-HT4 receptor and may increase the amount of food intake and shorten the time to the appearance of first flatus and defecation after abdominal surgery. The aim of the present study was to evaluate whether mosapride shortened the duration of postoperative ileus after colectomy.

Patients and Methods

Patients

From April 2008 to March 2010, a total of 30 patients who underwent laparoscopic colectomy for colon cancer participated in this study. In addition, inclusion criteria were (1) age younger than 80 years, (2) no signs of distant metastases, (3) no presence of ascites, (4) a technically resectable primary tumor, and (5) satisfactory cardiorespiratory status. The exclusion criteria were (1) age younger than 20 years, (2) presence of renal or liver failure, (3) presence of ascites, (4) history of allergic reaction for mosapride, and (5) presence of active infectious disease.

After surgery, an epidural tube was used for pain control and was maintained for 48 h. In all patients, the nasogastric tube was removed 1 day after surgery. Patients were randomly assigned to receive mosapride (15 patients) or to serve as controls (15 patients). The mosapride group received mosapride 15 mg by mouth with 40 ml of tap water three times a day from the afternoon of postoperative day 1 to the evening of postoperative day 7. The control group received 40 ml of tap water on the same schedule. Oral feeding was allowed on the morning of postoperative day 4. To avoid confounding the results with the effects of other potential prokinetic agents, no patient received metoclopramide, erythromycin, or other agents that might modify gastrointestinal motility during the study period. Postoperative use of prophylactic antiemetics was prohibited. All patients gave written informed consent, and this study was approved by the institutional review board at the Gunma University Hospital.

Evaluation of Clinical Findings

The amount of food intake and postoperative time to the first passage of flatus and defecation were evaluated by one of the investigators who was blinded as to whether the patient had received mosapride.

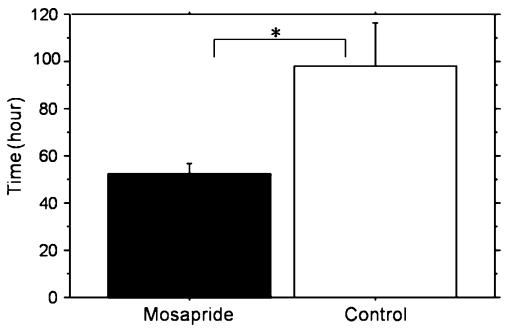

Fig. 1 Time to the appearance of first flatus after surgery in the mosapride group and the control group. *P<0.05

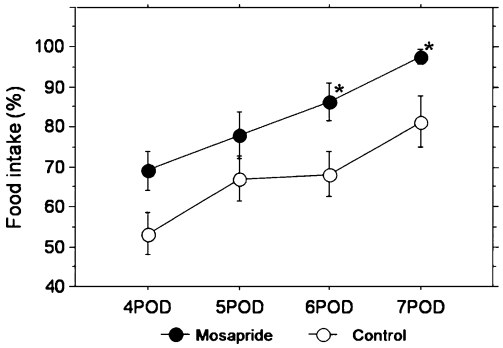

Fig. 3 Changes in the amount of food intake in the mosapride group and the control group. *P<0.05

Motility Study

A 6-mm-diameter flexible probe containing four strain gauge pressure transducers was used to monitor intestinal motor activity (GMMS-600; Star Medical, Tokyo, Japan). The pressure transducers measured intraluminal pressure in the esophagus, stomach, and duodenum. The most proximal pressure transducer was positioned in the esophagus. The two middle pressure transducers were positioned in the gastric body and antrum. The most distal pressure transducer, 15 cm distal from the third pressure transducer, was positioned in the proximal duodenum. The manometric studies were carried out 8 days after surgery. All subjects were required to stop taking medication known to affect gastrointestinal motility for at least 48 h prior to the study. After the subjects had fasted for at least 12 h overnight, the manometry assembly was inserted through the nostril and the two middle pressure transducers were placed in the stomach under fluoroscopic control. Recording started at 9:00 AM in all patients and lasted for 4 h, first for 2 h in the fasted state and then for 2 h after a 360-kcal meal. All patients ingested the entire meal.

Analysis of Motor Activity

Analysis was visual and computerized. Visual analysis was performed for both the fasted and fed states. Determination

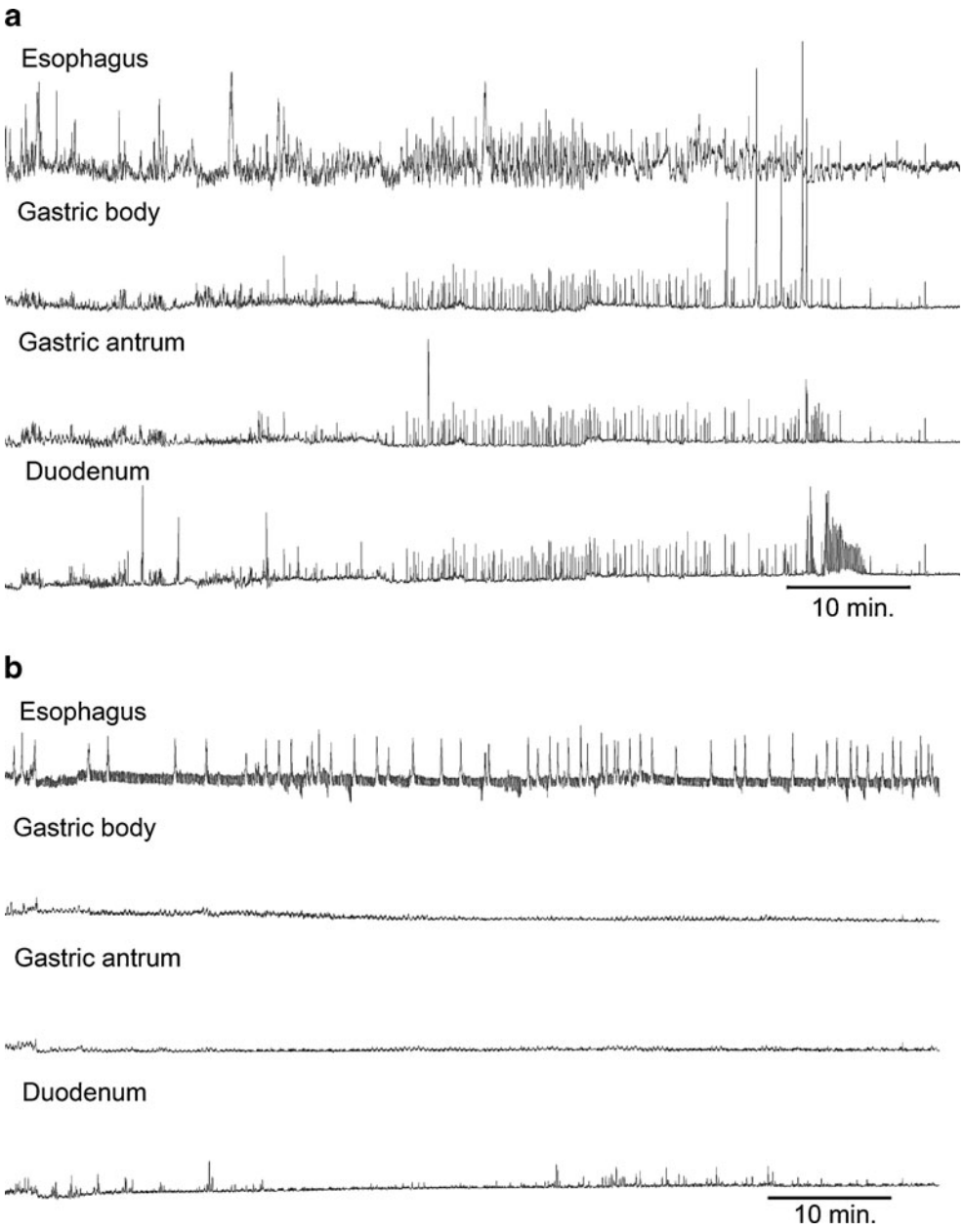

Fig. 4 Representative tracings of upper gut motility at postoperative day 8 in the fasted state. The fasted contractions in the mosapride group (**a**) were stronger than those in the control group (**b**) in the gastric body, antrum, and duodenum

of each phase of contractile activity was made according to the following criteria. Phase I was defined as a quiescent period. Phase II consisted of clusters of irregular contractions that followed phase I and preceded phase III. Phase III was a period of strong contractions lasting more than 5 min. Phase IV was a very short period of subsiding contractions that immediately followed phase III. Data were recorded on a computer (Adif1412. Dll; Star Medical, Tokyo, Japan) for analysis. To measure motor activity quantitatively, the motility index (MI) was determined. The signals from the manometric assembly, which were stored by a data recorder (GMMS-TB; Star Medical), were digitized at a sampling frequency of 500 ms and analyzed by the same system, which was controlled by a computer (Adif1412. Dll; Star Medical) according to methods described previously.[8] The MI given by the processing system corresponded to measurements of the area surrounded by the contraction wave and baseline, or in other words, to the product of amplitude and the time in minutes during a certain fixed period. The MIs of the esophagus, gastric body, antrum, and duodenum were calculated for each sequential 2 h of the fasted and fed states.

Statistical Analysis

Food intake data are expressed as mean±standard error, and the other data are expressed as mean±standard error of the mean (SEM). The relationships between each group and characteristic data were determined using the chi-squared test and Fisher's exact test. Quantitative data were subjected to detailed statistical analysis to obtain repeated measures of analysis of variance followed by Fisher's protected least significant difference method. The paired data were compared using Student's *t* test. Differences at *P* values lower than 0.05 were considered to be significant. The statistical calculations were carried out using Stat View® software (version 5.0; Abacus Concepts, Inc., Berkeley, CA).

Results

Patient Characteristics

Patients' characteristics and perioperative data are summarized in Table 1. The age, sex, height, weight, and tumor location did not differ between the mosapride and control groups. The operative time was 154±48 min in the mosapride group and 170±35 min in the control group, and blood loss was 70±44 ml in the mosapride group and 89±68 ml in the control group. There was no complication associated with the ingestion of mosapride.

Time to the Appearance of First Flatus

Postoperative time to the first flatus was significantly shorter in the mosapride group than in the control group (52.2±4.6 vs. 98.1±18.2 h, respectively, $P=0.0248$; Fig. 1).

Time to the Appearance of First Defecation

Postoperative time to the first defecation was significantly shorter in the mosapride group than in the control group (84.7±6.7 vs. 122.7±16.2 h, respectively, $P=0.0438$; Fig. 2).

Food Intake

On postoperative days 4 and 5, the amount of food intake in the mosapride group was higher than that in the control group, but no significant difference was detected (69.0±4.9% vs. 53.3±5.3% and 78.0±5.9% vs. 67.1±5.7%, respectively; $P=0.0526$ and $P=0.1983$). Furthermore, on postoperative days 6 and 7, the amount of food intake in the mosapride and control groups was significantly different (86.3±4.6% vs. 68.2±5.7% and 97.5±1.9% vs. 81.3±6.3%, respectively; $P=0.0238$ and $P=0.0236$). Food intake in the mosapride group was significantly higher than that in the control group at almost every time point at which the subjects were examined (Fig. 3).

Motility Study

In the fasted state, the gastrointestinal contractions of the gastric body, antrum, and duodenum in the mosapride group were stronger than those in the control group (Fig. 4a, b). The MIs in the antrum and duodenum in the mosapride group were significantly larger than those in the

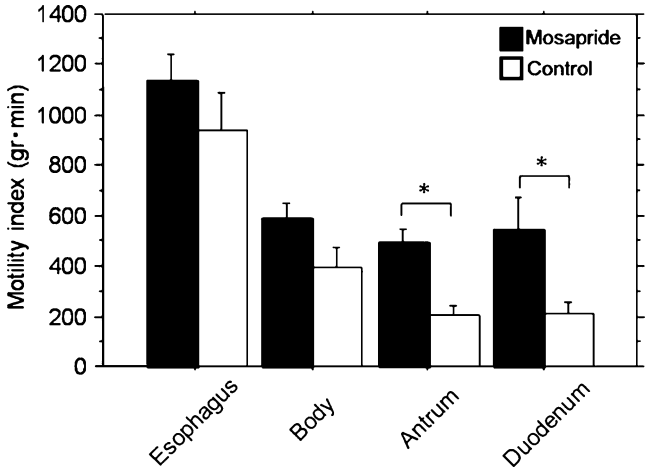

Fig. 5 MI in the fasted state in the mosapride group and the control group. *$P<0.05$

control group (Fig. 5). The MIs in the esophagus and gastric body in the mosapride group were not different from those in the control group. The appearance ratio of phase III in the mosapride group was significantly higher than that in the control group (80% vs. 47%, respectively). In the fed state, the gastrointestinal contractions of the gastric antrum and duodenum in the mosapride group were stronger than those in the control group (Fig. 6a, b). The MIs in the antrum and duodenum in the mosapride group were significantly larger than those in the control group (Fig. 7). The MIs in the esophagus and gastric body in the mosapride group were not different from those in the control group.

Discussion

In this study, we demonstrated that the times to the appearance of the first flatus and defecation in the mosapride group were shorter than those in the control group, and the amounts of food intake on postoperative days 6 and 7 in the mosapride group were higher than those in the control group.

We first reported about gastrointestinal motility after surgery with or without mosapride by means of a manometer. Mosapride has been considered to increase the amplitude of the antral and duodenal motor activities in the fed state in conscious dogs.[1] The data from our

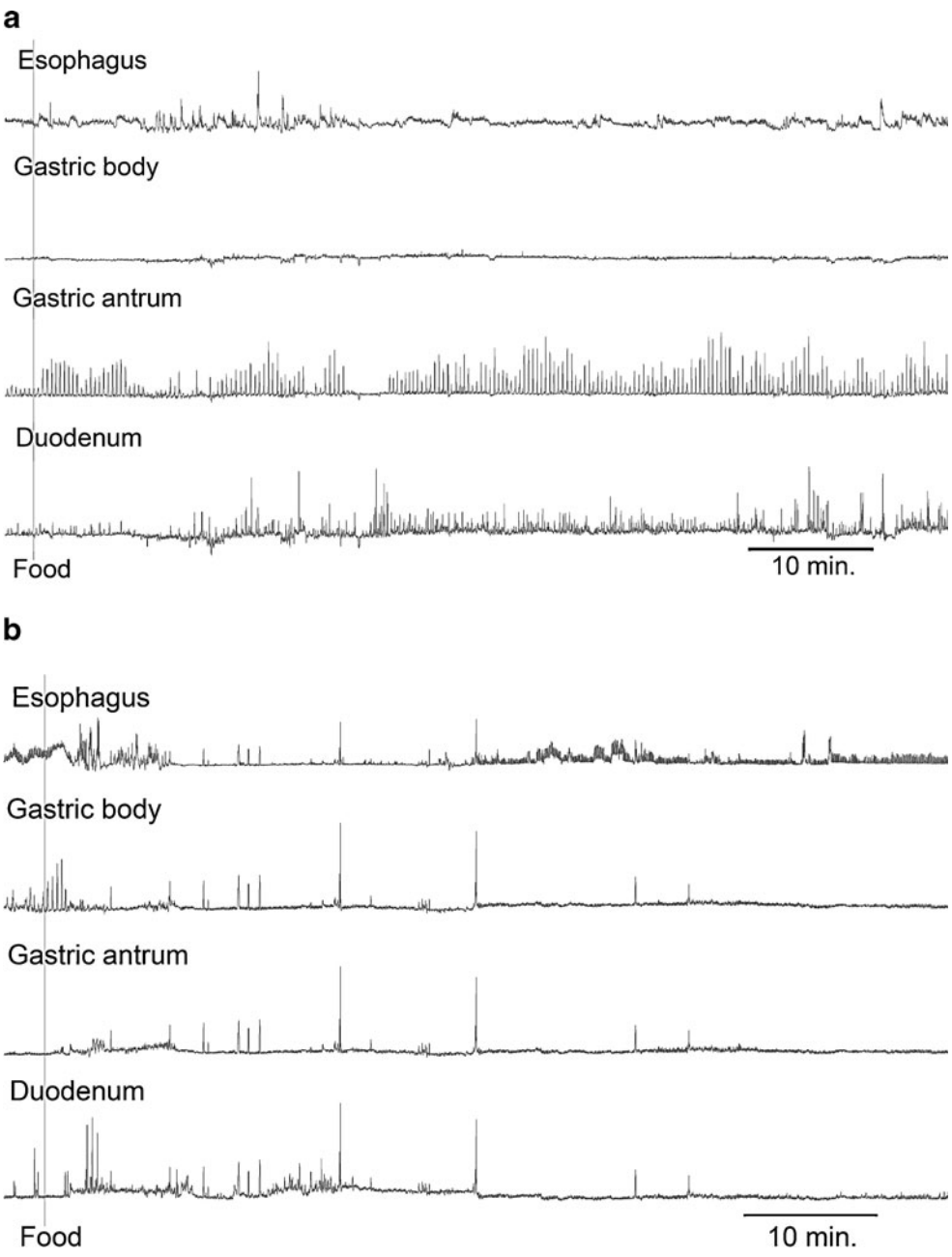

Fig. 6 Representative tracings of upper gut motility at postoperative day 8 in the fed state. The fed contractions in the mosapride group (**a**) were stronger than those in the control group (**b**) in the gastric antrum and duodenum

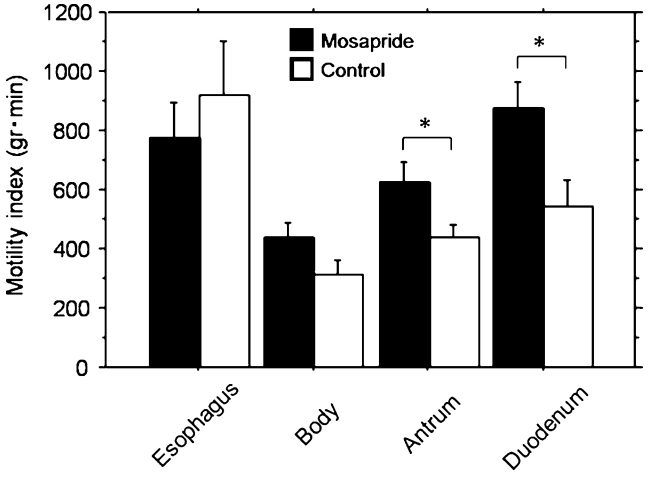

Fig. 7 The MI in the fed state in the mosapride group and the control group. *$P<0.05$

motility study in the fed state is in line with the results of the previous study. However, the effect of mosapride on fasted gastrointestinal motility has not been investigated sufficiently. TKS159 and CJ-033, a novel 5-HT4 agonist, increased the MI in the antrum in the fasted state in conscious dogs.[9,10] In addition, mosapride possesses the ability to bind to 5-HT4 receptors of the human stomach.[11] These results agree with our data in the fasted state. No study has reported that mosapride accelerates the appearance of phase III. We postulate that the antral and duodenal motor activities that were accelerated by mosapride might have enhanced the propulsion of the intraluminal contents and modulated the regularity of gastrointestinal motility, so that the appearance ratio of phase III in the mosapride group was higher than that in the control group.

In a previous report, gastric emptying concerned with antroduodenal motility.[12] Therefore, we speculate that antroduodenal motor activity accelerated by mosapride in the fed state may contribute to the acceleration of gastric emptying. Oral mosapride improves gastric emptying in patients with nonerosive gastroesophageal reflux disease[13] and in patients after colectomy.[14] These reports strongly support our speculation. Thus, improved gastric emptying seems to contribute to the increase of food intake postoperatively.

Mosapride had been considered to have no effect on the colonic motility of conscious dogs.[5] However, the 5-HT4 receptor has been reported to enhance the propulsion in the rat distal colon.[3] We hypothesize that the earlier appearance of the first flatus in the mosapride group resulted from colonic motor activity accelerated by mosapride because it was reported that mosapride enhanced the MI[2] and shortened the transit time in the guinea pig proximal colon.[4] Interestingly, the localization of the 5-HT4 receptor in the guinea pig colon is similar to that in the human colon.[6] These reports support our hypothesis.

The mechanism of defecation is composed of two reflexes, reflex contraction in the rectum and reflex relaxation in the internal anal sphincter.[15] Recently, mosapride has been reported to enhance these reflexes via 5-HT4 receptors,[7] strongly supporting our result that the time to the appearance of first defecation in the mosapride group was shorter than that in the control group.

In conclusion, oral mosapride shortens the time to the appearance of first flatus and first defecation and enhances food intake after colectomy. These results suggest that mosapride may enhance early recovery from postoperative ileus and may contribute to shorter hospital stays.

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ORIGINAL ARTICLE

Clinically Enlarged Lateral Pelvic Lymph Nodes Do Not Influence Prognosis after Neoadjuvant Therapy and TME in Stage III Rectal Cancer

Sekhar Dharmarajan · Dandan Shuai · Alyssa D. Fajardo · Elisa H. Birnbaum · Steven R. Hunt · Matthew G. Mutch · James W. Fleshman · Anne Y. Lin

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Abstract
Purpose The significance of lateral pelvic lymph nodes (LPLN) in rectal cancer remains unclear. The purpose of this study was to determine the outcome of patients with LPLNs identified on pretherapy imaging who were treated with neoadjuvant therapy followed by proctectomy without LPLN dissection.
Methods Pretherapy imaging of patients with stage III rectal cancer was reviewed to determine perirectal and LPLN enlargement. Data were collected on preoperative therapy, operative resection, adjuvant therapy, and patient outcomes and were correlated to the presence or absence of preoperatively identified LPLNs (LPLN+ and LPLN−).
Results Of the 53 patients identified who were treated between 2000 and 2005, 30 (57%) were LPLN+ on preoperative imaging. All patients received preoperative radiation therapy and total mesorectal excision. The local recurrence was 13%, and there was no difference related to LPLN status. A comparison of the overall and disease-free survival in patients with and without enlarged LPLNs revealed no difference.
Conclusions The LPLNs that were identified on pretherapy imaging do not affect the overall or disease-free survival after the neoadjuvant therapy and proctectomy in stage III rectal cancer. A lateral pelvic lymph node dissection does not appear to be justified in stage III patients with LPLNs on pretherapy imaging who receive neoadjuvant therapy.

Keywords Rectal cancer · Lateral pelvic lymph nodes · Preoperative radiotherapy · Total mesorectal excision

Introduction

Colorectal cancer is the third most prevalent cancer and the second leading cause of cancer deaths in the United States, with rectal cancer accounting for approximately one third of these cases.[1] Rectal cancer, particularly low rectal cancer (below the peritoneal reflection), is the cause of significant morbidity and mortality because of its increased rates of local recurrence owing to its anatomic location within the bony confines of the pelvis. A local recurrence of rectal cancer can be devastating, as it is often the source of significant pain and generally not amenable to treatment.

Recent advances in the treatment of rectal cancer have reduced local recurrence rates and, in some instances, improved overall survival. A total mesorectal excision (TME), first described by Heald, has become the gold standard for surgical therapy of rectal cancer and has been shown to dramatically lower local recurrence rates and also improve disease-free survival.[2–4] TME, however, does not remove lateral pelvic lymph nodes (LPLN) which may contain disease and be the source of local recurrence. Tumor-bearing LPLN are found in approximately 10–20% of patients with low rectal cancer.[5,6]

Different treatment strategies have evolved in Eastern and Western countries to reduce local recurrence rates of

S. Dharmarajan (✉) · A. D. Fajardo · E. H. Birnbaum · S. R. Hunt · M. G. Mutch · J. W. Fleshman · A. Y. Lin
Department of Surgery,
Washington University School of Medicine,
Campus Box 8109, 660 South Euclid Avenue,
St. Louis, MO, USA
e-mail: dharmarajans@wudosis.wustl.edu

D. Shuai
Department of Radiology,
Washington University School of Medicine,
St. Louis, MO, USA

rectal cancer due to tumor spread beyond the mesorectum. In the East, and Japan in particular, extended lymphadenectomy or LPLN dissection, is performed at the time of TME to remove potential tumor-bearing LPLNs. A number of reports have confirmed that the addition of LPLN dissection to TME can reduce local recurrence rates and improve overall survival.[7,8] LPLN dissection, however, is associated with a significant morbidity in terms of urinary and sexual dysfunction (50–75%).[9] In Western countries, neoadjuvant therapy, especially preoperative radiation therapy (RT), is most commonly employed in conjunction with TME to reduce local recurrence due to tumor spread beyond the mesorectum. This strategy has been well studied in large randomized trials and has also been shown to reduce local recurrence rates when combined with TME for the treatment of rectal cancer.[10–13] While neoadjuvant therapy is associated with less morbidity than LPLN dissection, the impact of preoperative radiation therapy on the subset of patients with involved LPLN has not been well studied. Specifically, it is unclear whether patients with involved LPLN who receive neoadjuvant therapy followed by TME have different outcomes than patients without involved LPLN. Recent reports have shown that pretherapy imaging using computed tomography (CT) and/or magnetic resonance imaging (MRI) of patients with rectal cancer can detect LPLN involvement with a high degree of accuracy.[14] The purpose of this study, therefore, was to determine the outcome of patients with enlarged LPLN identified on pretherapy imaging who were treated with neoadjuvant therapy followed by TME and compare these outcomes to patients without enlarged LPLN identified on pretherapy imaging. Our hypothesis is that neoadjuvant therapy followed by TME yields local recurrence and survival rates that are no different for patients with and without enlarged LPLN on pretherapy imaging.

Material and Methods

This study was conducted as an IRB-approved retrospective review performed on a prospectively maintained database of patients undergoing colorectal surgery at Washington University School of Medicine in St. Louis, MO. The database was queried for patients undergoing proctectomy for rectal cancer from July of 2000 through January of 2005. Only patients with clinical stage III rectal cancer as determined by transrectal ultrasound or pretherapy imaging (CT and/or MRI) were included in the study. Furthermore, patients that did not receive neoadjuvant radiation therapy were excluded from the study. Any patient that had evidence of distant metastases either during neoadjuvant treatment or at proctectomy were excluded from the study. Finally, for inclusion in the study, patients needed a pretherapy imaging study (CT with 5-mm thick sections or MRI) that was readily available for review.

All pretherapy imaging was independently reviewed by an experienced radiologist (D.S.) to determine the presence of LPLN enlargement. LPLN enlargement was defined as any lymph node greater than 5 mm in diameter in the lateral area, i.e., the iliac lymph node area outside of the mesorectum.[7,15] The lateral area was further subdivided into six regions as previously described in other reports.[7,16] The data were then collected on preoperative therapy, operative resection, postoperative therapy, and patient outcomes and were correlated to the presence or absence of LPLN enlargement on pretherapy imaging (Fig. 1). The primary endpoints of the study were local recurrence and overall and disease-free survival. Local recurrence was defined as any recurrence of rectal cancer in the pelvis diagnosed by clinical, radiographic, or histologic means.

A statistical analysis was performed using the GraphPad5 Prism software (San Diego, CA). Comparisons were made between two groups: those with enlargement of LPLN on pretherapy imaging (LPLN+) and those without (LPLN−). Continuous variables were compared using unpaired two-tailed t tests, and categorical variables were compared using Fisher's exact test. The survival was estimated using the Kaplan–Meier method with a log rank estimation used to assess differences in survival outcomes between groups. The statistical significance was set at $p<0.05$. The results are presented as mean ± standard deviation for quantitative variables and as percentages for categorical variables.

Results

Study Subjects

Fifty-three patients with clinical stage III rectal cancer treated between 2000 and 2005 who had pretherapy imaging available for review were identified. Of these, 30

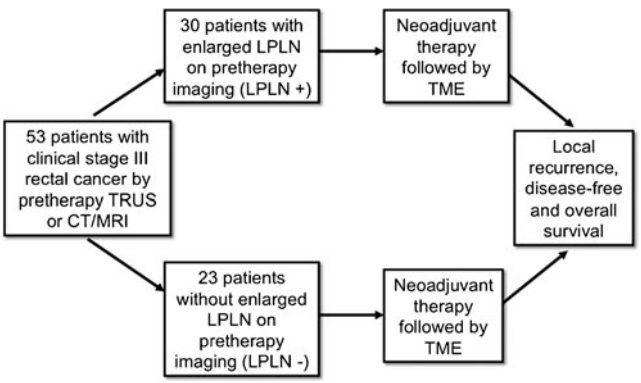

Fig. 1 Study design

patients (57%) had enlarged LPLN identified on pretherapy imaging (LPLN+) and 23 (43%) did not (LPLN−). A comparison of the demographic characteristics and details of preoperative therapy between the LPLN+ and LPLN− groups is presented in Table 1. The groups were evenly matched in terms of age, gender, preoperative CEA, and BMI. The mean distance of the tumor from the anal verge was <7 cm in both groups, indicating that the rectal cancers selected for the study were indeed low rectal cancers (below the peritoneal reflection) with potential for an LPLN spread. All patients received preoperative radiation therapy. Three patients (13%) in the LPLN− group and four patients (13.3%) in the LPLN+ group underwent a short course preoperative radiation therapy (2,000 Gy for 5 days). The remainder of the patients underwent long course radiation therapy with either 4,500 or 5,400 Gy of radiation delivered over 5.5 weeks. Radiation therapy portals included clinically enlarged LPLNs noted on pretherapy imaging. Twenty-three patients in the LPLN+ group (77%) and 11 patients in the LPLN− group (48%) received preoperative chemotherapy in conjunction with radiation (p=0.04). The majority of the patients received 5-fluorouracil (5-FU)-based therapy, with four patients receiving irinotecan or oxaliplatin in addition.

Operative and Pathologic Data

Table 2 shows the operative data regarding proctectomy and the final pathologic assessment for the rectal cancers included in the study. There was no difference in the rates of sphincter preservation, estimated blood loss, or complications between the two groups. Importantly, there was no operative mortality in this series and no patient died as an immediate result of a postoperative complication. Therefore, the survival data are unaffected by perioperative events.

On pathologic assessment, only one patient in the series (2%) had a complete pathologic response as defined by no evidence of tumor anywhere in the operative specimen (rectum or lymph nodes). Three patients in the LPLN+ and four patients in the LPLN− group had either no residual tumor or only a microscopic focus of tumor remaining in the rectum at the time of resection. Poor histologic features, tumor size, margins, and lymph node harvest and involvement were similar between the two groups. A pathologic downstaging occurred in 28.3% of all the patients and was not significantly different between the two groups. Finally, the majority of the patients in each group received adjuvant chemotherapy. Adjuvant therapy generally consisted of 5-FU, leucovorin and oxaliplatin, although some patients received irinotecan, bevacizumab, or erbitux.

LPLN Classification

Next, patients with enlarged LPLN on pretherapy imaging had the radiographic location of their lymph nodes classified into one of six regions according to the convention described by Ueno et al.[7] This classification is seen in Table 3. The external iliac and presacral nodal regions were the most common regions of involvement in patients with enlarged LPLN. The average radiographic diameter of the largest LPLN in the region was calculated to demonstrate pathologic enlargement in each of the LPLN nodal regions. There were no patients with internal pudendal lymph node enlargement in this series.

Outcomes

The rates of local recurrence, disease-free, and overall survival were compared for each group as shown in Table 4. The average length of follow-up was 3.1 years in the LPLN− group and 2.7 years in the LPLN+ group (median times, 3.1 and 2.8 years, respectively). Four patients had a local recurrence in the LPLN+ group and three patients in the LPLN− group for an overall recurrence rate of 13.2%. There was no significant difference between the groups in local recurrence, disease-free, or overall survival rates. While 5-year survival rates are presented, 1- and 2-year disease-free and overall survival rates were also calculated and these did not differ significantly between the two groups. The Kaplan–Meier survival curves for the two groups depicting this data graphically are presented in Fig. 2.

Table 1 Demographic characteristics and preoperative therapy in LPLN+ and LPLN− groups

	LPLN+ (n=30)	LPLN− (n=23)	p value
Age	59.6±16.7	64.1±16.0	0.32
Gender (% male)	70%	56.5%	0.47
BMI	26.6±3.7	25.8±7.0	0.63
Percent with fixed tumor	36.7%	39.1%	0.85
Distance from anal verge	6.9±3.2	6.6±4.1	0.75
Preoperative CEA	6.8±9.9	7.3±19.7	0.92
Percent receiving preoperative chemotherapy	76.7%	59.4%	0.04
Average radiation dose (Gy)	4,295±1,034	4,295±1,060	1.0

CEA carcinoembryonic antigen, *BMI* body mass index

Table 2 Operative and pathologic data for LPLN+ and LPLN− groups

	LPLN+ (n=30)	LPLN− (n=23)	p value
Operation			
Sphincter sacrificing (end stoma)	7 (23.3%)	11 (47.8%)	0.08
Sphincter preserving	23 (76.7%)	12 (52.2%)	
Lap assisted	9 (30%)	6 (26.1%)	1.0
EBL (ml)	438±305	398±371	0.68
LOS (days)	8.7±3.4	8.6±4.0	0.96
Percent with complications	46.7%	39.1%	0.79
Complete or near complete tumor downstaging	3 (10%)	4 (17.4%)	0.92
Histologic features			
Poorly differentiated/mucinous or signet ring histology	7 (23.3%)	6 (26.1%)	1.0
Tumor diameter (cm)	2.9±1.6	2.7±1.5	0.69
Tumor thickness (cm)	1.22±0.8	1.09±0.6	0.55
Distal margin (cm)	2.9±1.8	3.0±2.1	0.94
Radial margin (cm)	0.81±0.6	0.81±0.9	1.0
Lymphatic invasion	12 (40%)	4 (17.4%)	0.14
Venous invasion	2 (6.7%)	3 (13.0%)	0.75
No. of LNs harvested	12±7.3	11.5±4.9	0.79
No. of LNs positive	2.6±3.4	2.1±2.7	0.56
Pathologic T stage			
ypTx	3	4	0.20
ypT2	2	1	
ypT3	23	15	
ypT4	2	3	
Pathologic N stage			
ypN0	9	6	0.94
ypN1	13	11	
ypN2	8	6	
Percent receiving adjuvant therapy	86.7%	78.3%	0.66

EBL estimated blood loss, *LOS* length of stay, *LNs* lymph nodes

Discussion

Lateral pelvic lymph nodes may be involved in up to 10–20% of lower rectal cancers.[5,6] LPLN are not removed by total mesorectal excision and can be the source of local pelvic recurrence that causes significant morbidity. Different treatment philosophies have evolved to reduce local recurrence from potentially involved LPLN in rectal cancer.[17] In Japan, an extended lymphadenectomy or LPLN dissection, is added to TME in an effort to remove the LPLN that may potentially be involved. While studies have shown this strategy to be effective in reducing the local recurrence in certain subsets of patients with advanced rectal cancer, it is associated with significant morbidity in

Table 3 Classification of LPLN according to location in patients with enlargement of LPLN noted on pretherapy imaging

Lateral pelvic nodal region	No. of patients having nodal enlargement (%)	Average diameter of largest enlarged LN in region (mm)
External iliac	16 (53.3%)	10.7±2.8
Presacral	16 (53.3%)	9.6±4.9
Internal iliac	7 (23.3%)	12.3±6.8
Common iliac	6 (20%)	8.1±1.9
Obturator	1 (3.3%)	14.0
Internal pudendal	0	–

Table 4 Local recurrence, disease-free, and overall survival in LPLN+ and LPLN− groups

	LPLN+ (n=30)	LPLN− (n=23)	p value
Local recurrence	13%	13%	0.73
5-year overall survival	54%	51%	0.64
5-year disease-free survival	42%	43%	0.73

terms of urinary and sexual dysfunction. Therefore, in the West, neoadjuvant radiotherapy is employed prior to TME to sterilize the pelvis and reduce local recurrence after surgery. Well-conducted studies have shown this to also be an effective strategy in preventing the recurrence of rectal cancer while incurring lower morbidity than LPLN dissection. However, the effect of neoadjuvant radiation on patients with involved LPLN has not been well studied. Therefore, the objective of this study was to compare the outcomes of rectal cancer patients with and without involved LPLN based on pretherapy imaging who were treated with neoadjuvant radiation followed by TME. The key finding of this study is that there is no difference in local recurrence or survival in patients with and without involved LPLN on pretherapy imaging when treated with neoadjuvant radiation and TME. This would suggest that neoadjuvant radiation effectively sterilizes the pelvis and obviates the need for extended lymphadenectomy or LPLN dissection in patients with advanced stage rectal cancer.

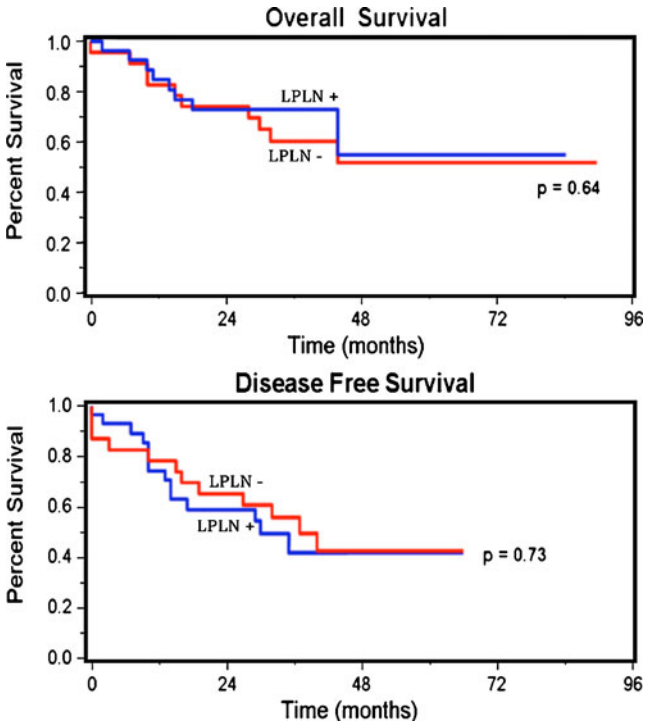

Fig. 2 Kaplan–Meier survival estimates for disease-free and overall survival in LPLN+ and LPLN− groups

The results of this study extend the findings of previous studies published in the literature. Initial studies from Japan indicated an improved survival in patients undergoing LPLN dissection in addition to TME in the treatment of low rectal cancer.[7,8] It is difficult to compare the outcomes in these studies to the Western experience because none of the patients in the Japanese studies received preoperative radiation therapy. Therefore, comparative studies were undertaken of the preoperative radiotherapy followed by TME versus TME with lateral pelvic lymph node dissection in the treatment of rectal cancer. Watanabe, in a retrospective study of 115 patients, found no significant difference in the overall survival, disease-free survival, and local recurrence between patients who received preoperative radiotherapy without LPLN dissection and patients who underwent LPLN dissection.[18] Nagawa et al. then conducted a prospective, randomized controlled trial of TME with or without LPLN dissection in 51 patients who received preoperative radiotherapy.[19] There was no difference between the groups in terms of overall or disease-free survival or local recurrence, but substantially increased urinary and sexual dysfunction in the group undergoing LPLN dissection. A related study by Kim compared postoperative chemoradiation versus LPLN dissection following TME in 485 rectal cancer patients.[20] Again, there was no difference in overall or disease-free survival between the two groups, and the local recurrence rate was 2.2-fold greater in the group undergoing LPLN dissection. Finally, Kusters et al. recently compared the Dutch experience with the preoperative RT + TME in 379 patients with 324 Japanese patients who received TME + LPLN dissection alone.[21] There was no difference between disease-free survival and local recurrence between the two groups. Taken in aggregate, these studies suggest that LPLN dissection does not confer additional benefit in terms of overall survival, disease-free survival, or local recurrence rates when patients with rectal cancer are treated with preoperative RT and TME. Our study confirms these findings as overall survival, disease-free survival, and local recurrence did not differ between patients with and without enlarged LPLNs on pretherapy imaging when all patients are treated with preoperative RT and TME. Furthermore, our study indicates that patients treated with RT and TME can avoid the increased morbidity associated with LPLN dissection (urinary and sexual dysfunction) without adverse effect on local recurrence and survival. The distinguishing feature of our study is the use of pretherapy imaging to identify patients with enlarged LPLNs, enabling us to examine the effect of preoperative RT on patients with enlarged LPLNs. Furthermore, our study, to the best of our knowledge, is the first Western

single institution review to study the effect of preoperative RT on enlarged LPLNs.

The primary limitations of this study are its retrospective nature and the number of patients studied, as it is likely underpowered to detect small differences in survival and local recurrence between the LPLN+ and LPLN− groups. However, the fact that survival and local recurrence are nearly identical in the two groups suggests that the effect of enlarged LPLN on survival after neoadjuvant radiation and TME for rectal cancer is minimal. The requirement for having a CT available for review limited the number of patients that could be included in the study as our practice environment is a tertiary institution and most patients have their imaging performed elsewhere. A significantly higher percentage of patients in the LPLN+ group received neoadjuvant chemotherapy in addition to radiation when compared to the LPLN− group (77% vs. 59%, respectively). This may have increased survival in the LPLN+ group and masked a difference in the survival curves or local recurrence. During the time period of this study (2000–2005), preoperative chemotherapy was not routinely administered in addition to radiation therapy for patients with locally advanced rectal cancer as it is currently. Finally, none of the patients underwent a lateral pelvic lymph node dissection and therefore the true denominator of patients with lateral lymph node metastases is unknown. In our study, we used radiologic enlargement of LPLNs as a surrogate marker for LPLN metastases. There is good evidence that pretherapy imaging can predict with great accuracy the presence of LPLN metastases. Certainly, however, false positives in the LPLN+ group or false negatives in the LPLN− group could have masked differences between the two groups in terms of survival and local recurrence. One issue that our study did not address is the response of enlarged LPLNs on pretherapy imaging to preoperative RT. Patients with persistently enlarged LPLNs after preoperative RT may have survival and recurrence rates different from patients whose LPLNs respond to neoadjuvant treatment. The response of enlarged LPLNs to preoperative RT could be examined on posttherapy imaging, with selective lymphadenectomy performed for persistently enlarged LNs. Our study did not address this issue, and this offers a topic for further investigation.

Conclusion

There is no difference in local recurrence or survival rates in patients with and without enlarged LPLNs on pretherapy imaging treated with preoperative RT and TME. This suggests that patients with locally advanced rectal cancer with enlarged LPLNs can avoid the sexual and urinary morbidity associated with LPLN dissection without incurring increased local recurrence or reduced survival rates when they are treated with preoperative RT and TME.

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ORIGINAL ARTICLE

A Meta-analysis of the Short- and Long-Term Results of Randomized Controlled Trials That Compared Laparoscopy-Assisted and Conventional Open Surgery for Rectal Cancer

Hiroshi Ohtani · Yutaka Tamamori · Takashi Azuma · Yoshihiro Mori · Yukio Nishiguchi · Kiyoshi Maeda · Kosei Hirakawa

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Abstract
Purpose We conducted a meta-analysis to evaluate and compare the short- and long-term results of laparoscopy-assisted and open rectal surgery for the treatment of patients with rectal cancer.
Methods We searched MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register for relevant papers published between January 1990 and April 2011 by using the search terms "laparoscopy," "laparoscopy assisted," "surgery," "rectal cancer," and "randomized controlled trials." We analyzed outcomes over short- and long-term periods.
Results We identified 12 papers reporting results from randomized controlled trials that compared laparoscopic surgery with open surgery for rectal cancer. Our meta-analysis included 2,095 patients with rectal cancer; 1,096 had undergone laparoscopic surgery, and 999 had undergone open surgery. In the short-term period, 13 outcome variables were examined. In the long-term period, eight oncologic variables, as well as late morbidity, urinary function, and sexual function were analyzed. Laparoscopic surgery for rectal cancer was associated with a reduction in intraoperative blood loss and the number of transfused patients, earlier resumption of oral intake, and a shorter duration of hospital stay over the short-term, but with similar short-term and long-term oncologic outcomes compared to conventional open surgery.
Conclusions Laparoscopic surgery may be an acceptable alternative treatment option to conventional open surgery for rectal cancer.

Keywords Meta-analysis · Laparoscopy-assisted rectal surgery · Rectal cancer

H. Ohtani (✉) · Y. Tamamori · T. Azuma · Y. Mori
Department of Surgery, Osaka City Sumiyoshi Hospital,
1-2-16, Higashi-Kagaya, Suminoe-ku,
Osaka 559–0012, Japan
e-mail: m5051923@msic.med.osaka-cu.ac.jp

Y. Nishiguchi
Department of Surgery, Osaka City General Hospital,
Osaka, Japan

K. Maeda · K. Hirakawa
Department of Surgical Oncology,
Osaka City University Graduate School of Medicine,
Osaka, Japan

Introduction

Laparoscopic surgery for rectal cancer has been reported to achieve superior short-term outcomes, including earlier postoperative recovery, less postoperative morbidity,[1,2] and better quality of life,[3] compared with conventional open surgery for rectal cancer. The use of laparoscopic surgery for rectal cancer has recently become more widespread, and several articles have described long-term outcomes associated with the procedure.[4–9] However, the curability of rectal cancer using laparoscopic surgery is controversial because the long-term oncologic outcomes of laparoscopic surgery, such as overall mortality, cancer-related mortality, and recurrence rate, remain uncertain. Laparoscopic surgery for rectal cancer is a technically demanding procedure because the surgical space

of the rectum is a narrow pelvic cavity surrounded by solid bones, which prevents the manipulation of laparoscopic instruments.

A radical excision of rectal cancers includes high ligation of the inferior mesenteric artery for adequate lymphatic clearance and total mesorectal excision. It is difficult to assess the quality of total mesorectal excision in rectal cancer surgery; however, the rates of circumferential resection margin and distal resection margin involvement are the best direct measure of total mesorectal excision.[10] The conventional versus laparoscopic-assisted surgery in colorectal cancer (CLASICC) trial reported the importance of the circumferential resection margin.[8] The study showed that a conversion to an open from a laparoscopic surgery was associated with a significantly worse overall, but not disease-free, survival. To accurately evaluate the efficacy of laparoscopic surgery for rectal cancer, the short- and long-term outcomes of laparoscopic surgery must be compared to those of open surgery. For short-term outcomes, perioperative variables, pathologic factors, and the cost of surgery should be examined. For long-term outcomes, long-term oncologic results are the primary endpoint of interest, followed by late morbidity and quality of life. Recently, several randomized controlled trials comparing laparoscopic surgery with open surgery for rectal cancer have been published.[11–18] We conducted a meta-analysis of the data from these randomized controlled trials to compare the short- and long-term outcomes of laparoscopic and open surgery for rectal cancer.

Materials and Methods

Literature Search

To identify papers relevant to our study, we searched the major medical databases MEDLINE, EMBASE, Science Citation Index, and the Cochrane Controlled Trial Register for studies published between January 1990 and April 2011. The following search terms were used: "laparoscopy," "laparoscopy assisted," "surgery," "rectal cancer," and "randomized controlled trials." We treated studies that were part of a series as a single study.[7–9,11,19,20] Appropriate data from such study series were used for this meta-analysis. This meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses statement[21] (Fig. 1).

Inclusion Criteria

To enter this meta-analysis, studies had to: (1) be described in English, (2) be a randomized controlled trial, (3) compare laparoscopic and open conventional surgery for rectal cancer, and (4) report on at least one of the outcome measures mentioned below.

Exclusion Criteria

Studies were excluded from this analysis if (1) the outcomes of interest were not reported for the two surgical techniques and if (2) they reported on rectal surgery for benign lesions.

Data Extraction

Three researchers (H.O., Y.T., and K.H.) extracted data from each article by using a structured sheet and entered the data into a database. Because this analysis was performed on the principle of intention-to-treat,[22] all patients converted from the laparoscopic group to the open group remained in the laparoscopic group for analysis. We conducted separate meta-analyses for two different post-operative time periods: short-term and long-term. For the short-term analysis, we collected data on operation time, estimated blood loss, number of transfused patients, number of dissected lymph nodes, hospital stay, time to oral diet, period of parenteral analgesic administration, overall complications, anastomotic leakage, perioperative mortality, circumferential resection margin, distal resection margin, and cost of surgery. The cost of surgery consisted of operating and hospitalization costs. We also examined the relationship between the conversion rate from laparoscopic to open surgery and

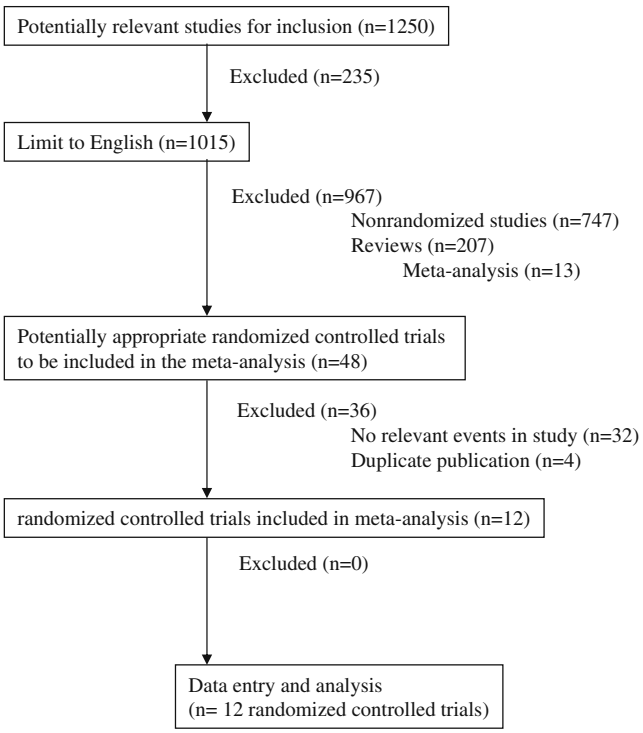


Fig. 1 Flow diagram of this meta-analysis in accordance with the QUOROM statement

Table 1 Characteristics of the randomized clinical trials

Authors	Year	Number of reference	Country	The type of institution	Study size (*n*)		Conversion rate (%)	Follow-up period (months)	Randomization	Double blinding	Withdraws and dropouts	Jadad's score
					LR	OR						
Araujo et al.	2003	[4]	Brazil	Single institution	13	15	U	47.2 (mean)	1	0	1	2
Baik et al.	2011	[5]	United States of America	Single institution	54	108	11 (6/54)	59 (median)	1	0	1	2
Braga at al.	2007	[6]	Italy	Single institution	83	85	7.2 (6/83)	53.6 (mean) 54.2 (median)	2	0	1	3
CLASICC	2010 2007 2005	[8] [7] [11]	United Kingdom	Multicenter (27 centers)	253	128	34 (82/242)	56.3 (median)	2	2	1	5
Gonzalez et al.	2006	[12]	Spain	Single institution	20	20	10 (2/20)	U	1	0	1	2
Kan et al.	2010	[3]	Korea	Multicenter (3 centers)	170	170	1.2 (2/170)	U (short-term)	2	2	1	5
Lujan et al.	2009	[13]	Spain	Single institution	101	103	7.9 (8/101)	32.8±18.9 (laparoscopic surgery) (mean) 34.1±20.0 (open surgery) (mean)	2	2	1	5
Ng (low) et al.	2008	[14]	China	Single institution	51	48	9.8 (5/51)	87.2 (laparoscopic surgery) (median) 90.1 (open surgery) (median)	2	2	1	5
Ng (upper) et al.	2009	[15]	China	Single institution	76	77	30.3 (23/76)	112.5 (laparoscopic surgery) (median) 108.8 (open surgery) (median)	1	0	1	2
Park et al.	2009	[16]	Korea	Single institution	107	72	0 (0/170)	36 months (mean)	1	0	1	2
Quah et al.	2002	[17]	Singapore	Single institution	86	84	12 (10/86)	U	2	0	1	3
Zhou et al.	2004	[18]	China	Single institution	82	89	U	1–16 months	1	0	1	2

U unknown

single-institution versus multicenter trials. For the oncologic results in the long-term analysis, we used data on the rate of overall recurrence, local recurrence, distant metastasis, wound site recurrence, cancer-related mortality, overall mortality, and disease-free survival at 3 and 5 years after surgery. For late morbidity in the long-term analysis, we used data on the rate of overall late morbidity, ileus, and incisional hernia. For quality of life in the long-term analysis, we used data on urinary and sexual dysfunction. Where necessary, we contacted the authors of the original papers to receive further information.

Assessment of Study Quality

The quality of the randomized controlled trials was assessed using Jadad's scoring system.[23] Two reviewers (H.O., Y.T.) assessed all studies that met the inclusion criteria (Table 1).

Statistical Analysis

Weighted mean differences and odds ratios were used for the analysis of continuous and dichotomous variables, respectively. Random effects models were used to identify heterogeneity between the studies,[24] and the degree of heterogeneity was assessed using the chi-square test. For the analysis of the conversion rate, the chi-square test was used. The confidence interval (CI) was established at 95%, and p values of less than 0.05 were considered to indicate statistical significance. As the cost data of one article[19] were precious and had neither a range nor any other measure of dispersion, the standard deviation was estimated by halving the mean.[25] One Euro and British pound were converted to US $1.4 and US $1.6, respectively. The statistical analyses were performed using the Review Manager (RevMan) software, version 5.1.1, provided by the Cochrane Collaboration, Copenhagen, Denmark.

Results

We identified 12 papers reporting results of randomized controlled trials that compared laparoscopic and open surgery for rectal cancer.[3–18] The characteristics of each randomized controlled trial are presented in Table 1. Our meta-analysis included 2,095 patients with rectal cancer; of these, 1,096 had undergone laparoscopic surgery, and 999 had undergone conventional open surgery. Short-term and long-term results are shown in Figs. 2 and 3, respectively. Late morbidity rate, urinary dysfunction, and sexual dysfunction are shown in Fig. 4.

Short-Term Outcomes

The operative time for laparoscopic surgery was significantly greater, by 40.96 min, than that for open surgery (weighted mean difference=40.96; 95% CI=25.53–56.38; $p<0.00001$). The intraoperative blood loss and the number of transfused patients in the laparoscopic group were significantly lower than in the open group. There was no significant difference in the number of harvested lymph nodes. The duration of hospital stay and the time to oral diet were significantly shorter with laparoscopic surgery than open surgery ($p=0.0001$ and 0.02, respectively). There was no significant difference in the period of parenteral analgesic administration. Overall complications and anastomotic leakage did not differ significantly between the two groups. We found no significant difference between patients who underwent laparoscopic surgery and those who underwent conventional open surgery for perioperative mortality.

Positive Circumferential Resection Margin

Seven articles reported data on the circumferential resection margin. Five of these compared data between laparoscopic and open groups. All five articles reported that there was no significant difference in the positive circumferential resection margin between the two groups. In an analysis of pooled data, we found that there was no significant difference in the positive circumferential resection margin between the two groups. There was no significant difference in the distal resection margin.

Cost of Surgery

In an analysis of the cost of surgery, there was no significant difference between the two groups. The cost of open surgery was similar among the three articles that assessed open surgery cost.

Conversion Rate

Ten articles reported data on the conversion rate from laparoscopic to open surgery, which ranged from 0% to 34% (Table 1). In an analysis of the conversion rate, there was no significant difference between the trials performed by a single institution and those performed on a multicenter basis ($p=0.51$).

Long-Term Outcomes

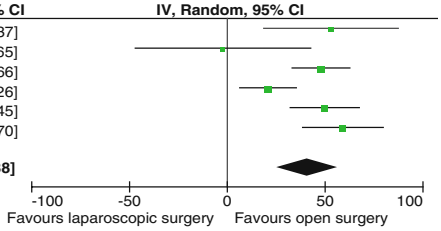
First, oncologic results of the long-term period were examined. Second, long-term morbidity and quality of life were evaluated.

Fig. 2 Meta-analysis of the short-term period for rectal cancer ▶

Operation time

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Braga et al.	262	72	83	209	70	20	11.4%	53.00 [18.63, 87.37]
Gonzalez et al.	236.3	51.9	20	238.5	88.2	20	8.2%	-2.20 [-47.05, 42.65]
Kan et al.	244.9	75.4	170	197	62.9	170	21.3%	47.90 [33.14, 62.66]
Lujan et al.	193.7	45.1	101	172.9	59.4	103	21.5%	20.80 [6.34, 35.26]
Ng (low) et al.	213.5	46.2	51	163.7	43.4	48	19.6%	49.80 [32.15, 67.45]
Ng (upper) et al.	213.1	59.3	76	154	70.3	77	18.0%	59.10 [38.50, 79.70]
Total (95% CI)			**501**			**438**	**100.0%**	**40.96 [25.53, 56.38]**

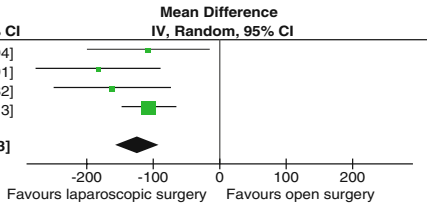
Heterogeneity: Tau² = 234.06; Chi² = 16.29, df = 5 (P = 0.006); I² = 69%
Test for overall effect: Z = 5.20 (P < 0.00001)



Blood loss

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baik et al.	313.2	260.9	54	420.6	314.7	108	12.9%	-107.40 [-198.86, -15.94]
Braga et al.	213	236	83	396	367	85	12.5%	-183.00 [-276.09, -89.91]
Gonzalez et al.	243.4	129.6	20	405	151.2	20	14.1%	-161.60 [-248.88, -74.32]
Lujan et al.	127.8	113.3	101	234.2	174.3	103	60.5%	-106.40 [-146.67, -66.13]
Total (95% CI)			**258**			**316**	**100.0%**	**-123.87 [-157.10, -90.63]**

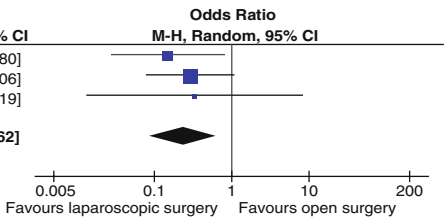
Heterogeneity: Tau² = 52.99; Chi² = 3.11, df = 3 (P = 0.37); I² = 4%
Test for overall effect: Z = 7.30 (P < 0.00001)



Number of transfused patients

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	3	13	10	15	34.0%	0.15 [0.03, 0.80]
Gonzalez et al.	7	20	13	20	56.7%	0.29 [0.08, 1.06]
Kan et al.	0	170	1	170	9.3%	0.33 [0.01, 8.19]
Total (95% CI)		**203**		**205**	**100.0%**	**0.23 [0.09, 0.62]**
Total events	10		24			

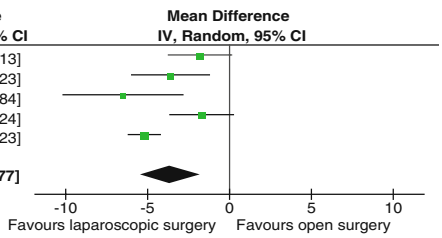
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.90 (P = 0.004)



Hospital stay

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baik et al.	7	3.8	54	8.8	8.7	108	21.2%	-1.80 [-3.73, 0.13]
Braga et al.	10	4.9	83	13.6	10	85	18.9%	-3.60 [-5.97, -1.23]
Gonzalez et al.	9.1	5.7	20	15.6	6.1	20	13.2%	-6.50 [-10.16, -2.84]
Lujan et al.	8.2	7.3	101	9.9	6.8	103	21.1%	-1.70 [-3.64, 0.24]
Zhou et al.	8.1	3.1	82	13.3	3.4	89	25.6%	-5.20 [-6.17, -4.23]
Total (95% CI)			**340**			**405**	**100.0%**	**-3.61 [-5.45, -1.77]**

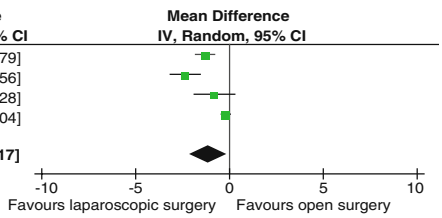
Heterogeneity: Tau² = 3.21; Chi² = 18.08, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 3.84 (P = 0.0001)



Time to oral diet

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Braga et al.	3.7	1.3	83	5	2	85	26.6%	-1.30 [-1.81, -0.79]
Gonzalez et al.	2.25	0.97	20	4.61	1.54	20	24.0%	-2.36 [-3.16, -1.56]
Lujan et al.	2.8	4.4	101	3.6	3.4	103	21.2%	-0.80 [-1.88, 0.28]
Zhou et al.	3.5	0.8	82	3.7	0.8	89	28.2%	-0.20 [-0.44, 0.04]
Total (95% CI)			**286**			**297**	**100.0%**	**-1.14 [-2.11, -0.17]**

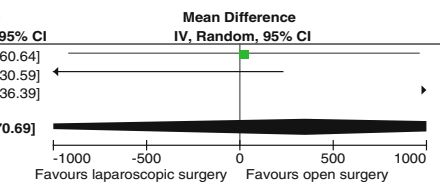
Heterogeneity: Tau² = 0.86; Chi² = 36.50, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.29 (P = 0.02)



Costs for surgery

Study or Subgroup	laparoscopic surgery Mean	SD	Total	open surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CLASICC	8,279.5	4,139.7	222	8,257.6	4,128.8	112	34.3%	21.90 [-916.84, 960.64]
Gonzalez et al.	5,828.2	1,757.1	20	7,153	3,083.5	20	30.0%	-1324.80 [-2880.19, 230.59]
Ng (low) et al.	9,588	1,683	51	7,517	1,693	48	35.7%	2071.00 [1405.61, 2736.39]
Total (95% CI)			**293**			**180**	**100.0%**	**350.23 [-1570.23, 2270.69]**

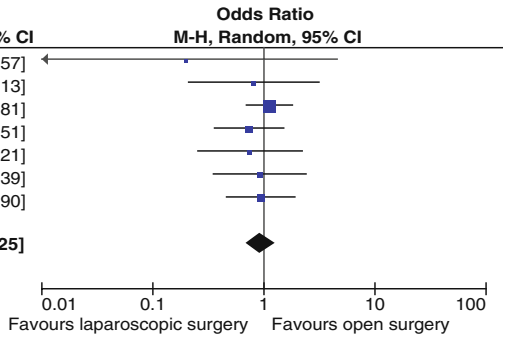
Heterogeneity: Tau² = 2571595.80; Chi² = 22.58, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 0.36 (P = 0.72)



Overall recurrence

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	2	15	0.9%	0.20 [0.01, 4.57]
Braga et al.	4	83	5	85	5.0%	0.81 [0.21, 3.13]
CLASICC	73	253	34	128	40.2%	1.12 [0.70, 1.81]
Lujan et al.	16	101	21	103	17.8%	0.74 [0.36, 1.51]
Ng (low) et al.	8	40	9	36	7.8%	0.75 [0.25, 2.21]
Ng (upper) et al.	9	59	11	67	9.9%	0.92 [0.35, 2.39]
Park et al.	24	107	17	72	18.2%	0.94 [0.46, 1.90]
Total (95% CI)		**656**		**506**	**100.0%**	**0.93 [0.68, 1.25]**
Total events	134		99			

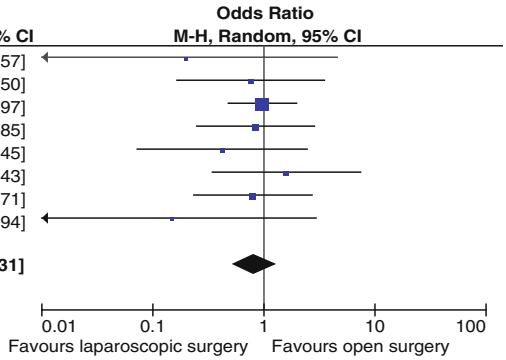
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 6 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.61)



Local recurrence

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	2	15	2.2%	0.20 [0.01, 4.57]
Braga et al.	3	83	4	85	9.1%	0.76 [0.16, 3.50]
CLASICC	25	253	13	128	42.4%	0.97 [0.48, 1.97]
Lujan et al.	5	101	6	103	14.2%	0.84 [0.25, 2.85]
Ng (low) et al.	2	40	4	36	6.8%	0.42 [0.07, 2.45]
Ng (upper) et al.	4	60	3	70	8.9%	1.60 [0.34, 7.43]
Park et al.	6	107	5	72	14.1%	0.80 [0.23, 2.71]
Zhou et al.	0	82	3	89	2.4%	0.15 [0.01, 2.94]
Total (95% CI)		**739**		**598**	**100.0%**	**0.83 [0.52, 1.31]**
Total events	45		40			

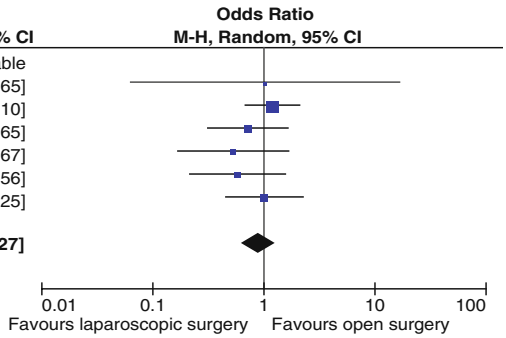
Heterogeneity: Tau² = 0.00; Chi² = 3.56, df = 7 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



Distant metastasis

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	0	15		Not estimable
Braga et al.	1	83	1	85	1.6%	1.02 [0.06, 16.65]
CLASICC	48	253	21	128	39.1%	1.19 [0.68, 2.10]
Lujan et al.	11	101	15	103	17.9%	0.72 [0.31, 1.65]
Ng (low) et al.	6	40	9	36	9.4%	0.53 [0.17, 1.67]
Ng (upper) et al.	7	60	13	70	12.6%	0.58 [0.21, 1.56]
Park et al.	18	107	12	72	19.4%	1.01 [0.45, 2.25]
Total (95% CI)		**657**		**509**	**100.0%**	**0.89 [0.63, 1.27]**
Total events	91		71			

Heterogeneity: Tau² = 0.00; Chi² = 2.91, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)



Wound-site recurrence

Study or Subgroup	laparoscopic surgery Events	Total	open surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Araujo et al.	0	13	0	15		Not estimable
Baik et al.	0	54	0	108		Not estimable
Lujan et al.	0	101	0	103		Not estimable
Ng (low) et al.	0	40	1	36	48.3%	0.29 [0.01, 7.40]
Ng (upper) et al.	0	60	0	70		Not estimable
Zhou et al.	2	82	0	89	51.7%	5.56 [0.26, 117.53]
Total (95% CI)		**350**		**421**	**100.0%**	**1.34 [0.07, 24.10]**
Total events	2		1			

Heterogeneity: Tau² = 1.78; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.20 (P = 0.84)

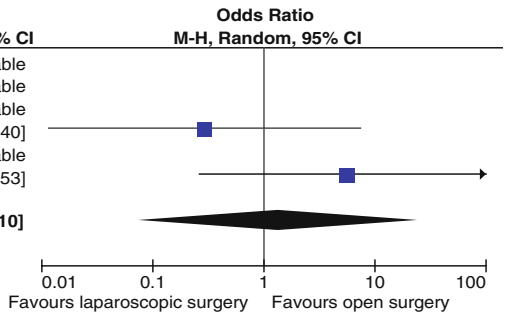
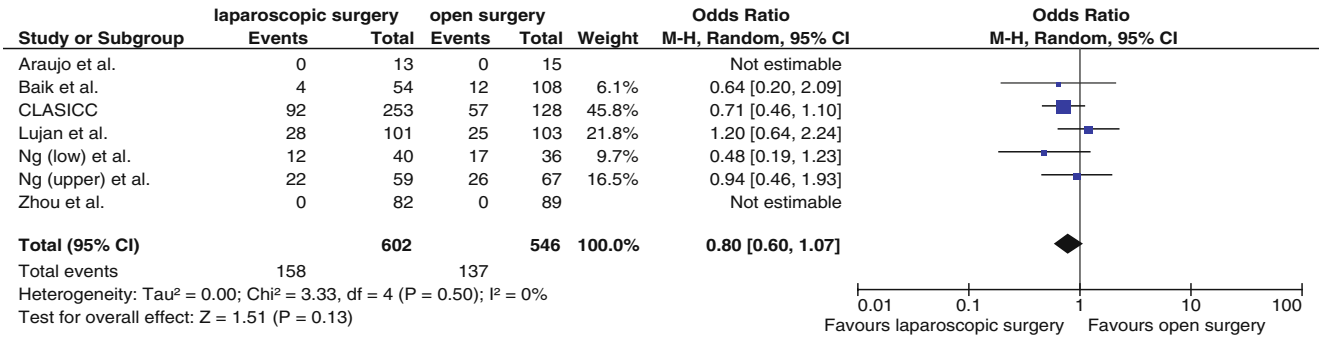
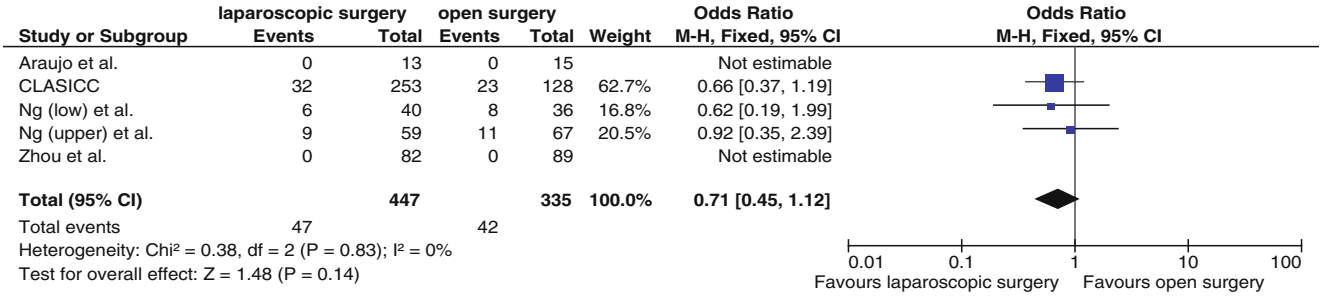


Fig. 3 Meta-analysis of the long-term oncologic results for rectal cancer

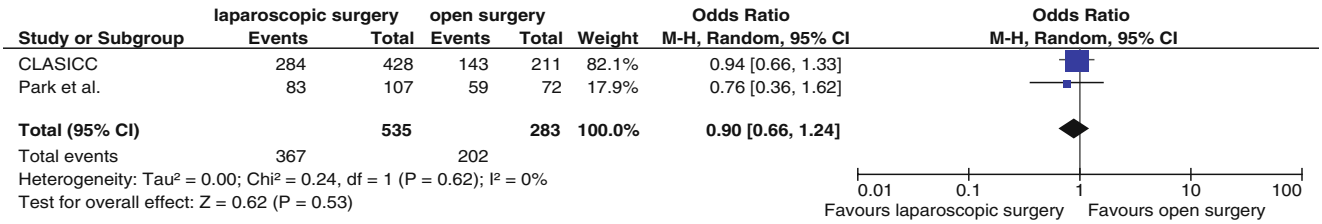
Overall mortality



Cancer-related mortality



Disease-free survival at 3 years after surgery



Disease-free survival at 5 years after surgery

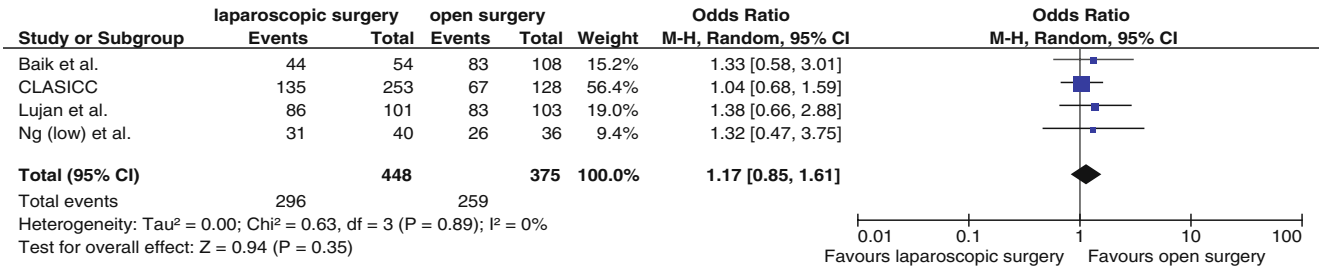
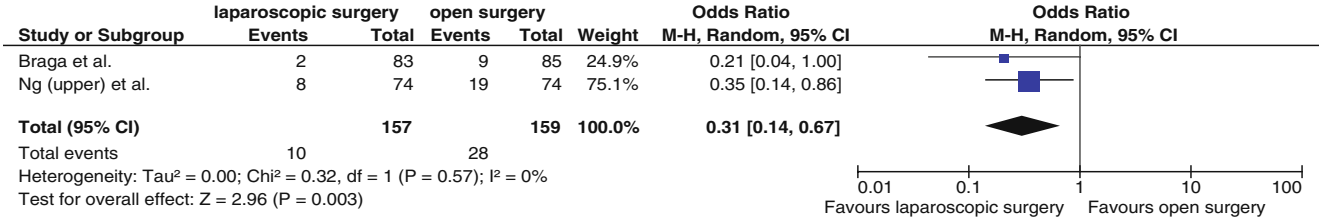


Fig. 3 (continued)

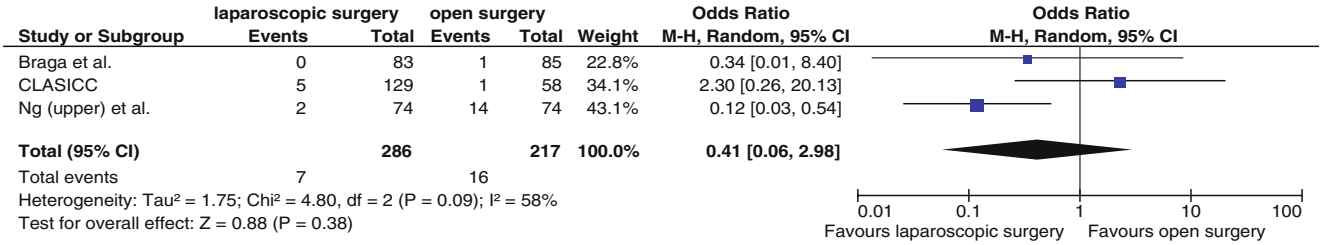
Tumor Recurrence

Eight, eight, and seven articles reported data on overall recurrence, local recurrence, and distant metastasis, respectively. Four, five, and four articles, respectively, compared these variables between laparoscopic and open surgery groups; none reported any significant difference. In an analysis of the pooled data, we found no significant difference in the overall recurrence, local recurrence, and distant metastasis between patients who underwent laparoscopic surgery and those who underwent open surgery. Further, no significant difference was found for wound site recurrence using the pooled data.

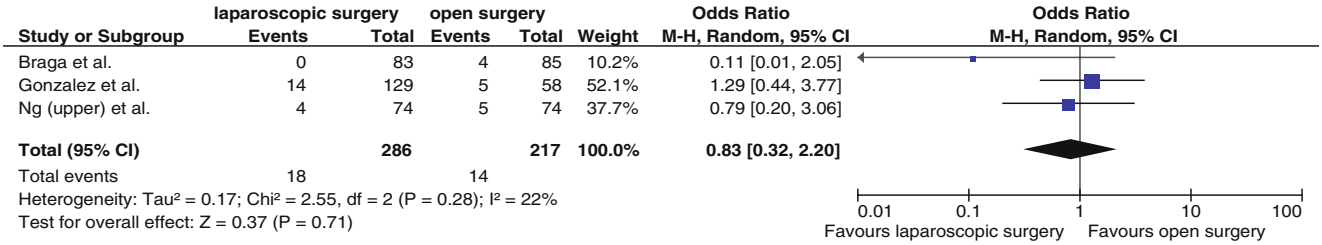
Overall late morbidity



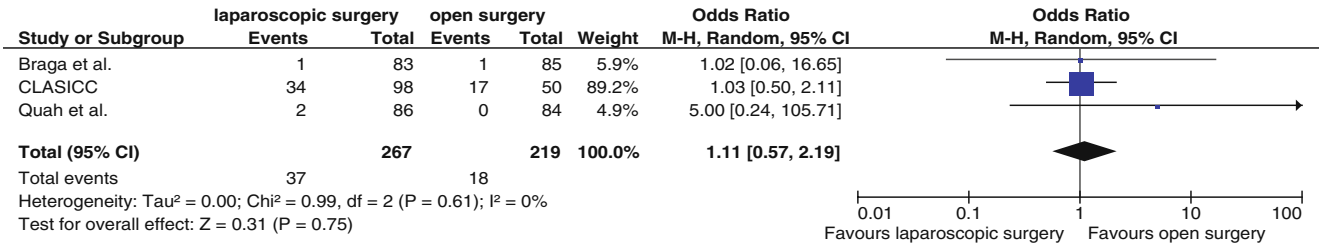
Ileus



Incisional hernia



Urinary dysfunction



Sexual dysfunction (both male and female)

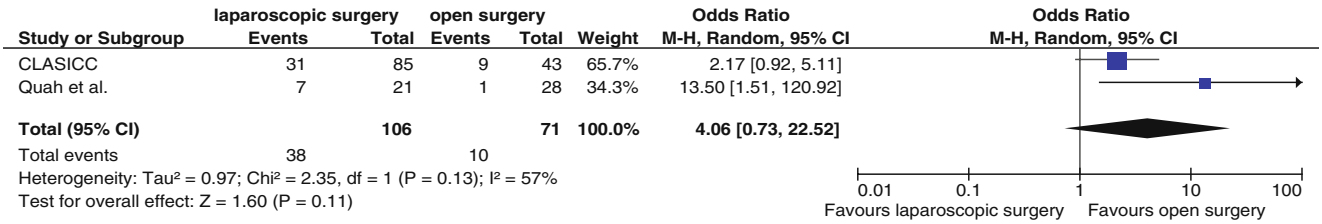


Fig. 4 Meta-analysis of the late morbidity and quality of life for rectal cancer

Mortality

Seven, five, two, and four articles reported data on overall mortality, cancer-related mortality, disease-free survival at 3 years after surgery, and that at 5 years, respectively. Five, two, one, and four articles, respectively, compared these variables between laparoscopic and open surgery groups; none reported any significant difference. In an analysis of the pooled data, we found no significant difference in the overall mortality, cancer-related mortality, and disease-free survival at 3 and 5 years after surgery between patients who underwent laparoscopic surgery and those who underwent conventional open surgery.

Long-Term Morbidity

Two, three, and three articles reported data on overall late morbidity, ileus, and incisional hernia, respectively. In an analysis of the pooled data, the rate of overall late morbidity in the laparoscopic group was significantly lower than that in the open group (odds ratio=0.31; 95% CI=0.14–0.67; p=0.003); however, we found no significant difference for ileus and incisional hernia between the two groups.

Long-Term Quality of Life

Three and two articles reported data on urinary and sexual dysfunction, respectively.

Urinary dysfunction did not differ significantly between the two groups (odds ratio=1.11; 95% CI=0.57–2.19; p=0.75). There was no significant difference in male, female, and both male and female sexual dysfunction between laparoscopic and open groups.

Heterogeneity

In the short-term period, a significant heterogeneity was found between studies with respect to operative time, duration of hospital stay, time to oral diet, and cost of surgery. In the long-term period, we found no significant heterogeneity between studies.

Discussion

In this meta-analysis, the examination of short-term outcomes showed that laparoscopic surgery for rectal cancer is associated with a significantly longer operative time, but significantly less intraoperative blood loss and the number of transfused patients compared with conventional open surgery. These results are consistent with those of recent randomized controlled trials.[3,6,12] Potential explanations for the abovementioned results include meticulous dissection facilitated by instruments for laparoscopic surgery and videoscopic magnification.[26–28] Patients who underwent laparoscopic surgery for rectal cancer resumed oral intake significantly earlier and had significantly shorter hospital stays than did patients who underwent conventional open surgery; this finding suggests that laparoscopic surgery for rectal cancer leads to faster recovery. In this meta-analysis, there was no significant difference in the period of parenteral analgesic administration between the two groups; however, Ng et al. reported that the number of postoperative analgesic requirements was significantly lower following laparoscopic surgery than conventional open surgery, both for upper and low rectal cancer.[14,15] The shorter surgical wound in laparoscopic surgery for rectal cancer may reduce the number of postoperative analgesic requirements, but not the duration of analgesic administration. No significant difference was found for overall perioperative complications, anastomotic leakage, and perioperative mortality between the two surgery groups; this finding suggests that the safety and feasibility of a laparoscopic surgery is similar to that of a conventional open surgery for rectal cancer. Further, the quality of laparoscopic surgery for rectal cancer appears to be similar to that of conventional open surgery, as shown by an insignificant difference in the number of dissected lymph nodes[16] and the rate of positive circumferential resection margin and distal resection margin[10] in this meta-analysis and previous studies.[5,13,15] In the analysis of the cost of surgery, we found no significant overall difference between laparoscopic and open surgery. The cost of open surgery for rectal cancer was similar among the three articles that assessed open surgery costs.[12,14,19] However, the operating costs were higher, and the hospitalization costs were lower for laparoscopic surgery compared with open surgery.

Several reports have shown that conversion from laparoscopic to open surgery is associated with inferior surgical outcomes.[11,29] In this analysis, the conversion rate was not significantly related to the type of study, i.e., single institution or multicenter. Both the CLASICC trial and Stohlein et al. reported that tumor infiltration/fixation and obesity were the most common reasons for conversion.[11,29]

In the long-term period, we found no significant difference in the overall recurrence, local recurrence, and distant metastasis between the two surgery groups. There was also no significant difference in wound site recurrence between the two groups, with the rate of wound site recurrence very small in the laparoscopic and open surgery groups. No significant difference was found in overall mortality, cancer-related mortality, and disease-free survival at 3 and 5 years after surgery. The abovementioned findings suggest that laparoscopic surgery for rectal cancer is comparable to conventional open surgery with respect to long-term oncologic results.

In the evaluation of long-term morbidity, the morbidity rate following laparoscopic surgery for rectal cancer was

found to be significantly lower than that following conventional open surgery. Similarly, Ng et al. and Braga et al. described a high rate of adhesion-related bowel obstruction[15] and incisional hernia[6] in the conventional open surgery group, respectively, compared with the laparoscopic surgery group. No significant difference was found in the analysis of pooled data for the incidence of ileus between the two groups. There also was no significant difference in the analysis of pooled data for the rate of incisional hernia between the two surgery groups.

Urinary dysfunction and sexual dysfunction were examined in this analysis to evaluate long-term quality of life. Injury to the autonomic nervous system causes variable symptoms of bladder and sexual dysfunction.[30–32] The incidence of bladder and sexual dysfunction in patients with rectal cancer has diminished since total mesorectal excision was introduced and the need to preserve the autonomic nervous system was recognized.[32,33] However, few randomized controlled trials have reported data on urinary and sexual dysfunction in this patient population.[17,20] No significant difference was found in the analysis of pooled data for urinary dysfunction between laparoscopic and open surgery groups, which compares favorably with other reports. Further, in this meta-analysis, no significant differences were detected in the analysis of pooled data for male, female, and male and female sexual dysfunction, whereas Jayne et al. reported a trend towards worse male sexual dysfunction[20] and Quah et al. described a higher rate of male sexual dysfunction[17] in laparoscopic surgery compared with open surgery groups. In the CLASICC trial, total mesorectal excision was found to be more commonly performed in laparoscopic surgery than conventional open surgery, which was postulated to be the reason for the worse postoperative sexual function in men who underwent laparoscopic surgery for rectal cancer.[20] On the other hand, there is an idea that laparoscopic total mesorectal excision will allow for better preservation of the pelvic nervous system because the magnified view of the pelvis under the laparoscope allows for easier identification of pelvic nerves.[34,35] Because of the limited data, it is difficult to accurately quantify the influence of laparoscopic surgery on sexual function.

A significant heterogeneity between studies was observed only for short-term outcomes, including operative time, duration of hospital stay, time to oral diet, and cost of surgery. In the long-term period, we found no significant heterogeneity between studies. The reason for the observed heterogeneity in operative time may be variations in the skill of the surgeon and the condition of the tumor. Differences in the clinical approach at different institutions may have caused the heterogeneity in the duration of hospital stay and time to oral diet. Reasons for the heterogeneity in the cost of surgery may include variations in operative time and the cost of laparoscopic instruments.

In conclusion, this meta-analysis showed that laparoscopic surgery for rectal cancer is associated with a reduction in intraoperative blood loss and the number of transfused patients, earlier resumption of oral intake, and shorter duration of hospital stay over the short-term, but is associated with similar short-term and long-term oncologic outcomes compared to conventional open surgery. Therefore, laparoscopic surgery may be an acceptable alternative treatment option to conventional open surgery for rectal cancer.

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ORIGINAL ARTICLE

Epidural Analgesia in Open Resection of Colorectal Cancer: Is there a Clinical Benefit? A Retrospective Study on 1,470 Patients

Rene Warschkow · Thomas Steffen · Andreas Lüthi · Miodrag Filipovic · Ulrich Beutner · Bruno M. Schmied · Sascha A. Müller · Ignazio Tarantino

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Abstract
Background Epidural analgesia (EA) is effective for postoperative pain relief and results in an earlier recovery from postoperative paralytic ileus. This study evaluated the influence of epidural analgesia on the postoperative 30-day mortality and morbidity after open colorectal cancer resection.
Methods A retrospective observational study was performed at a single, tertiary hospital. All patients with an open colorectal cancer surgery between 1991 and 2008 were identified from the hospital database.
Results Of the 1,470 patients included in the study, 838 (57.0%) received an EA. Mortality was lower after EA (1.5% vs. 5.7%, $p<0.001$). Risk of pneumonia was reduced after EA (odds ratio (OR), 0.45; 95% confidence interval (CI), 0.28–0.74; $p=0.001$), but not the risk of anastomotic leakage (OR, 1.18; 95% CI, 0.76–1.81; $p=0.465$) or surgical site infections (OR, 1.09; 95% CI, 0.74–1.60; $p=0.663$). A subgroup analysis of 427 patients operated on after 2002 (reflecting improved perioperative management) yielded similar results. However, no significant reduction in mortality was observed in the subgroup analysis.
Conclusion For patients with open colorectal cancer surgery, the application of EA leads to a reduction in pneumonia. Although this is only a retrospective study, it strongly supports the use of EA.

Keywords · Epidural analgesia · Colorectal cancer · Postoperative · Pneumonia · Mortality

Introduction

Although epidural analgesia (EA) is widely used, it remains controversial. It has been proven to be the most effective method for postoperative pain relief,[1] resulting in an earlier recovery from postoperative paralytic ileus.[2] EA has a low procedure-related complication rate; however, various practical issues limit its general application. Among these issues are cost, theater delays, high postoperative demand for analgesics when stopping EA or in case of failure, and complications such as hypotension.[3]

For the effect of EA on postoperative mortality or morbidity, little evidence is available. Most studies addressing this issue suffer from small sample sizes or heterogeneous patient selection.[4] In particular, the effect on the anastomotic leakage rate, a major concern after colorectal surgery, is controversial.[5–7] A randomized multicenter trial with 915 patients undergoing major abdominal surgery reported a reduction of pulmonary complications with EA (23 vs. 30%, $p=0.02$). In contrast,

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R. Warschkow · T. Steffen · U. Beutner · B. M. Schmied · S. A. Müller · I. Tarantino (✉)
Department of Surgery, Kantonsspital St. Gallen,
9007 St. Gallen, Switzerland
e-mail: Ignazio.Tarantino@kssg.ch

R. Warschkow
Institute of Medical Biometry and Informatics,
Universität Heidelberg,
69120 Heidelberg, Germany

A. Lüthi · M. Filipovic
Department of Anaesthesia, Kantonsspital St. Gallen,
9007 St. Gallen, Switzerland

other studies focusing on colorectal surgery could not find such a relationship.[8,9] Concerning cardiovascular events, there is also a lack of evidence to confirm a diminished risk in patients with EA.

The aim of this study was to evaluate the effect of EA on mortality and morbidity in a large cohort of patients with open colorectal cancer surgery.

Methods

For this retrospective, single-institution observational study, patients with histologically proven colorectal adenocarcinoma who had received primary colorectal cancer resection between July 1991 and August 2008 were identified from the institutional database. The search yielded 1,533 patients of which 25 were excluded due to missing documentation about epidural analgesia and 38 were excluded because they were operated on elsewhere and postoperatively transferred to our institution.

Data Collection and Definitions

Data regarding the patients' demographics, operative details, postoperative mortality, morbidity, and histological results were gathered from medical files. All patients who had received preoperative EA were counted in the EA group, regardless of efficacy.

Operating time was taken from the operation protocol. Mortality was defined as any death within 30 days of surgery. Anastomotic leakage was defined as the presence of an intraabdominal abscess with proof of anastomotic leakage by rectal examination, sigmoidoscopy, extravasation of endoluminally administered water-soluble contrast on radiography or computed tomography, or proof of anastomotic leakage on reoperations. Surgical site infections were defined as all abscesses, wound infections, and intraabominal abscesses not related to anastomotic leakages. Pneumonia was counted when mentioned explicitly as a diagnosis in the medical file or as a radiological finding. Cardiac events included perioperatively occurring myocardial infarction, angina, cardiogenic shock, heart block and arrhythmias, such as atrial fibrillation.

Epidural Analgesia

Epidural catheters were placed in a lower thoracic vertebral space (thoracic 8/9 or 9/10) by the loss of resistance technique using an 18-G Tuohy needle. A local anesthetic (1.25–2.5 mg/ml of bupivacaine) and an opioid (2–4 μg/ml of fentanyl) were given continuously at a rate of 4–8 ml/h during surgery and for 3–4 days postoperatively. Postoperative analgesia was standardized at the authors' institution. Independent of the application of EA, all patients received 3 g paracetamole and 4 g metamizole per day if no contraindications were present. In addition, in patients without EA, postoperative analgesia was achieved with patient- or physician-controlled intravenous morphine administration.

Statistical Analysis and Authorization

Statistical analysis was performed using the software R (http://www.rproject.org). A two-tailed p value <0.05 was considered statistically significant. Continuous data are expressed as the mean±standard deviation or interquartile range as appropriate. Confidence intervals (95% CI) of binominal proportions were estimated according to a modified Wilson method.[10] For comparing proportions, chi-square statistics were applied. Mann–Whitney tests were used for comparisons of continuous data. For multivariate analysis, generalized linear mixed models with the year of operation as a random intercept to adjust for time effects were performed. Regression analyses were applied with adjustments for the year of operation (random effect), age, body mass index, gender, American Society of Anesthesiologists (ASA) stage, cancer localization, Union for International Cancer Control (UICC) stage, and elective vs. urgent surgery. Multivariate p values were calculated with restricted maximum likelihood tests. To assess the effects of EA on mortality and pneumonia conditionally on age, locally weighted scatterplot smoothing regressions were performed.[11]

The study was approved by the Swiss Federal Expert Commission for Physician Confidentiality and by the institutional ethical review board.

Results

Baseline Characteristics

Of the 1,470 patients included in the study, 838 received an epidural analgesia (57.0%; 95% CI, 54.5–59.5%). The patient characteristics are summarized in Table 1. Patients receiving epidural analgesia were more likely male, slightly younger, and more obese. They had lower ASA and UICC tumor stages, but more rectal carcinomas and therefore, more left-sided colorectal surgeries. Epidural analgesia was applied more often in elective surgery. In 1991, the beginning of the study period, 13.8% of the patients received an EA. This rate increased during the whole study period culminating at 80.1% (p<0.001).

Univariate Outcome Analysis

Overall 30-day mortality was 3.3% (48/1,470; 95% CI: 2.5–4.3%). Mortality was significantly lower in patients receiving

Table 1 Baseline characteristics

		Total N=1,470	EA N=838	No EA N=632	p
Age	(years)	67.0±12.2	66.1±12.3	68.1±12.1	0.001[a]
Body mass index	(kg/m^2)	25.4±4.3	25.8±4.3	25.0±4.3	0.001[a]
Gender	Male	907 (61.7%)	543 (64.8%)	364 (57.6%)	0.005[b]
	Female	563 (38.3%)	295 (35.2%)	268 (42.4%)	
ASA stage	I/II	998(67.9%)	626 (74.7%)	372 (58.9%)	<0.001[a]
	III	447 (30.4%)	206 (24.6%)	241 (38.1%)	
	IV	23 (1.6%)	5 (0.6%)	18 (2.8%)	
	n.d[c]	2 (0.1%)	1 (0.1%)	1 (0.2%)	
Cancer Localization	Colon	764 (52.0%)	383 (45.7%)	381 (60.3%)	<0.001[b]
	Rectal	706 (48.0%)	455 (54.3%)	251 (39.7%)	
UICC stage	I	279 (19.0%)	183 (21.8%)	96 (15.2%)	<0.001[a]
	II	411 (28.0%)	228 (27.2%)	183 (29.0%)	
	III	384 (26.1%)	221 (26.4%)	163 (25.8%)	
	IV	358 (24.4%)	187 (22.3%)	171 (27.1%)	
	n.d[c]	38 (2.6%)	19 (2.3%)	19 (3.0%)	
Principal operation	Ileocoecal resection	7 (0.5%)	1 (0.1%)	6 (0.9%)	<0.001[b]
	Right hemicolectomy	314 (21.4%)	150 (17.9%)	164 (25.9%)	
	Transverse colectomy	14 (1.0%)	7 (0.8%)	7 (1.1%)	
	Left hemicolectomy	90 (6.1%)	51 (6.1%)	39 (6.2%)	
	Anterior resection	322 (21.9%)	228 (27.2%)	94 (14.9%)	
	Low anterior resection	540 (36.7%)	327 (39.0%)	213 (33.7%)	
	Total colectomy	70 (4.8%)	28 (3.3%)	42 (6.6%)	
	Abdominoperineal resection	73 (5.0%)	36 (4.3%)	37 (5.9%)	
	Segmental resection	16 (1.1%)	6 (0.7%)	10 (1.6%)	
	Transanal resection	24 (1.6%)	4 (0.5%)	20 (3.2%)	
Operation time	(hours)	165.4±74.0	168.9±79.6	160.4±65.1	0.360[a]
Surgery	Elective	1,346 (91.6%)	817 (97.5%)	529 (83.7%)	<0.001[b]
	Urgency	124 (8.4%)	21 (2.5%)	103 (16.3%)	

[a] Mann–Whitney test

[b] Chi-square test

[c] n.d. no data available

EA (1.4%, 95% CI: 0.8–2.5% vs. 5.7%; 95% CI, 4.1–7.8%; p <0.001; Table 2). After EA the rate of pneumonia (6.7%, 95% CI 5.2–8.6% vs. 11.6%, 95% CI 9.3–14.3%; p=0.001) and cardiac events was significantly reduced (4.3%, 95% CI 3.1–5.9% vs. 6.6%, 95% CI 4.9–8.9%; p=0.047). No statistically significant effects could be found for the rate of anastomotic leakages (p=0.239 for colon cancer and p= 0.723 for rectal cancer) and surgical site infections (p=0.504).

Table 2 Univariate outcome analysis

	Total N=1,470	EA N=838	No EA N=632	p
30-Day mortality	48 (3.3%)	12 (1.4%)	36 (5.7%)	<0.001[a]
Surgical morbidity				
Leakage colon cancer[b]	26/761 (3.4%)	16/382 (4.2%)	10/379 (2.6%)	0.239[a]
Leakage rectal cancer[b]	93/606 (15.3%)	65/414 (15.7%)	28/192 (14.6%)	0.723[a]
Surgical site infection	158 (10.7%)	94 (11.2%)	64 (10.1%)	0.504[a]
General morbidity				
Pneumonia	129 (8.8%)	56 (6.7%)	73 (11.6%)	0.001[a]
Cardiac events	78 (5.3%)	36 (4.3%)	42 (6.6%)	0.047[a]
Length of hospital stay (days)	18 (14–24)	18 (14–24)	19 (15–25)	0.053[c]

N (%), median (interquartile range)

[a] Chi-square test

[b] Analysis of leakage limited to patients with anastomosis and stratified for colon and rectal cancer

[c] Mann–Whitney U test

Mortality and pneumonia were significantly correlated (odds ratio (OR) 4.24, 95% CI: 2.09–8.10; $p<0.001$).

Multivariate Outcome Analysis

The odds of death were threefold lower after EA ($p=0.004$), while the odds of death increased significantly for older patients ($p=0.023$) and patients with higher ASA stages ($p=0.001$; Fig. 1). At any age, mortality was lower when EA was performed (left panel in Fig. 2).

Table 3 summarizes the results of a multivariate regression analysis for morbidity. After adjustment for baseline variables, EA did not influence the rate of anastomotic leakage or surgical site infections. Anastomotic leakages and surgical site infections occurred more often in patients with rectal cancer. The incidence of surgical site infections increased after urgent surgery. In the multivariate analysis, EA remained an independent predictor of pneumonia with an odds reduction of about twofold. Furthermore, a protective effect against pneumonia was found for female gender. At any age the pneumonia rate was lower after EA (right panel in Fig. 2). In multivariate analysis, EA was no independent predictor of cardiac events (OR 0.69; 95% CI, 0.42–1.13; $p=0.157$).

Since during the long study period, peri-operative management has certainly changed, we tried to assess the effect of such changes by a multivariate analysis restricted to patients operated after 2002. For this subgroup of 427 patients, EAwas still an independent predictor for reduced odds of pneumonia (OR 0.33; 95% CI, 0.14–0.78; $p=0.016$). However, the reduced mortality after EA was no longer a statistically significant effect (OR 0.27; 95% CI, 0.04–1.77, $p=0.184$). Application of EA did not correlate with the rate of anastomotic leakage, surgical site infections, or cardiac events. However, mortality and rate of pneumonia were significantly correlated (OR 7.34; 95% CI, 1.68–29.88; $p<0.001$).

Discussion

In this large retrospective study of patients with colorectal cancer surgery, we could show that application of epidural analgesia reduces the odds for pneumonia about twofold. Since pneumonia was strongly correlated with mortality, use of EA also reduced mortality significantly in the whole cohort. However in patients operated on after 2002 with presumably better peri-operative management, the reduction in mortality rate was no longer statistically significant. EA had no effect on anastomotic leakage rate, surgical site infections, or cardiac events.

It must be considered that these results are limited to a single-center patient cohort between 1991 and 2008 at a tertiary referral hospital with standardized medical care concerning EA and surgical treatment of colorectal cancer.

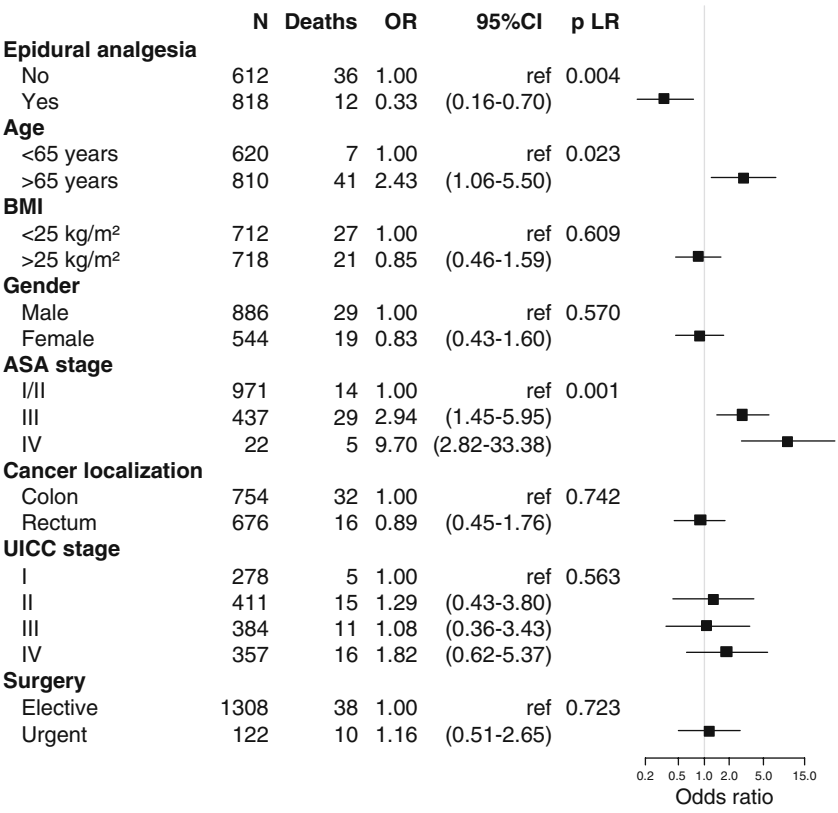

Fig. 1 Multivariate regression analysis for mortality. Analysis limited to 1430 patients with complete data

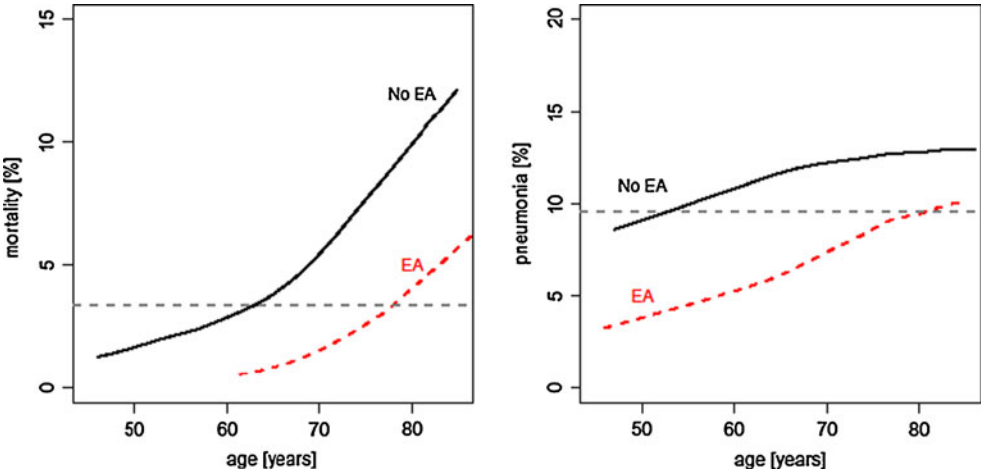

Fig. 2 Locally weighted scatterplot smoothing regression curves for mortality and pneumonia (degree of polynomials=1, degree of smoothing=0.8). *Dashed horizontal line* overall event rate

Furthermore, EA was applied in healthier patients with lower peri-operative risk. Due to the retrospective study design and the long study period, manifold forms of biases could not be ruled out, although some biases were anticipated in multivariate and subgroup analyses, which accounted for baseline variables and time effects. To overcome these limitations, a randomized controlled study would be necessary; however, this would be difficult to perform for ethical reasons due to other previously proven benefits of EA.

Nevertheless, the findings in this study suggest widening the use of EA, especially to include patients with higher-risk profiles.

Procedure-Related Morbidity of Epidural Analgesia

There were no cases of transient neurological injury, which typically is associated with a risk of one in 1,700 patients.[12] Due to the difficulties of the retrospective design, this study did not assess the adverse effects of EA such as pruritus, nausea and vomiting, or postoperative hypotension, which are proven to be associated with EA.[1,3,13,14]

Pneumonia

In the present study, EA reduced the risk of pneumonia. An odds ratio of 0.45 corresponded to a number needed to treat (NNT) of 18. This finding corresponded well with the proven effect of EA on postoperative pain relief[1] and the postoperative pain-related loss of respiratory mechanics resulting in hypoventilation.[15] A review denied that EA yielded measurable changes in clinical pulmonary signs or symptoms in patients with colorectal surgery[3]; however, a recent meta-analysis including 19 trials with 3,504 patients after abdominal or thoracic surgery estimated an odds ratio of 0.54 for pneumonia after EA.[13] Interestingly, the authors of the meta-analysis demonstrated a shift of the OR toward unity over the past 35 years as a consequence of a reduced baseline risk of pneumonia due to changes in systemic analgesia towards multimodal analgesia methods. Thus, the NNT shifted from four in the 1970s to 25 from 2000 to 2006. While the beneficial effect has decreased over the last 35 years, the efficiency of EA concerning pneumonia has remained stable. Consistently, a decreased incidence of respiratory failure occurred in 915 patients undergoing major abdominal surgery, while a beneficial effect of EA was not proven for seven other morbidity endpoints.[16] Since pneumonia has a high mortality,[17] a reduced pneumonia rate provides a reasonable explanation for the decreased mortality in this study.

Mortality

The overall mortality rate of 3.3% in this study was comparable to that of other studies.[18] Mortality was significantly lower in patients with EA. The odds ratio after multivariate adjustment was 0.33, which corresponded to a NNT of 27. This reduction in mortality may be attributable to a reduction of adverse organ system outcomes, such as pneumonia. Nevertheless, when limiting the analysis to patients operated after 2002, EA did not significantly influence mortality. One possible explanation for this discrepancy is a decreased power in the subgroup analysis which may have prevented significant results. The more likely explanation is the changes of clinical practice over the long study. A two third reduction of mortality by EA alone is clinically implausible. When the analysis was restricted to a recent time period after the introduction of early postoperative enteral feeding, routine deep vein thrombosis prophylaxis with low-molecular weight heparin, and intraoperative warming among others, only a non-significant reduction in mortality occurred. This discrepancy between main analysis and subgroup analysis concerning mortality is also reflected in the literature. While trends for a reduction of mortality in patients with EA were observed in previous studies, other studies demonstrated increased mortality rates. A recent meta-analysis of seven randomized

Table 3 Multivariate regression analysis of morbidity

Surgical morbidity						General morbidity			
		Anastomotic leakage[a]		Surgical site infection		Pneumonia		Cardiac events	
		OR (95% CI)	*p* LR	OR (95% CI)	*p* LR	OR (95% CI)	*p* LR	OR (95% CI)	*p* LR
Epidural analgesia	No	1.00[b]	0.465	1.00[b]	0.663	1.00[b]	0.001	1.00[b]	0.156
	Yes	1.18 (0.76–1.81)		1.09 (0.74–1.60)		0.45 (0.28–0.74)		0.69 (0.42–1.13)	
Age	<65 years	1.00[b]	0.932	1.00[b]	0.675	1.00[b]	0.166	1.00[b]	0.001
	>65 years	0.98 (0.65–1.48)		0.93 (0.65–1.33)		1.34 (0.89–2.02)		4.96 (2.4–10.27)	
Body mass index	<25 kg/m^2	1.00[b]	0.102	1.00[b]	0.878	1.00[b]	0.133	1.00[b]	0.750
	>25 kg/m^2	1.40 (0.93–2.09)		1.03 (0.73–1.46)		0.75 (0.51–1.09)		0.93 (0.57–1.50)	
Gender	Male	1.00[b]	0.803	1.00[b]	0.240	1.00[b]	0.001	1.00[b]	0.778
	Female	1.05 (0.70–1.59)		0.80 (0.56–1.16)		0.46 (0.29–0.72)		0.99 (0.60–1.63)	
ASA stage	I/II	1.00[b]	0.998	1.00[b]	0.158	1.00[b]	0.756	1.00[b]	0.013
	III	0.99 (0.61–1.60)		1.38 (0.93–2.04)		1.00 (0.65–1.53)		2.00 (1.20–3.32)	
	IV	0.95 (0.12–7.79)		2.32 (0.71–7.56)		1.62 (0.47–5.51)		3.41 (0.89–12.99)	
Cancer localization	Colon	1.00[b]	<0.001	1.00[b]	0.001	1.00[b]	0.351	1.00[b]	0.466
	Rectum	4.84 (3.01–7.77)		3.10 (2.11–4.54)		1.21 (0.81–1.81)		1.21 (0.74–1.99)	
UICC stage	I	1.00[b]	0.930	1.00[b]	0.348	1.00[b]	0.887	1.00[b]	0.416
	II	0.85 (0.49–1.49)		0.86 (0.51–1.44)		1.08 (0.62–1.88)		0.71 (0.36–1.39)	
	III	1.00 (0.58–1.73)		0.95 (0.58–1.58)		0.88 (0.49–1.57)		0.89 (0.45–1.73)	
	IV	0.96 (0.54–1.70)		1.30 (0.79–2.14)		1.02 (0.57–1.83)		0.56 (0.26–1.21)	
Surgery	Elective	1.00[b]	0.696	1.00[b]	0.041	1.00[b]	0.057	1.00[b]	0.122
	Urgency	1.19 (0.51–2.80)		1.91 (1.05–3.47)		0.48 (0.22–1.08)		0.48 (0.18–1.28)	

Analysis limited to 1,430 patients with complete data

[a] Analysis of anastomotic leakage limited to 1,343 patients with complete data

[b] Reference category mixed effects ordinary logistic regression with the year of operation as a random intercept

controlled trials (RCT) including 711 patients with intra-abdominal surgery failed to show a significant improvement of mortality or morbidity after EA.[19] Another meta-analysis of high-risk cardiac patients demonstrated reduced mortality in patients receiving EA (3.1% vs. 4.4%), but this result was not statistically significant due to a small sample size.[20] A Cochrane Library meta-analysis in elective open abdominal aortic surgery demonstrated mortality rates of 3.5% vs. 4.3% in favor of EA, but this result was also not statistically significant due to a sample size of only 1,224 patients.[21] The discrepancy between this and other studies may also have been a result of selection bias, e.g., for ASA classification or hidden confounders due to the retrospective observational design.

Unfortunately, no adjustment does ensure a reliable exclusion of these variables. On the other hand, this study assessed a large and homogeneous cohort treated according to day-to-day clinical practices. Therefore, the results presented in this observational study do not necessarily have a lower clinical impact than results from RCT[22,23] especially when considering that RCT are often limited to defined subgroups under near-ideal circumstances.[24,25]

Anastomotic Leakage

The present study revealed a fivefold increased risk of anastomotic leakage in patients with rectal cancer compared to colon cancer, which is consistent with recent research.[6] Stratifying for cancer localization yielded a similar leakage rate in patients with and without EA. Combining these findings with the higher incidence of EA in rectal cancer patients indicated that an increased risk of anastomotic leakage after EA is mainly due to a biased incidence of EA in distinct entities of colorectal cancer. This result may explain the contradictory results from other studies.[5,6]

Surgical Site Infections

Because most studies and meta-analyses of EA have included different surgical procedures, they are limited in the assessment of surgical outcome. However, consistent with previous investigations, this study did not reveal an effect of EA on the incidence of surgical site infections.[3]

Cardiac Events

The decreased risk of cardiac events in patients receiving EA observed using univariate analysis did not persist after multivariate adjustment. Age and the ASA stage were the only independent significant influential factors. Therefore, the decreased incidence of cardiac events in patients with EA must be interpreted as a result of bias because patients with EA were younger and had lower ASA stages. This interpretation is contradictory to a meta-analysis that included 14 trials with a total of 2,675 patients and estimated an OR of 0.55 for EA; however, this meta-analysis did not assess all cardiac events but only myocardial infarction and included patients with different surgical procedures.[13] Other meta-analyses either did not reach statistical significance regarding the influence of EA on cardiac events or the influence was restricted to subgroups.[20,26]

Length of Hospital Stay

The long length of hospital stay in this cohort reflected the hospital policy in Switzerland, where reimbursements were not yet based on Diagnosis Related Groups. Similar to RCT that showed small or no effects[2,27–29] of EA on the length of hospital stay, this study did not demonstrate a significant shortening of the length of hospital stay after EA.

Conclusion

Although this was a retrospective study over a long study period, it showed substantial evidence for a reduction in pneumonia in colorectal cancer surgery with patients receiving EA. EA did not increase the risk for anastomotic leakage or surgical site infections. The results of this study indicate that EA should be applied whenever possible.

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SSAT POSTER PRESENTATION

Does Adiponectin Upregulation Attenuate the Severity of Acute Pancreatitis in Obesity?

Hayder H. Al-Azzawi · Kathryn M. Ziegler · Deborah A. Swartz-Basile · Sue Wang · Henry A. Pitt · Nicholas J. Zyromski

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Abstract
Introduction Obesity is an independent risk factor for severe acute pancreatitis, though the mechanisms underlying this association are unknown. The powerful anti-inflammatory adipokine adiponectin is decreased in obesity. We recently showed that the severity of pancreatitis in obese mice is inversely related to circulating adiponectin levels, and therefore hypothesized that adiponectin upregulation would attenuate the severity of pancreatitis in obese mice.
Methods Forty congenitally obese mice were studied. Seven days prior to study, 20 mice received a single tail vein injection of adenovirus expressing recombinant murine adiponectin (APN; 2×10^8 plaque forming unit (pfu)), and the remainder received a control adenoviral vector expressing β-galactosidase (β-gal; 2×10^8 pfu). Half of the mice in each group had pancreatitis induced by cerulein injection (50 mcg/kg IP hourly for 6 h). The other half received saline on the same schedule. Serum APN concentration and pancreatic tissue concentrations of interleukin (IL)-6, IL-1β, and MCP-1 were measured by ELISA. Histologic pancreatitis score was calculated based on the degree of inflammation (0–4), edema (0–4), and vacuolization (0–4). Data were analyzed by ANOVA and Tukey's tests; $p<0.05$ was considered significant.
Results No difference in body weight was observed between groups. Serum APN was significantly upregulated in the APN group compared with the β-gal group. Pancreatic tissue concentration of IL-6 was significantly decreased in the APN group compared with the β-gal group. No change either in pancreatic tissue concentration of IL-1β and MCP-1 or in the severity of histologic pancreatitis were observed.
Conclusion Adiponectin upregulation modulates the pancreatic cytokine milieu but does not attenuate pancreatitis in this model of mild acute pancreatitis.

Keywords Adiponectin · Obesity · Pancreatitis · Adipokine · Adenovirus

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H. H. Al-Azzawi · K. M. Ziegler · D. A. Swartz-Basile · S. Wang · H. A. Pitt · N. J. Zyromski (✉)
Department of Surgery, Indiana University School of Medicine, 535 Barnhill Drive, RT 130, Indianapolis, IN 46202, USA
e-mail: nzyromsk@iupui.edu

Introduction

Acute pancreatitis (AP) represents a substantial clinical problem, accounting for over 240,000 hospital admission annually in the USA, at a cost of over $2.3 billion.[1] The spectrum of pancreatitis severity is broad. Fifteen to 20% of patients with AP develop severe pancreatitis associated with a massive systemic inflammatory response and mortality rates that reach 10–20%.[2,3] However, the pathophysiology of AP is poorly understood and little is known about which subset of patients will develop severe AP. Epidemiological studies have clearly shown obesity to be an independent risk factor for developing severe AP.[4–6]

Obesity is epidemic in the twenty-first century; currently, over one third of adult Americans are considered to be clinically obese resulting in more than $120 billion in yearly health care costs.[7,8] Obesity is associated with fatty infiltration in the heart, kidney, liver, and pancreas. This situation leads to a generalized proinflammatory milieu and subsequent organ dysfunction.[9–12] The role of adipose tissue as a metabolic organ has been increasingly appreciated. Adipocytes secrete many biologically active substances called adipokines.[13] Adipokines have a wide variety of endocrine, paracrine, and autocrine effects, including regulation of satiety, immune function, and energy metabolism. In addition, adipokines are important mediators of the inflammatory response.

Adiponectin is the most abundant circulating adipokine and has a potent anti-inflammatory effect. In contrast to leptin (which is predominantly a proinflammatory adipokine), circulating adiponectin concentration paradoxically decreases as obesity progresses.[14–16] The status of the adipokine milieu associated with obesity contributes to the generalized proinflammatory state observed in obesity.[17] We have recently developed a murine model of acute pancreatitis in the setting of obesity. In this murine model, similar to the human situation, congenitally obese mice develop more severe pancreatitis than lean wild-type animals.[18] In these experiments, we observed that circulating adiponectin concentration inversely mirrored the severity of AP. Based on these observations, we hypothesized that upregulating adiponectin concentration would attenuate the severity of acute pancreatitis.

Modulating the adipokine milieu (specifically increasing adiponectin) has been shown to alter the inflammatory process associated with certain inflammatory diseases like rheumatoid arthritis, Crohn's disease, and atherosclerosis.[19–22] Adiponectin upregulation may be achieved by simple intravenous or intraperitoneal administration of the protein. On the other hand, dietary modification with fish oil[23] or pharmacologic blockade of the cannabinoid receptor-1[24] have also been shown to upregulate circulating adiponectin. Adiponectin circulates in micrograms per dilliliter concentration; the dosage of synthetic adiponectin necessary to achieve physiologic concentration in in vivo models is prohibitively expensive. Indirect methods of adiponectin upregulation are less than ideal because of concomitant metabolic changes. An alternative, relatively inexpensive method to upregulate adenovirus expressing recombinant murine adiponectin (APN) expression utilizes adenovirus in which the APN gene has been incorporated.[25–27]

The current experiments were, therefore, designed to test the hypothesis that adenovirus-mediated upregulation of circulating APN would attenuate AP severity in congenitally obese mice.

Materials and Methods

All studies were performed with the approval of the Indiana University Institutional Animal Care and Use Committee and were in accordance with the National Research Council guide for the care and use of laboratory animals.

Animals and Diets

Forty obese leptin-resistant (Lep^{Db}) female mice were obtained from Jackson Laboratories (Bar Harbor, ME) at 7 weeks of age. Animals were allowed to acclimate for 1 week in a climate-controlled room with a 12:12-h light–dark cycle. At 8 weeks of age, all of the mice were fed our standard diet consisting of (% calories) 25% fat (23% soybean oil/2% corn oil), 55% carbohydrate (30% complex and 20% simple carbohydrate), and 20% protein-derived calories (diet # 180627, Dyets Inc., Bethlehem, PA). The fat in this diet contains about 8.5% n3 free fatty acid in the form of α-linolenic acid. Animals and food were weighed weekly to monitor growth and dietary intake, and the animals were studied at 14 weeks of age.

Experimental Design

The design of the experiment is shown in Fig. 1. Eight-week-old animals were placed on diet for 6 weeks. At 13 weeks of age, half of the animals (n=20) received a single 100 μl tail vein injection of adenovirus expressing full-length recombinant murine adiponectin (AD-APN; 2×10^8 plaque forming unit (pfu)); the other half (n=20) received a single tail vein injection of 100 μl of a control adenoviral vector expressing

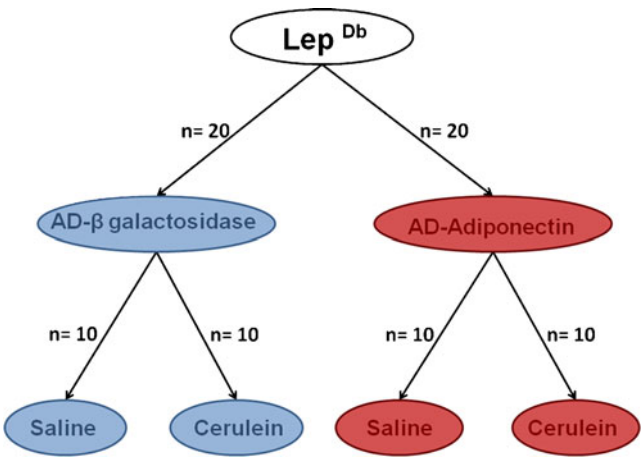

Fig. 1 Experimental design. Leptin-resistant (Lep^{db}) obese mice were randomly allocated to receive a single tail vein injection of adenovirus expressing either murine recombinant adiponectin (*AD-APN*) or β-galactosidase (*AD-β-gal*; 2×10^8). After 1 week, acute pancreatitis was induced by intraperitoneal (IP) injection of cerulein (50 μg/kg hourly, ×6). Control animals received IP saline on the same schedule

Table 1 Body weight and diet consumption

Values are mean±SEM, $n=10$ in each group. Diet consumption is grams of diet per week per mouse

	AD-β-gal		AD-adiponectin	
	Saline	Cerulein	Saline	Cerulein
Body weight (g)	49.3±0.6	48.0±0.3	47.8±0.8	47.6±0.7
Diet consumption (g/week)	24.2±1.3	25.3±1.5	23.4±1.6	24.3±1.5

β-galactosidase (AD-β-gal; $2*10^8$ pfu). Both the adenovirus expressing APN and β-gal were kindly donated from Dr. Giamila Fantuzzi (University of Illinois, Chicago). Adenovirus was amplified and purified by Vector Biolab, Philadelphia PA. Seven days later (14 week of age), half of the mice ($n=10$) in each group (AD-APN and AD-β-gal) had acute pancreatitis induced by pancreatic overstimulation with the cholecystokinin agonist cerulein (Sigma-Aldrich, St. Louis, MO). The remaining half ($n=10$) received intraperitoneal injection of saline on the same schedule.

Induction of Pancreatitis and Tissue Procurement

Acute pancreatitis was induced by administering 50 μg/kg cerulein intraperitoneally hourly for 6 h. Nine hours after the first injection, mice were anesthetized with an intraperitoneal injection of xylazine (15 mg/kg) and ketamine (50 mg/kg). The animals then underwent laparotomy and total pancreatectomy. A small portion of each pancreas was preserved in 10% formalin for histological analysis, and the remainder was immediately snap frozen in liquid nitrogen and stored at −80°C for further analysis. Blood was collected at the same time via ventricular puncture. Blood was centrifuged at 15,000 rpm for 5 min, and serum was stored for subsequent analysis.

Microscopy and Histological Analysis

Formalin-preserved pancreas was embedded in paraffin blocks, sectioned into 5-μm segments, and stained with hematoxylin and eosin. Sections of pancreas were taken from a standard location, the mid-body of the gland. Histological severity of pancreatitis was determined by two separate observers who were blinded to the animals' treatment. A total pancreatitis score was determined by a validated method based on the degree of inflammation, vacuolization, and edema.[18,28]

Chemical Assays

Pancreatic tissue was homogenized in buffer containing 50 mM Tris, 250 mM NaCl, 5 mM EDTA, 1 mM NaF, 20 mM $Na_4P_2O_7$, 0.02% NaN_3, proprietary detergent, and protease inhibitor (Sigma, St. Louis, MO) at a volume of 50 μl per gram tissue. Homogenates were centrifuged at 10,000 rpm at 4°C for 15 min, and protein concentration of the supernatant was assayed (Bio-Rad, Hercules, CA). Pancreatic tissue concentration of the cytokines interleukin (IL)-1β and IL-6, and the chemokine monocyte chemoattractant protein-1 (MCP-1) were determined with commercially available ELISA (R&D Systems, Minneapolis, MN). Serum concentration of adiponectin was determined by ELISA (Linco Research, St. Charles, MO); in our hands, this assay is highly reproducible.[18,24]

Statistical Analysis

Statistical analyses were performed with Sigma Stat software (Jandel, San Rafael, CA). Data are expressed as means±standard error of the mean (SEM). ANOVA and Tukey's tests were applied as appropriate. A p value of <0.05 was accepted as statistically significant.

Results

Animal Weight and Diet Consumption

No difference in body weight was observed among groups. No difference was observed in diet consumption among groups throughout the entire study (Table 1).

Hepatic β-gal Expression

RT-PCR confirmed β-gal expression in the liver of control mice as a negative control (data not shown).

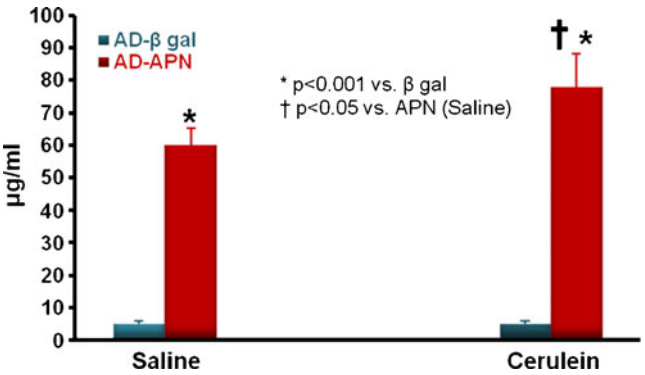

Fig. 2 Serum adiponectin. Circulating adiponectin concentration substantially increased in the AD-APN group compared with the control AD-β-gal group. Interestingly, between the two groups injected with AD-APN, the cerulein-induced pancreatitis group had significantly higher serum adiponectin concentration compared with the saline (no pancreatitis) group. Data are mean±SEM, $n=10$ in each group

Table 2 Pancreatic tissue inflammatory milieu

	AD-β-gal		AD-adiponectin	
	Saline	Cerulein	Saline	Cerulein
IL-1β (pg/mg)	9.7±1.0	266.8±45.5*	14.9±3.6	201.8±27.1*
IL-6 (pg/mg)	5.8±0.9	262.7±41.1*	6.1±0.8	127.2±40.3*, **
MCP-1 (pg/mg)	15.7±1.8	854.4±126.3*	22.5±3.7	658.9±136.6*

Values are mean±SEM, $n=10$ in each group

*$p<0.001$ vs. saline. **$p<0.02$ vs. AD-β-gal (cerulein)

Circulating Adiponectin Concentration

Animals injected with AD-APN had a significant ($p<0.001$) increase in circulating adiponectin concentration compared with those that received the control AD-β-gal (Fig. 2) Interestingly, between the two groups injected with AD-APN, the cerulein-induced pancreatitis group had significantly ($p<0.05$) higher serum adiponectin concentration compared with the saline (no pancreatitis) group (Fig. 2).

Pancreatic Inflammatory Milieu (Biochemical Pancreatitis)

Table 2 shows biochemical markers of acute pancreatitis. Induction of pancreatitis upregulated the pancreatic tissue inflammatory markers IL-1β, MCP-1, and IL-6 in both AD-β-gal and AD-APN compared with the saline-injected mice (no pancreatitis). The pancreatic tissue concentration of IL-1β and MCP-1 was similar in AD-β-gal and AD-APN groups. In contrast, the pancreatic tissue of the AD-APN mice had significantly less IL-6 than that of the mice injected with AD-β-gal subjected to pancreatitis.

Histologic Pancreatitis

The histologic severity of pancreatitis was measured with a validated scale (pancreatitis score) based on the degree of edema, vacuolization, and inflammatory cell infiltration. The total pancreatitis score was significantly higher in the groups receiving cerulein to induce pancreatitis compared with the groups receiving saline. The histologic pancreatitis severity was similar in the AD-β-gal group and the AD-APN group (Fig. 3).

Discussion

In this study, a single tail vein injection of AD-APN significantly upregulated circulating adiponectin concentration in congenitally obese Lep^{Db} mice. After induction of mild acute pancreatitis, adiponectin upregulation modulated the pancreatic inflammatory milieu by significantly decreasing the proinflammatory cytokine IL-6 concentration. This alteration of the pancreatic inflammatory milieu did not translate into attenuation of histologic acute pancreatitis.

The altered adipokine milieu of obesity is associated with inflammatory diseases in many organ systems including rheumatologic, gastrointestinal, and cardiovascular.[29–33] Epidemiologic studies have consistently shown obesity to be a risk factor for increased severity of pancreatitis; the incidence of acute pancreatitis is more frequent in obese patients (body mass index (BMI)>30) when compared with non-obese patients (odds ratio, 2.9).[4–6] Therefore, it is logical to speculate that the altered adipokine milieu of obesity may contribute to this association. The powerful anti-inflammatory adipokine adiponectin is of particular interest.

Adiponectin exerts its anti-inflammatory effects through several distinct mechanisms including suppression of proinflammatory cytokine production[34] and upregulation of anti-inflammatory cytokine production.[35] In addition, adiponectin alters macrophage and lymphocyte function[35–37] and downregulates chemokines and adhesion molecules.[38,39] Adiponectin upregulation has shown a beneficial effect on several inflammatory diseases. For example, Lee et al. showed that adiponectin mitigated arthritis severity in rats.[20] In addition, local adiponectin treatment has also been shown to suppress the development of atherosclerosis in rabbits.[22] Furthermore, Valentini et al. showed that both active and inactive Crohn's disease patients have decreased circulating adiponectin compared with controls.[21]

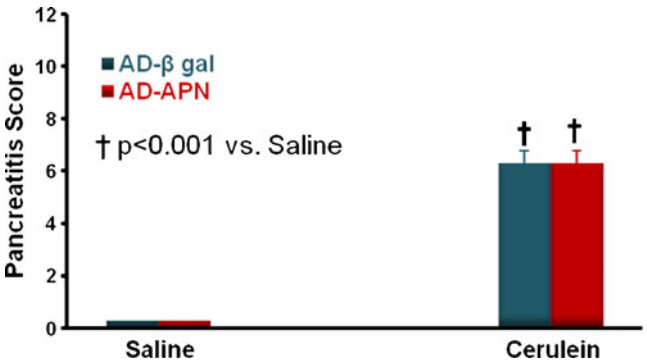

Fig. 3 Pancreatitis score. Total pancreatitis score was determined by degree of pancreatic edema, vacuolization, and inflammatory cell infiltrate. Pancreatitis score is significantly higher in the groups receiving cerulein to induce pancreatitis compared with the groups receiving saline. No difference was observed in the histologic severity of pancreatitis between the AD-APN group and the AD-β-gal group. Data are mean±SEM, $n=10$ in each group

Our laboratory has developed a murine model of acute pancreatitis in the setting of obesity.[18] In this model, similar to the human situation, congenitally obese mice develop more severe pancreatitis than wild-type lean mice when subjected to cerulein hyperstimulation.[18] In this model, we observed that serum adiponectin concentration inversely mirrored the severity of pancreatitis.[18] We have also demonstrated previously that blockade of the cannabiniod receptor-1 significantly increased circulating adiponectin and attenuated the severity of cerulein-induced acute pancreatitis.[24] If adiponectin is to be used with therapeutic intent, it will be important to show that adiponectin administration (or upregulation) is effective *after* the initiation of acute pancreatitis. To date, these experiments have not been done.

The association of the anti-inflammatory adipokine adiponectin and pancreatitis has been examined in three clinical studies.[40–43] Adryc et al. showed no difference in circulating adiponectin concentration between healthy individuals and patients with chronic pancreatitis.[41] However, Schäffler et al. showed that patients with mild pancreatitis have marginal but statistically significant higher levels of circulating adiponectin than patients with severe acute pancreatitis.[42] In a 3rd clinical study, no difference in admission of adiponectin concentration was seen in 12 lean patients (BMI of 27) with severe AP compared with BMI-matched patients with mild AP.[43] The logistical challenges of studying patients with acute pancreatitis are evident in all three of these reports.

One animal study has directly examined the effects of adiponectin in acute pancreatitis. In a nicely designed experiment, Araki et al. showed that adiponectin had a protective role in cerulein-induced AP in adiponectin knockout (APN-KO) mice fed a high fat diet.[27] The APN-KO phenotype is lean, which leads to question the direct translation of adiponectin effects in the obese phenotype.

The question of differential adipokine effects in specific phenotypes (i.e., lean versus obese) is important, though the specific effects of adiponectin on lean mice with pancreatitis are not clear. We have administered exogenous adiponectin to lean and obese mice prior to initiating acute pancreatitis; adiponectin administration changed the pancreatic chemokine and cytokine milieu in obese mice but had no effect in lean animals (unpublished data, manuscript under review). Similarly, central cannabinoid receptor blockade increased adiponectin concentration and decreased pancreatitis severity in obese mice; however, this intervention did not change adiponectin concentration or pancreatitis severity in lean animals (with the caveat that this technique certainly affected additional metabolic pathways).[24]

In the present study, adiponectin upregulation altered the pancreatic inflammatory milieu in the setting of mild acute pancreatitis. Specifically, pancreatic tissue concentration of the proinflammatory cytokine IL-6 was decreased in AD-APN mice compared with the control group. In contrast, the pancreatic tissue concentration of IL-1β and MCP-1 in the APN group decreased, though not to levels that reached statistical significance. The gold standard method for measuring the severity of pancreatitis currently is microscopic scoring of histologic specimens. In our study, upregulation of adiponectin did not affect the histologic severity of AP when measured by experienced observers using a validated method of pancreatitis score.

The reason why the observed pancreatic biochemical alterations did not result in histologic changes is not entirely clear; however, the simplest and most logical explanation is that pancreatitis severity induced by this model was quite mild. No perfect experimental model of acute pancreatitis exists. Cerulein-induced AP is a simple, reproducible, and reliable method of inducing AP but it results in a mild edematous interstitial AP, and in addition the clinical relevance is questionable. Another method of inducing pancreatitis involves retrograde pancreatic duct injection of the bile salt sodium taurocholate.[44,45] While this method results in a more severe pancreatitis than the cerulein-induced method and may be more physiologic, it is more invasive and technically challenging especially in small animals like mice.

In conclusion, adenovirus expressing full-length adiponectin significantly upregulated the circulating adiponectin concentration in congenitally obese mice. Increased circulating adiponectin modulated the pancreatic inflammatory cytokine milieu by significantly decreasing the proinflammatory cytokine IL-6 but did not alter histologic pancreatitis severity in this model of mild acute pancreatitis.

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ORIGINAL ARTICLE

Influence of Visceral Obesity for Postoperative Pulmonary Complications After Pancreaticoduodenectomy

Atsushi Shimizu · Masaji Tani · Manabu Kawai · Seiko Hirono · Motoki Miyazawa · Kazuhisa Uchiyama · Hiroki Yamaue

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Abstract
Background We conduct this study to determine whether postoperative complications, including postoperative pulmonary complications (PPCs), are associated with BMI and visceral fat area (VFA) after pancreaticoduodenectomy.
Methods A total of 317 patients undergoing pancreaticoduodenectomy were enrolled. VFA was measured using a cross-sectional computed tomography (CT) scan at the level of the umbilicus by FatScan software version 3.0 (N2 systems Inc., Osaka, Japan). Clinicopathological variables, intraoperative outcomes, and postoperative courses were analyzed.
Results Of all patients, 130 (41.0%) had postoperative complications and PPCs occurred in 14 patients (4.4%). VFA were significantly higher in patients who developed postoperative pancreatic fistula (POPF), PPCs, and mortality than in those patients who did not (P=.0282, P=.0058, and P=.0173, respectively). Multivariate analysis demonstrated that high BMI and high VFA were not independent predictive risk factors for POPF grade B/C and mortality; only high VFA was an independent risk factor influencing PPCs (P=.0390, odds ratio 4.246, 95% confidence interval 1.076–16.759).
Conclusions Visceral obesity was the independent risk factor for the incidence of PPCs after pancreaticoduodenectomy. Preoperative VFA measurement using CT scan is a useful tool for the prediction of the development of PPCs compared to BMI calculation.

Keywords Visceral fat area (VFA) · Body mass index (BMI) · Pancreaticoduodenectomy · Postoperative complications · Postoperative pulmonary complications (PPCs)

Introduction

The prevalence of overweight and obesity is increasing in the general population and reached over 60% in U.S. populations having higher than 25 kg/m^2 body mass index (BMI).[1] Overweight and obesity are associated with numerous complications such as cardiovascular, pulmonary, and metabolic disorders; therefore, surgeons have agreed that generalized obesity is a potential risk factor for operative morbidity and mortality.[2–5] Although BMI is a convenient measure and is useful for assessing the consequence of obesity, it is often unreliable for the evaluation of an individual's status because the proportion and distribution of fat tissue differ greatly from each other. Accordingly, in recent years, excessive visceral fat has been noteworthy in its association with postoperative complications.[6–8]

Postoperative pulmonary complications (PPCs) are common complications after all digestive surgery. Previous reports demonstrated that the incidence of PPCs was 2–13% after pancreaticoduodenectomy,[9–13] which was less than the incidence of postoperative pancreatic fistula (POPF), postpancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE).

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A. Shimizu · M. Tani · M. Kawai · S. Hirono · M. Miyazawa · K. Uchiyama · H. Yamaue (✉)
Second Department of Surgery, School of Medicine,
Wakayama Medical University,
811-1, Kimiidera,
Wakayama 641-8510, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

However, one should consider that PPCs are lethal complications frequently requiring extended intensive care, including reintubation and continuous positive airway pressure.

Smetana et al. interestingly reported that BMI was not associated with increased clinical PPCs after surgery in a systematic review.[14] However, obesity is thought to be a risk factor for PPCs and may lead to restrictive pulmonary physiology and further reduction of lung volume.[15, 16] Thus, obesity interrupts the ability to take a deep breath after surgery, and visceral fat (VF) plays an important factor in obesity. Patients with a high volume of VF have high abdominal pressure, resulting in a risk factor for PPCs. Therefore, a new strategy is required for evaluating obesity for the improvement of surgical outcomes after pancreaticoduodenectomy. We conducted this study to determine whether postoperative complications, including PPCs, are associated with BMI and visceral fat area (VFA) after pancreaticoduodenectomy.

Material and Methods

Patients

Between February 2003 and December 2009, 324 consecutive patients underwent pancreaticoduodenectomy in Wakayama Medical University Hospital (WMUH). In the present study, seven patients were excluded because of undergoing hepatopancreaticoduodenectomy (n=3), additional pancreatic tail resection (n=2), total gastrectomy (n=1), or splenectomy (n=1). The 317 enrolled patients in the present study have a median age of 70 years (range 35–91); 181 are male and 136 are female. Patients' characteristics and perioperative and postoperative parameters were reviewed for the following clinical variables: age, gender, concomitant disease, including cardiovascular disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, recent smoking history (smoking within 4 weeks prior to surgery),[17] pulmonary function on spirograms (percentage predicted vital capacity, %VC, and the ratio of forced expiratory volume in 1 s to forced vital capacity, FEV1/FVC), preoperative biliary drainage, type of resection (pylorus-preserving pancreaticoduodenectomy, PpPD, or conventional pancreaticoduodenectomy, PD), additional portal vein resection, BMI, VFA, operative time, intraoperative bleeding, red blood cell transfusion, pancreatic texture (soft or hard), and histologic diagnosis (malignant or benign). Informed consents were obtained from all the patients in accordance with the guidelines of the Ethical Committee on Human Research of WMUH.

BMI and Visceral Fat Area

BMI was calculated by patient height and body weight measured preoperatively. The World Health Organization criteria for overweight and obesity were used (overweight, BMI 25.0–29.9; obesity, BMI≥30.0).[18] VFA was measured using a cross-sectional CT scan at the level of the umbilicus by FatScan software version 3.0 (N2 systems Inc., Osaka, Japan),[19] and patients were classified into a high-VFA group (VFA≥130 cm^2) and a low-VFA group (VFA<130 cm^2). In Fig. 1, we show samples in this study population of the amount of visceral fat by FatScan

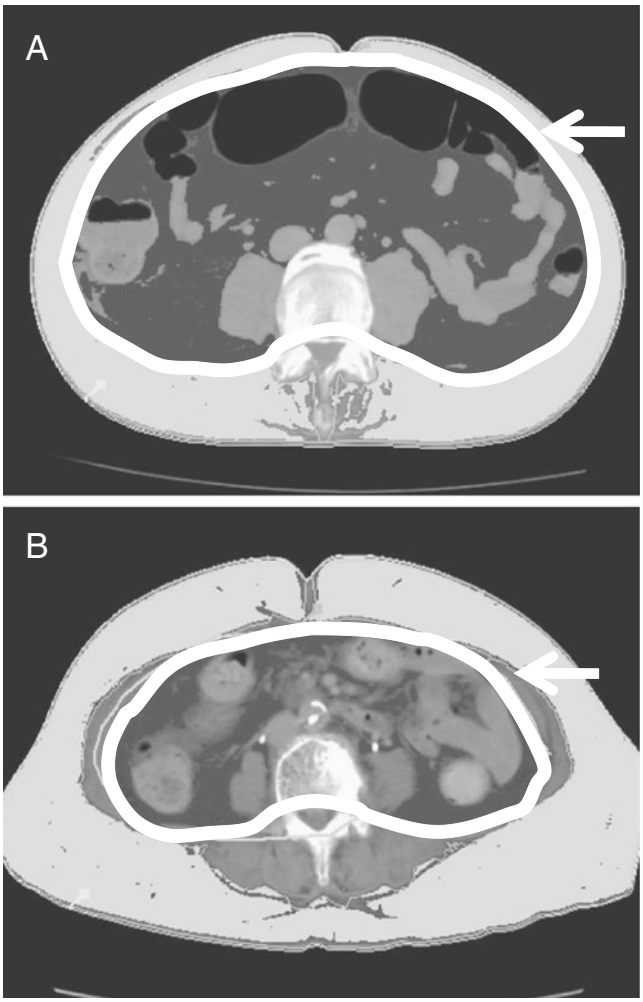

Fig. 1 Distribution of visceral fat area (VFA) by FatScan software on preoperative CT scan. The white line (*white arrow*) outlines the intraperitoneal area. Visceral fat tissue was calculated in the region outlined by the white line by FatScan software. A, VFA was 194.4 cm^2 and body mass index (BMI) was 19.6 kg/m^2, representing high VFA but low BMI. B, VFA was 71.1 cm^2 and BMI was 25.3 kg/m^2, representing low VFA but high BMI (high VFA≥130 cm^2 and low VFA<130 cm^2 and high BMI≥25 kg/m^2 and low BMI<25 kg/m^2)

software on preoperative CT scan. We have no financial relationship to disclose with the FatScan software used.

Surgical Treatment

All patients underwent PpPD with Traverso reconstruction or PD with Child reconstruction, with various extents of lymph node dissection, as described previously.[20, 21] All operations were performed by two experienced pancreatic surgeons (H.Y. and M.T.). Pancreaticojejunostomies were performed with duct-to-mucosa, end-to-side anastomosis in all patients.[22] A 5-French polyethylene pancreatic duct drainage tube (Sumitomo Bakelite, Tokyo, Japan) was used in an external or internal drainage stent for pancreaticojejunostomy. Hepaticojejunal anastomosis was performed end-to-side without stent, followed by pancreaticojejunostomies. Reconstruction of the duodenojejunostomies was performed by the antecolic route.[20] A single prophylactic closed-suction drain was routinely placed in the right upper quadrant around the pancreatic and biliary anastomosis.

Postoperative Complications

POPFs were defined according to the definition of the International Study Group on Pancreatic Fistula.[23] DGE and PPH were also defined according to definitions of the International Study Group of Pancreatic Surgery.[24, 25] In detail, POPF was defined as a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity.[23] DGE was defined by the need for maintenance of the nasogastric tube (NGT) for 3 days, need for reinsertion of NGT for persistent vomiting after postoperative day 3, or inability to tolerate a solid diet by postoperative day 7.[24] PPH is defined by three parameters: onset, location, and severity. The onset is either early (≤24 h after the end of the index operation) or late (<24 h), the location is either intraluminal or extraluminal, and the severity of bleed may be either mild or severe. Three different grades of PPH (grades A, B, and C) are defined according to these parameters.[25] PPCs were defined as pneumonia with evidence by radiologic pulmonary infiltrates and/or the presence of pathogenic bacteria in the sputum culture, and pulmonary atelectasis required frequent bronchoscopic toilet or prolonged ventilator support.[26] Pulmonary edema, pulmonary embolus, and acute respiratory distress syndrome were excluded, similar to previous reports.[27] Other postoperative complications were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v.3.0). In this study, adverse events of grades 2–5 within 30 days after surgery were expediently judged as postoperative complications. Adverse events of grade 1 were excluded because no medical treatment was required. Mortality was defined as death within 30 days after surgery.

Statistical Analysis

Any significance in the correlation between all variables and two variables (BMI and VFA) was evaluated by Mann–Whitney U test and linear regression analysis, where applicable. A P value of less than 0.05 was considered statistically significant. Risk factors for complications were analyzed by logistic regression analysis. Multivariate logistic regression analysis was performed incorporating all factors with $P<0.20$ on univariate analysis. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS, Chicago, Illinois).

Results

Clinicopathological Characteristics

Table 1 shows the clinicopathological characteristics of patients. Median BMI and VFA were 21.5 kg/m^2 (range 14.8–33.5) and 77.5 cm^2 (range 9.2–261.2), respectively. Association between characteristics and BMI/VFA were summarized in Table 2. BMI was significantly lower in patients with %VC<80 on spirogram (P=.0429) and was higher in patients of benign disease than malignant disease (P=.0334). Otherwise, gender and diabetes mellitus were demonstrated to have significant differences in VFA (P <.0001 and P=.0177, respectively). Other variables were statistically identical with both BMI and VFA.

Surgical Outcome

Median operative time was 358 min (range 185–723) and median estimated blood loss was 735 ml (range 45–9,100; Table 1). Relations between intraoperative outcome and BMI/VFA are shown in Table 3. The linear relationship was demonstrated to have a significant correlation between operative time and both BMI and VFA (P=.0088 and P<.0001, respectively). Estimated blood loss and required red blood cell transfusion were also demonstrated to have a significant correlation with VFA (P=.0008 and P=.0276), whereas for BMI the relation of estimated blood loss was only marginally correlated (P=.0575), and there was no difference between blood transfusion and BMI (P=.3341).

Table 1 Clinicopathological characteristics and intraoperative outcome of patients after pancreaticoduodenectomy

Variable	*N*=317
Age (years), median (range)	70 (35–91)
Gender (male/female)	181/136
Concomitant disease (yes/no)	
Cardiovascular disease	21/296
COPD	15/302
Diabetes mellitus	98/219
Recent smoking history[a] (yes/no)	87/230
Pulmonary function on spirogram	
%VC<80 (yes/no)	31/286
FEV1/FVC ratio<0.70 (yes/no)	64/253
Preoperative biliary drainage (yes/no)	127/190
Type of resection (PpPD/PD)	269/48
Additional portal vein resection (yes/no)	43/274
Pancreatic texture (soft/hard)	137/180
Histologic diagnosis (malignant/benign)	232/85
BMI median (range)	21.5 (14.8–33.5)
BMI (≥25/<25)	46/271
VFA median (range)	77.5 (9.2–261.2)
VFA (≥130/<130)	60/257
Operative time (min), median (range)	358 (185–723)
Estimated blood loss (ml), median (range)	735 (45–9100)
Red blood cell transfusion (yes/no)	114/203

COPD chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history means smoking within 4 weeks prior to surgery[17]

Postoperative Complications

Of all patients, 130 patients had postoperative complications (41.0%). The complications are listed in Table 4. The most common postoperative complication was POPF in 92 patients (29.0%), consisting of 61 grade A (19.2%), 27 grade B (8.5%), and four grade C (1.3%). The incidence of DGE was 35 patients (11.0%), consisting of six grade A (1.9%), ten grade B (3.2%), and 15 grade C (4.7%), and the incidence of PPH was 11 patients (3.5%), consisting of six grade B (1.9%) and five grade C (1.6%). PPCs occurred in 14 patients (4.4%). In the 14 patients with PPCs, seven were unexpectedly admitted to the intensive care unit, and the other five patients required intensive therapy by continuous positive airway pressure in the surgical ward. Mortality occurred in five patients (1.6%); causes were extraluminal hemorrhage (2), sepsis (1), disseminated intravascular coagulation (1), and nonobstructive mesenteric ischemia (1).

Differences Between Postoperative Complications and BMI/VFA

Table 5 shows the statistical differences between the occurrence of postoperative complications and variables of BMI/VFA. Both BMI and VFA in patients with complications were significantly higher than in those without complications (P=.0434 and P=.0189, respectively). Regarding POPF, BMI and VFA demonstrated no significant differences; however, the patients who developed grade B/C POPF had higher VFA than the patients who did not develop POPF (P=.0282). BMI and VFA were demonstrated

Table 2 Association between clinicopathological characteristics and BMI/VFA

Variable	BMI (median, range)	*P* value	VFA (median, range)	*P* value
Age, years (≥70/<70)	21.5 (15.4–33.5)/21.6 (14.8–30.5)	.8392	81.5 (9.2–261.2)/75.7 (10.4–241.1)	.2856
Gender (male/female)	21.5 (15.4–31.2)/21.5 (14.8–33.5)	.6235	93.5 (10.9–261.2)/68.8 (9.2–201.0)	<.0001
Concomitant disease (yes/no)				
Cardiovascular disease	21.1 (15.4–31.2)/21.5 (14.8–33.5)	.7506	81.3 (16.5–183.3)/76.2 (9.2–261.2)	.2040
COPD	21.2 (15.4–26.1)/21.5 (14.8–33.5)	.1443	88.1 (16.5–144.2)/77.1 (9.2–261.2)	.9290
Diabetes mellitus	21.5 (15.8–33.5)/21.5 (14.8–30.0)	.3623	90.6 (10.4–261.2)/75.8 (9.2–230.9)	.0177
Recent smoking history (yes/no)	21.3 (15.8–31.2)/21.6 (14.8–33.5)	.9967	86.1 (18.5–241.1)/75.2 (9.2–261.2)	.1201
Pulmonary function on spirogram				
%VC<80 (yes/no)	21.0 (15.4–26.7)/21.6 (14.8–33.5)	.0429	89.4 (16.5–241.1)/77.0 (9.2–261.2)	.5670
FEV1/FVC ratio<0.70 (yes/no)	21.6 (14.8–30.5)/21.5 (15.4–33.5)	.2694	75.9 (16.0–252.0)/78.8 (9.2–261.2)	.8427
Preoperative biliary drainage (yes/no)	21.4 (15.8–30.5)/21.6 (14.8–33.5)	.7919	74.5 (10.4–241.1)/81.7 (9.2–261.2)	.5363
Type of resection (PpPD/PD)	21.6 (14.8–33.5)/20.6 (15.4–31.2)	.0731	77.5 (10.0–261.2)/78.2 (9.2–209.3)	.3410
Additional portal vein resection (yes/no)	21.4 (16.2–28.3)/21.5 (14.8–33.5)	.8756	84.7 (10.4–208.5)/76.2 (9.2–261.2)	.7399
Pancreatic texture (soft/hard)	21.6 (14.8–31.2)/21.4 (15.4–33.5)	.4697	76.5 (10.0–241.1)/78.9 (9.2–261.2)	.6291
Histologic diagnosis (malignant/benign)	21.2 (15.4–33.5)/22.4 (14.8–30.0)	.0334	75.5 (10.4–252.0)/87.4 (9.2–261.2)	.1853

Table 3 Relation with intraoperative outcome

Variable	BMI			VFA		
	Regression coefficient	R^2	*P* value	Regression coefficient	R^2	*P* value
Operative time (min)	3.878	.022	.0088	0.377	.054	<.0001
Estimated blood loss (ml)	65.417	.011	.0575	7.023	.035	.0008
Red blood cell transfusion (units)	.088	.003	.3341	.012	.015	.0276

BMI body mass index, *VFA* visceral fat area

to have no statistical differences regardless of the occurrences of DGE and PPH. Median VFA of patients with PPCs was 135.7 (range 49.2–174.3), significantly higher than patients without PPCs (75.9; range 9.2–261.2) (P=.0058), whereas there was no difference in BMI. Both BMI and VFA showed no significant differences regardless of the occurrence of the other complications including intra-abdominal abscess, cardiovascular complication, bile leakage, sepsis, bowel obstruction, and wound infection. The mortality group had significantly higher BMI and VFA compared with the nonmortality group (P=.0143 and P=.0173, respectively).

Risk Factors Influencing the Incidence of POPF Grade B/C

BMI and VFA were categorized into two groups and assessed; 46 patients (14.5%) were categorized to high BMI (≥25.0 kg/m^2) and the other 271 patients (85.5%) were categorized to low BMI (<25.0 kg/m^2); similarly, 60 (18.9%) patients were categorized into high VFA (≥130 cm^2) and the other 257 (81.1%) into low VFA (<130 cm^2). Of all 31 patients with POPF grade B/C, five patients were in the high-BMI and high-VFA groups; however, two patients were in only the high-BMI group and two patients were in only the high-VFA group. Multivariate analysis demonstrated that preoperative biliary drainage and soft pancreas predicted the independent risk factor for POPF grade B/C (P=.0407 and P=.0004, respectively; Table 6).

Table 4 Incidence of postoperative complications after pancreaticoduodenectomy

Complication	Number of patients	%
Overall complications	130	41.0
POPF		
All grades	92	29.0
Grade A/B/C	61/27/4	19.2/8.5/1.3
DGE	32	10.1
PPH	11	3.5
Extraluminal hemorrhage	5	1.6
Intraluminal hemorrhage	6	1.9
Intra-abdominal abscess	38	12.0
PPCs	14	4.4
Cardiovascular complication	10	3.2
Bile leakage	9	2.8
Sepsis	11	3.5
Bowel obstruction	10	3.2
Wound infection	19	6.0
Mortality	5	1.6

POPF postoperative pancreatic fistula, *DGE* delayed gastric empting, *PPH* postpancreatectomy hemorrhage, *PPCs* postoperative pulmonary complications

Risk Factors Influencing the Incidence of PPCs

In the 14 patients who developed PPCs, four patients were in the high-BMI group (8.7%). On the other hand, eight patients were in the high-VFA group (13.3%). Six parameters that had a P value ≤ 0.20 by univariate analysis were selected for multivariate analysis, gender, additional portal vein resection, high BMI, high VFA, operative time, and estimated blood loss, and only high VFA was predicted as an independent risk factor influencing the incidence of PPCs (P=.0390, odds ratio 4.246, 95% confidence interval 1.076–16.759; Table 7).

Risk Factors Influencing Mortality

There were five postoperative mortalities (1.6%). Three patients were in the high-BMI group and two were in the low-BMI group, whereas four patients were in the high-VFA group and one was in the low-VFA group. Multivariate analysis demonstrated that recent smoking history (smoking within 4 weeks prior to surgery) was the only independent predictive factor (P=.0321, odds ratio 28.954, 95% confidence interval 1.332–629.405), although high BMI and high VFA were not consequently risk factors for postoperative mortality (P=.1145 and P=.7514, respectively; Table 8).

Discussion

In this study, VFA was demonstrated to be the independent risk factor for the incidence of PPCs after pancreaticoduo-

Table 5 Difference of BMI and VFA in postoperative complications

Complication	BMI (median, range)			VFA (median, range)		
	(+)	(−)	*P* value	(+)	(−)	*P* value
Overall complications	21.9 (15.6–33.5)	21.3 (14.8–31.2)	.0434	86.8 (15.0–261.2)	73.0 (9.2–252.0)	.0178
POPF						
All grades	21.7 (15.8–29.8)	21.4 (14.8–33.5)	.1364	87.7 (9.2–261.2)	74.0 (10.0–252.0)	.1420
Grade B/C	22.2 (16.2–29.8)	21.5 (14.8–33.5)	.0814	93.5 (20.1–261.2)	75.2 (9.2–252.0)	.0282
DGE	21.5 (15.6–28.4)	21.5 (14.8–33.5)	.7626	93.1 (22.3–201.0)	75.9 (9.2–261.2)	.1895
PPH						
Extraluminal hemorrhage	23.0 (19.4–26.6)	21.5 (14.8–33.5)	.3934	93.5 (73.5–160.9)	76.6 (9.2–261.2)	.2498
Intraluminal hemorrhage	24.9 (15.8–28.4)	21.5 (14.8–33.5)	.0507	144.6 (19.9–208.5)	76.6 (9.2–261.2)	.1219
Intra-abdominal abscess	22.2 (15.8–29.8)	21.5 (14.8–33.5)	.3191	89.6 (19.4–261.2)	75.8 (9.2–252.0)	.1088
PPCs	21.6 (19.6–28.3)	21.5 (14.8–33.5)	.1668	135.7 (49.2–174.3)	75.9 (9.2–261.2)	.0058
Cardiovascular complication	20.8 (18.7–28.6)	21.5 (14.8–33.5)	.9972	61.1 (28.7–261.2)	78.3 (9.2–252.0)	.9650
Bile leakage	19.3 (16.8–29.8)	21.5 (14.8–33.5)	.2588	79.3 (19.4–209.3)	77.1 (9.2–261.2)	.5888
Sepsis	20.6 (19.3–30.5)	21.5 (14.8–33.5)	.9306	114.2 (49.6–162.8)	76.2 (9.2–261.2)	.0680
Bowel obstruction	21.4 (19.6–28.6)	21.5 (14.8–33.5)	.6650	78.7 (18.8–261.2)	77.5 (9.2–252.0)	.6727
Wound infection	21.9 (16.8–33.5)	21.5 (14.8–31.2)	.4235	81.2 (15.0–194.8)	76.6 (9.2–261.2)	.8323
Mortality	25.3 (22.6–30.5)	21.5 (14.8–33.5)	.0143	142.7 (73.5–208.5)	76.6 (9.2–261.2)	.0173

Table 6 Univariate and multivariate analyses of risk factors for POPF grade B/C

Variable	Univariate analysis		Multivariate analysis	
	P value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)
Age, years (≥70 or <70)	.4370	1.346 (0.636–2.851)	–	–
Gender (male/female)	.6199	1.212 (0.567–2.591)	–	–
Concomitant disease (yes/no)				
Cardiovascular disease	.4353	0.443 (0.057–3.422)	–	–
COPD	.7067	1.236 (0.410–3.720)	–	–
Diabetes mellitus	.1490	0.506 (0.201–1.276)	.4037	0.661 (0.251–1.746)
Recent smoking history[a] (yes/no)	.1447	0.478 (0.178–1.289)	.1291	0.451 (0.161–1.261)
Pulmonary function on spirogram				
%VC<80% (yes/no)	.5154	0.611 (0.139–2.695)	–	–
FEV1/FVC ratio<0.70 (yes/no)	.7272	1.172 (0.481–2.855)	–	–
Preoperative biliary drainage (yes/no)	.0348	2.248 (1.060–4.771)	.0407	2.292 (1.036–5.071)
Type of resection (PpPD/PD)	.3771	1.743 (0.508–5.978)	–	–
Additional portal vein resection (yes/no)	.9099	0.938 (0.311–2.828)	–	–
Pancreatic texture (soft/hard)	.0002	5.296 (2.208–12.703)	.0004	5.100 (2.084–12.481)
Histologic diagnosis (malignant/benign)	.9263	0.975 (0.564–1.683)	–	–
BMI (≥25 or <25)	.1849	1.847 (0.746–4.576)	.0685	2.508 (0.932–6.743)
VFA (≥130 or <130)	.5854	1.282 (0.525–3.133)	–	–
Operative time (min; ≥350 or <350)	.5205	1.283 (0.600–2.741)	–	–
Intraoperative bleeding (ml; ≥1,000 or <1,000)	.7384	1.141 (0.525–2.481)	–	–
Red blood cell transfusion (yes/no)	.9534	0.977 (0.450–2.120)	–	–

COPD chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area, *CI* confidence interval

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

Table 7 Univariate and multivariate analyses of risk factors for PPCs

Variable	Univariate analysis		Multivariate analysis	
	P value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)
Age, years (≥70 or <70)	.3300	1.742 (0.570–5.318)	–	–
Gender (male/female)	.0435	4.757 (1.047–21.625)	.1863	2.956 (0.592–14.750)
Concomitant disease (yes/no)				
Cardiovascular disease	.9365	1.088 (0.135–8.748)	–	
COPD	.6666	1.588 (0.194–13.015)	–	–
Diabetes mellitus	.4367	0.597 (0.163–2.190)	–	–
Recent smoking history[a] (yes/no)	.4808	1.497 (0.487–4.600)	–	–
Pulmonary function on spirogram				
%VC<80% (yes/no)	.7354	0.700 (0.088–5.541)	–	–
FEV1/FVC ratio<0.70 (yes/no)	.5763	0.648 (0.141–2.971)	–	–
Preoperative biliary drainage (yes/no)	.7345	0.824 (0.270–2.519)	–	–
Type of resection (PpPD/PD)	.5053	0.640 (0.172–2.383)	–	–
Additional portal vein resection (yes/no)	.1059	2.708 (0.810–9.057)	.2929	2.034 (0.542–7.635)
Pancreatic texture (soft/hard)	.2712	0.515 (0.158–1.679)	–	–
Histologic diagnosis (malignant/benign)	.4451	0.646 (0.210–1.985)	–	–
BMI (≥25 or <25)	.1384	2.486 (0.745–8.291)	.8179	0.841 (0.193–3.673)
VFA (≥130 or <130)	.0009	6.436 (2.142–19.333)	.0390	4.246 (1.076–16.759)
Operative time (min; ≥350 or <350)	.0216	11.018 (1.423–85.304)	.0678	7.258 (0.865–60.932)
Intraoperative bleeding (ml; ≥1,000 or <1,000)	.1697	2.124 (0.725–6.224)	.6801	0.778 (0.236–2.566)
Red blood cell transfusion (yes/no)	.2692	1.832 (0.626–5.361)	–	–

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

denectomy. Additionally, BMI did not statistically correlate with the incidence of PPCs. Smetana et al. concluded that obesity was not a risk factor for PPCs[14] because many studies reported that obesity had not increased the risk for PPCs after noncardiothoracic surgery.[28, 29] However, obesity was defined by BMI. As shown in Fig. 1, visceral fat has an individual distribution. In the high-VFA group, 29 patients (48.3%) were interestingly of normal BMI, and 15 patients of high BMI (32.6%) had VFA less than 130 cm^2; these results indicate that BMI and VFA are independent factors from each other for evaluation of the obesity status, and BMI could not always reflect the amount of visceral fat for surgeons.

After abdominal surgery, various factors have been considered to modify postoperative pulmonary dysfunction, that is, rapid shallow breathing, prolonged supine position,[30] pain and anesthesia-induced diaphragmatic dysfunction,[31] and impaired mucociliary clearance.[32] Visceral fat accumulation increases intra-abdominal pressure[33] to pump the diaphragmatic muscle upward, compressing the parenchyma of the lung. Consequently, patients with visceral obesity are affected by a restrictive respiratory impairment with decreased expiratory reserve volume and functional residual capacity.[15, 16] It was considered that the restrictive respiratory impairment caused by visceral fat accumulation may further impair pulmonary function in the perioperative period and lead to PPCs.

In the present study, overall POPF were not associated with BMI and VFA; however, the patients who developed POPF grade B/C showed significantly higher VFA than patients without grade B/C POPF, regardless of risk factors for POPF grade B/C. House et al. showed that the patients with retrorenal visceral fat thickness were associated with the incidence of pancreatic fistula after pancreaticoduodenectomy.[34] Moreover, fatty infiltration into the pancreatic parenchyma was demonstrated as a risk factor for POPF after pancreaticoduodenectomy;[35, 36] therefore, further studies are expected to associate VFA, fatty infiltration, and POPF.

Patients with postoperative mortality had significantly higher BMI and higher VFA than other patients, whereas neither BMI nor VFA was a risk factor for mortality.

Table 8 Univariate and multivariate analyses of risk factors for mortality

Variable	Univariate analysis		Multivariate analysis	
	P value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)
Age, years (≥70 or <70)	.6097	0.625 (0.103–3.794)	–	–
Gender (male/female)	.3201	3.051 (0.337–27.615)	–	–
Concomitant disease (yes/no)				
Cardiovascular disease	.9796	NE	–	–
COPD	.9828	NE	–	–
Diabetes mellitus	.9690	NE	–	–
Recent smoking history[a] (yes/no)	.0329	11.036 (1.216–100.187)	.0321	28.954 (1.332–629.405)
Pulmonary function on spirogram				
%VC<80% (yes/no)	.4513	2.350 (0.254–21.716)	–	–
FEV1/FVC ratio<0.70 (yes/no)	.2844	2.688 (0.440–16.440)	–	–
Preoperative biliary drainage (yes/no)	.3719	2.274 (0.375–13.809)	–	–
Type of resection (PpPD/PD)	.9795	NE	–	–
Additional portal vein resection (yes/no)	.1101	4.407 (0.714–27.176)	.0695	14.656 (0.807–266.262)
Pancreatic texture (soft/hard)	.3185	0.326 (0.036–2.950)	–	–
Histologic diagnosis (malignant/benign)	.1191	0.238 (0.039–1.448)	.0684	0.048 (0.002–1.258)
BMI (≥25 or <25)	.0158	9.384 (1.523–57.805)	.1145	26.257 (0.453–1520.454)
VFA (≥130 or <130)	.0100	18.286 (2.005–166.773)	.7514	1.695 (0.065–44.353)
Operative time (min; ≥350 or <350)	.9763	NE	–	–
Intraoperative bleeding (ml; ≥1,000 or <1,000)	.2148	3.134 (0.515–19.053)	–	–
Red blood cell transfusion (yes/no)	.0761	7.345 (0.811–66.545)	.1175	15.023 (0.505–447.051)

CI confidence interval, *NE* not able to estimate, *COPD* chronic obstructive pulmonary disease, *%VC* percentage predicted vital capacity, *FEV1/FVC ratio* ratio of forced expiratory volume in 1 s to forced vital capacity, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PD* pancreaticoduodenectomy, *BMI* body mass index, *VFA* visceral fat area

[a] Recent smoking history = smoking within 4 weeks prior to surgery[17]

Fortunately, our study had a low incidence of mortality (n= 5, 1.6%); therefore, the influence of VFA on mortality cannot be evaluated.

The limitations of our study include the facts that the racial responses to relative levels of obesity with the population in Japan differ across much of the Western countries. WHO defines obesity as BMI≥30.0, but the prevalence of the population with such a BMI is less than 3% of the general population in Japan.[37] The Western Pacific Region of the WHO has recommended lowering the BMI cutoff levels for Asian people to 25.0 for obesity[37] because of occurring of obesity-related disorders at a much lower BMI than in Caucasian populations. For this point, we defined high BMI as BMI≥25.0 kg/m^2 in this study.

In the present study, we categorized the patients into high- and low-VFA groups using the cutoff value of VFA determined to be 130 cm^2 for logistic regression analysis because VFA≥130 cm^2 has been reported to be a risk factor for cardiovascular disease,[38] metabolic syndrome,[39] and the complication of laparoscopic sigmoidectomy.[40] However, the optimal cutoff value for VFA still remains unclear, and it is essential to determine the optimal cutoff value of VFA for pancreatic surgery.

It has been demonstrated that adipose tissue is not only for fat storage but is also a metabolically active organ secreting several hormones, adipocytokines, including adiponectin, leptin, tumor necrosis factor-α, interleukin-6, angiotensinogen, and plasminogen activator inhibitor 1. Circulating adiponectin levels correlate inversely with VFA, and hypoadiponectinemia with visceral adiposity is associated with a low-grade systemic inflammatory environment.[41] Indeed, a low preoperative adiponectin level was an independent risk factor for the development of postoperative infections after colorectal cancer surgery.[42] These results suggest that adipocytokines with visceral obesity may influence postoperative complications, including PPCs.

To prevent PPCs, prophylactic respiratory physiotherapy, management of immune status, and fast-track recovery pathways including early mobilization are thought to be effective; therefore, careful perioperative management may be more essential for patients with visceral obesity.

In conclusion, visceral obesity was the independent risk factor for the incidence of PPCs after pancreaticoduodenectomy. Preoperative VFA measurements using CT scan may be a useful tool for the prediction of the development of PPCs compared to BMI calculation and may reduce the incidence of PPCs through careful management of patients with high VFA.

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ORIGINAL ARTICLE

The Influence of Prognostic Factors and Adjuvant Chemoradiation on Survival After Pancreaticoduodenectomy for Ampullary Carcinoma

Timothy N. Showalter · Tingting Zhan · P. Rani Anne · Inna Chervoneva · Edith P. Mitchell · Charles J. Yeo · Ernest L. Rosato · Eugene P. Kennedy · Adam C. Berger

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Abstract

Introduction The prognosis after pancreaticoduodenectomy (PD) for ampullary carcinoma (AC) is superior to that of pancreatic cancer. Decisions regarding adjuvant therapy are influenced by factors such as nodal status, stage, and grade, but the influence of these individual variables on survival is unclear.

Methods A prospective tumor registry database was queried to identify patients who underwent PD for AC at Thomas Jefferson University between Jan 1997 and Apr 2009. The study was conducted with the approval of the institutional review board. Data were collected through review of hospital and departmental charts. Overall survival (OS) was analyzed using univariate and multivariate Cox proportional hazard models. The proportional hazard assumption was verified for the overall model and individual covariates.

Results A total of 61 patients underwent PD for AC at our institution. There were five perioperative deaths (8.2%). Mean age was 70 years (62% male). Median survival time (MST) was 50 months for all patients. Only primary tumor stage, T1/T2 versus T3/T4 (American Joint Committee on Cancer Staging, version 6), was associated with OS in univariate analyses ($p=0.003$). The association of nodal status with OS was borderline-significant ($p=0.08$), with the MST being 84 months for node-negative and 17 months for node-positive patients. The remaining covariates were not predictors of OS. In the multivariate analysis, only primary tumor stage (HR, 5.1; $p<0.001$) and age (HR, 1.04; $p=0.06$), but not nodal status or adjuvant therapy, were associated with overall survival.

Conclusions Advanced primary tumor stage and age were associated with inferior OS after PD for AC. Adjuvant therapy did not impact survival. Patients with advanced tumor stage should be considered for clinical trials of adjuvant therapy after PD with novel compounds and optimized radiation therapy strategies.

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T. N. Showalter · P. R. Anne
Department of Radiation Oncology, Jefferson Medical College of Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, PA, USA

T. Zhan · I. Chervoneva
Division of Biostatistics, Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA, USA

E. P. Mitchell
Department of Medical Oncology, Jefferson Medical College of Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, PA, USA

C. J. Yeo · E. L. Rosato · E. P. Kennedy · A. C. Berger
Department of Surgery, Jefferson Medical College of Thomas Jefferson University, and the Jefferson Pancreas, Biliary and Related Cancer Center, Philadelphia, PA, USA

A. C. Berger (✉)
1100 Walnut Street, MOB, Suite 500, Philadelphia, PA 19147, USA
e-mail: adam.berger@jefferson.edu

Keywords Ampullary cancer · Adjuvant therapy · Ampulla of Vater · Adenocarcinoma

Introduction

Carcinoma of the ampulla of Vater is a relatively uncommon malignancy and accounts for approximately 10% to 20% of pancreaticoduodenectomies (PDs) performed for periampullary cancers.[1–3] Prognosis after PD for ampullary carcinoma (AC) is superior to that of pancreatic cancer (PC), with higher rates of complete surgical resection, lower recurrence rates, and longer survival.[1] Published 5-year overall survival (OS) rates for ampullary carcinoma range from 38% to 68%.[1–7] There are less published data available for AC than for PC to assist with decisions regarding adjuvant therapy. The only randomized, prospective trial of adjuvant radiotherapy and concurrent chemotherapy to include patients with AC was the one reported by the European Organization for Research and Treatment of Cancer (EORTC).[8] This study randomized patients with cancers of the pancreatic head or the periampullary region, defined as the distal common bile duct, ampulla of Vater, or duodenum, to the addition of adjuvant chemoradiotherapy (CRT) after surgery versus surgery alone. The study results showed that CRT did not improve OS rates in this trial. Results of this study are controversial, but they do not lend support for adjuvant therapy for either PC or AC.[8] Retrospective, single-institution studies have suggested conflicting results for the role of CRT in AC; most notably that adjuvant CRT extends survival either only in patients with involved lymph nodes,[5] or only in patients with advanced tumor stage.[9]

Table 1 Pathologic staging system for ampullary carcinoma used in the seventh edition of the American Joint Committee on Cancer staging system

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined in ampulla of Vater or sphincter of Oddi
T2	Tumor involves duodenal wall
T3	Tumor invades pancreas
T4	Tumor invades peripancreatic soft tissue or other organs
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 2 Stage grouping for ampullary carcinoma used in the seventh edition of the American Joint Committee on Cancer staging system

Stage grouping			
Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Previous retrospective studies have identified clinical and pathologic factors that predict poorer outcome after PD for AC, in an effort to identify high-risk patients who may benefit most from adjuvant therapy. Reported prognostic factors include specimen lymph node involvement, poor histologic

Table 3 Age, tumor, and adjuvant therapy information for 61 ampullary carcinoma patients who were treated with pancreaticoduodenectomy

Factor	Value
Age	
Mean (year (interquartile range))	70 (54–76)
Grade (*N* (%))	
Well differentiated	6 (10%)
Moderately differentiated	36 (59%)
Poorly differentiated	16 (26%)
Unknown	3 (5%)
Stage (*N* (%))	
I	19 (31%)
II	29 (48%)
III	12 (20%)
IV	1 (2%)
Nodal status (*N* (%))	
N0	20 (33%)
N1	41 (67%)
Surgical margin status (*N* (%))	
R0 (negative)	58 (95%)
R1 (microscopic positive)	3 (5%)
R2 (macroscopic positive)	0 (0%)
Adjuvant chemoradiotherapy (*N* (%))	
Yes	16 (26%)
No	36 (59%)
Unknown	9 (15%)
Adjuvant chemotherapy (*N* (%))	
Yes	25 (41%)
No	28 (46%)
Unknown	8 (13%)

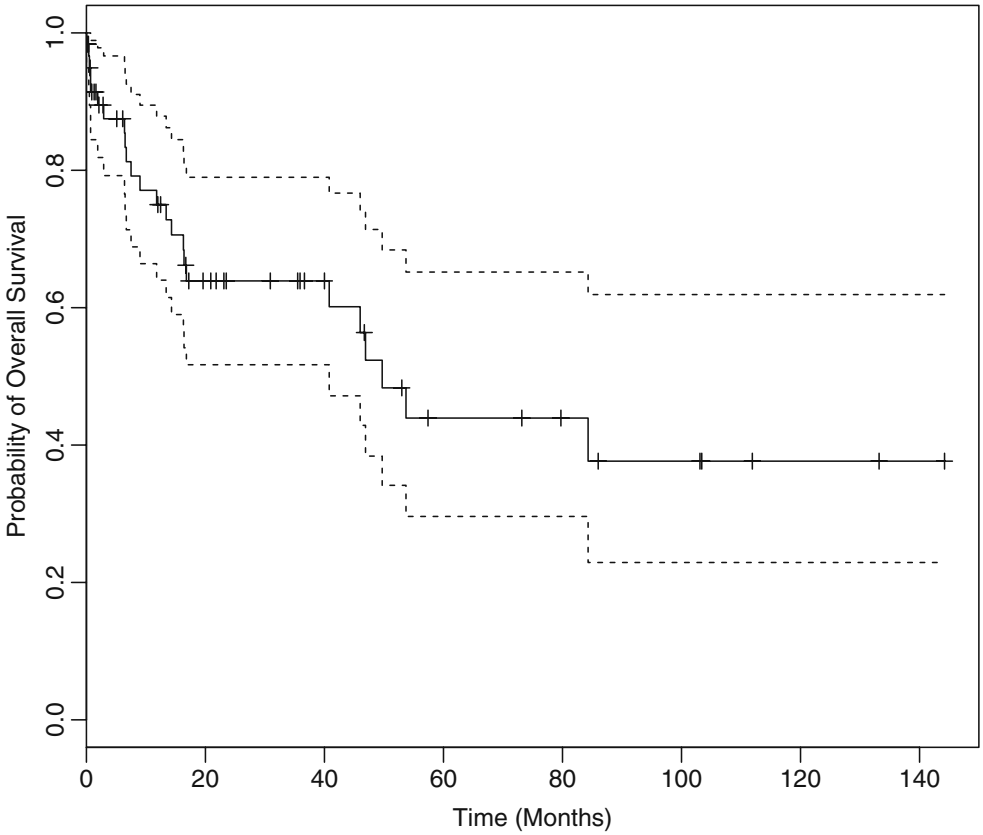

Fig. 1 Kaplan–Meier plot of overall survival (*solid line*) for all ampullary carcinoma patients (n=61) after pancreaticoduodenectomy, with 95% confidence interval (*dashed line*)

grade, positive resection margins, and higher tumor stage (T3/T4 vs. T1/T2).[1,3,5,7,10,11] This analysis of outcomes for patients treated for AC at Thomas Jefferson University Hospital was performed to evaluate the associations of reported prognostic factors with overall survival after PD, and to assess the impact of adjuvant CRT on overall survival.

Methods

A prospective tumor registry database was queried to identify patients who underwent PD for AC at Thomas Jefferson University between Jan 1997 and Apr 2009. The study was conducted with the approval of the institutional review board. Data were collected through chart review and included age, gender, perioperative complications, margin status, stage, adjuvant therapy, survival, and recurrence. Tumor staging was performed according to the 7th edition of the American Joint Committee on Cancer Staging Manual (Tables 1 and 2). During the study period, decisions regarding adjuvant therapy were made by the treating physicians without a consistent policy, but the tendency was to reserve CRT for those patients with high-risk features such as positive nodes. Based on institutional treatment policies, intraoperative radiation therapy (IORT) was also considered in addition to CRT for any patient who

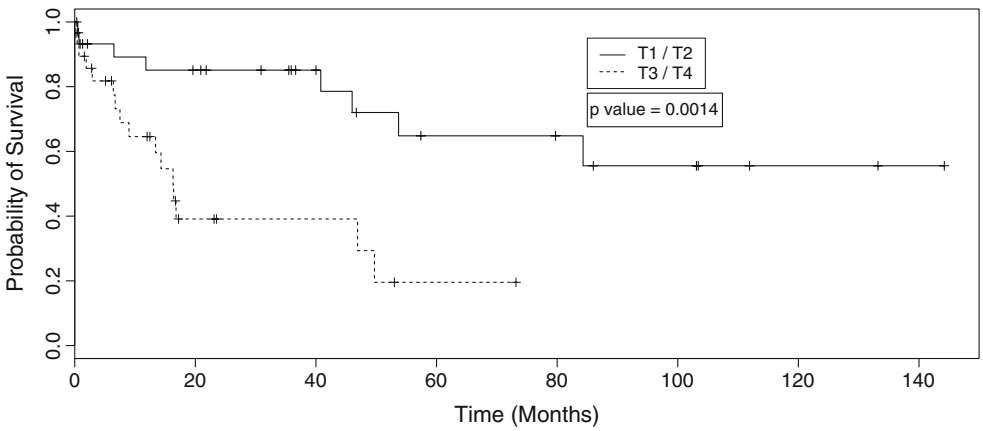

Fig. 2 Kaplan–Meier plot of overall survival for ampullary carcinoma patients after pancreaticoduodenectomy by primary tumor stage, comparing T1/T2 tumors (*solid line*, n=33) to T3/T4 tumors (*dashed line*, n=28; p=0.003)

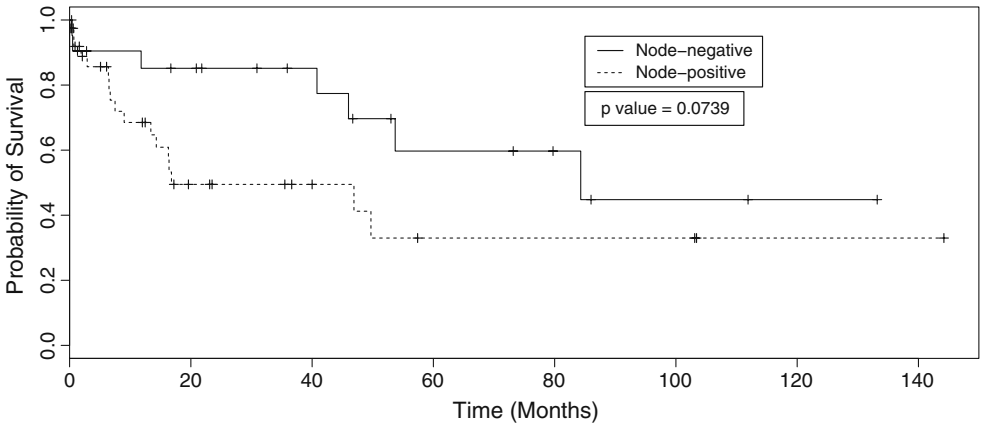

Fig. 3 Kaplan–Meier plot of overall survival for ampullary carcinoma patients after pancreaticoduodenectomy by nodal status, comparing lymph node negative (N0, *solid line*, $n=20$) to lymph node positive (N1, *dashed line*, $n=41$; $p=0.081$)

received PD at our institution until 1998 and was subsequently reserved for those patients thought to have higher risk of positive margins.[12]

Time to recurrence was estimated from the date of surgical resection, and the location of first recurrence was recorded. The recurrence rate for node-positive tumors was compared with node-negative tumors using Fisher's exact test. Overall survival (OS) was estimated from the date of surgical resection. The overall survival was analyzed using univariate and multivariate Cox proportional hazard models and reported including 95% confidence interval (CI). For statistical analysis, tumor (T) stage was dichotomized as "low" (T1/T2) versus "high" (T3/T4), and the histological grade was dichotomized as "low" (well and moderately differentiated) versus "high" (poorly differentiated). Factors included in the multivariate analysis were age, primary tumor stage (T1/T2 vs. T3/T4), grade, nodal status (N0 vs. N1), adjuvant CRT, and adjuvant chemotherapy. The final multivariate Cox model was selected using the Akaike Information Criterion.[13] The proportional hazard assumption was verified for the overall model and for the individual covariates. Data were analyzed in R 2.10 (R Foundation for Statistical Computing, http://www.R-project.org).

Results

Sixty-one patients were identified who underwent PD for AC at our institution between Jan 1997 and Apr 2009. There were five perioperative deaths (8.2%), with the causes being pulmonary embolism in one patient, respiratory failure in one patient, and cardiac events in three patients. Median follow-up of surviving patients was 22.4 months. Average age was 70 years and 62% were male. Negative microscopic margins (R0) were achieved in 58 patients (95%). Positive margins ($n=3$) were identified at the uncinate ($n=1$) and circumferential ($n=2$) margins of resection. Sixteen patients (29%) received adjuvant RT, which was delivered in combination with concurrent 5-fluorouracil (5-FU) or capecitabine. External beam RT doses used during CRT were 45–52.2 Gy in daily fractions of 1.8 Gy, with a median dose of 50.4 Gy. Five patients treated with adjuvant CRT also received IORT boost (median dose, 15 Gy) after completion of external beam RT. A total of 25 patients received adjuvant chemotherapy alone, with or without CRT, including gemcitabine or 5-FU (Table 3).

Recurrence

Tumor recurrence was observed in 20 patients (36%) at a median of 10.5 months after surgery. Distant metastases were present at the time of first recurrence in 13 patients, including liver in 11 patients and lungs in three patients. Regional lymph nodes were involved at time of first recurrence for six patients. Initial recurrence of AC was noted to be locoregional only, without any distant

Table 4 Univariate Cox proportional models of overall survival

Variable	Hazard ratio (95% confidence interval)	*p* value
Tumor stage (T1/2 vs. T3/4)	4.05 (1.6–10.1)	0.003
Grade (well/moderate vs. poor)	1.8 (0.8–4.5)	0.183
Age	1.0 (1.0–1.1)	0.225
Nodal status (negative vs. positive)	2.2 (0.9–5.4)	0.081
Adjuvant chemoradiotherapy (yes vs. no)	1.2 (0.5–3.0)	0.713
Adjuvant chemotherapy alone (yes vs. no)	0.9 (0.4–2.0)	0.741
Gender (male vs. female)	0.6 (0.2–1.4)	0.235

dissemination, for four patients. Three of 20 (15%) node-negative patients developed recurrence, which occurred in regional lymph nodes (n=1) and liver (n=2). Seventeen of 41 (41%) node-positive patients developed recurrence, which occurred in regional lymph nodes (n=5), liver (n=9), and lungs (n=3). The recurrence rate for node-negative patients was significantly lower than for node-positive patients (p=0.03).

Survival

The median survival time (MST) was 50 months for all patients, with 2- and 5-year OS rates of 64% (95% CI, 52–80%) and 44% (95% CI, 30–65%), respectively (Fig. 1). The 2- and 5-year OS rates were 85% (95% CI, 73–100%) and 65% (95% CI, 46–92%), respectively, for T1/T2 tumors (n=33) versus 39% (95% CI, 23–67%) and 20% (95% CI, 6–60%) for T3/T4 tumors (n=28) (p=0.003). The MST was not reached for the T1/T2 group, and was 16 months for the T3/T4 group (Fig. 2). The MST, 2- and 5-year OS rates were 84 months, 85% (95% CI, 71–100%) and 60% (95% CI, 38–94%), respectively, for node-negative tumors, versus 17 months, 50% (95% CI, 34–72%) and 33% (95% CI, 17–65%) for node-positive tumors (Fig. 3) (p=0.081). As concerns OS, by univariate analyses, neither tumor grade, age, gender, adjuvant chemotherapy, nor adjuvant CRT were associated with overall survival. However, tumor stage was associated with OS (p=0.003), and nodal status demonstrated a borderline-significant association (p=0.08) (Table 4). In multivariate analysis, only tumor stage (T1/2 vs. T3/4) was significantly associated with OS, with HR 5.08 (95% CI, 1.95–13.25, p<0.001), and age had borderline-significant association, with HR 1.04 (95% CI 1.00–1.08, p=0.06). Tumor grade, nodal status, adjuvant CRT, and adjuvant chemotherapy were not significant independent predictors of survival.

Discussion

In the current study, tumor stage and age were associated with OS, and the MST was not reached for T1/T2 tumors. A similar association between tumor stage and OS has been reported in previous series, including recent reports from MD Anderson Cancer Center[9] and Johns Hopkins Hospital[14] that showed inferior OS for T3 and T4 AC tumors compared with T1 and T2 tumors. The median survival seen in the current series compares favorably with that found at Hopkins (50 vs. 36 months). Additionally, 5-year survival rates were similar for lymph node-negative (60%) and T1/T2 tumors (65%) to those seen in the group reported by M.D. Anderson. The significant association between age and OS differs from the findings of other investigators, including Krishnan et al. and Yeh et al., who found that advanced age was not associated with inferior survival after PD for AC.[9,15] Conclusions regarding the influence of age on OS for AC are limited due to the relatively small numbers of patients in these series. Lymph node involvement, which has been shown to be associated with OS in multiple series,[1,3,5,16,17] was a borderline-significant predictor of OS in the current series, with median survival time of 84 months for N0 patients versus 17 months for N1 patients. In our experience, lymph node-negative AC patients had lower rates of recurrence and better overall survival than patients with nodal involvement. The current study is limited by its retrospective design, with non-randomized treatment allocation, as well as the relatively small number of patients treated for this uncommon cancer diagnosis. It is possible that a significant association between nodal status and OS would be revealed with a larger population of AC patients.

The role of adjuvant CRT in the management of AC is not clear. In the present study, adjuvant CRT did not influence OS. Interpretation of the observed lack of effect of CRT on OS is limited by the small number of patients in this study; less than 50% of patients in our series received any adjuvant therapy. The EORTC prospective trial of CRT for periampullary cancers included 92 patients with AC. In this EORTC trial, which comprised the only prospective, randomized data for CRT in AC, CRT did not improve OS, with a 2-year survival rate of 70% versus 64% with and without CRT, respectively.[8] Similarly, Zhou and colleagues, in their 2009 report of 111 AC patients treated at the Johns Hopkins Hospital, also observed no clinical benefit from CRT.[14] A recent report by Krishnan et al., from MD Anderson, observed that CRT improved survival for AC patients with T3/T4 tumors, but not for patients with involved lymph nodes.[9] On the other hand, adjuvant CRT has been reported by other authors to improve survival for AC patients with positive lymph nodes.[5,18] Future studies that include a larger number of patients may provide further insight into which subsets of AC patients will benefit from adjuvant CRT.

Previous reports have focused on the identification of high-risk factors that predict for higher rates of recurrence, using either models of multiple pathologic factors or lymph-node-based parameters, such as number of positive nodes and lymph node ratio.[10,16,17] Given the influence of lymph node status on rates of recurrence and survival after PD for AC, it seems reasonable to consider closely these lymph node parameters when evaluating prognosis. Recent data have demonstrated that primary tumor stage and nodal status are correlated in AC, with increased risk of nodal metastasis for T3/4 (71.1–77.3%) versus T1/2 (28.0–50.9%) tumors.[19] It is unclear whether these prognostic approaches may be used as the basis for decisions regarding adjuvant CRT for AC patients. Although the current analysis suggests that tumor stage, age,

and lymph node involvement are associated with overall survival, the addition of adjuvant CRT after PD did not improve survival. Since they are associated with inferior survival after PD, these adverse factors should be considered when developing novel strategies for adjuvant therapy for AC patients.

In conclusion, only primary tumor stage, and not nodal status or the use of adjuvant CRT, was associated with OS after PC for AC. Patients with advanced primary tumor stage should be considered for clinical trials of adjuvant therapy with novel compounds and optimized RT strategies, while observation following surgical resection may be considered for patients with T1/2 and node-negative AC.

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ORIGINAL ARTICLE

Therapeutic Management of Hemorrhage from Visceral Artery Pseudoaneurysms after Pancreatic Surgery

Xiangjiu Ding · Jiankang Zhu · Min Zhu · Caixia Li · Wencheng Jian · Jianjun Jiang · Zhanmin Wang · Sanyuan Hu · Xusheng Jiang

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Abstract
Introduction Hemorrhage from pseudoaneurysms after pancreatic surgery is a rare but life-threatening and complicated complication. The study presents our experience to provide therapeutic management for this rare condition.
Methods Between February 1994 and January 2011, 35 patients experienced hemorrhage from pseudoaneurysms in our hospital. Medical data of this rare complication were analyzed retrospectively.
Results The prevalence of hemorrhage from pseudoaneurysms was 3.2% (35/1,102). Sixteen patients (45.7%) experienced sentinel bleeding. Pancreatic fistula (74.3%) and intra-abdominal abscess (57.1%) were two common complications prior to hemorrhage. Of 35 patients, 20 underwent endovascular intervention, 14 received surgical re-laparotomy, and bleeding stopped spontaneously in one. The overall mortality rate was 22.9%. Technical success rate of endovascular treatment was 87%. There were significant differences in the mortality rate (10.0% vs 42.9%), operation time (72.8 vs 123.9 min), estimated blood loss (1,835 vs 3,000 ml), and intensive care unit stay (3.6 vs 8.6 days) between endovascular and surgical treatment. Mean follow-up was 19.2±17.0 (range, 5–63 months).
Conclusion Endovascular intervention represents the first-line treatment for hemorrhage from pseudoaneurysms after pancreatic surgery. Endovascular embolization or stent-graft placement should be selected individually depending on the involved artery and its vascular anatomy.

Keywords Hemorrhage · Pseudoaneurysm · Pancreatic surgery

Introduction

The mortality after pancreatic surgery has decreased significantly over the last two decades,[1–4] however, the morbidity remains considerably high, ranging from 36% to 55%.[3–6] Hemorrhage after pancreatic surgery is a less common but serious complication with an incidence of 1.5% to 15%.[7–9] Postoperative hemorrhage may result from insufficient intraoperative hemostasis, peptic ulcer, marginal ulcer, anastomotic dehiscence, or pseudoaneurysm rupture.[10] Hemorrhage from ruptured pseudoaneurysms is a rare entity,[11,12] however, it's usually massive, rapidly progressive, and life-threatening, which is associated with a high mortality rate of up to 54%.[13–15]

Management of hemorrhage from pseudoaneurysms is usually difficult. Surgical hemostasis would be difficult and hazardous because of postsurgical adhesions and critical general condition.[13] Endovascular embolization may stop bleeding immediately but often sacrifices the involved

Xiangjiu Ding and Jiankang Zhu contributed equally to this work.

X. Ding · J. Zhu · M. Zhu · J. Jiang · Z. Wang · S. Hu (✉) · X. Jiang (✉)
Department of General Surgery,
Qilu Hospital of Shandong University,
107 Wenhua Xi Road,
Jinan 250012, China
e-mail: husanyuan1962@hotmail.com

X. Jiang
e-mail: jiangxusheng@yahoo.com.cn

C. Li · W. Jian
Department of Radiology, Qilu Hospital of Shandong University,
107 Wenhua Xi Road,
Jinan 250012, China

artery, which may lead to fatal ischemia or necrosis of the supplied organ or tissue.[14,15] Endovascular stent-graft placement is still a new technique for ruptured pseudoaneurysms.[16–18] The optimal treatment for hemorrhage from pseudoaneurysms remains unclear and controversial. The aim of the current study was to summarize our experience in 35 patients from 1994 to 2011 to propose therapeutic strategies for the management of this rare condition. Special focus was given to endovascular techniques. To our knowledge, most literature was limited to case reports or small series,[11–18] and we believe it is the largest single-institution series to date.

Patients and Methods

Patients

From February 1994 to January 2011, 1,102 patients underwent pancreatic surgery in our hospital. All patients included were those who experienced hemorrhage after pancreatic surgery. Postoperative hemorrhage from pseudoaneurysms was confirmed by angiography or open surgery. The study excluded patients with postoperative hemorrhage which was caused by insufficient hemostasis, peptic ulcer, anastomotic ulcer, or anastomotic dehiscence. These causes were usually demonstrated by surgery or endoscopy. Also, we excluded patients with postoperative hemorrhage of unknown etiology. Medical data for clinical characteristics, management, outcomes, and follow-up data were analyzed retrospectively.

Intra-abdominal abscess was defined as intra-abdominal fluid collection which was proven by computed tomography (CT), or ultrasonography, in association with clinical characteristics of abdominal pain, temperature of higher than 38°C, or leukocyte counts of more than 15×10^9/L.[15] A drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity was considered to be pancreatic fistula.[19] Intermittent minor bleeding from the gastrointestinal tract or surgical drains which occurred 12 h before massive hemorrhage was regarded as "sentinel" bleeding.[20]

Therapeutic Management

All patients received prompt resuscitation with fluids, packed red blood cells, or plus fresh frozen plasma, when hemorrhage or hypovolemic shock was identified. Vital signs were observed by blood pressure measurement and electrocardiographic monitoring. Surgical hemostasis and endovascular treatment including embolization and stent-graft placement were employed in this study.

Surgical Intervention

At the early stage of this study, surgical intervention was the conventional treatment because of unavailability of endovascular expertise (n=5). Then, surgical treatment was usually performed in those patients who could not be resuscitated for endovascular treatment or in whom endovascular attempts failed. Surgical procedures included removal of hematoma, ligation or repair of the involved arteries, and reconstruction of the anastomosis or external drainage of pancreatic duct if possible.

Endovascular Intervention

Endovascular treatment was usually performed in patients whose condition could be maintained stable with fluid loading and blood transfusion. Informed consent was obtained from all patients before endovascular procedures. Technical success was defined as successful deployment of coils, stent-grafts or coils plus *N*-butyl-2-cyanoacrylate in the targeted artery, exclusion of the pseudoaneurysm without evidence of contrast extravasation, and cessation of bleeding.[21]

Diagnostic Angiography

Endovascular procedures were performed under local anesthesia. The femoral artery was usually punctured firstly. A 0.035-inch guidewire was introduced via the femoral artery. A 4F pigtail or Cobra catheter was advanced over the guidewire. The celiac axis, its branches (the hepatic and splenic arteries), and the superior mesenteric artery (SMA) were selectively catheterized, and angiography was performed to identify the bleeding site. After localization of the bleeding site, the treatment choice was mainly based on the involved artery and its vascular anatomy. Stent-graft implantation was not performed in several potentially suitable patients due to unavailability of expertise in stent-graft placement at that time.

Transcatheter Arterial Embolization

Two embolization techniques were used in our series: (1) embolization of the outflow and inflow arteries of the pseudoaneurysm, the so-called "isolation technique"[22]; (2) embolization of the inflow artery of the pseudoaneurysm. Thirteen patients were embolized with stainless steel coils alone (Cook Inc, Bloomington, Ind).

A combination of coils and *N*-butyl-2-cyanoacrylate (BNCA; Cordis Neurovascular, Miami, FL) was used in two patients with pseudoaneurysms of the gastroduodenal artery (GDA).

Stent-Graft Placement

In order to facilitate delivering the stent-grafts, the brachial artery was also punctured in two patients with pseudoaneurysms of the SMA. The diameter of the parent artery was measured according to intraoperative angiography or preoperative CT images. The stent-graft was usually 1 mm larger in diameter than the involved artery. A Fluency stent-graft (CR Bard Inc, Murray Hill, NJ) was negotiated into the involved artery over a 0.035-inch/260-cm stiff guidewire (Terumo, Tokyo, Japan). The stent-graft was centered on the bleeding site and then deployed. Subsequently, repeat angiography was performed to confirm exclusion of the pseudoaneurysm and patency of the targeted artery. The puncture site was closed with an arterial closure devise or manually compressed.

Postoperative Management

All patients were observed closely for potential re-bleeding and other complications. Antibiotic therapy was performed to treat or prevent bacterial infection in all patients. Patients who underwent stent-graft placement received dual antiplatelet therapy to maintain the patency of the stent-grafts. Clopidogrel (75 mg/day) and aspirin (100 mg/day) were usually given 24 h after stent-graft implantation. Pancreatic fistula or intra-abdominal abscess in endovascular patients was managed by ultrasonography or CT-guided percutaneous drainage or re-laparotomy.

Follow-Up

Patients were followed up at 1, 3, 6 months, and then annually after discharge. Clinical manifestations and laboratory tests were monitored, which included blood cell counts, liver function, and tumor makers. CT or ultrasonography was performed to assess recurrence of the primary diseases, the liver and spleen, and the patency of stent grafts. Clopidogrel (75 mg/day) was usually taken for 3–6 months. Aspirin (100 mg/day) was recommended as a lifelong medicine.

Statistical Analysis

SPSS 13.0 software was used for statistical analysis in the study. Comparisons of the results of surgical and endovascular treatment were performed using the Fisher exact test and the Mann–Whitney *U* test. A *P* value of less than 0.05 was considered statistically significant.

Results

Clinical Characteristics

Of 1,102 patients who underwent pancreatic surgery, 52 (4.7%) experienced postoperative hemorrhage. Thirty-five patients (35/52, 67.3%) were diagnosed with hemorrhage from visceral artery pseudoaneurysms. Of 35 patients, 19 were male and 16 were female. Median age was 56 years (range, 35–72 years). Hemorrhage mostly occurred after pancreaticoduodenectomy (71.4%) for pancreatic cancer, ampullary cancer, and distal bile duct cancer (Table 1). Pancreatic fistula (n=26, 74.3%) and intra-abdominal abscess (n=20, 57.1%) were two common abdominal complications which occurred before hemorrhage. Sentinel bleeding was noted in 16 patients (45.7%).

Postoperative hemorrhage was observed from surgical drains in 22 patients (62.9%), gastrointestinal tract in nine patients (25.7%), and both in four patients (11.4%). Mean interval between initial surgery and hemorrhage was 15.7±7.2 days (range, 7–33 day). All patients received an average of 11.2±3.0 units of packed red blood cells (range, 6–18 units) after hemorrhage. Twenty-nine patients received fresh frozen plasma transfusion (mean, 8.9±2.2 packages). The pseudoaneurysms originated from the GDA in 13 patients (Fig. 1a), hepatic artery in eight (Fig. 1b), splenic artery in seven (Fig. 1c), SMA in four (Fig. 1d), inferior pancreaticoduodenal artery in two, and jejunal artery in one. Treatment modalities and in-hospital outcome of these pseudoaneurysms are shown in Table 2.

Table 1 Clinical data of patients with hemorrhage from pseudoaneurysms

Characteristics, *n* (%)	
Indications for surgery	
Pancreatic cancer	18 (51.4)
Ampullary cancer	8 (22.9)
Distal bile duct cancer	5 (14.3)
Benign tumor of pancreas	2 (5.7)
Pancreatic trauma	2 (5.7)
Surgical procedures	
Conventional pancreaticoduodenectomy	19 (54.3)
Pylorus-preserving pancreaticoduodenectomy	6 (17.1)
Distal pancreatectomy (or plus splenectomy)	6 (17.1)
Segmental resection of the pancreas	4 (11.4)

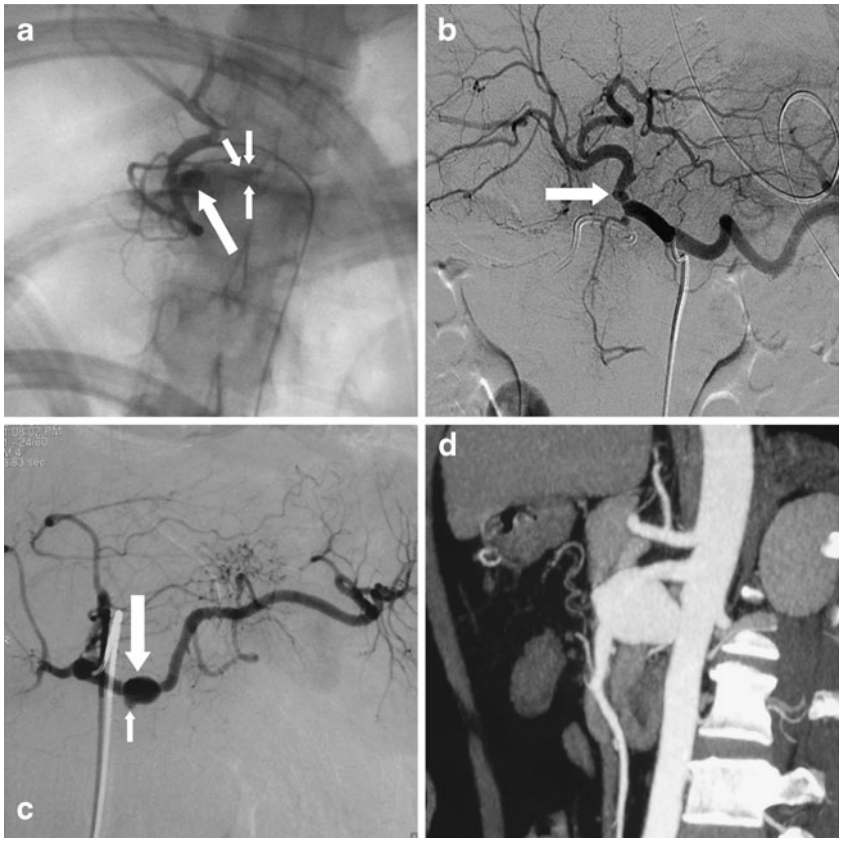

Fig. 1 Angiograms and computed tomographic (CT) angiogram before treatment. **a** Angiogram shows extravasation of contrast medium (*small arrows*) from a pseudoaneurysm (*large arrow*) originating from the gastroduodenal artery (GDA). **b** Angiogram demonstrates a pseudoaneurysm (*arrow*) of the proper hepatic artery. **c** Angiogram shows extravasation of contrast medium (*small arrow*) from the pseudoaneurysm (*large arrow*) of the proximal splenic artery. **d** Preoperative CT image demonstrates a superior mesenteric artery (SMA) pseudoaneurysm

Diagnosis

Twenty-one patients (60%) underwent emergency angiography after bleeding was identified. Eleven patients (31.4%) received surgical re-laparotomy directly without angiography. CT was performed in three stable patients (8.6%) with minor hemorrhage, and then they were treated by endovascular intervention.

Endovascular Intervention

Endovascular treatment was attempted in 24 patients (68.6%). During the endovascular procedure, repeat angiography before coil placement revealed the GDA pseudoaneurysm occluded spontaneously in one patient (Fig. 2). No further bleeding was identified, and no pseudoaneurysm

Table 2 Treatment and in-hospital outcomes of different pseudoaneurysms

Arteries with pseudoaneurysms	Treatment (*n*)	Outcome (*n*)
Gastroduodenal artery (*n*=13)	Surgical hemostasis (5)	Died (2), alive (3)
	Embolization (7)	Died (1), alive 6)
	Spontaneous occlusion (1)	Alive (1)
Hepatic artery (*n*=8)		
Common and proper hepatic artery (*n*=7)	Surgical hemostasis (3)	Died (2), alive (1)
	Embolization (3)	Died (1), alive (2)
	Stent-graft placement (1)	Alive (1)
Left hepatic artery (*n*=1)	Embolization (1)	Alive (1)
Splenic artery (*n*=7)	Surgical hemostasis (2)	Died (1), alive (1)
	Embolization (3)	Alive (3)
	Stent-graft placement (2)	Alive (2)
Superior mesenteric artery (*n*=4)	Surgical hemostasis (2)	Died (1), alive (1)
	Stent-graft placement (2)	Alive (2)
Inferior pancreaticoduodenal artery (*n*=2)	Surgical hemostasis (1)	Alive (1)
	Embolization (1)	Alive (1)
Jejunal artery (*n*=1)	Surgical hemostasis (1)	Alive (1)

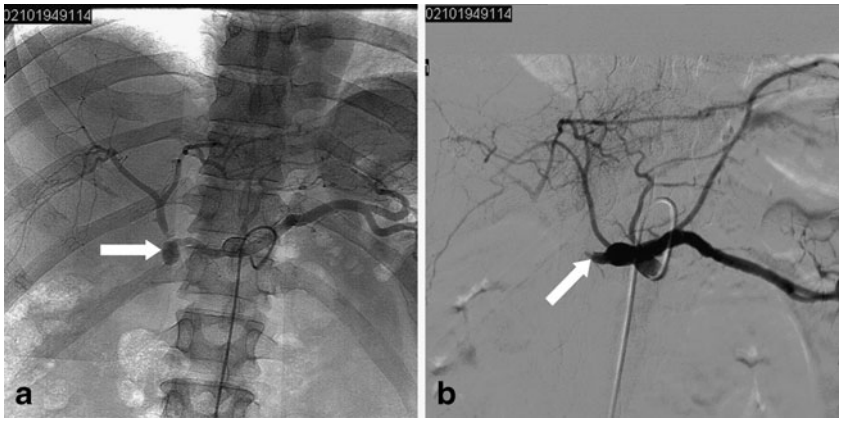

Fig. 2 Spontaneous occlusion of a GDA pseudoaneurysm. **a** Angiogram shows a pseudoaneurysm (*arrow*) at the stump of the GDA. **b** Repeat angiogram reveals no contrast extravasation from the GDA stump (*arrow*)

was found on CT scans 3 days after angiography. The patient recovered uneventfully. Three patients were converted to open surgical hemostasis after failed attempts at embolization. Of these three patients, selective catheterization of the involved artery (the GDA and the inferior pancreaticoduodenal artery) was not achieved in two patients. For the third one, the splenic artery pseudoaneurysm was close to the celiac trunk. Coils migrated into the femoral artery via the celiac trunk, and they were taken out after femoral arteriotomy. Further embolization was abandoned.

Hemostasis was achieved in the remaining 20 patients by embolization ($n=15$) or stent-graft placement ($n=5$; Fig. 3a–d). The technical success rate of endovascular intervention was approximately 87% (20/23). Of three patients who underwent embolization of the proper or common hepatic artery, one had a right subphrenic artery from the celiac trunk (Fig. 3b) and another one had a replaced right hepatic artery originating from the SMA (Fig. 3e). Re-bleeding occurred in one patient with a GDA pseudoaneurysm because of recanalization, and it was successfully treated by a second embolization.

Clinical outcomes of endovascular therapy are shown in Table 3. Two patients died in the endovascular group. One died suddenly 2 days after embolization for a GDA pseudoaneurysm, and the autopsy was not performed. The other one died of hepatic failure after embolization of the proper hepatic artery. Increase in total bilirubin and transaminase was detected after embolization in two patients. The incidence of splenic infarction following embolization was almost 33.3% (1/3). Postembolization syndrome was noted in one patient (6.7%). They were successfully treated by conservative therapy.

Surgical Re-laparotomy

Surgical re-laparotomy was performed in 14 patients (40%), which included three patients in whom an embolization attempt failed. Of 11 patients who underwent surgical hemostasis directly without angiography, endovascular treatment was not considered in five due to unavailability of endovascular expertise at that time. Other six patients suffered emergent massive bleeding and could not be resuscitated for endovascular intervention. Simple ligation of the involved artery was performed in ten patients. Four patients underwent repair of the hepatic artery or the SMA. Clinical outcomes of surgical hemostasis are shown in Table 3. The causes of death of six patients were as follows: hemorrhagic shock ($n=3$), septic shock ($n=1$), multiple organ failure ($n=1$), and disseminated intravascular coagulation ($n=1$). Of six dead patients, one had a failed attempt at embolization. The mortality after failure of embolization was almost 33.3% (1/3). The most common complication was pulmonary infection ($n=3$). Myocardial infarction occurred in one patient. One patient developed inflammatory ileus. They were managed by non-surgical treatment.

Overall Outcome

The overall outcomes are shown in Table 3. Compared with surgical intervention, endovascular therapy was associated with a low mortality rate ($P=0.026$). Endovascular intervention had significantly shorter operation time and intensive care unit stay than surgical intervention ($P<0.05$). Estimated blood loss was obviously less in the endovascular group than in the surgical group ($P=0.017$). There was no significant difference in the overall length of hospital stay between two groups ($P=0.062$).

Follow-up

Twenty-seven patients survived to discharge home with a mean follow-up of 19.2±17.0 months (range, 5–63 months). The stent grafts were patent in five patients during follow-up. Twenty-two patients died from cancer-associated causes after discharge (mean, 11.6±4.1 months). Five patients were alive during follow-up (mean, 52.4±10.2 months).

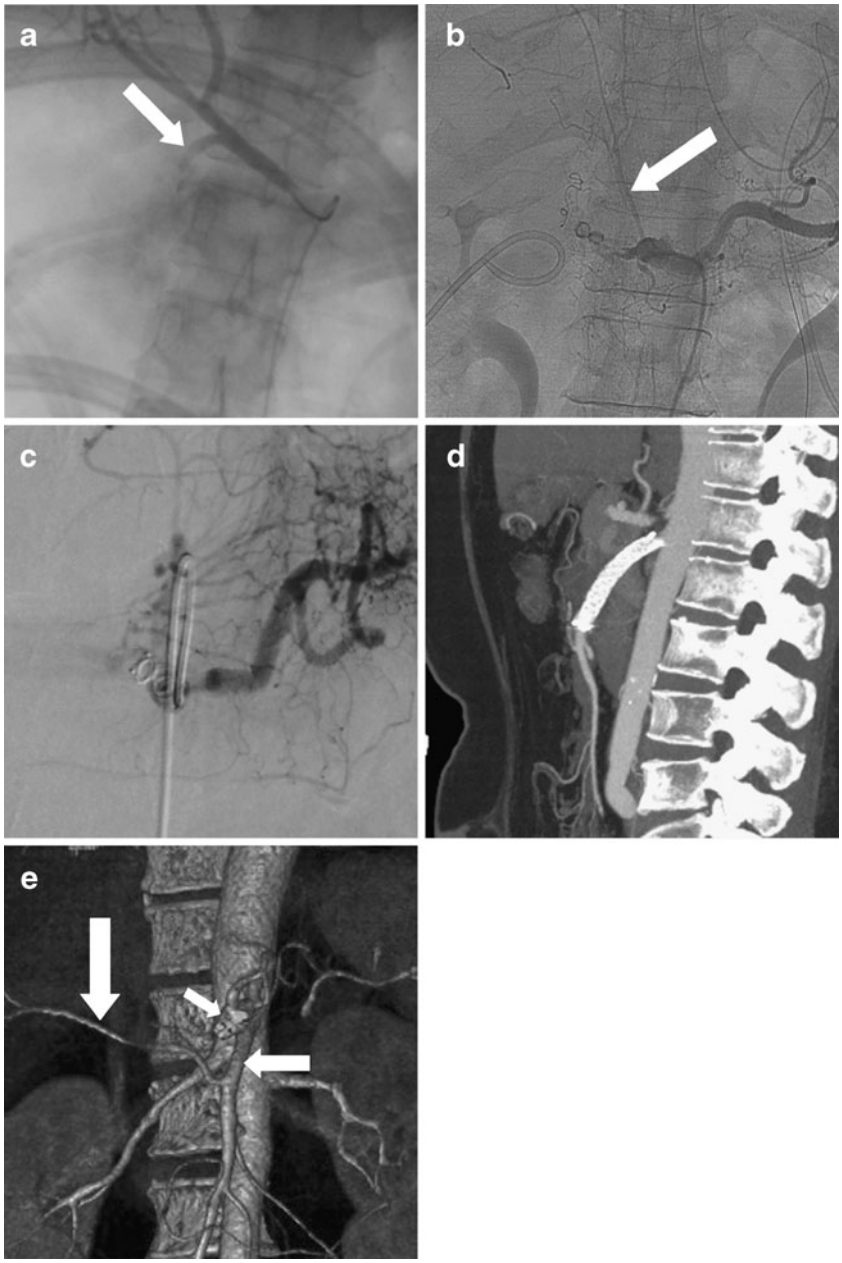

Fig. 3 Angiograms and CT angiograms after treatment. **a** Completion angiogram shows no contrast extravasation from the proximal GDA (*arrow*). **b** Angiogram shows the common hepatic artery is embolized, and the right subphrenic artery (*arrow*) originates from the celiac trunk. **c** Angiogram shows embolization of the proximal splenic artery and no contrast extravasation. **d** CT angiogram at 6-month follow-up shows the patency of the SMA. **e** CT image with three-dimensional reconstruction at 12-month follow-up shows the replaced right hepatic artery (*large arrow*) arises from the SMA (*middle arrow*), and the common hepatic artery (*small arrow*) is embolized

Discussion

Hemorrhage from visceral artery pseudoaneurysms after pancreatic surgery is a rare complication with a high mortality rate.[12–14] The current study had the largest number of patients to date. In this study, the incidence and mortality rates were 3.2% and 22.9%, respectively. Postoperative hemorrhage usually occurred 1 to 4 weeks after surgery from surgical drains or gastrointestinal tract in the current and previous studies.[13,18] Hemorrhage from

Table 3 Clinical outcomes of patients with hemorrhage from pseudoaneurysms

	Total, n=35	Surgical, n=14	Endovascular, n=20	P value
Mortality	22.9%	42.9%	10.0%	0.026
Operation time (min)	92.4±39.4	123.9±35.8	72.8±25.6	<0.0001
Estimated blood loss (ml)	2271±1179	3000±1265	1835±830	0.004
Length of ICU stay (days)	5.5±5.2	8.6±7.0	3.6±1.4	0.017
Length of hospital stay (days)	47.8±12.2	55.6±14.3	45.3±9.5	0.062

ICU intensive care unit

pseudoaneurysms was usually rapid and massive, which required a large amount of blood transfused. Sentinel bleeding was identified in almost half of our series. In a recent study, it reached 77.8%.[13] More attention should be paid to sentinel bleeding because it is an important clinical sign prior to massive hemorrhage. Angiography has been recommended in patients with sentinel bleeding.[23,24]

The etiology of pseudoaneurysms after pancreatic surgery remains unclear. Vascular injury during dissection was considered one possible cause, especially in patients who underwent lymphadenectomy for malignant tumors.[25,26] Pancreatic fistula and intra-abdominal abscess may erode the arterial wall.[27–29] In this study, the incidence rates of these two complications were 74.3% and 57.1%, respectively. Since they have been proven to be risk factors of postoperative massive hemorrhage,[28,29] early identification and management of these complications may help to prevent pseudoaneurysm formation after pancreatic surgery.

Several approaches have been used in the treatment of postoperative hemorrhage from pseudoaneurysms, including endovascular intervention, surgical re-laparotomy, and conservative therapy. In our series, 20 patients received endovascular treatment, 14 patients were treated surgically, and bleeding stopped spontaneously in one patient. Spontaneous occlusion of visceral artery pseudoaneurysms is exceptionally rare in the literature, and the exact mechanism is still unclear. It may be related to catheter-induced vasospasm and spontaneous thrombosis within the aneurysmal lumen.[30–32]

Endovascular treatment has been gradually accepted as the first choice for hemorrhage from pseudoaneurysm, which includes embolization and stent-graft placement.[11–13,18] Compared with surgical intervention, endovascular intervention was associated with a lower mortality rate in our series. It had an immediate effect on hemostasis in our experience. Patients had a shorter recovery in the endovascular group than in the surgical group. However, it is not exempt from complications. End-organ ischemia and in-stent thrombosis have been reported in previous studies.[12–14] In this study, one patient died of hepatic failure due to ischemia, and one patient developed splenic infarction. No thrombotic occlusion of the stent grafts was identified in our five patients. In order to prevent thrombosis, antiplatelet therapy has been recommended for patients treated by stent-graft placement.[12,18]

Visceral artery pseudoaneurysms should be managed individually in endovascular treatment, which depends on the involved artery and its vascular anatomy. In our series, the most common pseudoaneurysms originated from the GDA, and embolization of the GDA was usually safe and relatively easy in the present and previous studies.[13] Embolization was also recommended for patients with pseudoaneurysms originating from branches of the SMA, for example, the inferior pancreaticoduodenal artery pseudoaneurysm in our study.

However, fatal ischemia or necrosis of the end-organ or tissue may occur after embolization of the splenic artery, the common or proper hepatic artery, or the main trunk of the SMA.[12–14] Moreover, it would be difficult to embolize the proximal splenic artery or the common hepatic artery in our experience due to the high blood flow. The coils migrated from the proximal splenic artery into the femoral artery in one of our series. Endovascular stent-graft placement not only excludes pseudoaneurysms from the circulation but also preserves blood flow of the involved arteries. Thus, stent-graft placement is considered the most appropriate treatment method for these patients if they have favorable vascular anatomy.[17,18,33] If stent-graft implantation is difficult due to anatomical reasons, such as tortuosity or variation, embolization can also be considered in patients with splenic artery pseudoaneurysms. However, embolization of the common or proper hepatic artery should be restricted to patients with collateral hepatic blood flow,[14,34] such as a right subphrenic artery (Fig. 3b) or a replaced hepatic artery (Fig. 3e). Embolization was not considered in patients with pseudoaneurysms of the main trunk of the SMA. If hemostasis cannot be achieved by endovascular techniques, temporary balloon occlusion of the involved artery may be a useful life-saving method in this critical condition.[35]

Surgical treatment was usually associated with a high mortality rate. The operative mortality reached 50% in Lee's study.[13] It was almost 42.9% in the current study. Surgical hemostasis produced large trauma with a slower recovery. It was always difficult because of postsurgical adhesions. Moreover, repair of the involved arteries was also difficult due to friability of the arterial wall. Thus, surgical hemostasis is only recommended for those patients who cannot be resuscitated for endovascular treatment or in whom endovascular attempts fail.

Conclusion

Hemorrhage from visceral artery pseudoaneurysms after pancreatic surgery is a rare but life-threatening complication. Early recognition and prompt management of abdominal complications may help to prevent massive hemorrhage. Endovascular treatment should be the first choice for hemorrhage from pseudoaneurysms. Endovascular approaches should be selected individually depending on the involved artery and its vascular anatomy. Surgical hemostasis remains an alternative for patients who cannot be resuscitated for endovascular treatment or in whom endovascular attempts fail. Further data from multiple centers with large populations

are required to evaluate the efficacy of endovascular intervention, especially for stent-graft placement.

Disclosure All authors have no competing interest to declare. We declare that we have no financial or personal relationships with other people or organizations that can inappropriately influence our work.

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ORIGINAL ARTICLE

Intra-abdominal Pressure and Abdominal Perfusion Pressure: Which is a Better Marker of Severity in Patients with Severe Acute Pancreatitis

Lu Ke · Hai-bin Ni · Zhi-hui Tong · Wei-qin Li · Ning Li · Jie-shou Li

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Abstract
Background Intra-abdominal hypertension is common in patients with severe acute pancreatitis. The aim of this study was to assess the clinical relevance of intra-abdominal pressure and abdominal perfusion pressure in the first 72 h after admission during severe acute pancreatitis.
Methods From January 2009 to February 2011, 50 patients admitted for severe acute pancreatitis were included in this prospective, observational study. The intra-abdominal pressure and abdominal perfusion pressure level were repeatedly measured every 12 h during the first 72 h. The maximum and the mean values of intra-abdominal pressure and the minimum and mean values of abdominal perfusion pressure were used for analysis.
Results Both the maximum and mean levels of intra-abdominal pressure were significantly different between patients with or without kinds of clinical variables. But for abdominal perfusion pressure, difference could only be detected in terms of need of vasoactive drugs. Besides that, different from abdominal perfusion pressure, intra-abdominal pressure is associated with high incidence rates of MODS and secondary infection.
Conclusion Compared with abdominal perfusion pressure, intra-abdominal pressure is much more valuable as an early marker of the evolution and complications of severe acute pancreatitis.

Keywords Intra-abdominal pressure · Abdominal perfusion pressure · Severe acute pancreatitis · Multiple-organ dysfunction syndrome · Pancreatic infection

Introduction

Despite recent evidence-based advances in the management of patients with severe acute pancreatitis (SAP), SAP remains a disease with an unpredictable clinical outcome and dramatic morbidity and mortality.[1] Up to one half of deaths from SAP are related to multiple-organ dysfunction syndrome (MODS).[2] In the later phase of the disease, death mostly results from secondary pancreatic infection and consequent septic complications.[3] Besides that, it is a disease with a wide clinical variability, and therefore risk factor evaluation at a very early stage is one of the main determinants for the appropriate treatment of the disease.

In patients with SAP, a tense abdomen is a common clinical finding during the acute phase. Several years before, the World Society of Abdominal Compartment Syndrome (WSACS) reviewed the literature and reached a consensus about the definitions of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS)[4] and the technique for the measurement of intra-abdominal pressure (IAP). So far, several studies about IAH/ACS and its clinical relevance in SAP patients have been published[5–8] and the association of elevated IAP and high occurrence rates of organ dysfunction and death has been proved for several times although most of these studies did not adopt the standard technique and definition of IAH/ACS recommended by WSACS in 2006.[4] But for abdominal perfusion

L. Ke · H.-b. Ni · Z.-h. Tong · W.-q. Li · N. Li · J.-s. Li
Department of General Surgery, Jinling Hospital,
Nanjing University School of Medicine,
Nanjing 210002, China

W.-q. Li (✉)
Department of SICU, Research Institute of General Surgery,
Jinling Hospital,
305 East Zhongshan Road,
Nanjing 210002 Jiangsu Province, China
e-mail: kkb9832@gmail.com

pressure (APP), which is defined as mean arterial pressure (MAP) minus IAP and proposed as an accurate predictor of visceral perfusion[9] in IAH/ACS patients, no study about its clinical relevance in SAP patients has been published yet.

In the present study, we aimed to evaluate and compare the utility of standard measured IAP and APP as markers of severity of SAP to accurately determine the subsequent development of organ dysfunction and pancreatic infection in a well-defined series of primary referral patients with SAP. In addition, the correlation between IAP, APP, and several clinical variables was studied as well.

Methods

In this prospective, observational study, we studied all consecutive adult patients (age ≥18 years) admitted because of SAP (within 3 days after the onset of the disease) to the Surgical Intensive Care Unit (SICU) of Institute of General Surgery, JinLing Hospital between January 2009 and February 2011. General inclusion criteria for SAP were based on the consensus of the international symposium on acute pancreatitis (Atlanta definition).[10] Patients who suffered prior attacks of acute pancreatitis, patients who were pregnant or with other factors which may affect the IAP level and patients who received early surgical treatment in the first 3 days after admission were excluded from the study. All patients were treated according to the practice guidelines in acute pancreatitis[11] and were followed until discharge from the hospital or hospital mortality.

The study was approved by the institutional ethics committee of Jinling Hospital. Written informed consent was obtained from all patients or their representative.

Data Collection

Baseline data collected included age, sex, etiology, the Ranson score, the APACHE II score were recorded on admission. IAP was measured with a catheter inserted into the bladder according to the standard technique established by WSACS in 2006[4]: 25 ml of 0.9% NaCl was instilled, and the midaxillary line was considered as level 0. The IAP was determined every 12 h during the first 72 h after admission. MAP was measured simultaneously, with APP calculated as MAP minus IAP. Maximum IAP and minimum APP were defined as the highest and lowest level reached in all measures, respectively, and the mean IAP and APP were defined as the mean value of all levels measured.

The incidence rate of organ dysfunction was recorded and defined based on a score of 2 or more in the Sequential Organ Failure Assessment scoring system[12]: (1) cardiovascular: requiring vasoactive medication (norepinephrine, dobutamine at any dose, or dopamine at doses above 5 μg/kg/min); (2) renal: serum creatinine above 2.0 mg/dl; (3) pulmonary: a PaO2/FiO2 ratio <300 or the need for mechanical ventilation. Multiple-organ dysfunction syndrome (MODS) was defined as the combined failure of two major organ systems. The diagnosis of secondary pancreatic infection is as follows: positive findings in bacterial culture of abdominal fluid and temperature increased consistently. Besides that, kinds of other outcome measures were also recorded during the course of disease, e.g., the development of systemic and local complications such as systemic inflammatory response syndrome and pseudocysts, computed tomography severity index (Balthazar), the application of vasoactive drugs and mechanical ventilation, the duration of hospital and ICU stay, and the need of surgical treatment were also recorded. Moreover, routine laboratory parameters such as C-reactive protein (CRP) were determined on a daily basis as well.

Statistical Analysis

Results were expressed as the median (interquartile range), unless mentioned otherwise. Categoric variables were described in absolute numbers and in percentages. Continuous variables were compared using the Mann–Whitney *U* test and categorical data were analyzed with the chi-squared test. Receiver operating characteristic (ROC) curve method was applied to yield an optimal threshold pressure for the development of MODS and secondary pancreatic infection. All statistical tests were two-tailed, and the significance level was set at $P<0.05$. Data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

During the 24-month period, 50 patients with a primary diagnosis of SAP were enrolled in the analysis. Table 1 shows the demographic and clinical data of these patients. The mean maximum IAP and minimum APP in this series were 13.1 mmHg (11.5 to 17.1 mmHg) and 74.5 mmHg (67.8 to 80 mmHg), respectively, and the mean IAP and APP were 11.5 mmHg (9.6 to 14.6 mmHg) and 80 mmHg (75.8 to 85 mmHg), respectively. The incidence of organ dysfunction during the episode of SAP was high: pulmonary dysfunction developed in 29 patients (58%), cardiovascular dysfunction in 10 (20%), and renal dysfunction in 15 patients (30%).

IAP, APP, and Presence or Absence of Clinical Variables

Table 2 shows that both the maximum and mean level of IAP were significantly higher in patients with MODS or secondary pancreatic infection and patients who required vasoactive drugs to maintain hemodynamic status or mechanical venti-

Table 1 Demographic data and clinical characteristics

Demographic and clinical variables	
Age(years)	48 (39 to 55)
Gender	29 males/21 females
Etiology	30 biliary origin (60%)
	8 alcohol abuse (16%)
	5 hyperlipidemia (10%)
	7 idiopathic (14%)
APACHE II score at admission	9 (8 to 11.5)
Ranson score48 h after admission	4 (3 to 5)
CRP level at admission (mg/dL)	154 (101 to 212)
Balthazar index	6 (5 to 8)
Hospital mortality (%)	5 (10%)
Pancreatic necrosis (%)	40 (80%)
Pancreatic infection (%)	14 (28%)
Organ dysfunction	34 (68%)
MODS (%)	17 (34%)
Surgical intervention (%)	8 (16%)
Hospital duration (days)	14 (10 to 24)
ICU duration (days)	9 (4.8 to 16.5)

APACHE Acute Physiology and Chronic Health Evaluation; *CRP* C-reactive protein; MODS: multiple-organ dysfunction syndrome; ICU: intensive care unit

lation to guarantee sufficient minute volume ($P<0.001$). Moreover, difference could also be detected in regard to other clinical variables such as incidence of pancreatic necrosis, positive blood culture result, requirement of surgical treatment and death although with a little weaker statistical significance. However, when it comes to APP, difference could only be seen in terms of need of vasoactive drugs for both minimum APP and mean APP and death for minimum APP only (Table 3). Therefore, the utility of IAP was much better than that of APP evaluating the severity of SAP regardless of mean or extreme value used.

IAP, APP, MODS, and Secondary Pancreatic Infection

As Figs. 1 and 2 show, patients who present MODS or secondary pancreatic infection during hospitalization had a constant higher level of IAP in the consecutive 72 h after admission. Besides that, MODS patients also showed significant lower APP after 36 h (Fig. 3). In contrast, no difference was detected regarding APP between patients with or without pancreatic infection (Fig. 4). To rule out potential factors which may influence the IAP/APP we measured such as age, gender, and body mass index (BMI), we compared demographic data between patients with and without MODS, as well as patients with and without pancreatic infection (Table 5). The results show no significant difference in terms of these demographic characteristics, therefore the elevated IAP should be pathological and caused by the disease.

Given the statistical significance we found for IAP, ROC curves were applied to yield an optimal threshold value for determining the occurrences of MODS and pancreatic infection. The results of ROC curves (Figs. 5 and 6) indicate that patients with a maximum IAP of 15 mmHg or above and a mean IAP of 12 mmHg or above are at greater risk of development of MODS and secondary infection. The detailed accuracy of maximum and mean IAP illustrated by specificity, sensitivity and area under curve (AUC) is shown in Table 4.

Discussion

Accurate assessment of the severity and reliable prediction of high risk and potentially fatal cases are of great

Table 2 Values of IAP (millimeters of mercury) level in relation to the presence or absence of clinical variables

Clinical variables	Presence			Absence			*P* value[a]	*P* value[b]
	n	Mean IAP	Max IAP	*n*	Mean IAP	Max IAP		
Death	5	16.5 (15.8 to 18.9)	20 (18.5 to 21.5)	45	10.5 (9.4 to 13.4)	12.3 (11.2 to 15.4)	0.002	0.002
Operative intervention	8	15.8 (14.3 to 18.7)	18.9 (16 to 21.5)	42	10.4 (9.5 to 13)	12.3 (10.8 to 14.8)	0.005	0.001
MODS	17	15.8 (13.7 to 18.3)	17.7 (15 to 20.8)	33	10.1 (9 to 12.4)	11.5 (10.8 to 13.8)	<0.001	<0.001
Vasoactive drugs	9	16.3 (14.6 to 18.5)	19.2 (16.6 to 21.5)	41	10.3 (9 to 12.9)	12.3 (10.8 to 14.6)	<0.001	<0.001
Secondary infection	14	15.4 (13.6 to 18.3)	17.7 (15.4 to 21.5)	36	10.2 (9 to 12.7)	11.9 (10.8 to 13.8)	<0.001	<0.001
Pancreatic necrosis	40	12.4 (9.9 to 15.4)	14.2 (11.5 to 17.7)	10	9.3 (8.4 to 10.8)	11.2 (9.6 to 12.7)	0.005	0.003
Mechanical ventilation	10	16.4 (14.9 to 18.8)	19.6 (17.1 to 21.5)	40	10.3 (9.2 to 12.9)	12.3 (10.8 to 14.6)	<0.001	<0.001
Positive blood cultures	7	16.3 (15.2 to 18.9)	20 (17.7 to 21.5)	43	10.3 (9.1 to 12.9)	12.3 (10.8 to 14.6)	0.001	<0.001

IAP intra-abdominal pressure, *Max* maximum, *MODS* multiple-organ dysfunction syndrome

[a] *P* for mean IAP

[b] *P* for maximum IAP

Table 3 Values of APP (millimeters of mercury) level in relation to the presence or absence of clinical variables

Clinical variables	Presence			Absence			*P* value[a]	*P* value[b]
	n	Mean APP	Min APP	*n*	Mean APP	Min APP		
Death	5	76 (54.5 to 81)	66 (48.5 to 74)	45	81 (76 to 86)	76 (68.5 to 80)	0.092	0.037
Operative intervention	8	78.5 (76 to 81.5)	74 (67.3 to 75.5)	42	81 (75 to 87)	76 (67.8 to 80)	0.327	0.347
MODS	17	77 (75.8 to 80.5)	72 (66.5 to 75.5)	33	82 (76 to 87)	76 (68 to 81)	0.069	0.093
Vasoactive drugs	9	76 (62.5 to 78.5)	71 (55.5 to 74)	41	81 (76 to 87)	76 (68.5 to 81)	0.012	0.006
Secondary infection	14	78 (75.8 to 82.8)	74 (69.8 to 76.8)	36	81 (75.3 to 87)	76 (67.3 to 81.5)	0.284	0.304
Pancreatic necrosis	40	80 (75 to 86.5)	74.5 (67 to 80)	10	80.5 (78.3 to 83)	75 (72.8 to 78.5)	0.734	0.627
Mechanical ventilation	10	77 (73 to 80.5)	72.5 (64.3 to 74.5)	40	81 (75.3 to 87)	76 (68 to 80)	0.112	0.114
Positive blood cultures	7	77 (76 to 80)	76 (68 to 80)	43	81 (75 to 87)	74 (66 to 74)	0.166	0.149

APP abdominal perfusion pressure, *Min* minimum, *MODS* multiple-organ dysfunction syndrome

[a] *P* value for mean APP

[b] *P* value for maximum APP

importance in the management of severe acute pancreatitis because early stratification enables the application of prompt aggressive intensive care measures for individual patients. The present study has demonstrated that measurement of IAP is a highly valuable marker for severity of SAP and correlates well with the development of MODS and secondary pancreatic infection. Irrespective of whether mean level or maximum level of IAP was used, excellent diagnostic accuracy was obtained. As for APP, although patients with or without MODS showed different level of APP during the 36-72 h period after admission, neither mean APP nor minimum APP was associated with the occurrences of MODS and pancreatic infection. To our knowledge, the underlying study evaluates the clinical relevance of APP for the first time in patients with SAP, but the results indicate that APP may not be a qualified marker of severity in the early phase of SAP.

IAH and ACS are increasingly recognized complications of SAP. Patients with SAP are at risk of elevated IAP due to

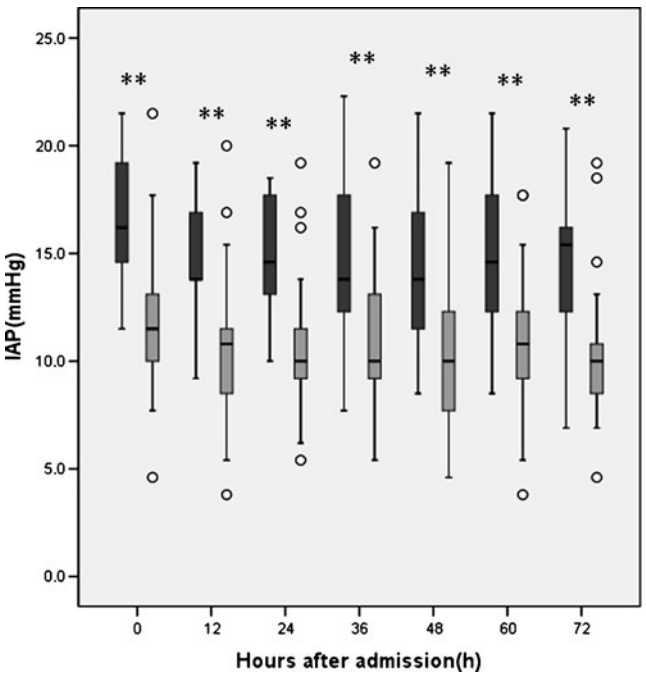

Fig. 1 Box plot of the IAP level in patients with and without MODS; *light boxes*, patients without MODS; *dark boxes*, patients with MODS;** $p<0.01$ between patients with and without MODS

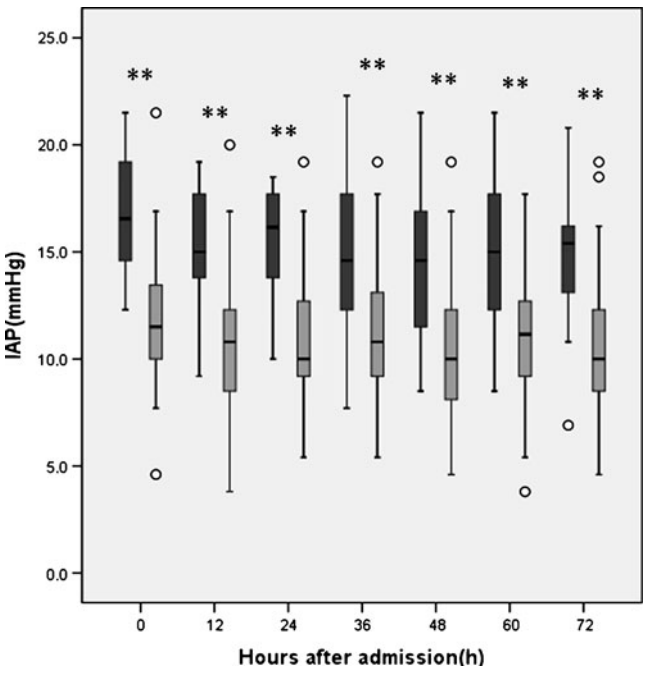

Fig. 2 Box plot of the IAP level in patients with and without secondary pancreatic infection; *light boxes*, patients without secondary pancreatic infection; *dark boxes*, patients with secondary pancreatic infection; ** $p<0.01$ between patients with and without pancreatic infection

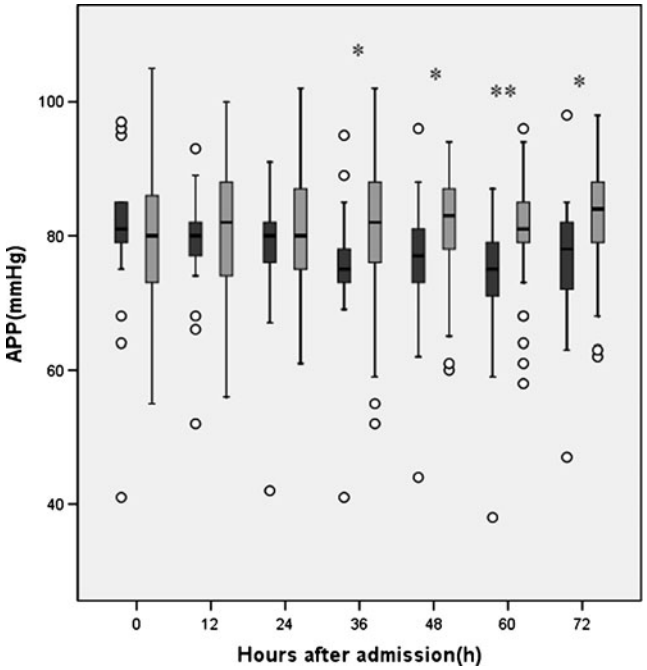

Fig. 3 Box plot of the APP level in patients with and without MODS; *light boxes*, patients without MODS; *dark boxes*, patients with MODS; * $p<0.05$ between patients with and without MODS;** $p<0.01$ between patients with and without MODS

the pancreatic or retroperitoneal inflammation, large volume of intra-abdominal and peripancreatic fluid collection, generalized and visceral edema caused by aggressive fluid resuscitation, gastrointestinal ileus or distension and other factors.[5,8] In the present study, the mean maximal IAP in all patients is 13.1 mmHg (11.5 to 17.1 mmHg), which seems lower than some previous reports.[5,13] The main reason that leads to this phenomenon lies in the new standard technique we adopted which allows a maximal instillation volume of 25-ml sterile saline into the bladder, whereas most previous studies instilled 50 or 100 ml instead. Additionally, although IAP varies widely among individuals with different age, gender, and BMI and could reach as high as 15–16 mmHg in some cases, WSACS has defined that normal IAP is approximate 5–7 mmHg in critically ill adults.[4] Accordingly, our results are in accordance with the real clinical condition as most of our patients are above the normal range. Besides

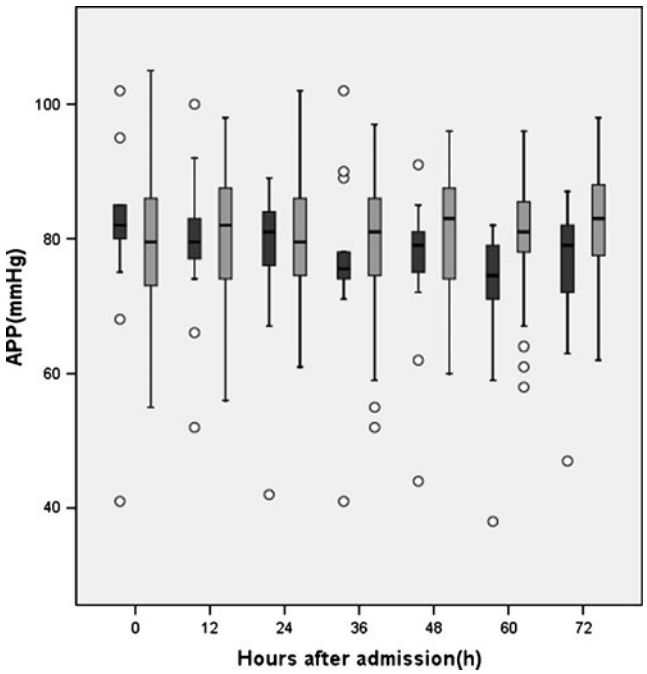

Fig. 4 Box plot of the APP level in patients with and without secondary pancreatic infection; *light boxes*, patients without secondary pancreatic infection; *dark boxes*, patients with secondary pancreatic infection

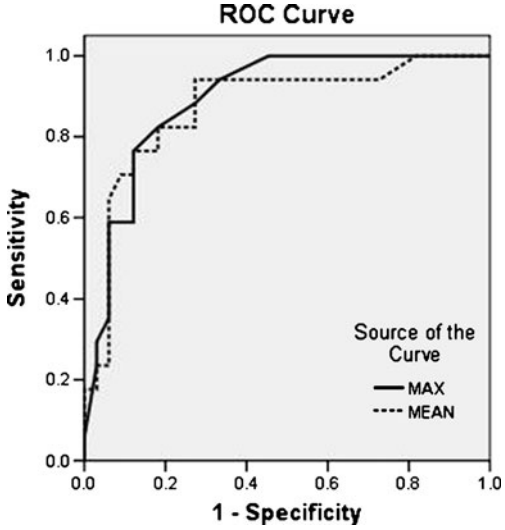

Fig. 5 Receiver operating characteristic curve for mean and maximum IAP and the development of MODS

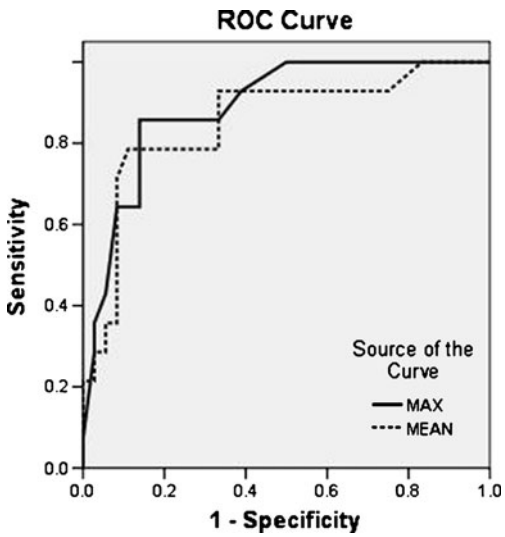

Fig. 6 Receiver operating characteristic curve for mean and maximum IAP and the development of secondary pancreatic infection

Table 4 Values derived from ROC curves regarding IAP (millimeters of mercury) and development of MODS and secondary infection

	Development of MODS				Development of secondary infection			
Variables	AUC	Cut-off value	Sn	Sp	AUC	Cut-off value	Sn	Sp
Maximum IAP	0.871	15.0	77%	88%	0.890	15.0	86%	86%
Mean IAP	0.844	12.1	81%	73%	0.853	11.5	93%	67%

MODS multiple-organ dysfunction syndrome, *Sn* sensitivity, *Sp* specificity, *IAP* intra-abdominal pressure, *AUC* area under curve

that, we have ruled out those potential influential factors mentioned before (Table 5) to make our results more reliable.

For IAH/ACS patients, it is thought that calculation of APP could not only address the severity of IAH present, but also reflect the adequacy of tissue perfusion.[14,15] Cheatham et al. suggested that APP appeared to be a clinically useful predictor of patient survival during the treatment for IAH/ACS.[14] However, in the present study, we only found a significant association between an increase in IAP and a variety kinds of clinical variables related to the process of SAP, such as the need of surgical intervention, vasoactive drugs and mechanical ventilation, the presence of pathogenic microorganisms and so on which is in consistent with several previous studies.[5,7,16,17] Differently, only a correlation with the need of vasoactive drugs could be found with respect to APP which means only patients with cardiovascular dysfunction presented lower APP in the first 72 h. This might mainly be because during the early phase of SAP, most patients even those with greatly increased level of IAP are still capable to maintain a reasonable APP level through increasing the level of MAP so that they could maintain sufficient visceral perfusion to avoid severe ischemia.

Once SAP has occurred, the most important determinant of ultimate outcome is the presence of multiple-organ dysfunction and bacterial contamination of pancreatic necrosis which could lead to kinds of other life threatening complications such as major bleeding and septic shock.[11,18] Therefore, precise anticipation of these two is of specific interest on account of the predominant roles they play during SAP.[19–21] A variety of prognostic factors and scoring systems have been developed for the early assessment of the severity of acute pancreatitis and reliable prediction of MODS and pancreatic infection, such as CRP,[22] hematocrit,[23] D-dimer[24,25] and APACHE II score.[26] In this investigation, analysis of ROC curve established optimal cut-off values of 15 mmHg (maximum IAP) and 12 mmHg (mean IAP) to classify patients at greater risk of both MODS and pancreatic infection. The results are in accordance with De Waele et al's study who also suggested a maximal IAP of 15 mmHg as a boundary of IAH and non-IAH in patients with SAP, but they did not calculate the mean IAP of each patient.[5] Nevertheless, no significant correlation could be detected between both minimum and mean APP and these two important complications.

A possible drawback of this study pertains to the relative shorter observation period, especially for APP because it is impossible for severe patients to maintain MAP at a high level for a long time and most of them may present lower APP over time. Our data also showed that after 36 h, patients with MODS presented lower APP than others. Despite all this, APP still should not be considered as a potential marker of severity because you could hardly

Table 5 Demographic data of patients with or without MODS and patients with or without pancreatic infection

	MODS		*P* value	Pancreatic infection		*P* value
	With MODS (n=17)	Without MODS (n=33)		With infection (n=14)	Without infection (n=36)	
Age (years)	46 (41 to 57)	49 (39 to 55)	0.846	55 (46 to 57)	47 (38 to 54)	0.154
Gender (M/F)	12/5	17/16	0.196	10/4	19/17	0.230
BMI (kg/m^2)	24.8 (24.0 to 27.0)	25.1 (23.9 to 26.8)	0.894	25.6 (24.0 to 27.4)	25.1 (23.7 to 26.6)	0.666
Etiology			0.291			0.337
Biliary	10	20		10	20	
Alcohol	4	4		3	5	
Hyperlipidemia	0	5		0	5	
Idiopathic	3	4		1	6	

MODS multiple-organ dysfunction syndrome, *BMI* body mass index

distinguish severe patients from mild ones with the aid of APP in the first 3 days and after that you might have missed the optimal timing for more aggressive treatment. In addition, as a single center study with limited sample size, we have to choose the nonparametric test which may bring in some uncertainty to the conclusion.

In general, compared with abdominal perfusion pressure, intra-abdominal pressure in the first 72 h after admission correlates much better with the evolution and complications of severe acute pancreatitis. Our results are different from previous studies about the clinical relevance of APP in other clinical settings[14,15] and a longer-lasting monitor of APP may yield different results, therefore further studies are warranted for that.

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Conflict of Interest The authors have not disclosed any potential conflicts of interest.

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ORIGINAL ARTICLE

Prognostic Impact of Preoperative the Branched-Chain Amino Acid to the Tyrosine Ratio in Hepatocellular Carcinoma Patients after Initial Hepatectomy

Toru Mizuguchi · Masaki Kawamoto · Makoto Meguro · Yukio Nakamura · Kohei Harada · Kazuharu Kukita · Koichi Hirata

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Abstract
Introduction The branched-chain amino acid/tyrosine ratio (BTR) reflects the amino acid balance and the severity of liver disease. The aim of the present study was to determine the relationship between BTR and liver function in patients with hepatocellular carcinoma (HCC). Furthermore, we evaluated the clinical usefulness of BTR as a prognostic indicator of disease-free and overall patient survival after initial hepatectomy.
Methods Between January 2004 and December 2008, 105 consecutive HCC patients who underwent initial hepatectomy were enrolled in this study. The correlation between BTR and preoperative liver functional indicators was evaluated. The cutoff levels of BTR for 2-year survival prediction were evaluated using a dot blot diagram. The patients were divided into high BTR (4.5 or higher) and low BTR (4.4 or lower) groups and these were compared in terms of clinical variables such as liver functional indicators, operative variables, and tumor characteristics.
Results The preoperative BTR level decreased according to the severity of liver disease. BTR was correlated with the albumin, bilirubin, and prealbumin levels, as well as the prothrombin time. Although the preoperative liver function was significantly different between the high BTR and low BTR groups, the operative variables and tumor-related variables were not found to be significantly different. Postoperative complications in the high BTR group were significantly less frequent than in the low BTR group ($p=0.003$). Disease-free and overall patient survival in the high BTR group were significantly longer than in the low BTR group ($p<0.001$ and $p=0.021$, respectively).
Conclusions BTR reflected the pathological liver background with a high correlation to the other liver functional indicators. BTR is thus considered to be a useful marker to predict postoperative complications, disease-free survival, and overall survival of HCC patients after initial hepatectomy. It is, therefore, a useful indicator of liver function and a predictor for the risk of cancer recurrence and overall survival in HCC patients.

Keywords Branched-chain amino acid/tyrosine ratio · Liver function · Hepatocellular carcinoma · Hepatectomy

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T. Mizuguchi (✉) · M. Kawamoto · M. Meguro · Y. Nakamura · K. Harada · K. Kukita · K. Hirata
Department of Surgery I, Sapporo Medical University Hospital, School of Medicine, Sapporo Medical University,
S-1, W-16, Chuo-Ku,
Sapporo, Hokkaido 060-8543, Japan
e-mail: tmizu@sapmed.ac.jp

Introduction

The incidence of hepatocellular carcinoma (HCC) has been increasing internationally due to epidemic viral hepatitis[1,2] and ranks as the third most common cause of cancer-related deaths worldwide.[3] The annual incidence of de novo carcinogenesis increases depending on the severity of liver disease, no matter what the etiology.[3,4] The severity of liver disease is well correlated with liver fibrosis and deteriorating liver function. Liver resection is one of the curative treatments to control HCC[5] in patients in whom liver function is maintained. However, the high recurrence rate after hepatectomy[6] prompted us to search for a reliable

predictive factor to identify high-risk patients who may have rapid recurrence.

Protein-calorie malnutrition, which is noted in patients with liver disease, is characterized by a low level of branched-chain amino acids (BCAA) and increased levels of aromatic amino acids (AAA).[7] BCAA consist of leucine, isoleucine, and valine, which are considered to be essential amino acids and must be obtained from the diet.[8] When liver function deteriorates for any reason, BCAA decrease due mainly to metabolism by the muscle.[8–10] On the other hand, tyrosine is a semiessential amino acid and can be derived from either the diet or the hydroxylation of phenylalanine.[11,12] More than 98% of tyrosine is degraded by the intrahepatic oxidative pathway.[13] Therefore, an imbalance of the metabolism of these amino acids is seen in the impairment of liver function.[9] It is largely reflected by increased BCAA uptake in the muscle due to decreased AAA uptake in the liver.[10]

A low BCAA/AAA ratio, which is known as the Fischer ratio,[9] reflects a low level of liver function. The BCAA/tyrosine ratio (BTR) is considered to be a substitute for the Fisher ratio and also reflects the amino acid balance in plasma.[14] Although analysis of the amino acid balance is relatively complicated, BTR can be measured and calculated using an automated analyzer.[14,15] BTR is correlated with many clinical factors such as the albumin (ALB) level, prothrombin time (PT), and cholinesterase.[14] Therefore, BTR may be a representative liver functional marker in patients with liver disease.

To our knowledge, no study has yet shown the precise relationship between BTR and prognosis in HCC patients after initial hepatectomy. The aim of the present study was to investigate the relationship between BTR and other liver function indicators. Furthermore, we divided the patients into two groups depending on the BTR value and compared their disease-free and overall survival times following the initial hepatectomy.

Patients and Methods

Patients

Between January 2004 and December 2008, 105 consecutive HCC patients who underwent initial hepatectomy were enrolled in this study. All the patients gave their informed consent. Routine laboratory tests before hepatectomy were conducted for the indocyanine green retention rate at 15 min ($ICGR_{15}$), hyaluronic acid, type IV collagen, retinol-binding protein, prealbumin (PreALB), the BTR, hepatocyte growth factor (HGF), alpha fetoprotein, des-gamma-carboxy prothrombin, and ^{99m}Tc-galactosyl serum albumin (GSA). The institutional normal ranges of these clinical variables are shown in Table 1. The tumor size, number of tumors, and vascular invasion were recorded at the time of the pathological examinations with the consent of two independent pathologists. All patients ate usual meals depending on what they wanted in the 2 days before hepatectomy. All laboratory tests were conducted in the early morning on the day of assessment at least 3 days before hepatectomy. Mortality was defined as any death in the hospital within 90 days after the operation. The postoperative complications were defined and classified by the modified Clavien–Dindo classification.[16] Briefly, grade I was any deviation from the normal postoperative course without any special treatment. Grade II required pharmacological treatment. Grade III required surgical or radiological intervention with (IIIb) or without (IIIa) general anesthesia. Grade IV was a life-threatening complication involving single (IVa) or multiple (IVb) organ dysfunction. Grade V was the death of the patient. Of the complications assessed as grade IV or higher, liver failure/dysfunction was defined as a serum bilirubin concentration of more than 10 mg/dl and a PT of <50%. Hepatic arterial aneurysm was present in one patient and was completely resolved after interventional coiling. Pneumonia was diagnosed if there were respiratory symptoms based on either X-ray examinations or proof of bacteria. Renal insufficiency was defined by oliguria (<400 ml/day) with sustained elevation of the serum creatinine level of more than 1.1 mg/dl or a blood urea nitrogen level of more than 20 mg/dl. Although no mechanical ileus requiring nasointestinal tube drainage occurred, paralytic ileus was observed with an oral intake of <500 ml/day for more than 3 days. Wound infection/dehiscence was defined as any wound that split open regardless of proof of bacteria. The presence of ascites was defined as a fluid discharge of more than 300 ml/day for more than 3 days.

Table 1 Institutional standard levels of each clinical variable

Factors	Units	Low limits	High limits
ALB	g/dl	3.7	5.2
Bilirubin	mg/dl	0.2	1.2
PT	%	80.0	120.0
PreALB	mg/dl	22	40
$ICGR_{15}$	%	0	10.0
BTR		4.41	10.05
Plt	$\times 10^4$/ml	12.7	35.6
HGF	ng/ml	0	0.39
AFP	ng/ml	0	8.5
DCP	mAU/ml	0	40

ALB albumin, *PT* prothrombin time, *Plt* platelet count, *$ICGR_{15}$* indocyanine green retention rate at 15 min, *BTR* branched-chain amino acid/tyrosine ratio, *HGF* hepatocyte growth factor, *AFP* alpha fetoprotein, *DCP* des-gamma-carboxy prothrombin

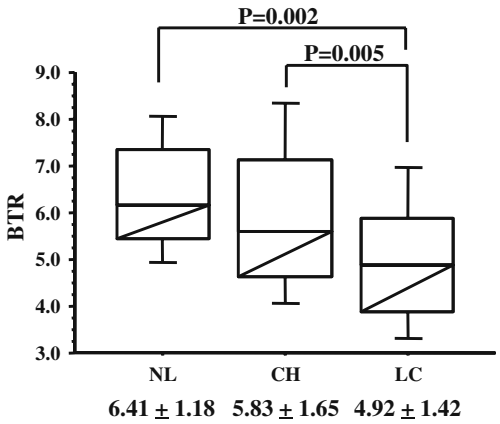

Fig. 1 Box and whisker plot for BTR and the severity of liver disease (*NL* normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis). The *central boxes* represent the values from the lower to upper quartiles (25 to 75 percentile). The *line in the middle* represents the median. The *horizontal line* extends from the minimum to the maximum values

The design of this study conformed to the ethical guidelines of the Declaration of Helsinki, and all the study patients gave their informed consent with individual signatures prior to enrollment in the study.

Statistical Analysis

The relationships between BTR and the pathological liver background are represented using a box and whisker plot. The relationships between BTR and other clinical data were examined using Spearman's rank correlation coefficient. Patient demographics and perioperative laboratory tests were extracted from the database, and differences between the groups were compared using the chi-squared test followed by a post hoc 2×2 Fisher exact test. Student's unpaired *t* test was used to compare the means of the two groups. The factors determining the overall survival were assessed using the Kaplan–Meier method and comparisons were made by the log-rank test. The calculations were performed using the StatView 5.0 software package (Abacus Concepts Inc., Berkeley, CA) or the SPSS 16.0 software program (SPSS Inc., Chicago, IL). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) was determined using the MedCalc software package (Version 8.0.1.0, Mariakerke, Belgium). All results are expressed as the mean±standard deviation. A p value of <0.05 was considered to be statistically significant.

Results

Preoperative BTR was compared among the groups depending on the postoperative pathological examinations in the nontumor region (Fig. 1). The preoperative BTR was significantly different according to the postoperative pathological backgrounds. We compared the laboratory test results to evaluate liver function and identify the relationship between BTR and other markers (Fig. 2). Although the Child–Pugh scores were significantly correlated with BTR, only ALB was strongly correlated with it (R=0.463, p< 0.001). PreALB (R=0.618, p<0.001) was also significantly

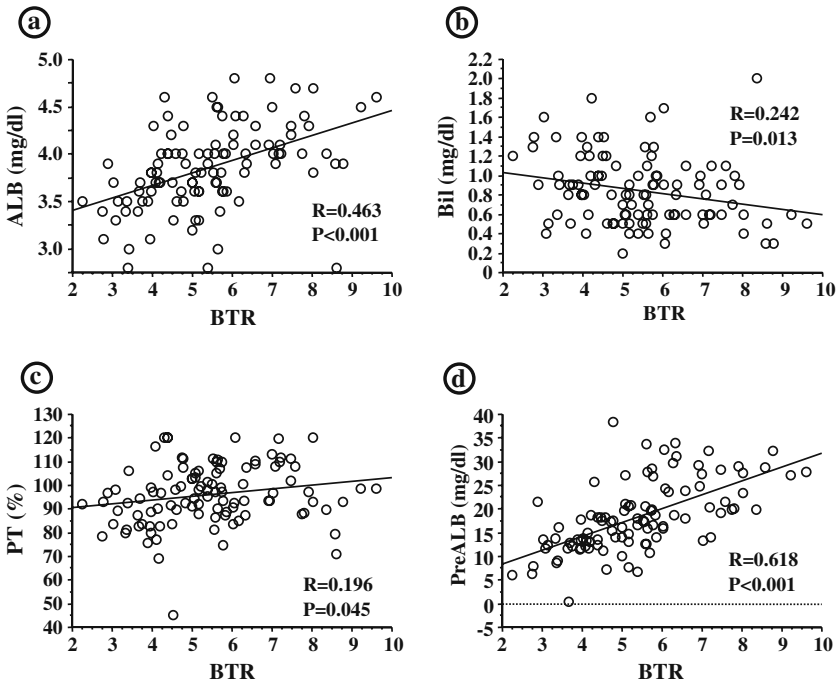

Fig. 2 Linear regression analyses for BTR and liver functional indicators such as ALB (**a**), bilirubin (**b**), PT (**c**), and PreALB (**d**)

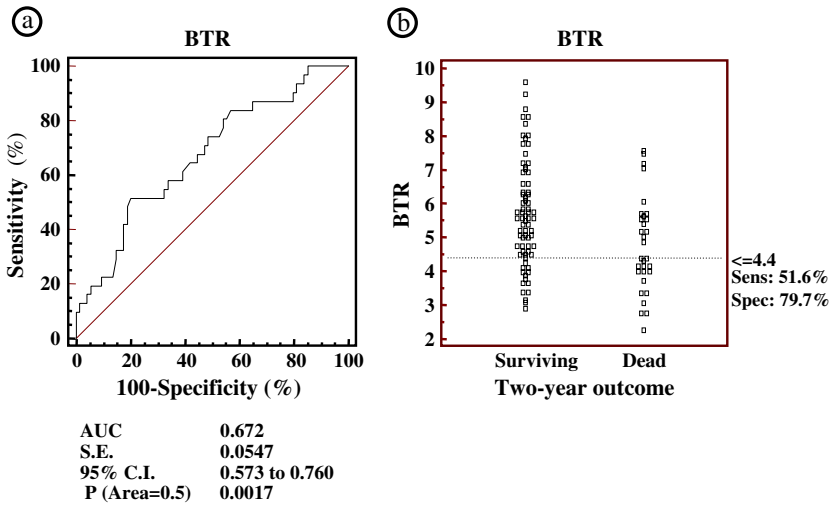

Fig. 3 Receiver operating curve analysis for BTR to predict 2-year patient survival (**a**). Interactive dot diagram for BTR to predict 2-year survival and to determine the cutoff value (**b**). *AUC* area under the ROC curve, *S.E.* standard errors, *C.I.* confidence interval, *Sens* sensitivity, *Spec* specificity

correlated with BTR among the tested markers. The 2-year patient survival probability was evaluated by ROC curve analysis and the dot plot diagram (Fig. 3). BTR was significantly useful to predict 2-year survival (AUC=0.672, p=0.0017). The cutoff value of BTR was 4.4 (sensitivity, 51.6%; specificity, 79.7%).

We divided the patients into two groups depending on the BTR value. Clinical variables were compared between the high BTR (higher than 4.4) and low BTR (4.4 or lower) groups. Although age and PT were not significantly different between the groups, the other clinical variables were found to be significantly different, including BTR. In particular, the number of female patients, the presence of type C hepatitis, and the number of LC patients in the low BTR group were significantly higher than in the high BTR group (p<0.001, p=0.001, and p=0.005, respectively). Tumor-related markers, such as HGF, tumor size, number of tumors, vascular invasion, and tumor markers, were not significantly different between the groups. In addition, operation-related factors such as operation time, intraoperative bleeding, and operation type, were not found to be significantly different between the two groups (Table 2).

Postoperative complications were recorded and compared between the two groups (Table 3). The overall complications in the high BTR group were significantly less frequent than those in the low BTR group (p=0.003). Furthermore, disease-free and overall survival (Fig. 4) in the high BTR group (mean disease-free survival, 41.6±3.5 and 53.1±2.9 months [p<0.001], respectively) were significantly longer than for patients in the low BTR group (mean overall survival, 19.8±2.8 and 41.4±5.2 months [p=0.021], respectively). Comparison of disease-free survival in each stage is shown in Fig. 5. Although disease-free survival in stage 4 was not significantly different between the groups, the disease-free survival rates of the high BTR group in the other stages were significantly longer than in the low BTR group (Table 4). Furthermore, multivariate analysis for independent risks of disease-free survival revealed that being female, BTR, tumor size, and tumor

Table 2 Clinical characteristics of patients in the high BTR and low BTR groups who received initial hepatectomy in a consecutive series

Factors	High BTR	Low BTR	p value
Age (years)	64.3±11.4	65.9±9.1	0.496
Sex (M:F)	61:10	16:18	<0.001*
Etiology B:C:alcohol	43:22:6	7:24:3	0.001*
Pathology N:CH:LC	11:31:29	1:8:25	0.005*
ALB	3.94±0.44	3.69±0.41	0.001*
Bilirubin	0.77±0.35	0.98±0.35	0.001*
PT	97.6±12.4	92.6±13.1	0.059
PreALB	20.6±7.2	13.6±5.4	<0.001*
$ICGR_{15}$	11.4±6.2	19.6±8.39	<0.001*
BTR	6.17±1.24	3.88±0.93	<0.001*
Plt	17.3±11.8	11.9±8.9	0.021*
HGF	0.34±0.18	0.38±0.14	0.293
T size	4.33±3.62	4.22±2.59	0.874
T number	1.4±0.9	1.5±1.0	0.643
VI Pos:Neg	19:52	12:22	0.369
AFP	2884±14279	1721±6226	0.656
DCP	2994±8375	3699±16232	0.772
Op time	350.5±175.2	357.6±272.7	0.874
Bleeding	726.4±850.9	833.1±1151.6	0.604
Op (Hr) (0:S:1:2:3)	29:18:14:8:2	17:12:2:2:1	0.230
Stage (1:2:3:4)	15:31:20:5	3:19:8:4	0.067

N normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis, *ALB* albumin, *PT* prothrombin time, $ICGR_{15}$ indocyanine green retention rate at 15 min, *BTR* branched-chain amino acid/tyrosine ratio, *Plt* platelet count, *HGF* hepatocyte growth factor, *T* tumor, *VI* vascular invasion, *Pos* positive, *Neg* negative, *AFP* alpha fetoprotein, *DCP* des-gamma-carboxy prothrombin, *Op* operation, *Hr* type of liver resection, *S* subsegmentectomy

Table 3 Postoperative complications in 105 HCC patients after initial hepatectomy

Complications	High BTR group (n=71) (minor/major)	Low BTR group (n=34) (minor/major)
Liver/biliary		
Liver failure/insufficiency	–/1	–/3
Bile leakage	1/1	1/–
Hepatic arterial aneurysm	–/–	–/1
Pulmonary		
Pleural effusion (symptomatic)	1/1	–/1
Pneumonia	–/–	1/–
Genitourinary		
Renal insufficiency/failure	2/–	–/–
Gastrointestinal		
Ileus	1/–	–/–
Miscellaneous		
Wound infection/dehiscence	2/–	4/2
Ascites	5/1	4/1
Intra-abdominal abscess	1/–	–/–
Total	13/4	10/8

Minor complications are graded as grades I, II, and III in the modified Clavien classification. Major complications are graded as grades IV and V in the modified Clavien classification. The chi-squared test followed by a Fisher's exact test (post hoc 2×2) was used to compare the two groups (p=0.003)

number were independent risk factors after initial hepatectomy (Table 5).

Discussion

We herein demonstrated that BTR reflected the pathological liver background and correlated with other liver functional markers. High BTR levels represented good liver function, although they did not reflect any tumor-related factors. In addition, BTR may be a good marker to predict postoperative complications, disease-free survival, and overall patient survival.

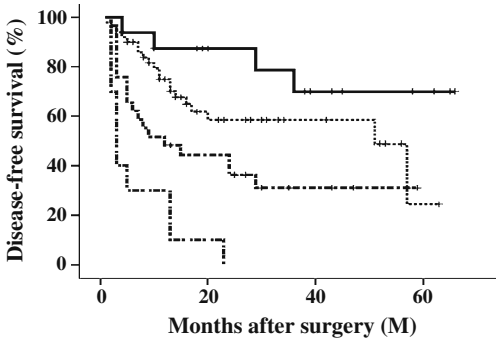

Fig. 5 Cumulative disease-free survival in HCC patients for stage 1 (*solid single line*), stage 2 (*dotted line*), stage 3 (*single chain line*), and stage 4 (*double chain line*)

BTR has been shown to correlate with the severity of liver disease.[14,15,17,18] Although the actual BTR values in the present results for the normal liver and chronic hepatitis are consistent with those described in a previous report,[15] the results shown in a liver cirrhosis (LC) study appeared to differ. This may be due to different study populations. Patients in the present study were waiting for surgery and fulfilled the criteria for tolerating the surgery. Therefore, the liver functions of the present patients were maintained. Another reason for these varying interstudy results may be different diagnostic criteria for LC. The present study may reflect a more accurate conclusion because all liver samples were pathologically investigated in detail. If the pathological severity of LC is identical, the liver function in LC patients should range widely depending on their conditions.

BTR was found to be correlated with other liver functional markers. However, the correlation with ALB was reported to vary widely from R=0.447[15] to R=0.538,[14] and the present results were within this range. BTR was correlated with serum protein levels rather than bilirubin levels,[14,17,19] which reflects the correlation between BTR and maintenance of serum protein levels. The reason why the correlation varied among the evaluated proteins could be that BTR only reflected a part of the activities of protein synthesis at the time of stable rest, and the serum protein level does not always determine the rate of synthesis.[20,21]

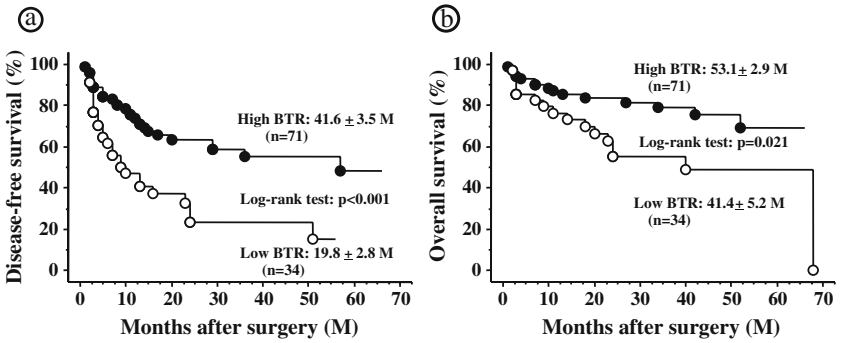

Fig. 4 Cumulative disease-free survival (**a**) and overall survival (**b**) curves in HCC patients for the high BTR and low BTR groups. *Closed circle* high BTR group (n=71), *open circle* low BTR group (n=34)

Table 4 Mean recurrence-free survival time in the high BTR and low BTR groups who received initial hepatectomy in each stage

Stage	Total patients	High BTR	Low BTR	*p* value
1	52.7±5.7	56.1±5.1	4.0±0	<0.001
2	38.5±3.9	44.3±4.9	28.9±5.5	0.026
3	25.1±4.6	30.3±5.8	11.2±3.3	0.049
4	6.9±2.2	5.2±2.1	8.6±4.2	0.618

Data are presented as the mean±standard error

On the other hand, BTR highly correlated with PreALB, which has a short half-life of only 1.9 days[22] and has one of the highest ratios of essential to nonessential amino acids of any protein,[23] making it a distinct marker for protein synthesis.[24] This indicated that BTR might be a rapid marker to evaluate protein synthesis and a sensitive indicator of any change affecting protein synthesis in liver disease.[22,24]

The prognostic factors in HCC patients after hepatectomy include operative factors, tumor-related factors, and liver functional factors.[25–29] Tumor-related factors include staging, the number of tumors, tumor size, vascular invasion, tumor markers, and the HGF level. Conversely, liver functional markers include the Child–Pugh class, GSA-Rmax, $ICGR_{15}$, and antithrombin III, among others. Besides these tumor-related factors, the preservation of liver function is important for the survival of patients with cancer recurrence,[30,31] where survival time may eventually be extended. The present results showed that disease-free and overall patient survival in the low BTR group were shorter than in the high BTR group. The clinical characteristics of the low BTR group in this study were being female, presence of type C hepatitis, LC, and low liver function. The survival difference between the groups could be due to differences in basal liver functions. However, the shorter disease-free survival in the low BTR group represented a high risk of recurrent HCC in this group. In fact, low BTR was one of the independent risk factor for disease-free survival. Further study will be needed to determine if BTR manipulation can prolong disease-free survival in these patients, i.e., female patients, patients with type C hepatitis, and LC patients.

Table 5 Relative risk of disease-free survival with Cox's proportional hazards model

Disease-free survival	Odds ratio	95% confidence interval	*p* value
Sex (female)	0.37	0.14–0.95	0.039
BTR	0.57	0.37–0.86	0.008
Tumor size	1.24	1.11–1.38	<0.001
Tumor number	1.53	1.19–1.97	0.001

The role of BCAA supplements has been investigated in many studies,[32–35] examining whether the incidence of recurrence can be reduced or liver function can be improved. However, treatment with supplements failed to decrease disease recurrence and prolong survival time,[34] although the serum ALB level was somewhat elevated and the event-free survival period was prolonged. The results of the present study showed no difference in tumor-related factors between the groups, although the recurrence rate in the low BTR group was significantly higher than in the high BTR group. Low BTR may represent not only low liver function but also cancer-activated status without cancer severity. A 1-year period of supplementation might not be long enough to deactivate cancer maintenance after hepatectomy. The present results indicated that the disease-free survival declined in a mostly linear manner within 2 years after hepatectomy. Therefore, it is recommended that supplementation of BCAA should be continued for more than 1 year in future studies.

Postoperative complications were related to tumor factors, operative procedures, the presence of other diseases, and overall liver function. The present results showed that none of the tumor factors or operative variables was significantly different between the groups. If surgical techniques and perioperative management are accomplished perfectly, host conditions, including liver function itself, could primarily be involved in the development of postoperative complications. In particular, high-grade complications were observed in the low BTR group. Therefore, further intensive care will be required for low BTR patients who undergo hepatectomy.

Conclusion

BTR reflects the pathological liver background with a high degree of correlation to other liver functional markers. In the low BTR group with a low level of liver function, patients who were female and those who had type C hepatitis or LC appear to have a higher risk for reduced survival. Furthermore, BTR seems to be a good marker to predict postoperative complications, disease-free survival, and overall patient survival after initial hepatectomy. Therefore, we must pay attention to the preoperative BTR levels for planning personal perioperative care. Future studies will implement long-term patient observation to examine whether prolonged BTR supplementation can improve the prognosis of HCC patients who have undergone an initial hepatectomy.

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ORIGINAL ARTICLE

Alkaline Phosphatase: Does it have a Role in Predicting Hepatocellular Carcinoma Recurrence?

Ming-Chin Yu · Kun-Ming Chan · Chen-Fang Lee · Yun-Shien Lee · Firas Zahr Eldeen · Hong-Shiue Chou · Wei-Chen Lee · Miin-Fu Chen

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Abstract
Backgrounds Surgical resection remains the first line of treatment for earlier stages of hepatocellular carcinoma (HCC), and it offers the best prognosis for long-term survival. Nevertheless, the recurrence rates after resection are still high in reports. Therefore, it is still essential to explore any potential prognostic factors to attain relatively longer-term survival of HCC patients.
Materials and Methods In the period from 1983 to 2005, 1,685 patients who underwent hepatectomy at Chang Gung Memorial hospital were enrolled in the study, and their clinicopathological data were retrospectively reviewed for survival analysis.
Results The 1-, 3-, 5-, and 10-year disease-free survival (DFS) rates in this series were 60.3%, 39.7%, 31.3%, and 24.0%, respectively, whereas the 1-, 3-, 5-, and 10-year overall survival (OS) rates were 80.1%, 59.1%, 46.6%, and 27.7%, respectively. Gross vascular invasion, tumor status, lymph node involvement, satellite lesion, positive surgical margin, alkaline phosphatase (ALP), albumin, presence of cirrhosis, and Child grade B or C were independent prognostic factors for prediction of DFS; while α-fetoprotein, ALP, surgical factors, including complications, blood transfusion, positive resection margin, and tumor characters including tumor status, vascular invasion, and lack of tumor encapsulation were found to be independent predicting factors for OS, as determined by Cox regression analysis. Interestingly, we found that preoperative level of ALP was one of the most important independent predictors of recurrence, even more important that α-fetoprotein (AFP) as we noticed that elevation of ALP above (82 U/L) predicted poor prognosis in patients where AFP levels was less than 66 ng/ml. It is worth to mention that ALP was statistically related to other liver function tests, but not tumor characters by hierarchical clustering; which means that we were able to correlate ALP with prognosis statistically, but not with pathological criteria of the tumor; to elucidate these finding, further basic science research is required.
Conclusion ALP among liver function tests, in addition to other tumor characters were independent factors for DFS and OS; our results suggest that preoperative ALP levels could be utilized to monitor and predict recurrence in high risk HCC patients.

Keywords Hepatocellular carcinoma · Hepatectomy · Alkaline phosphatase · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and accounts for 5.6% of all human cancers. Primary liver cancer is also the third leading cause of cancer death with yearly fatality ratio of

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M.-C. Yu · K.-M. Chan · C.-F. Lee · F. Z. Eldeen · H.-S. Chou · W.-C. Lee (✉) · M.-F. Chen
Department of Surgery,
Chang Gung Memorial Hospital, Linkou No. 5, Fu-Hsing Street,
Kuei Shan Hsiang,
Taoyuan county 333, Taiwan
e-mail: weichen@cgmh.org.tw

M.-C. Yu
Graduate Institute of Clinical Medical Sciences,
Chang Gung University, Taoyuan, Taiwan

Y.-S. Lee
Genomic Medicine Research Core Laboratory,
Chang Gung Memorial Hospital, Taoyuan, Taiwan

Table 1 Clinical, operative, and pathologic data of 1,685 HCC patients

	No. of patients (%)
Age (years)	57 (46–66)
Gender	
Male/female	1,326 (78.7)/359 (21.3)
OP year	
Before 2000/After 2000	916 (54.4)/769 (45.6)
Viral hepatitis serology	
HBV/HCV/HBV and HCV/none	676/297/129/125
Diabetes (yes)	261 (15.5)
Alcohol (yes)	503 (36.1)
Symptoms (yes)	988 (59.1)
Signs (yes)	380 (22.8)
CTP status	
A/B and C	1,529 (91.9)/134 (8.1)
Complication (yes)	424 (25.2)
Mortality (yes)	93 (5.5)
Bleeding (>550 ml)	836 (52.4)
OP duration (>245 min)	852 (52.1)
Blood transfusion (yes)	593 (35.2)
ICG (%)	9.4 (5.5–15.7)
AST (U/L)	43 (30–72)
ALT (U/L)	42 (27–70)
ALP (U/L)	82 (64–113)
Albumin (g/dl)	4.0 (3.6–4.3)
AFP	66.5 (9.0–908.3)
Tumor size (cm)	4.5 (2.6–8.0)
Rupture	171 (10.2)
Cirrhosis	902 (55.0)
Macrovacular/microvascular invasion	339 (21.6)/203 (12.9)
Satellite lesions	443 (27.0)
Resection margin positive	81 (5.1)
Grade	
Well and moderate differentiated/poorly and undifferentiated	737 (51.1)/706 (48.9)

Data are presented as number of patients (% of total patients) or median (25–75 percentile)

OP operation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

approximately 1.[1]. In Taiwan, as a high-risk area, primary liver cancer ranked first in cancer mortality in men and second in women in 2007 (39.3 in men and 14.7 in women of standardized death rates). Moreover, HBV infection is more prevalent than hepatitis C virus (HCV) infection in Taiwan and it is present in 58.9% of the male HCC patients;[2] therefore, improvement of long-term outcomes imposes a challenge to researchers and clinicians.

The recurrence rate of HCC after resection is still frustratingly high at 50–60%; thus, several variables were studied to predict prognosis of HCC; such as the clinicopathologic features of HCC, including larger tumor size, satellite lesions, vascular invasion, and tumor rupture; these factors when present indicate poor prognosis.[3,4] Blood transfusion, serum factors, and viral load have also been proposed as independent factors in some reports.[3,5] In the aforementioned studies, the sensitivity and specificity of α-fetoprotein (AFP) are poor; however, it remains a biomarker that is universally utilized for monitoring HCC in high-risk patients in clinical practice. Besides, fucosylated fraction of AFP and des-gamma-carboxy prothrombin were reported to be a more useful marker than total AFP.[6,7]

Alkaline phosphatase (ALP) is a hydrolase enzyme, which is present in all tissues throughout the entire body, but particularly concentrated in the liver, bile duct, kidney, bone, and placenta.[8] ALP is also included in the standard liver function panel and has also been found to have a significant impact as a poor predictor in the outcome of

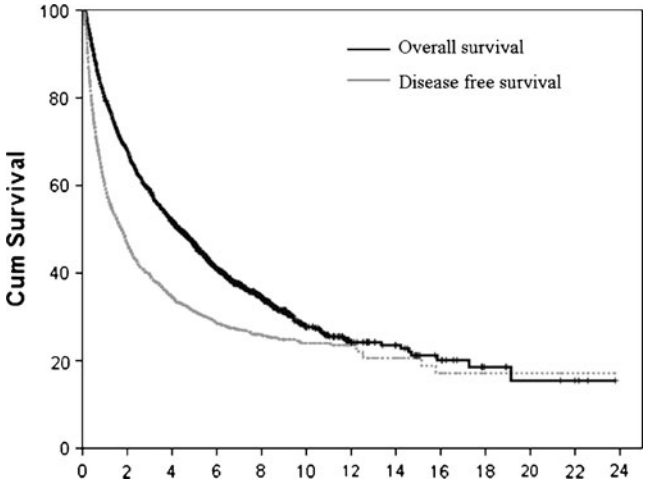

Fig. 1 The overall and disease free survival curves of 1,592 HCC patients underwent hepatectomies. The 5-year overall and disease-free survival rate for HCC patients were 46.6% and 31.3%, respectively

HCC in our previous studies;[9,10] however, long-term follow-up results have not been reported. ALP has also been included in the Chinese University Prognostic Index (CUPI), an HCC staging system that assigns a score of 3 when ALP is higher than 200 IU/L.[11] A review of the available literature revealed that the correlation between the pathologic factors and the clinical outcome of HCC patients has been analyzed in several medical centers worldwide; however, the preoperative liver function tests specifically ALP and its value in the long-term follow-up of HCC patients have seldom been mentioned;[4,12] therefore, in this study, we analyze the impact of ALP and its interrelations with other pathological and biological variables on survival and long-term outcome.

We collected detailed data of 30 clinicopathologic factors and were analyzed by hierarchical clustering analysis to determine the most important factors predicting the long-term outcome. The clinical impact of ALP and other liver function parameters on the survival of HCC patients has also been discussed.

Patients and Methods

In the period from 1983 to 2005, data of 1,685 patients who underwent partial hepatectomy for HCC at Chang Gung Memorial Hospital was retrospectively reviewed. The operative mortality rate was 5.5% (93 patients), and 424 patients (25.2%) had surgical complications. Among these patients, 1,592 were enrolled for survival analysis. All patients were regularly followed-up at 3-month intervals for laboratory data collection and image study. Median follow-up period was 49 months; patients with incomplete data or lost during follow-up were excluded. Regarding the serological data for viruses, 65.6% of the patients were positive for HBV and 34.7% patients were positive for HCV; however, some data were unavailable because the serology test for hepatitis C virus was not available before 1993.

The HCC was staged according to the criteria of the seventh edition (2007) of the American Joint Committee on Cancer (AJCC) staging system. Recurrence if suspected was confirmed by angiography; repeated resection, local ablation therapy, or systemic chemotherapy was implemented singularly or in combination as a common strategy for treatment; complications including bile leakage, intractable ascites, intra abdominal infection, postoperative bleeding, pleural effusion, hepatic failure, and others for which necessary intervention treatment were recorded.

A series of 30 clinicopathologic and biologic variables were selected for analysis; continuous data were expressed as the medians and 25–75 percentiles. Mean values were compared by unpaired Student's t test, and the chi-square test was used to compare percentages. All the variables were performed with hierarchical clustering using Cluster and TreeView software.[13] Survival was analyzed by the Kaplan–Meier method and survival curves were compared by the generalized Wilcoxon test and log-rank test. A value of $p<0.05$ was considered statistically significant. The significance of the prognostic value of the variables was estimated with Cox's multivariate proportional hazards model. Analysis was performed with SPSS for Windows 17.0.

Results

Survival Analysis

The demographic data of the 1,685 patients are shown in Table 1. Of the 1,685 patients, 711 (42.2%), and 974 (57.8%) patients underwent major hepatectomy (≥3 Couinaud segments) and minor hepatectomy, respectively. The Child–Turcotte–Pugh (CTP) grade was A in more than 91% of the patients and 55.0% had liver cirrhosis. More than 900 (54.4%) patients had hepatectomy for HCC before 2000 and 769 (45.6%) patients underwent surgery after 2000. In 746 (47.8%), 211 (12.5%), 555 (32.9%), and 50 (2.9%) patients the tumor-node-metastasis stage were I, II, III, and IV, respectively (Table 1). The 1-, 3-, 5-, 8-, and 10-year disease-free survival (DFS) rates in this series were 60.3%, 39.7%, 31.3%, 26.0%, and 24.0%, respectively, while the 1-, 3-, 5-, 8-, and 10-year overall survival (OS) rate were 80.1%, 59.1%, 46.6%, 34.4%, and 27.7%, respectively (Fig. 1).

Table 2 Cox proportional hazard models on disease-free survival

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% CI	*p* Value
Symptoms					
Yes	926	27.1	0.000	0.88–1.28	0.539
No	654	36.9			
Signs					
Yes	339	26.2	0.012	0.75–1.15	0.488
No	1,235	32.6			
Operation era					
~2000	861	27.4	0.000	0.77–1.14	0.491
2001~	731	35.6			
Cirrhosis					
Yes	837	28.6	0.002	1.05–1.52	0.013
No	713	34.8			
AST (43 U/L)					
>43	730	21.6	0.000	0.84–1.32	0.684
≤43	795	39.3			
ALT (42 U/L)					
>42	721	25.7	0.000	0.95–1.45	0.145
≤42	756	37.0			
ALP (82 U/L)					
>82	693	22.6	0.000	1.14–1.63	0.001
≤82	755	38.1			
Albumin (4.0 g/dl)					
≤4.0	730	24.3	0.000	1.04–1.50	0.014
>4.0	714	37.8			
CTP					
B or C	107	17.1	0.000	1.05–2.20	0.027
A	1,465	32.3			
Duration (min)					
>250	754	28.2	0.001	0.85–1.23	0.851
≤250	790	33.5			
Bleeding (ml)					
>600	707	25.0	0.000	0.89–1.39	0.338
≤600	799	35.9			
Transfusion					
Yes	539	23.9	0.000	0.80–1.31	0.338
No	1,053	34.8			
Complication					
Yes	331	25.7	0.001	0.87–1.31	0.533
No	1,261	32.6			
AFP					
>66.5	742	27.8	0.000	0.96–1.37	0.142
≤66.5	753	35.4			
Tumor size					
>5 cm	669	22.7	0.000	0.97–1.52	0.086
≤5 cm	923	37.2			
Satellite lesion					
Yes	407	20.8	0.000	1.00–1.54	0.048
No	1,149	35.2			
Vascular invasion					
Yes	311	22.6	0.000	1.08–1.69	0.007
No	1,182	34.3			

Table 2 (continued)

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% CI	*p* Value
Rupture					
Yes	152	17.1	0.000	0.72–1.60	0.735
No	1,433	32.7			
Encapsulation					
No	439	25.1	0.000	0.97–1.42	0.091
Yes	963	34.8			
Tumor status					
T3-4	556	17.1	0.000	1.01–1.75	0.042
T1-2	1,021	38.5			
Margin					
Positive	72	10.8	0.000	1.53–3.41	<0.001
Negative	1,438	32.6			
Lymph node status					
Yes	16	0	0.000	1.38–5.49	0.004
No	1,519	32.1			
Grade					
Grade III or IV	663	31.0	0.012	0.80–1.15	0.670
Grade I or II	710	33.3			

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

To predict the DFS, most clinical, surgical, and pathologic factors were significantly related to tumor recurrence in the follow-up study. Besides, aspartate aminotransferase (AST; >43 U/L), alanine aminotransferase (ALT; >42 U/L), ALP (>82 IU/L, normal range<94 IU/L), AFP (>66 ng/mL), and albumin (≤4.0 g/dL) were found to be significant prognostic factors according to the results of the univariate log-rank tests, while age, gender, positivity of viral hepatitis, and diabetes were not found to be significant (Table 2). The results of ROC curve analysis in blood tests were close to the median of continuous variables; therefore, we chose the median values as our new cutoff levels (data not shown). Moreover, gross vascular invasion (p=0.007), tumor status (T3 and T4 vs. T1 and T2, p=0.042), lymph node involvement (p=0.004), and satellite lesions (p=0.048) were independent prognostic factors for DFS. A positive surgical margin (p<0.001) had a significant impact on tumor recurrence. Liver function status, including ALP (p=0.001), albumin (p=0.014), presence of cirrhosis (p=0.013), and CTP grade B or C (p=0.027) were also independent factors in the multivariate analysis but not AFP (Table 2).

Most clinicopathologic features, except age, gender, and positivity of viral infection, were significantly related to OS in the univariate analysis (Table 3). Surgical factors, including operation complication (p=0.023), transfusion at surgery (p=0.017), positive resection margin (p=0.002), and tumor characters, including tumor status (p<0.001), vascular invasion (p<0.001), and lack of tumor encapsulation (p=0.001), were prognostic factors as determined by the Cox regression analysis. AFP (p=0.038), ALP (p=0.001), albumin (p=0.003), and CTP grade B or C (p=0.001) also predicted the long-term outcome independently (Table 3).

Elevation of ALP Predicted Recurrence and Outcome after Resection

ALP was an independent predictive factor for both DFS and OS. The 5-year DFS and OS rates for patients with higher ALP levels (≥82 IU/L, median) were 22.6% and 38.5%, respectively, whereas the 5-year survival rates for patients with lower ALP levels were 38.1% and 56.2%, respectively (Fig. 2a, b). Moreover, the outcome of HCC patients was remarkably good when ALP was lower than 82 U/L in DFS and OS (vs. ALP=82–200 IU/L and ALP >200 IU/L). To analyze the impact of ALP on survival, Kaplan–Meier survival analysis of four different subtypes stratified according to the ALP (82 IU/L) and AFP (66 ng/mL) levels before operation revealed significant differences in both the DFS and the OS outcomes. Patients with higher ALP had a poorer outcome than patients with higher AFP (Fig 2c, d). In conclusion, ALP among the liver function tests, in addition to other tumor characters were

Table 3 Cox proportional hazard models on overall survival

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% C.I.	*p* Value
Symptoms					
Yes	926	38.2	<0.001	0.87–1.30	0.561
No	654	57.8			
Signs					
Yes	339	36.9	<0.001	0.71–1.12	0.326
No	1,235	48.9			
Operation era					
~2000	861	35.9	<0.001	0.66–1.01	0.058
2001~	731	59.6			
Cirrhosis					
Yes	837	45.9	0.078	0.93–1.34	0.1.137
No	713	47.4			
AST (43 U/L)					
>43	730	38.1	<0.001	0.99–1.66	0.052
≤43	795	55.1			
ALT (42 U/L)					
>42	721	45.5	0.005	0.71–1.14	0.377
≤42	756	49.3			
ALP (82 U/L)					
>82	693	35.8	0.000	1.13–1.68	0.001
≤82	755	56.2			
Albumin (4.0 g/dl)					
≤4.0	730	37.7	0.000	0.61–0.90	0.003
>4.0	714	57.5			
CTP					
B or C	107	21.3	0.000	1.23–2.51	0.001
A	1,465	48.9			
Duration (min)					
>250	754	40.5	0.001	0.88–1.31	0.477
≤250	790	51.8			
Bleeding (ml)					
>600	707	34.2	0.000	0.92–1.47	0.218
≤600	799	56.7			
Transfusion					
Yes	539	28.9	0.000	1.06–1.74	0.017
No	1,053	55.8			
Complication					
Yes	331	37.4	0.001	1.04–1.59	0.023
No	1,261	48.9			
AFP					
>66.5	742	38.8	0.000	1.01–1.48	0.038
≤66.5	753	56.2			
Tumor size					
>5 cm	669	33.6	0.000	0.86–1.38	0.467
≤5 cm	923	55.9			
Satellite lesion					
Yes	407	33.1	0.000	0.88–1.37	0.401
No	1,149	52.1			
Vascular invasion					
Yes	311	25.5	0.000	1.31–2.05	<0.001
No	1,182	54.2			

Table 3 (continued)

Clinicopathologic variables	No. of patients	Univariate analysis 5-year survival rate (%)	*p* Value	Multivariate analysis HR 95% C.I.	*p* Value
Rupture					
Yes	152	25.5	0.000	0.72–1.61	0.727
No	1,433	48.9			
Encapsulation					
No	439	38.3	0.000	1.15–1.69	0.001
Yes	963	53.1			
Tumor status					
T3-4	556	24.1	0.000	1.29–2.26	<0.001
T1-2	1,021	59.0			
Margin					
Positive	72	29.5	0.000	1.28–3.00	0.002
Negative	1,438	48.8			
Lymph node status					
Yes	16	6.3	0.000	0.93–3.70	0.081
No	1,519	47.7			
Grade					
Grade III or IV	663	46.1	0.007	0.78–1.16	0.618
Grade I or II	710	51.7			

HR hazard ratio, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CTP* Child–Turcotte–Pugh, *ICG* indocyanine green, *AFP* α-fetoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

found to be independent factors in both DFS and OS of HCC patients; therefore, our results strongly suggest that high ALP could be related to recurrence and poor prognosis in HCC patients.

Interrelationships between Clinicopathologic Variables

Thirty clinicopathologic factors were analyzed for the interaction between the variables by hierarchical clustering analysis as shown in (Fig. 3). The red bands represent risk of recurrence in DFS analysis, whereas the green bands represent lower risk of recurrence (Fig. 3). Interestingly, the tumor status (T3 and T4 vs. T1 and T2) of HCC was associated with vascular invasion, satellite lesions, and lack of tumor encapsulation but not with tumor grade, AFP, or liver function tests. Since measurement of ALP activity is included in the liver function panel; not surprisingly, ALP was associated with AST, ALT, bilirubin, presence of cirrhosis, and HCV carrier state, while AFP was associated with tumor grade. In Cox regression analysis, ALP was the only powerful predictor in liver function tests for HCC prognosis after hepatectomy (Table 2); however, it was not statistically related to the pathologic tumor criteria. Moreover, surgical factors such as operation duration, transfusion, and bleeding during surgery were statistically in close relation with each other (Fig. 3). Taken together, ALP and the liver function tests had no close interaction or correlation with the tumor status, especially when recurrence was considered.

Discussion

The relatively large-scale study that we conducted depicts the interrelationship of clinical and pathologic factors to show their value in predicting recurrence and to reveal their impact on long-term survival; therefore, it is not surprising that most pathological factors were found to be significant predictive factors in univariate survival analysis; for example, positive resection margin, tumor status, vascular invasion, and satellite lesions were found to be important in prognosis; while transfusion and surgical complications were found to affect OS; however, multivariate analysis revealed that tumor status and lack of tumor encapsulation were the most powerful pathologic predictors. A multicenter study on HCC using international database revealed that tumor size and number of nodules were associated with microvascular invasion and that tumor size predicts the histologic grade of tumor.[14] Also, surgical factors such as blood loss, blood transfusion, operation duration, surgical resection margin, and complications were reported to be of predictive value.[12] Besides, the tumor–lymph node–metastasic status system still had enough predictive value in surgical patients[15]

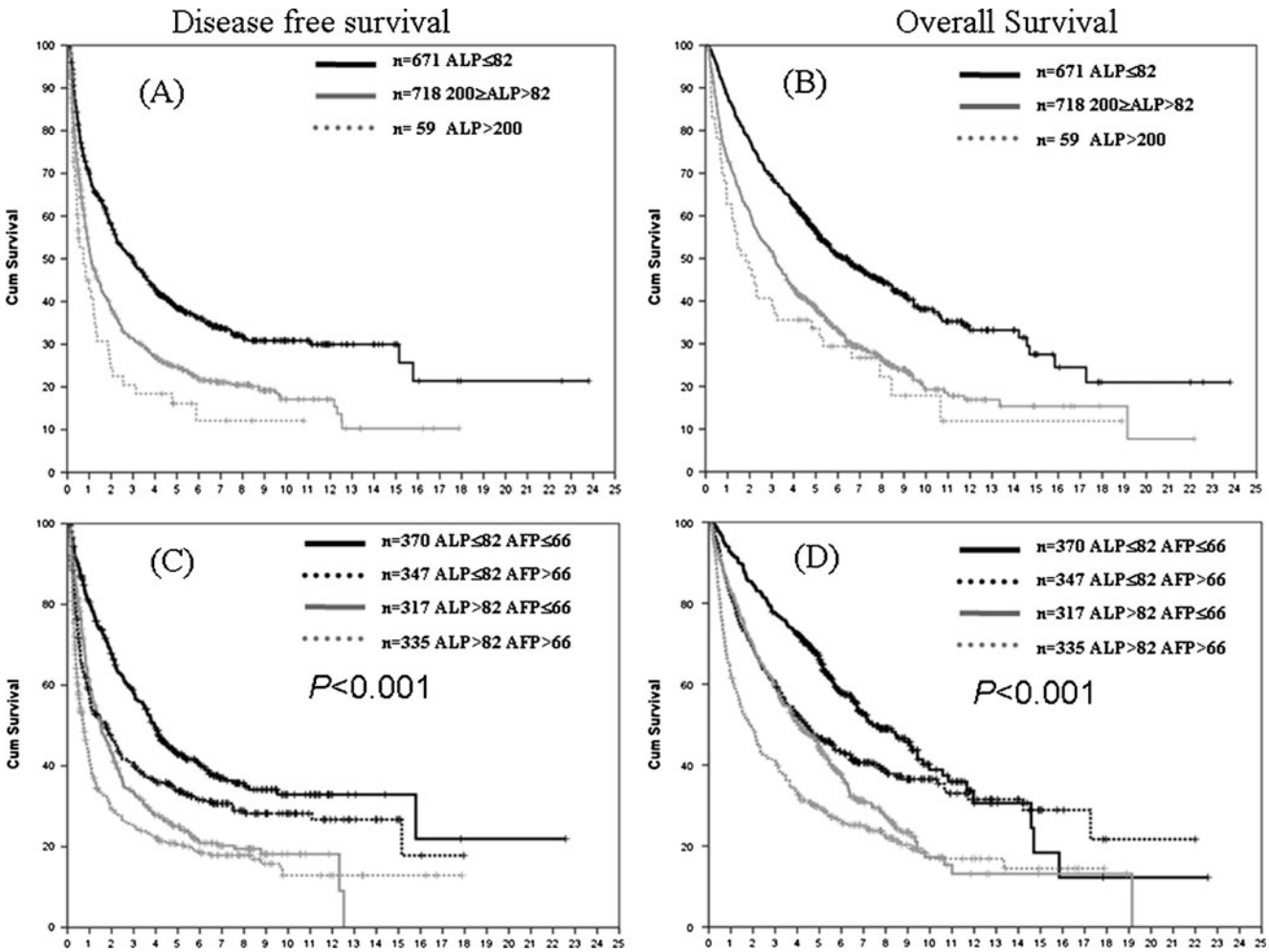

Fig. 2 **a**, **b** The serum level of alkaline phosphatase (ALP) and the long-term outcome. Elevation of ALP is related to poor outcome in both recurrence and overall survival, comparing level ≤82 U/L and 82–200 U/L or >200 U/L ($p<0.001$) but there is no significant difference in overall survival when comparing ALP levels between 82 and 200 U/L and >200 U/L in $p=0.182$. **c**, **d** The disease-free and overall survival is better when patients had lower ALP and AFP. However, elevation of ALP (82 U/L) predicts poor prognosis even AFP level is less than 66 ng/ml

Among the parameters of the current staging systems, serum levels of albumin and bilirubin are included in the Okuda staging system, while ALP is included in the CUPI system and considered to be poor prognostic factor if levels were higher than 200 U/L.[11,16] Moreover, AST has been proposed to be linked to poor outcome when AST was more than twice the upper normal limits before surgery.[17]

Cumulative data derived from Asian population with HCC revealed that elevation of ALP was associated with poor outcome.[9,10,18,19] This has been suggested in four previous studies; the first cohort study of 254 patients with HCC with no cirrhosis, ALP was found to be one of the independent prognostic factors for recurrence.[10] In another study of 218 patients with HCC and cirrhosis, ALP, tumor size (2 cm), multiplicity, and vascular invasion were found to be independent predictors for overall survival.[9] A third large-scale study in Taiwan also showed that ALP could predict the outcome. Lastly but not the least, a western study of Asian Americans with HCC showed that AFP and ALP were independent baseline predictors of survival.[18,19]. In our study, we also found that preoperative level of ALP was one of the most important independent predictors of recurrence even more important that AFP as we found that elevation of ALP above (82 U/L) predicted poor prognosis even when AFP level was less than 66 ng/ml.

Liver ALP is an isoform of tissue-nonspecific alkaline phosphatase and is identical to the mesenchymal stem cell antigen.[20] Furthermore, it is a differentiation marker for embryonic stem cell and other stem cells derived from the bone and adipose tissue. A previous study on rat liver regeneration revealed that ALP was transiently elevated

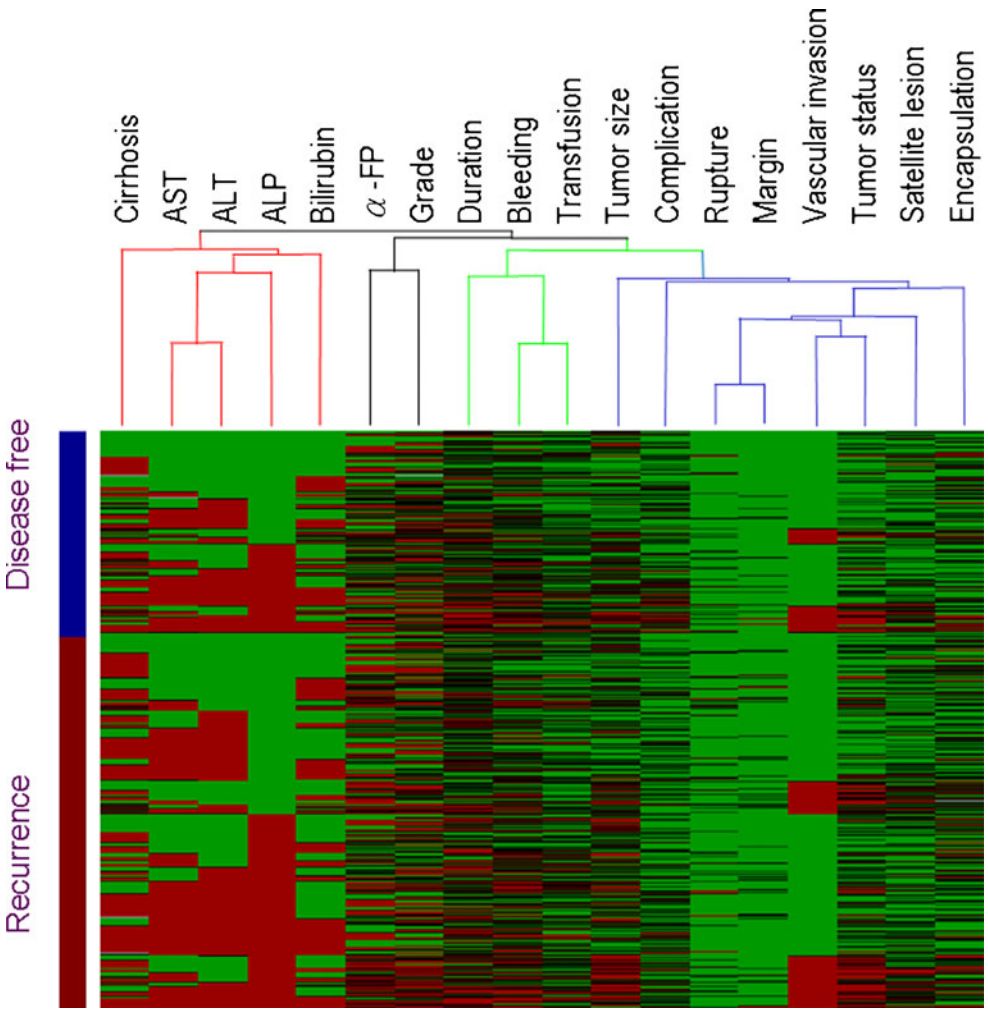

Fig. 3 Hierarchical clustering of 18 clinicopathologic variables for hepatocellular carcinoma. The variables were dichotomized into two zones; a higher risk recurrence zone represented by the red bands and a lower risk recurrence zone represented by green bands. For simplicity, we gathered related cluster of variables under bundles of lines having the same color. *Red lines bundle* represent a cluster of variables related to liver status, namely, liver function tests (AST, ALT, ALP, and bilirubin) and cirrhosis; *blue lines bundle* represent another cluster of variables related to tumor characters, namely, vascular invasion, satellite lesions, tumor size, tumor status, and encapsulation. However the two groups of variable are not closely related. Finally, *green lines bundle* represent a cluster of variables related to surgical procedure, namely, operative time, bleeding, and blood transfusion. According to disease-free survival, patients were categorized longitudinally into two groups recurrence and disease free

after surgery; however, no subsequent study was conducted to support this finding.[21] ALP was found to possibly indicate cancer cell proliferation in nucleolar localization in an electron microscopic cytochemistry study.[22] Cancer cells, including Hep-G2, A-375, and Bx-PC3 cells, showed higher ALP activity in the nucleolus and change in the localization during cell cycles. Taken together, the role of ALP in HCC setting may not only be related to cholestasis or hepatitis per se but also might be related to cancer proliferation or promotion mechanisms; however, this relation needs to be elucidated by further research.

Interestingly, hierarchical clustering analysis showed that ALP was statistically in close relation to AST, ALT, bilirubin level, and cirrhosis but not to albumin. Also, biochemical variables were clustered in one group along with cirrhosis, while pathologic variables represented another cluster that was statistically not closely related to liver function tests; however, a study from southern Taiwan showed that ALT elevation and AST/ALT ratio were poor prognostic factors in HCC, which was comparable with the outcome in western countries.[23] Taken together, from our and other authors' results, the independent prognostic factors mentioned above were found to be important prognostic factors; however, they were not included in the tumor–lymph node–metastasis system of the seventh edition (2007) of the AJCC staging system. Hopefully, future basic science research could find explanations—rather than statistical correlation alone—for that complex interaction between the clinical parameters, laboratory data, and pathologic factors; and to elucidate their impact on HCC prognosis, which undoubtedly should be considered in future staging systems once validated.

Conclusion

ALP among the liver function tests, in addition to other tumor characters were independent factors for DFS and OS; we found that elevated ALP (>82 U/L) in HCC patients indicates poor prognosis; therefore, our results suggest that preoperative ALP levels could be utilized to monitor and predict recurrence in high-risk HCC patients. May be future

basic research could find explanation for the complex interaction between the clinical parameters, laboratory data, and pathologic factors to elucidate their impact on HCC prognosis.

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ORIGINAL ARTICLE

Surgical Outcomes for Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease

Toshifumi Wakai · Yoshio Shirai · Jun Sakata · Pavel Vladimirovich Korita · Yoichi Ajioka · Katsuyoshi Hatakeyama

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Abstract
Background The present study investigated outcomes following surgical resection of hepatocellular carcinoma (HCC) in nonalcoholic fatty liver disease (NAFLD).
Methods Patients (n=225) undergoing resection for HCC were divided into three groups: hepatitis C viral group (n=147), hepatitis B viral group (n=61), and NAFLD group (n=17). Clinicopathological characteristics and surgical outcomes were analyzed retrospectively.
Results Patients in the NAFLD group were older (P<0.001), with a higher body mass index (P<0.001) and larger tumors (P=0.002) than patients who were positive for hepatitis viral markers. Eight patients in the NAFLD group were found to have nonalcoholic steatohepatitis (NASH) histologically. Postoperative morbidity and 30-day mortality rates were significantly higher in the NAFLD group (59% and 12%, respectively) than in the hepatitis C viral (31% and 0.7%, respectively) and hepatitis B viral (28% and 3.3%; P=0.043 and P=0.016, respectively) groups. All deaths in the NAFLD group were in patients with NASH-related cirrhosis who had undergone right hemihepatectomy. Survival after resection was comparable among the three groups (P=0.391), but patients with NAFLD showed better disease-free survival on univariate (P=0.048) and multivariate (P=0.020) analyses.
Conclusions Surgical resection may provide a survival benefit for patients with NAFLD-related HCC. Patients with NASH-related cirrhosis undergoing major hepatic resection should be treated carefully.

Keywords Hepatocellular carcinoma · Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Hepatic resection · Prognosis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic nonviral liver disease.[1–3] NAFLD comprises a wide spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH),[2] which is an important cause of cirrhosis and hepatocellular carcinoma (HCC).[4–8] Prior to the recognition of NASH as a significant cause of chronic liver disease, some cases of cirrhosis caused by NASH may have been labeled as cryptogenic cirrhosis, thus underestimating the true prevalence of NASH-related cirrhosis. The incidence of HCC due to nonviral causes has increased gradually over recent years.[7–9] In a nationwide survey of 33,379 Japanese patients with liver cirrhosis, 1.6% of HCC was caused by NASH-related cirrhosis.[9] Tokushige et al.[10] reported that post-treatment survival and recurrence rates in patients with NASH-related HCC are similar to those for HCC patients infected with hepatitis C virus (HCV). In contrast, others reported higher frequencies of intrahepatic recurrences and lower survival rates for patients with HCV-related HCC compared to patients infected with hepatitis B virus or with

T. Wakai (✉) · Y. Shirai · J. Sakata · K. Hatakeyama
Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences,
1-757 Asahimachi-dori, Chuo-ku,
Niigata 951-8510, Japan
e-mail: wakait@med.niigata-u.ac.jp

P. V. Korita · Y. Ajioka
Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences,
Niigata, Japan

non-B non-C hepatitis.[11–15] There is little information in the literature regarding comparative analyses of surgical outcomes between patients with NAFLD-related HCC and patients with hepatitis virus-related HCC. Thus, there is no consensus concerning differences in surgical outcomes in patients with HCC depending on the underlying liver disease.

Kleiner et al.[16] proposed an NAFLD activity scoring system to discriminate between NASH and non-NASH fatty liver disease based on histological assessment of steatosis, lobular inflammation, and ballooning. In the present study, we evaluated NAFLD activity scores in resected specimens of NAFLD-related HCC and compared surgical outcomes among patients with different underlying liver diseases using univariate and multivariate analyses. The aim of the present retrospective study was to determine surgical outcomes for HCC in NAFLD.

Patients and Methods

Patient Population

From January 1990 to December 2007, a total of 317 consecutive Japanese patients underwent curative hepatic resection for HCC at the Division of Digestive and General Surgery, Niigata University Medical and Dental Hospital (Niigata, Japan). Curative hepatic resection was defined as resection of all grossly visible hepatic tumors. Prior to undergoing surgical resection, all patients were tested for the presence of hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (anti-HCV). Three patients who tested positive for both HBsAg and anti-HCV were excluded from the study, as were 42 patients who underwent repeat hepatectomy for intrahepatic recurrence of HCC. The remaining 272 patients were divided into three groups on the basis of hepatitis viral status as follows: the C viral group, who tested positive for anti-HCV only (n=147); the B viral group, who tested positive for HBsAg only (n=61); and the non-B non-C group, who tested negative for both HBsAg and anti-HCV (n=64). In the non-B non-C group, 24 patients had underlying alcoholic liver injury, 17 patients had NAFLD, four patients had primary biliary cirrhosis, one patient had Budd–Chiari syndrome, one patient had autoimmune hepatitis, 11 patients had cryptogenic hepatitis or cirrhosis, and six patients had an almost normal liver. The diagnostic criteria for NAFLD included alcohol intake of <20 g/day, negative hepatitis serology (viral, autoimmune, metabolic), and histological features consistent with NAFLD, characterized by the presence of hepatic steatosis involving >5% of hepatocytes, lobular inflammation, and hepatocellular ballooning.[16] The present retrospective study included 147 patients in the C viral group, 61 patients in the B viral group, and 17 patients with NAFLD. The study protocol was approved by the Institutional Review Board of Niigata University Medical and Dental Hospital.

Laboratory Evaluation

Prior to surgical resection, HBsAg, anti-HCV, Child–Pugh classification, and serum α-fetoprotein (AFP) levels were determined. Serum HBsAg and anti-HCV were detected by radioimmunoassay (Lumipulse II HBsAg; Fujirebio, Tokyo, Japan) and a second-generation ELISA (Lumipulse II Ortho HCV; Ortho-Clinical Diagnostics, Tokyo, Japan), respectively. Serum concentrations of AFP were determined by enzyme immunoassay (Luminomaster AFP; Sankyo Yell Yakuhin, Tokyo, Japan), with a reference range of <21 ng/mL. In the present study, the retention of indocyanine green (Diagnogreen; Dai-ichi Pharmaceutical, Tokyo, Japan) 15 min after injection (0.5 mg/kg) was used as an indicator of hepatic functional reserve (reference range, ≤10%).

Hepatectomy Procedures

Hepatectomy procedure was selected individually for each patient, taking into account the status of the primary tumor (i.e., size, number, and location), the hepatic functional reserve, and the patient's general condition.[17] The tendency was to select a more extensive hepatectomy procedure for patients with larger tumors, more deeply located tumors, better hepatic functional reserve, and/or a better general condition. In the present study, the term *limited* hepatectomy refers to nonanatomic partial hepatectomy, monosegmentectomy, and bisegmentectomy, whereas *major* hepatectomy refers to central hepatectomy, hemihepatectomy, and more extensive hepatectomy.

Pathological Evaluation

Resected specimens were submitted to the Department of Surgical Pathology (Niigata University Medical and Dental Hospital) for evaluation. Each specimen was examined to determine the presence of cirrhosis, the number of hepatic tumors, the size of the largest hepatic tumor, the histological grade, gross or microscopic vascular invasion, hepatectomy margin status, and NAFLD activity score. A median number of 12 microscopic slides of the resected liver from each patient was reviewed (range, 2–55 slides). For the histological evaluation of hepatic fibrosis, two or three paraffin-embedded blocks were selected from each resected specimen. Two serial 3-μm sections were re-cut and prepared from each block, one for haematoxylin–eosin

staining and one for Masson's trichrome staining to evaluate hepatic fibrosis. The pathological findings were described according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[18] Hepatectomy margin status was classified as either R0 (no residual tumor) or R1 (microscopic residual tumor)[18] when histologically verified tumor cells were absent or present, respectively, on the resection margin.

In the present series, the number of hepatic tumors was determined by gross examination of multiple slices from each resected specimen, but did not include satellite nodules. In patients with multiple tumors, the largest tumor was chosen as representative. Cirrhosis in the adjacent (nontumorous) liver was diagnosed microscopically based on the presence of regenerative nodules surrounded by fibrous septa. Histological grade was determined according to the Edmondson–Steiner classification [19] and was based on the areas of the tumor with the highest grade. Vascular invasion in the present study refers to both portal and hepatic venous invasion. Using the previously published NAFLD activity scoring system, [16] we calculated an NAFLD activity score, defined as the unweighted sum of the scores for steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2). In the present study, a score of 5–8 indicates NASH.[16]

Patient Follow-Up after Resection

Postoperative morbidity was defined as any postoperative complication that lengthened hospital stay.[17] Postoperative mortality was defined as any death occurring within 30 days following resection of the HCC. Approximately 1 month after resection, serum AFP concentrations were measured, and abdominal ultrasonography and/or contrast-enhanced computed tomography were performed in all patients. Thereafter, patients were followed up every 3 months in outpatient clinics and were monitored for disease recurrence by measurement of AFP serum concentrations and/or imaging studies. The median follow-up time after resection was 87 months (range, 1–239 months). At the time of assessment of disease status, 94 patients had died of tumor recurrence, and 27 had died of other causes with no evidence of disease. The remaining 104 patients were alive. In the present series, 154 (68%) patients had disease recurrence during the follow-up period.

Prognostic Factors

To determine factors influencing long-term outcome after resection, 13 conventional variables (Table 1),[18,20,21] together with underlying liver disease, were tested in all 225 patients. The cutoff levels for patient age (65 years) and indocyanine green retention rate at 15 min (ICG R15; 15%) were determined based on respective median values, whereas the size of the primary tumor (cutoff, 5 cm) was determined according to the AJCC Cancer Staging Manual.[18] The cutoff level for preoperative serum AFP (20 ng/mL) was determined on the basis of a reference range of serum AFP levels <21 ng/mL. The cutoff level for body mass index

Table 1 Clinicopathological characteristics of 225 patients with hepatocellular carcinoma according to underlying liver disease

Variable	Underlying liver disease			*P* value
	C viral (*n*=147)	B viral (*n*=61)	NAFLD (*n*=17)	
Age (≤65/>65 years)	63/84	47/14	4/13	<0.001
Sex ratio (M/F)	107/40	43/18	10/7	0.496
BMI (≤25/>25 kg/m^2)	123/24	49/12	6/11	<0.001
Child–Pugh classification (A/B+C)	123/24	56/5	16/1	0.195
Cirrhosis (absent/present)	63/84	22/39	8/9	0.611
ICG R15 (≤15/>15%)	73/74	48/13	9/8	<0.001
Serum AFP (≤20/>20 ng/mL)	64/83	22/39	9/8	0.409
Hepatectomy procedure (limited/major)	113/34	36/25	9/8	0.009
Tumor number (solitary/multiple)	105/42	40/21	14/3	0.371
Tumor size (≤5/>5 cm)	122/25	40/21	9/8	0.002
Edmondson–Steiner grade (I+II/III+IV)	118/29	48/13	15/2	0.685
Vascular invasion (absent/present)	106/41	34/27	10/7	0.060
Hepatectomy margin status (R0/R1)	132/15	50/11	14/3	0.289

C viral hepatitis C viral, *B viral* hepatitis B viral, *NAFLD* nonalcoholic fatty liver disease, *BMI* body mass index, *ICG R15* indocyanine green retention rate at 15 min, *AFP* α-fetoprotein, *R0* no residual tumor, *R1* microscopic residual tumor

(BMI; 25 kg/m^2) was determined according to World Health Organization criteria.[22]

Statistical Analysis

Medical records and survival data were obtained for all patients. Categorical variables were compared by Pearson's chi-squared test. Causes of death were determined from the medical records and deaths from other causes were treated as censored cases. The Kaplan–Meier method was used to estimate the cumulative incidence of events, and differences between groups were evaluated using the log-rank test. Cox's proportional hazards regression model was used to identify factors that were independently associated with survival and disease-free survival. In this model, stepwise selection was used for variable selection, with entry and removal limits of $P<0.05$ and $P>0.10$, respectively. The stability of each model was confirmed using a step-backward and step-forward fitting procedure, and variables identified as having an independent influence on survival and disease-free survival were identical in both procedures. All statistical analyses were performed using PASW Statistics 17 software (SPSS Japan, Tokyo, Japan). All tests were two-sided, and $P<0.05$ was considered significant.

Results

Patient Characteristics

There were 160 men and 65 women, with a median age of 65 years (range, 16–83 years). The median values of BMI, ICG R15, and serum AFP were 22.3 kg/m^2 (range, 13.5–35.2 kg/m^2), 14% (range, 1–48%), and 43 ng/mL (range, 1–770,000 ng/mL). The median size of the primary tumor was 3.3 cm (range, 0.9–17 cm).

Hepatectomy Procedures

Intraoperative ultrasonography was routinely used to evaluate the liver remnant for additional tumors. Intermittent clamping of the portal pedicle (15 min clamping followed by 5 min unclamping) was used during hepatic resection. Surgical procedures included nonanatomic partial hepatectomy in 69 patients, monosegmentectomy (removal of one Couinaud segment) in 37 patients, bisegmentectomy (removal of two Couinaud segments) in 51 patients, central hepatectomy (removal of Couinaud segments IV, V, and VIII) in three patients, right hemihepatectomy (removal of Couinaud segments V–VIII) in 35 patients, left hemihepatectomy (removal of Couinaud segments II–IV) in eight patients, and more extensive hepatectomy in 22 patients.

Clinicopathological Characteristics According to Underlying Liver Disease

Comparisons of clinicopathological characteristics among the three groups (Table 1) revealed that patient age was significantly higher in the NAFLD group and that this group also had a significantly higher BMI and larger tumor size. The C viral group was characterized by impaired ICG R15 and limited hepatectomy. These findings indicate that impaired hepatic function was more common in the C viral group. The B viral group was characterized by a younger age.

NAFLD Activity Score

The NAFLD activity scores in 17 patients with NAFLD are summarized in Table 2. Using the NAFLD activity scoring system of Kleiner et al.[16] the median score in the present series was 4 (range, 2–7). NASH was verified histologically in eight patients who had scores of ≥5. Cirrhosis was verified histologically in six of eight (75%) patients with NASH.

Postoperative Morbidity and Mortality According to Underlying Liver Disease

The incidence of postoperative morbidity and 30-day mortality in the present study was 32% (72/225 patients) and 1.8% (4/225 patients), respectively. Postoperative morbidity was significantly higher in the NAFLD group (10/17; 59%) compared to the C and B viral groups [45/147 (31%) and 17/61 (28%), respectively; $P=0.043$]. In the NAFLD group, hepatic insufficiency ($n=4$) was the most common complication, followed by biliary fistula ($n=3$), ascites ($n=1$), paralytic ileus ($n=1$), and acute respiratory insufficiency ($n=1$). In addition, the incidence of postoperative 30-day mortality was significantly higher in the NAFLD group compared with the C and B viral groups [2/17 (12%), 1/147 (0.7%), and 2/61 (3.3%), respectively; $P=0.016$]. Two patients with NASH-related cirrhosis in the NAFLD group who had undergone right hemihepatectomy died in hospital. The causes of deaths ($n=2$) in the NAFLD group were hepatic failure and multiple organ failure (MOF).

Factors Influencing Survival after Resection

The overall cumulative survival rates 5 and 10 years after resection were 59% and 41%, respectively. Univariate analysis identified serum AFP levels, tumor size, Edmondson–Steiner grade, vascular invasion, and the number of hepatic tumors as significant prognostic factors for survival. Variables that were significant prognostic factors in the univariate analyses were

Table 2 Nonalcoholic fatty liver disease activity score

Variable	Definition	Number of patients
Degree of steatosis	Low to medium power of parenchymal involvement by steatosis	
0	<5%	0
1	5–33%	10
2	>33–66%	5
3	>66%	2
Lobular inflammation	Overall assessment of all inflammatory foci	
0	No foci	0
1	<2 foci per×200 field	9
2	2–4 foci per×200 field	8
3	>4 foci per×200 field	0
Ballooning		
0	None	2
1	Few balloon cells	8
2	Many cells/prominent ballooning	7

entered into multivariate analyses, which revealed that Edmondson–Steiner grade ($P<0.001$), tumor size ($P<0.001$), serum AFP levels ($P=0.010$), and the number of hepatic tumors ($P=0.020$) remained as independent prognostic factors for survival (Table 3).

Factors Influencing Disease-Free Survival after Resection

The overall cumulative disease-free survival rates 5 and 10 years after resection were 34% and 20%, respectively. Univariate analyses identified tumor size, Edmondson–Steiner grade, serum AFP levels, vascular invasion, cirrhosis, the number of hepatic tumors, Child–Pugh classification, and underlying liver disease as significant prognostic factors for disease-free survival. Subsequent multivariate analysis revealed that tumor size ($P<0.001$), Edmondson–Steiner grade ($P=0.001$), cirrhosis ($P=0.014$), underlying liver disease ($P=0.020$), and serum AFP levels ($P=0.028$) remained as independent prognostic factors for disease-free survival (Table 4).

Long-Term Outcome of Patients with NAFLD

The cumulative survival rate 5 years after resection was 59% in the NAFLD group, compared with 57% and 63% in the C and B viral groups, respectively. Survival after resection was comparable among the three groups ($P=0.391$; Fig. 1). Cumulative disease-free survival 5 years

Table 3 Independent factors significantly influencing survival after resection

Variable	Number of patients	Survival rate (%)		Univariate analysis	Multivariate analysis	
		5 years	10 years	*P* value	Hazard ratio (95% CI)	*P* value
Edmondson–Steiner grade						
I–II	181	66	46	<0.001	1.000	
III–IV	44	27	18		2.495 (1.550–4.015)	<0.001
Tumor size						
≤5 cm	171	66	47	<0.001	1.000	
>5 cm	54	35	22		2.201 (1.413–3.429)	<0.001
Serum AFP						
≤20 ng/mL	95	72	53	<0.001	1.000	
>20 ng/mL	130	50	32		1.804 (1.149–2.833)	0.010
No. hepatic tumors						
Solitary	159	67	47	0.002	1.000	
Multiple	66	39	26		1.696 (1.086–2.648)	0.020

95% CI 95% confidence interval, *AFP* α-fetoprotein

Table 4 Independent factors significantly influencing disease-free survival after resection

Variable	Number of patients	Disease-free survival (%)		Univariate analysis	Multivariate analysis	
		5 years	10 years	*P* value	Hazard ratio (95% CI)	*P* value
Tumor size						
≤5 cm	171	38	22	<0.001	1.000	
>5 cm	54	20	15		2.135 (1.418–3.216)	<0.001
Edmondson–Steiner grade						
I–II	181	39	24	<0.001	1.000	
III–IV	44	14	5		1.995 (1.311–3.035)	0.001
Cirrhosis						
Absent	93	43	32	0.003	1.000	
Present	132	28	9		1.605 (1.100–2.342)	0.014
Underlying liver disease						0.020
NAFLD	17	66	66	0.048	1.000	
C viral	147	29	12		2.645 (1.060–6.598)	0.037
B viral	61	39	29		1.820 (0.712–4.651)	0.211
Serum AFP						
≤20 ng/mL	95	46	25	0.001	1.000	
>20 ng/mL	130	26	16		1.493 (1.043–2.138)	0.028

95% CI 95% confidence interval, *NAFLD* nonalcoholic fatty liver disease, *C viral* hepatitis C viral, *B viral* hepatitis B viral, *AFP* α-fetoprotein

after resection was 66% in the NAFLD group, compared with 29% and 39% in the C and B viral groups, respectively. Disease-free survival after resection was significantly better in the NAFLD group (P=0.048; Fig. 2). In the NAFLD group, the cumulative disease-free survival curve plateaued 2 years after resection, whereas it continued to decrease steadily in the other two groups, suggesting a low risk of tumor recurrence in the NAFLD group (Fig. 2). In the subgroup of patients with cirrhosis (n=132), underlying liver disease was not associated with either survival (P=0.819) or disease-free survival (P=0.268). Furthermore, comparing patients with NAFLD-related cirrhosis (n=9) and HCV-related cirrhosis (n=84), there was no significant difference in either survival (P=0.576) or disease-free survival (P=0.109) between the two groups.

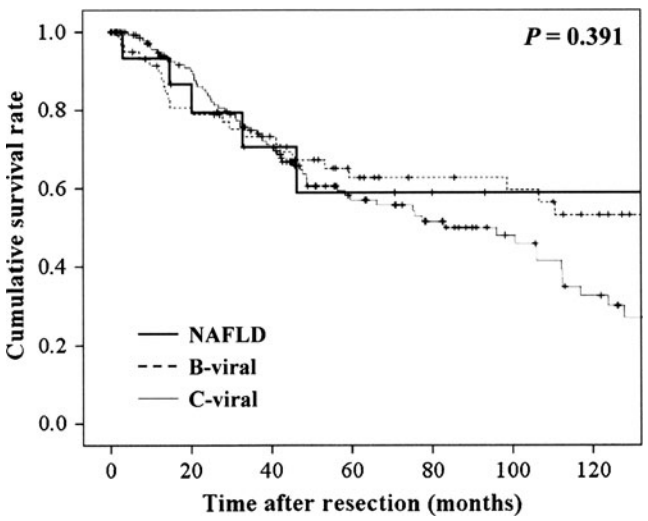

Fig. 1 Kaplan–Meier survival estimates according to underlying liver disease: nonalcoholic fatty liver disease (NAFLD; n=17), hepatitis B viral (n=61), and hepatitis C viral (n=147). Cumulative survival after resection was comparable among the three patient groups (P=0.391)

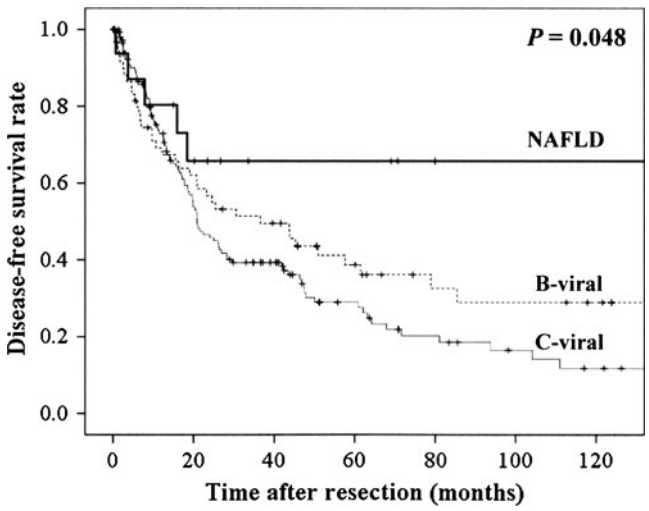

Fig. 2 Kaplan–Meier disease-free survival estimates according to underlying liver disease: nonalcoholic fatty liver disease (NAFLD; n=17), hepatitis B viral (n=61), and hepatitis C viral (n=147). Cumulative disease-free survival after resection was significantly better in the NAFLD group (P=0.048)

Discussion

NAFLD, especially NASH-related cirrhosis, is recognized as a critical risk factor for the development of HCC.[4–8] Although there are reports that the incidence of NAFLD-related HCC is increasing gradually,[7–9,23] there is little information regarding the comparative analysis of surgical outcomes between patients with NAFLD-related HCC and patients with hepatitis virus-related HCC. This prompted us to undertake the present study, which revealed that patients with NAFLD-related HCC had acceptable surgical outcomes, despite being older and having larger tumors than patients in the hepatitis viral groups. However, the frequencies of postoperative morbidity and mortality were greater in the present NAFLD group. This may be explained, in part, by the greater number of elderly patients and patients with a higher BMI in the NAFLD group. Because several studies have suggested that hepatic steatosis is a critical risk factor for major hepatic resection,[24–26] patients with NAFLD-related HCC, especially underlying NASH-related cirrhosis, should be treated carefully to avoid postoperative complications.

Although hepatic steatosis is considered to be a significant risk factor for major hepatic surgery, there is no consensus regarding how to adjust the extent of liver resection in patients with hepatic steatosis.[27] The systematic review and meta-analysis by de Meijer et al.[28] suggested a significant association between severe hepatic steatosis and increased risk of postoperative complications and mortality. We also confirmed this. In the NAFLD group of the present study, hepatic insufficiency was the most common complication and the deaths (n=2) in patients with NASH-related cirrhosis were related to hepatic failure following right hemihepatectomy. Thus, patients with NASH-related cirrhosis undergoing major hepatectomy should be approached with due caution. Nakamuta et al.[29] proposed that a short-term combination therapy for a protein-rich (100 kcal/day) diet, exercise (600 kcal/day), and bezafibrate (400 mg/day) is effective for reducing hepatic steatosis in potential living donor liver transplant candidates. This might be an effective approach to reduce steatosis-associated complications after major hepatectomy.

Most NASH-related HCCs are believed to develop against the background of a cirrhotic liver.[4,5,30–33] In 2004, Bencheqroun et al.[34] reported for the first time a case of NASH-related HCC arising from a non-cirrhotic liver. Since then, several studies focusing on NASH-related HCC have reported some HCCs arising from non-cirrhotic liver.[35–39] In the present study, two of eight (25%) patients with NASH-related HCC had a non-cirrhotic liver. Together, these findings suggest that patients with non-cirrhotic NASH should be recognized as being at risk of developing HCC.

Intrahepatic recurrence after resection of HCC can result from either intrahepatic metastases from the primary tumor or multicentric new lesions.[14] Previous studies[14,15,30–43] indicate that early recurrence (i.e., within approximately 2 years of resection) includes both intrahepatic metastases from primary and multicentric lesions, whereas late recurrence (i.e., >2 years after resection) is predominantly of multicentric origin. In the present study, cumulative disease-free survival plateaued 2 years after resection in the NAFLD group (Fig. 2), after which there were no further recurrences. Takuma et al.[39] reported similar findings in 11 patients with NASH-related HCC who underwent potentially curative treatment, including ablation therapy and surgical resection. However, in the present study, cumulative disease-free survival continued to decrease steadily throughout the duration of follow-up of patients in both hepatitis viral groups (Fig. 2), suggesting that multicentric carcinogenesis may have contributed to the development of tumor recurrence in these patients. Assuming that the incidence of multicentric lesions is constant with time, it seems that multicentric carcinogenesis is uncommon in patients with NAFLD-related HCC. Therefore, most tumor recurrences after resection in the NAFLD group are perhaps of metastatic rather than multicentric origin.

Disease-free survival after resection was significantly better in patients with NAFLD-related HCC, as determined by univariate and multivariate analyses (Table 4), whereas survival after resection was comparable among the three groups (Fig. 1). Postoperative screening for recurrence, and subsequent successful treatment for tumor recurrence, may explain the prolonged survival of patients in the two hepatitis viral groups. In the present study, the cumulative 5-year disease-free survival rate in the NAFLD group after resection was 66%, which is comparable with the 5-year recurrence-free survival rate of 60% in patients with NASH-related HCC reported by Takuma et al.[39] Considering that late recurrence caused by multicentric carcinogenesis was less common in the NAFLD group, surgical resection would seem to provide a survival benefit for patients with NAFLD-related HCC.

The small number of patients in the present retrospective analysis limited the statistical power of the study, and the short follow-up time in some patients and the relatively small number of patients with NAFLD-related HCC (n=17) precluded firm conclusions being drawn. However, to our knowledge, this remains one of the largest series comparing surgical outcomes between patients with NAFLD-related HCC and those with hepatitis virus-related HCC. In addition, we believe that the stated limitations were unlikely to significantly affect the outcome of the present study because the differences between the groups were too marked to have resulted from any bias.

Conclusions

Surgical resection may provide a survival benefit for patients with NAFLD-related HCC. Patients undergoing resection for NAFLD-related HCC have an increased risk of postoperative morbidity and mortality. Patients with NAFLD-related HCC, especially underlying NASH-related cirrhosis, should be treated carefully to avoid postoperative complications.

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ORIGINAL ARTICLE

Differential Bone Marrow Hematopoietic Stem Cells Mobilization in Hepatectomized Patients

Carmen Herencia · Antonio Rodríguez-Ariza · Antonio Canalejo · Álvaro Naranjo · F. Javier Briceño · Pedro López-Cillero · Manuel De la Mata · Juan R. Muñoz-Castañeda

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Abstract
Background The involvement of bone marrow hematopoietic stem cells (BMHSC) mobilization during liver regeneration from hepatectomized patients is under debate. The main aim of this study was to investigate the role of BMHSC mobilization after hepatic resection in 33 patients with liver disease.
Methods and Results Mobilization of $CD34^+$ BMHSC after 72 h of surgery was found in peripheral blood of some, but not all, of the hepatectomized patients. These $CD34^+$ cells co-expressed other stem cells markers. The patients without BMHSC mobilization showed high levels of circulating and liver tissue BMHSC ($CD34^+$ cells) previous to surgery. Therefore, two types of patients: "mobilizers" and "non-mobilizers" were distinguished based on the values of $CD34^+$ cells before and after surgery. Changes in cytokines involved in the hepatic regeneration (HGF and TGF-β), and in BMHSC mobilization process (SCF, SDF-1, IL-12, or MMP-2), were detected in both groups. In addition, a higher activation previous to surgery of the SDF-1/CXCR4 axis in liver tissue was observed in non mobilizers patients compared to mobilizer patients.
Conclusion BMHSC mobilization seems to be associated with variations in the levels of cytokines and proteolytic enzymes involved in hepatic regeneration and bone marrow matrix degradation. Hepatectomy may be an insufficient stimulus for BMSHC mobilization. The pre-hepatectomy higher levels $CD34^+$ cells in peripheral blood and liver, associated to the activation of hepatic SDF-1/CXCR4 axis, suggest a BMHSC mobilization process previous to surgery in non mobilizer patients.

Keywords Bone marrow hematopoietic stem cells · Hepatic regeneration · Mobilization · SDF-1/CXCR4- axis

Introduction

Liver regeneration after partial hepatectomy is a very complex and well-orchestrated phenomenon associated with signaling cascades involving growth factors, cytokines, chemokines, matrix remodeling, and several feedbacks stimulating and inhibitory cell growth-related signals.[1,2] During this process, the source of new hepatocytes remains as a key unanswered question.[3] Hepatocytes themselves have been proposed as the main cells involved in this hepatic regeneration.[4] Many studies have described the capability of these cells to modulate the final hepatic mass after an orthotopic liver

C. Herencia · A. Rodríguez-Ariza · M. De la Mata · J. R. Muñoz-Castañeda
Instituto Maimónides de Investigación Biomédica de Córdoba, (IMIBIC), Hospital Universitario Reina Sofía,
Córdoba, Spain

A. Canalejo
Departamento de Biología Ambiental y Salud Pública,
Universidad de Huelva,
Huelva, Spain

Á. Naranjo · F. J. Briceño · P. López-Cillero
Servicio de Cirugía, Hospital Universitario Reina Sofía,
Córdoba, Spain

F. J. Briceño · P. López-Cillero · M. De la Mata
Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd),
Madrid, Spain

J. R. Muñoz-Castañeda (✉)
Instituto Maimónides de Investigación Biomédica de Córdoba, (IMIBIC), Hospital Universitario Reina Sofía,
Avda. Menéndez-Pidal s/n.,
Córdoba, Spain 14004
e-mail: juanr.munoz.exts@juntadeandalucia.es

transplant or hepatectomy.[5] However, under specific conditions of liver damage, these hepatocytes lose substantially the capability to regenerate the liver.[6] In these circumstances, other types of cells, such as bone marrow hematopoietic stem cells (BMHSC) or hepatic progenitors cells contribute to hepatic regeneration,[3,6,7] serving as an alternative source of hepatocytes in damaged livers.[8,9] Bone marrow has a heterogeneous population of stem and progenitor cells, which have the capacity to differentiate into hepatocytes. These cells might participate in hepatic regeneration after hepatectomy through a BMHSC mobilization process.

In renal and cardiac injury models, it has been reported that BMHSC are mobilized from the bone marrow to the bloodstream with destination to the damaged organ.[10,11] In relation to hepatectomy, some studies have shown an involvement of BMHSC in hepatic regeneration after hepatic resection or chronic hepatic diseases[12,13] while others did not.[14,15] Therefore, the mobilization of stem cells from bone marrow to bloodstream after hepatectomy is unclear.

Based on the hypothesis that BMSHC may contribute to liver repair after hepatectomy, and that these cells must be present in the circulation before reaching the liver, we have investigated the number and type of $CD34^+$ cells in peripheral blood from hepatectomized patients. Once the $CD34^+$ hematopoietic stem cells are released into peripheral blood, these cells migrate and anchor to the liver in response to stress signals, to changes in the levels of cytokines and/or after activation of SDF-1/CXCR4 axis.[16] SDF-1 was the first chemoattractant reported for human $CD34^+$ hematopoietic stem cells and SDF-1/CXCR4 interaction regulates the homing and repopulation of stem cells into injured organ.[17] An altered response to SDF-1 may be associated with $CD34^+$ progenitor cells mobilization.[18]

In this study, we analyzed the relationships between BMHSC mobilization, cytokines associated to hepatic regeneration and bone marrow matrix degradation, and the activation of the SDF-1/CXCR4 axis in hepatectomized patients.

Material and Methods

Patients

The study included 33 consecutive patients admitted to the hospital for medically indicated hepatectomy. Hepatic biopsies (during the surgery) and blood samples before (0 h) and 72 h after surgery were obtained from all the patients. All patients underwent anesthesia and laparotomy. The clinical characteristics of the patients included in this study are included in Table 1. The study protocol was approved by the local ethics committee of the Reina Sofia University Hospital and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

Hepatectomy Procedure

Liver anatomy terms used are based on Couinaud's classification. Liver parenchymal transection was accomplished using an ultrasonic dissector. Intermittent inflow occlusion was applied when necessary. The cut surface of the liver was secured with TissueLink (TissueLink Medical Inc, Dover, NH, USA), electrocautery, and clips. Vessels more than 2 mm in diameter were ligated or sutured with 4/5-0 stitches. At the end of hepatectomy, the raw surface of the liver was carefully assessed to rule out bleeding or bile leakage.

Flow Cytometry Analysis

The presence of $CD34^+$ cells, at 0 and 72 h after of surgery, was quantified in peripheral blood using flow citometry. The immunophenotype of the $CD34^+$ circulating cells in peripheral blood was also evaluated by conventional dual color immunofluorescence using fluorescein isothiocyanate (FITC)-conjugated CD34 and phycoerythrin (PE)-conjugated monoclonal antibodies: anti-CD45 from Sigma Aldrich (Sigma, Saint Louis, MI, USA), anti-CD90 and anti- CXCR4 from Becton Dickinson (Becton, Dickinson, Franklin Lakes, NJ, USA) and anti-CD117 and anti- CD133 from Miltenyi Biotec (Bergisch Gladbach, Germany). To this end, 5×10^4 cells were acquired by flow cytometry (FACSCalibur; Becton Dickinson) excluding cellular debris in a side scatter/forward scatter dot plot and analyzed using CellQuest software. The percentage of positive cells was calculated after subtraction of background fluorescence as measured with the appropriate isotype control mouse PE-IgG2a and mouse FITC-IgG1 (Miltenyi Biotec).

Cytokine Levels Determination

Serum and plasma levels of cytokines, stem cell factor (SCF), stromal derived factor 1 (SDF-1), interleukine 12 (IL-12), hepatocyte growth factor (HGF), transforming growth factor-β (TGF-β), and MMP-2 protease were measured at 0 and 72 h after surgery by using high-sensitivity ELISA. TGF-β and IL-12 kits were purchased from BenderMedsystems (Vienna, Austria), SCF, SDF-1, and MMP-2 kits were purchased from R&D Systems (Wiesbaden, Germany), and HGF kit was purchased from Biosource International (Camarillo, CA).

Table 1 Characteristics of the patients included in the study

	n	Gender	Age	Mob.	%Hx	% CD34 cells 0 h	Cirrhosis	Mob. Patients in the group (%)
Primary tumors								
HCC	1	Female	63	+	20	15.08	−	14
	2	Male	71	−	25	13.80	−	
	3	Male	61	−	25	4.16	+	
	4	Male	57	−	2	9.03	+	
	5	Female	58	−	25	34.50	+	
	6	Male	63	−	20	15.15	+	
	7	Male	74	−	10	10.13	+	
CHOL	1	Male	72	+	60	2.18	−	40
	2	Male	57	+	30	10.00	−	
	3	Male	76	−	60	13.19	−	
	4	Male	71	−	60	19.42	−	
	5	Female	50	−	35	10.47		
Gallbladder cancer	1	Female	72	+	15	5.40	−	67
	2	Female	66	+	15	9.65	−	
	3	Female	77	−	15	25.5	−	
Secundary tumors								
Metastasis	1	Female	66	+	15	2.62	−	40
	2	Male	70	+	10	4.89	−	
	3	Female	63	+	30	10.56	−	
	4	Female	48	+	60	11.73	−	
	5	Female	69	−	60	19.07	−	
	6	Female	60	−	30	15.73	−	
	7	Male	40	−	25	14.95	−	
	8	Female	41	−	15	28.08	−	
	9	Female	28	−	15	20.37	−	
	10	Female	70	−	30	23.96	−	
Benign tumors								
FNH	1	Male	27	+	60	3.8	−	50
Adenoma	2	Femal	76	+	10	1.62	−	
FNH	4	Female	13	−	30	8.74	−	
Hemangioma	5	Female	56	−	10	11.76	−	
No tumoral lesions								
Hydatic abscess	1	Male	76	+	60	6.09	−	60
Hydatic abscess	2	Female	46	+	60	6.18	−	
Hydatic abscess	3	Male	43	+	20	12.1	−	
Caroli	4	Male	65	−	60	13.33	−	
Hematoma	5	Male	52	−	60	13.53	−	

Immunohistochemical Analysis

Liver samples obtained from biopsies at 0 h were immunostained in a DakoCytomation Autostainer Universal Staining System (Glostrup, Denmark), using anti-SDF-1 (5 μg/ml) and anti-CXCR4 (10 μg/ml) from eBioscense, and anti-CD34 (1/100) and Ki67 (10 μg/ml) from Dako. Labeled polymer-HRP anti-mouse and anti-rabbit from Dako Envision + Dual Link System-HRP (DAB+) was used. The quantification of positive staining in digital images was performed using ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD, USA).

Statistical Analysis

Results are expressed as mean±standard error. The data were analyzed with the Wilcoxon's test for paired data and

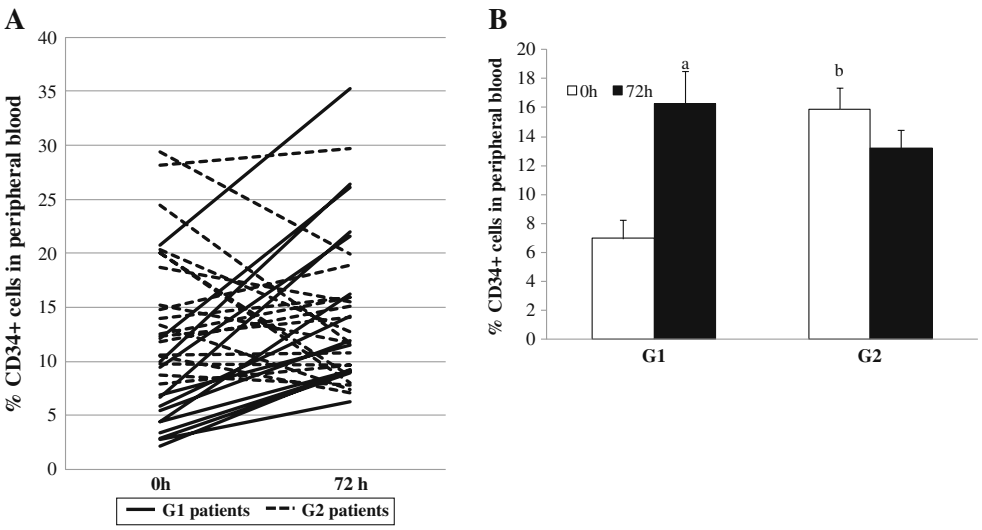

Fig. 1 Bone marrow stem cells mobilization in patients undergoing hepatic resection. **a** Individual values of circulating $CD34^+$ cells in peripheral blood before and after hepatectomy in 33 patients with liver disease. **b** Circulating levels of $CD34^+$ cells in the peripheral blood before (0 h) and 72 h after hepatectomy in G1 and G2 patients (see text for details). Values are expressed as mean± standard error. [a]$p<0.001$ vs. G1 at 0 h; [b]$p=0.002$ vs. G1 at 0 h

the Mann–Whitney's test. A $p<0.05$ was considered statistically significant. Data processing was performed with the SPSS statistical package for Windows (11.0.1, Chicago, IL, USA, http://www.spss.com).

Results

Circulating Levels of $CD34^+$ Cells in Hepatectomized Patients

Circulating $CD34^+$ cells levels were measured before and 72 h after surgery in 33 consecutive hepatectomized patients with different types of liver diseases. In 14 of 33 patients, the levels of circulating $CD34^+$ cells increased 72 h after hepatectomy as compared with the pre-hepatectomy levels (0 h), whereas in the other 19 patients, these values were lower or similar (Fig. 1a). Accordingly, the group of patients with an increase in circulating $CD34^+$ cells after 72 h of hepatectomy was designated as group 1 (G1), and the group of patients with lower or similar levels of $CD34^+$ cells after 72 h was named as group 2 (G2). The mean values of $CD34^+$ cells in peripheral blood from both groups of patients are shown in Fig. 1b. Interestingly, G2 patients showed significant higher pre-hepatectomy levels of $CD34^+$ cells than G1 patients. The clinical characteristics of the patients are shown in Table 1. It is interesting to note that the lowest percentage of mobilizer patients was observed in the HCC group (14%) compared with other liver pathologies. A large portion of the HCC patients (71%) had cirrhosis as underlying liver disease. No significant differences in BMHSC mobilization were observed among other liver pathology groups.

Immunophenotype Analysis of $CD34^+$ Cells

$CD34^+$ cells detected in peripheral blood of G1 and G2 patients co-expressed other surface proteins and BMSC markers such as CD45, CD90, CD117, CD133, and CXCR4 (Table 2). An increase in $CD34^+CD45^+$, $CD34^+CD90^+$,

Table 2 Immunophenotype analysis of $CD34^+$ cells

		G1 patients	G2 patients	G1 vs. G2 patients
% CD34+/CD45+	0 h	5.7±1.19	4.7±0.73	ns
	72 h	9.6±1.88[a]	1.8±0.31	$p=0.003$
% CD34+/CD90+	0 h	4.6±0.94	3.4±1.28	ns
	72 h	7.1±1.59[a]	0.6±0.17	$p=0.003$
% CD34+/CD117+	0 h	0.5±0.07	0.3±0.05	ns
	72 h	0.8±0.08[a]	0.2±0.03	$p=0.005$
% CD34+/CD133+	0 h	0.4±0.04	0.5±0.09	ns
	72 h	0.7±0.09[a]	0.3±0.06	$p=0.040$
% CD34+/CXCR4+	0 h	6.1±1.24	5.3±0.88	ns
	72 h	9.6±1.84[a]	1.9±0.40	$p=0.031$

Immunophenotype of $CD34^+$ cells detected in peripheral blood at 0 and 72 h after hepatectomy in G1 and G2 patients. The percentages were determined by two-color flow cytometry. Values are expressed as mean ± standard error

[a]$p<0.001$ vs. 0 h

$CD34^+CD117^+$, $CD34^+CD133^+$, and $CD34^+CXCR4^+$ levels was observed in G1 patients after 72 h of hepatectomy. Significantly, G2 patients showed higher pre-hepatectomy levels of CXCR4, the single receptor for stromal-derived factor-1 (SDF-1) than G1 patients (73%±16.7% vs. 47%±5.7%, $p<0.05$; Table 2).

Presence of $CD34^+$ Cells in the Liver

The potential presence of a $CD34^+$ hematopoietic stem cell population in the liver previous to hepatectomy was immunohistochemically evaluated in both groups of patients. In all patients, a positive staining of $CD34^+$ cells was observed in the hepatic parenchyma and sinusoids. However, the $CD34^+$ immunostaining was remarkably higher in G2 compared to G1 patients (Fig. 2).

Levels of $CD34^+$ Cells and the SDF-1/CXCR4 Axis

The relationship between $CD34^+$ stem cells mobilization and SDF-1/CXCR4 axis was studied in both groups of patients G1 and G2. We analyzed the expression of SDF-1 and CXCR4 by immunohistochemistry. SDF-1 staining was positive in the bile ducts and parenchyma of livers from both groups of patients, but it was significantly higher in those from G2 patients (Fig. 3a, b). CXCR4 staining was similar to that observed for SDF-1, with expression around the central vein and parenchyma of livers from both groups of patients. Similarly, a higher CXCR4 staining was observed in livers from patients with lower levels of circulating $CD34^+$ cells after 72 h of hepatectomy (G2), (Fig. 3c, d). Figure 3e shows these significant differences in SDF-1 and CXCR4 expression between G1 and G2 patients.

$CD34^+$ Cells Mobilization and Changes in Circulating Levels of Cytokines

The circulating levels of cytokines involved in BMHSC mobilization (SDF-1, SCF, IL-12, and MMP-2) and hepatic regeneration (HGF, TGF-β) were evaluated. A distinct cytokine profile was observed in both groups of patients (G1 and G2; Fig. 4). Previous to hepatectomy, higher levels of SDF-1, SCF, IL-12, and MMP-2 were found in G2 compared to G1 patients. On the contrary, after 72 h of hepatectomy, the levels of cytokines involved with hepatic regeneration such as HGF or TGF-b and MMP-2 were lower in G2 patients than in G1 patients.

Association of BMHSC Mobilization and Hepatic Regeneration

The presence of Ki67, as a marker of hepatocyte regeneration, was analyzed by immunohistochemistry in liver tissue of all the studied patients. The nuclear Ki67 staining was positive in both G1and G2 patients. In G1 patients, the Ki67 expression was mainly observed around central vein and in sinusoidal cells. Comparatively, the Ki67 staining in G2 patients was significantly more intense and localized in

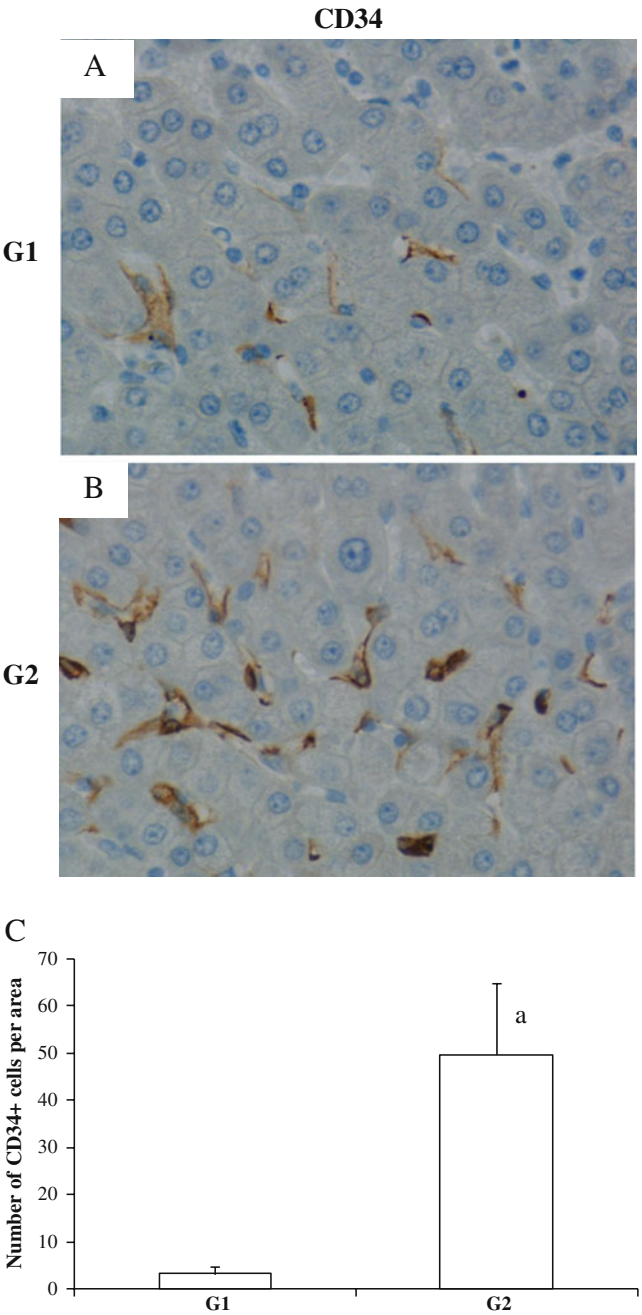

Fig. 2 Presence of a $CD34^+$ hematopoietic stem cell population in liver. $CD34^+$ immunohistochemical staining in liver tissue from G1 patients (**a**) and G2 patients (**b**). A representative image from each group of patients is displayed. Magnification: ×20. Quantitative analysis of $CD34^+$ immunohistochemical staining (**c**). $CD34^+$ staining was quantified with Image J software $^a p<0.001$ vs. G1 patients

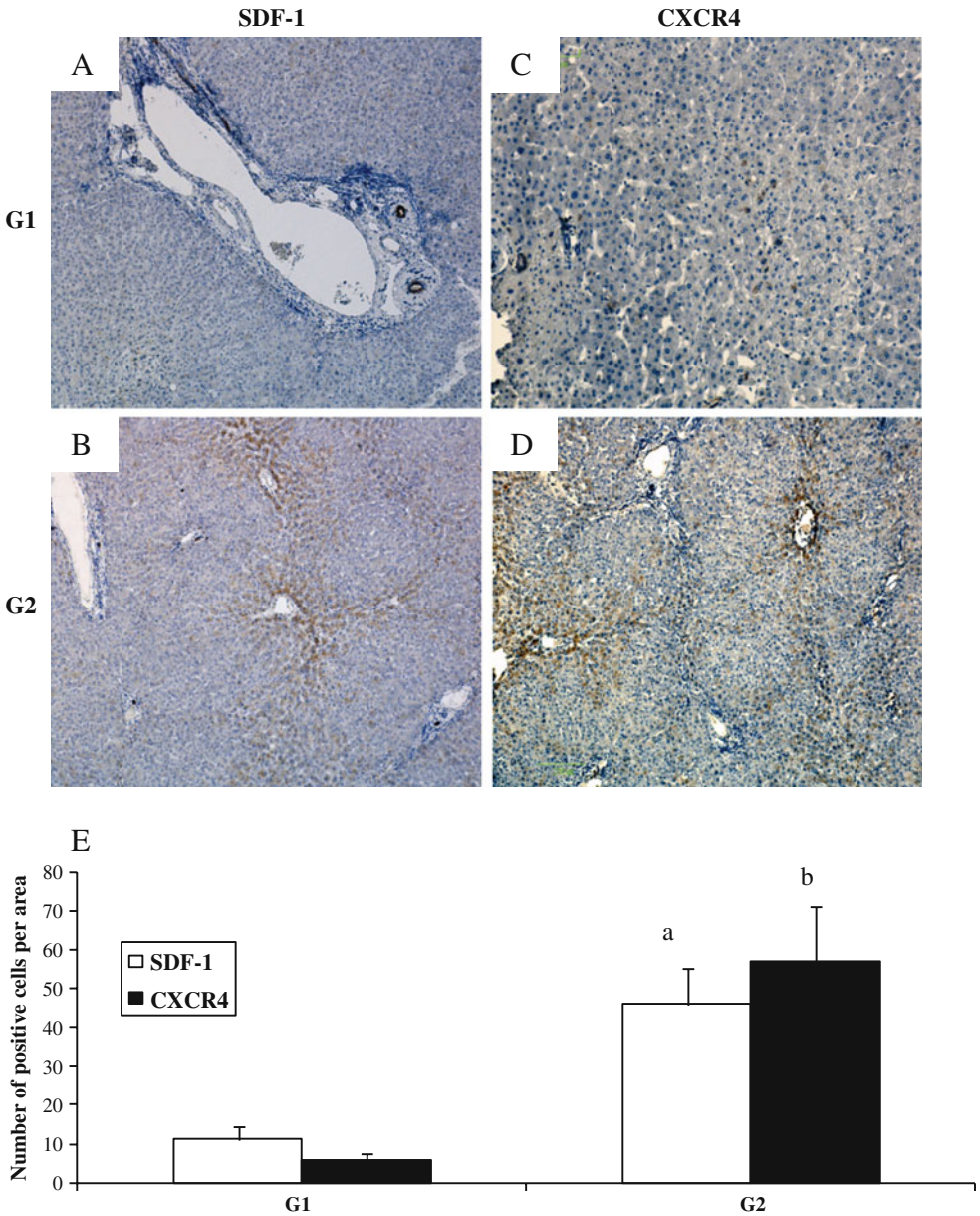

Fig. 3 Expression of SDF-1 and CXCR4 in liver. **a**, **b** SDF-1 immunohistochemistry from liver tissue of G1 and G2 patients. **c**, **d** CXCR4 immunohistochemistry from G1 and G2 patients. **e** Levels of SDF-1 and CXCR4 were quantified from immunohistochemical staining in the livers G1 and G2 patients. SDF-1 and CXCR4 staining was quantified with Image J software. Biopsies were obtained during surgery (0 h). Values are expressed as mean±standard error. [a]$p<0.001$ vs. G1 patients group and [b]$p<0.001$ vs. G1 patients group. Magnifications: ×20

the parenchymal hepatocytes and in sinusoidal cells (Fig. 5).

Discussion

This study was aimed to investigate the role of BMHSC mobilization after hepatectomy in patients with hepatic disease. A mobilization of $CD34^+$ BMHSC in some (14 from 33) but not all of the hepatectomized patients was found. The pattern of co-expression of other surface proteins and stem cell markers (CD45, CD90, CD117, CD133, and CXCR4) with $CD34^+$ revealed their bone marrow origin. Interestingly, the pre-hepatectomy levels of circulating $CD34^+$ cells were significantly higher in patients without BMHSC mobilization (G2). Two distinct types of patients (mobilizers and no mobilizers) were found after hepatectomy. Our results suggest that hepatectomy is an insufficient stimulus to induce BMHSC mobilization in patients with hepatic disease and that not all hepatectomized patients share the same stimuli to activate a BMHSC mobilization process.

These data are in agreement with other studies, although conflicting results have arisen regarding the role of the mobilization of BMHSC in the hepatic regeneration. Some studies have reported BMHSC mobilization in patients subjected to hepatectomy,[16,19] while in others, this mobilization process was not observed.[20,21] Thus, Di Campli et

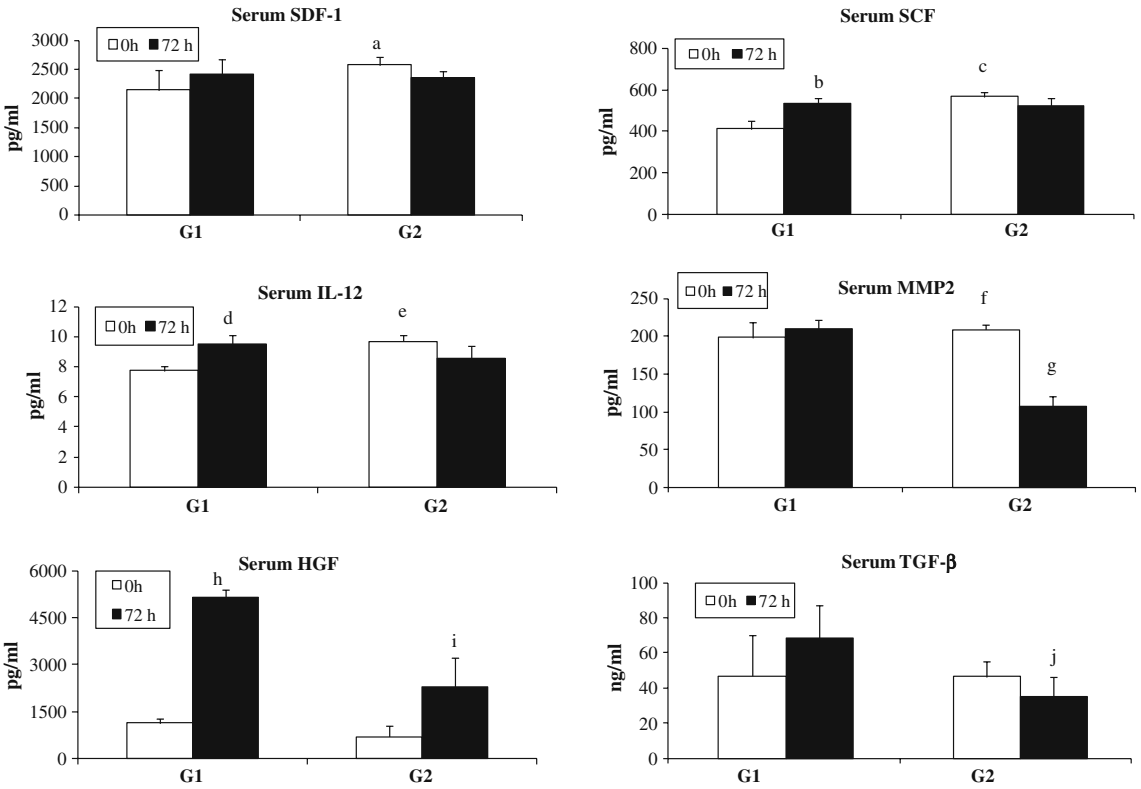

Fig. 4 Circulating levels of cytokines and proteolytic enzymes involved in stem cell mobilization and hepatic regeneration. Serum and plasma levels of cytokines and proteolytic enzymes were measured before (0 h) and after (72 h) hepatectomy in G1 and G2 patients. Values are mean± standard error. [a]p=0.045 vs. G1 at 0 h; [b]p<0.00 vs. G1 at 0 h; [c]p=0.007 vs. G1 at 0 h; [d]p=0.042 vs. G1 at 0 h; [e]p=0.034 vs. G1 at 0 h; [f]p=0.016 vs. G1 at 0 h; [g]p=0.044 vs. G1 at 72 h. [h]p=0.004 vs. G1 at 0 h; [i]p=0.013 vs. G1 at 72 h; [j]p=0.037 vs. G1 at 72 h

al.[20] did not find evidences of hematopoietic stem cell mobilization in six hepatectomized patients or in eight patients with acute and chronic liver failure. In other study,[16] only six from 13 hepatectomized patients augmented the levels of $CD34^+$, $CXCR4^+$ $CD90^+$ in peripheral blood 72 h after the surgery. On the contrary, Gehling et al.[19] found an increase in $CD133^+$ $CD45^+$ $CD14^+$ cells but not in $CD34^+$ cells in living donors submitted to liver resection. Other authors have shown that cirrhotic patients without hepatectomy are able to mobilize bone marrow stem cells to the bloodstream.[22] Menegazzo et al. have shown that the type of the hepatic lesion influences the regenerative response after hepatic resection, with a reduced mobilization of HSC in the malignant liver diseases.[21] In the present study, the analysis of a comparatively higher number of patients has shown no association between the levels of $CD34^+$ cells and the clinical characteristic of the patients. However, it is interesting to note that the patients with hepatocellular carcinoma and metastasis showed lower percentages of BMSC mobilization (14% and 40%, respectively) compared to other type of pathologies. It is tempting to speculate that the underlying cirrhosis in the HCC patients may contribute to a previous BMHSC mobilization. This may explain the very low number of mobilizer patients observed in this group compared with the other liver pathologies.

However, other differences between G1 and G2 patients were found. Hepatic tissue of G2 patients showed pre-hepatectomy higher levels of expression of $CD34^+$, SDF-1, and CXCR4. Interestingly, in G2 patients, these data correlated with the observed levels of these proteins in peripheral blood at 0 h. The presence of $CD34^+$, SDF-1, and CXCR4 in liver tissue before surgery suggests that hepatectomy is not necessary to trigger a $CD34^+$ stem cells mobilization and might explain why some patients (G2) do not mobilize BMHSC after hepatectomy. In this sense, activation and modulation of the SDF-1/CXCR4 axis is critical for the induction of the BMHSC mobilization process.[17,23,24] SDF-1 is involved in the recruitment of HSC toward the hepatic tissue,[17,25,26] and other studies have related an increase of SDF-1 levels with the capacity of mobilization of BMHSC in patients without hepatectomy and cirrhosis.[22]

Differences in the cytokine profile and in the levels of proteolytic enzymes involved in hepatic regeneration and BMHSC mobilization were also found between G1 and G2

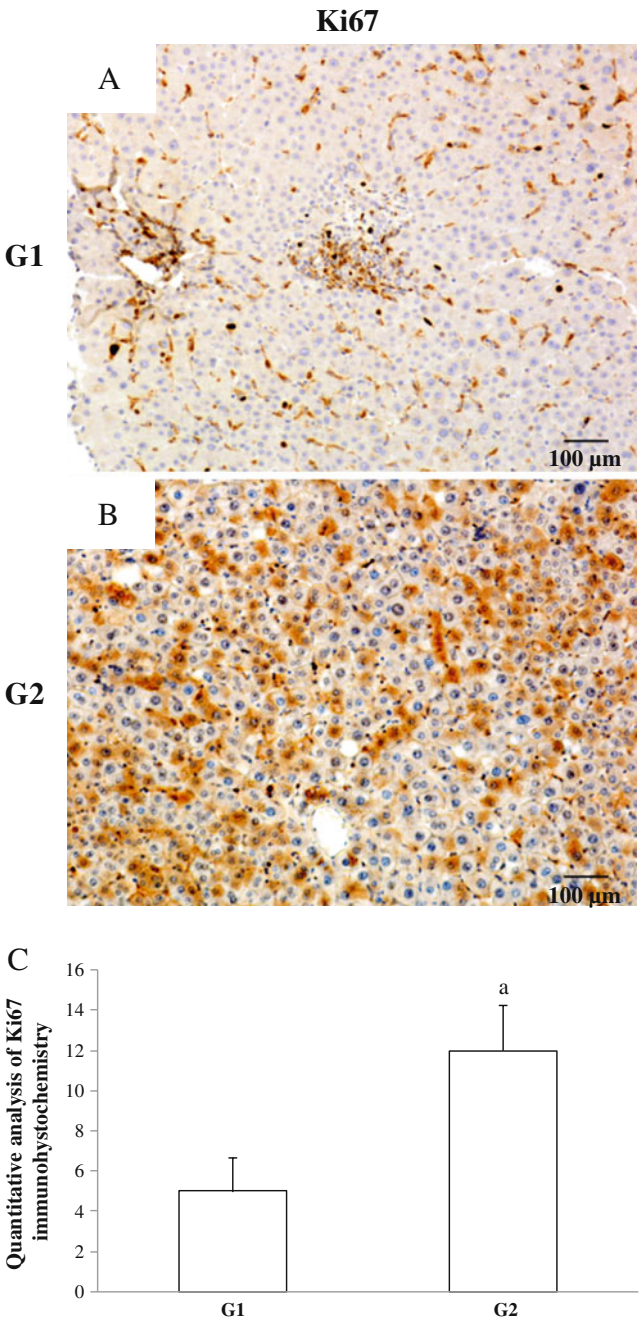

Fig. 5 Association of BMHSC mobilization and hepatic regeneration. Ki67 immunohistochemistry from liver tissue of G1 (**a**) and G2 (**b**) patients. A representative image of each group is shown. Ki67 staining was quantified in the livers of G1 and G2 patients (**c**). Ki67 staining was quantified with Image J software. Values are expressed as mean± standard error. Biopsies were obtained during surgery (0 h). $^{a}p<0.001$ vs. G1 patients group. Magnifications: ×20

patients. The different levels of cytokines found might explain the differences in the mobilization process observed between G1 and G2 patients. In no mobilizer patients (G2), the higher levels of cytokines related to a BMSC mobilization process were observed before surgery (SCF, SDF-1, IL-12, and MMP-2), and these elevated levels were not altered after 72 h. However, a positive increase in the levels of these cytokines was observed in mobilizer patients (G1) 72 h after surgery. A lower bone marrow extracellular matrix degradation and release of hematopoietic stem cells into the bloodstream was observed in G2 patients compared to G1 patients. These data might explain the different degree of BMHSC mobilization among hepatectomized patients.

BMHSC mobilization is finely regulated by several cytokines and its triggering depends on the levels of specific cytokines.[10,25] SCF has a key role in the stimulation of HSC proliferation and mobilization,[27] and its levels may be influenced by liver injury.[28] The activation of proteolytic enzymes, such as MMP-2, MMP-9, or Cathepsin L, as well as the modulation of IL-6 and IL-12, have also been related with the increase of SCF levels.[29] SCF modulates SDF-1 concentration, causing the release of $CD34^{+}$ cells from the bone marrow into peripheral blood.[10,25,30]

After 72 h of surgery, non-mobilizer patients (G2) showed lower levels of cytokines involved with hepatic regeneration (HGF and TGF-β) than mobilizer patients (G1). This might explain the lower capability of BMHSC mobilization observed in G2 patients. HGF participates in hepatic regeneration and is also responsible for the events of regeneration and migration of human $CD34^{+}$ stem cells.[31,32] Kollet and coworkers demonstrated that HGF also induces cytoskeleton rearrangement, increases cell motility, and enhances the response of immature $CD34^{+}$ cells to SDF-1 signaling by inducing CXCR4 up-regulation and synergizing with SCF.[25]

An early BMHSC mobilization process in G2 patients is suggested by the high levels of CD34 cells, SDF-1, and CXCR4 previous to surgery and the significant variations in the levels of cytokines that are key for this mobilization process, such as stem cell factor, interleukin-12, matrix metalloproteinase 2, HGF, or TGF-β. Moreover, our data of Ki67 staining suggest that this previous BMHSC mobilization process might be associated with the higher hepatic regeneration observed in G2 patients.

In summary, hepatectomy may be an insufficient stimulus to trigger the BMSHC mobilization process. This process seems to be associated with variations in the levels of cytokines and proteolytic enzymes involved in bone marrow matrix degradation and hepatic regeneration. The pre-hepatectomy higher levels of $CD34^{+}$ cells in peripheral blood and liver, associated to an increased expression of SDF-1/CXCR4 axis and Ki67 in non-mobilizer patients, might suggest a BMHSC mobilization process previous to surgery in non-mobilizer patients.

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Conflict of Interest No potential and real conflicts of interest.

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HOW I DO IT

A Technique of Gastrojejunostomy to Reduce Delayed Gastric Emptying after Pancreatoduodenectomy

Adeel S. Khan · William G. Hawkins · David C. Linehan · Steven M. Strasberg

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Abstract Delayed gastric emptying (DGE) through a gastroenterostomy is a clinical problem that affects many patients who have a standard Whipple procedure. A new method, which is associated with a low rate of DGE, is described.

Keywords Whipple procedure · Pancreatoduodenectomy · Gastroenterostomy · Delayed gastric emptying

Introduction

Delayed gastric emptying (DGE) after pancreatoduodenectomy is a common problem.[1–6] DGE is not life-threatening, but it prolongs hospital stay, increases the need for TPN, and raises cost.[1–6]

DGE occurs both in patients who have standard Whipple resections and pylorus-sparing Whipple procedures.[1–6] It may be caused by mechanical problems at the gastrojejunostomy or duodenojejunostomy such as anastomotic edema; it may also be produced by perigastric inflammation related to the procedure or due to postoperative abscess or fistula. Drugs especially narcotics or gastric atony due to pre-existing conditions, such as diabetes mellitus, may also be contributory.

This paper describes a method of gastrojejunostomy used in performance of a standard pancreatoduodenectomy with antrectomy, which has been associated with a low incidence of DGE.

A. S. Khan · W. G. Hawkins · D. C. Linehan · S. M. Strasberg (✉)
Section of Hepato-Pancreato-Biliary Surgery, Department of Surgery, Washington University in Saint Louis, Suite 1160, Northwest Tower, 4990 Children's Place, Box 8109, St. Louis, MO 63110, USA
e-mail: strasbergs@wustl.edu

Methods

Rationale and Technique

Rationale

Based upon serial observation of cases of delayed gastric emptying (DGE), it seemed that DGE was usually due to anastomotic swelling (Fig. 1), perigastric inflammation caused by the procedure itself, or inflammation resulting from complications such as adjacent abscesses or fistulae. Although theoretically fistulae or abscesses may originate from the gastroenterostomy, they are almost always due to pancreatic anastomotic failure.

The method to be described aims to reduce inflammation in and around the gastroenterostomy. The anastomosis is performed using fine absorbable sutures with the outer seromuscular layer on the back row of the anastomosis set at a greater distance than usual from the inner full-thickness layer. When completed, the anastomosis is placed in the retrocolic position, the rationale being that most dissection in a Whipple procedure takes place in the supracolic compartment and therefore more inflammation can be expected above the mesocolon than below.

Technique

The gastric resection is an antrectomy which removes 40–50% of the stomach. The lesser omentum is opened and the left gastric vessels are divided close to the stomach approximately halfway between the esophagogastric junction and the pylorus. The gastroepiploic

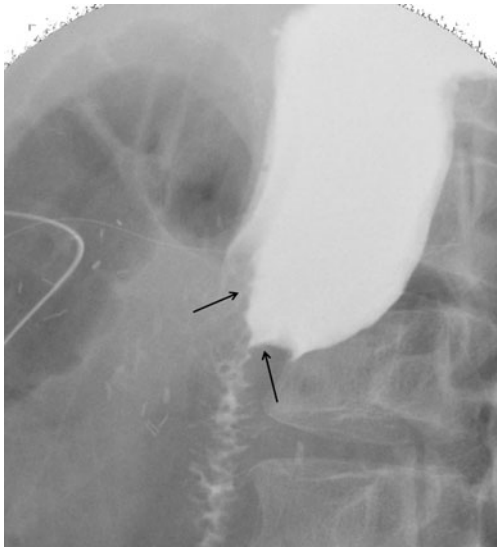

Fig. 1 Abdominal radiograph from postoperative upper gastrointestinal series with demonstration of anastomotic edema (*arrows*) and delayed gastric emptying

arcade is divided 3–4 cm closer to the pylorus. The stomach is divided with two firings of a GIA 60 mm stapler (Autosuture/Covidien, Mansfield, MA), using a blue load unless the stomach is very thick, in which case a green load is used. For the first firing, the stapler is placed at 90° to the greater curvature and a 4.5–5.0 cm length of the stapler is applied to the stomach and fired (Fig. 2). This will be the future stoma of the gastroenterostomy. The short terminal portion of the staple line, which has not been cut by the staple knife, is now cut with scissors to the end of the staple line. The stapler is then placed between the end of the first staple line and the point on the lesser curvature previously selected, and fired. The angle between staple lines is approximately 135° (Fig. 2).

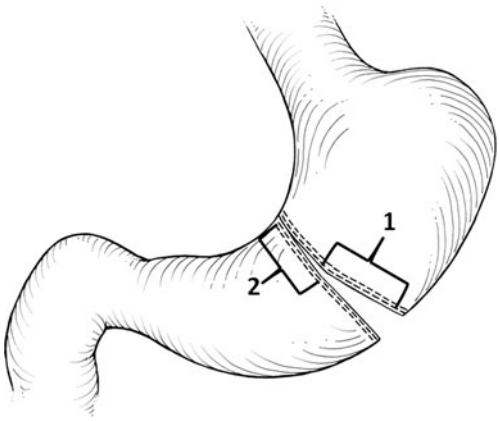

Fig. 2 Transection of the stomach with GIA stapler. Two firings are used in the positions shown. The second firing is placed to create an angle of about 135° between the staple lines

Occasionally, it takes a third staple load to reach the lesser curvature.

An opening is made in the mesocolon to the left of the middle colic vessels. A loop of jejunum 60 cm distal to the hepaticojejunostomy is marked with cautery along the antimesenteric border for 5 cm or slightly less and brought up through the opening in the mesocolon to rest beside the first gastric staple line to usually lie in an antiperistalic position. There is no preference of antiperistaltic over isoperistalltic except that the former seems to lie better than the latter. Two running, locking, seromuscular posterior row suture lines of 3–0 polydioxanone (PDS) suture are started between the stomach and jejunum, one running to the left and the other to the right until they come to the corner of the posterior row, where they are locked with an in-line knot (Fig. 3). The first bites of this suture line are taken so that the knots are tied projecting posteriorly. These bites and subsequent ones are taken so that there is about 8 mm of jejunal wall between the suture line and the antimesenteric border previously marked with cautery, and 8 mm of gastric wall left between the suture line and the staple line (Fig. 3).

The jejunum is opened along the previously marked line with cutting/blended current for a distance of 4.5–5.0 cm, and the gastric staple line is resected so that a slightly larger gastric stoma results. The inner row is a

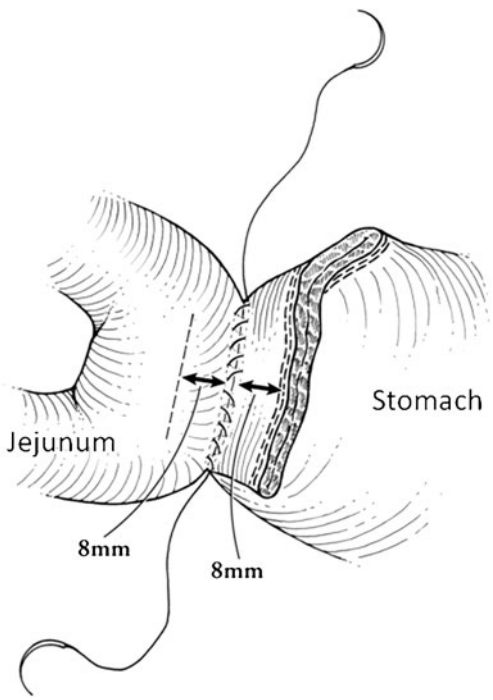

Fig. 3 Posterior seromuscular row is taken to leave 8 mm between the seromuscular suture line and the proposed opening in the jejunum on the antimesenteric border (*dashed line*) and as well the same distance between the seromuscular suture line and the staple closure on the stomach

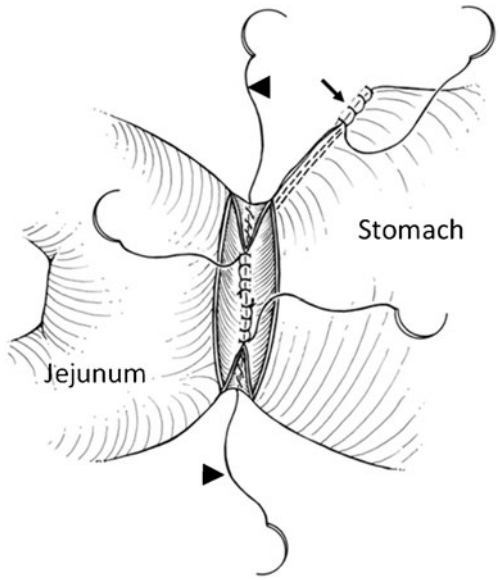

Fig. 4 The inner full-thickness layer placed as a running locking stitch is shown partially completed. After this suture line is completed posteriorly and anteriorly the posterior seromuscular sutures (*arrowheads*) are used to complete the anterior seromuscular row. The lesser curve is underrun with a running locking suture (*arrow*)

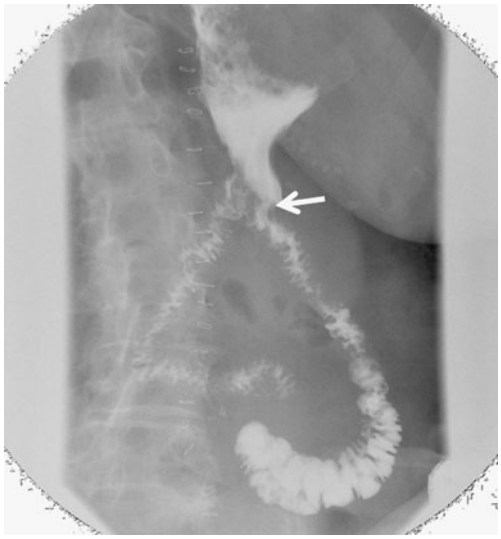

Fig. 6 Film from postoperative upper gastrointestinal series in 65-year-old female who began to vomit and had NG tubing placed. Study demonstrated rapid emptying of contrast from a nondistended stomach. This patient was treated successfully with antiemetics and a reduction in narcotic analgesics and was not considered to have DGE. *Arrow* is at gastroenterostomy

full thickness running 3–0 PDS suture. It is placed as a locking suture on the back row (Fig. 4). The bites are 3–4 mm in depth so that a space remains between inner and outer suture lines on the posterior row. The corners are performed with a baseball stitch and the anterior row with a simple running suture (not locked). The anastomosis is completed by an anterior seromuscular row using the two posterior seromuscular row sutures, which had been locked at the corners (Fig. 4) see arrowheads). The staple line on lesser curvature is underrun with a running, locking 4–0 polydioxanone suture from the lesser curvature to the edge of the anastomosis. (Fig. 4; see arrow)

The anastomosis is dislocated into the infracolic compartment. The edge of the mesocolon is sutured to the anterior and posterior surfaces of the stomach about 1 cm

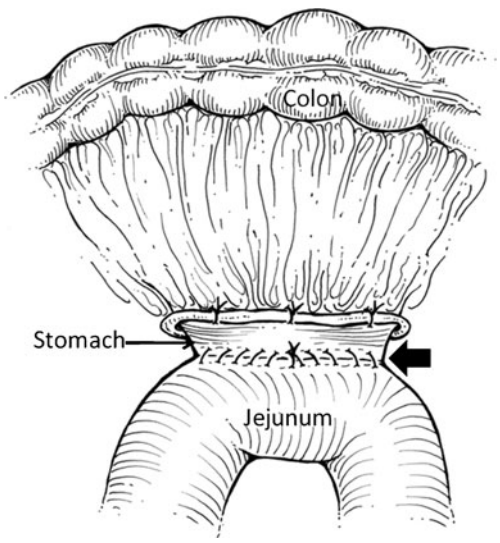

Fig. 5 The stomach is dislocated into the infracolic compartment where it is held by sutures to the mesocolon. The anterior sutures are shown. The *large arrow* points to the gastrojejunostomy

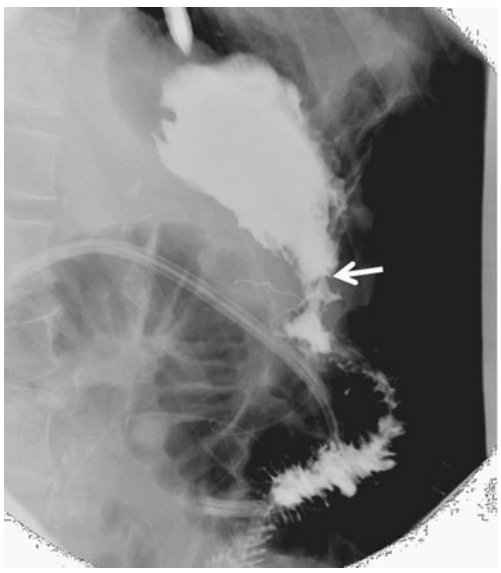

Fig. 7 Postoperative upper gastrointestinal series in 70-year-old male showing slight delay in empting from a nondistended tapering stomach. *Arrow* is at gastroenterostomy. Drain runs to site of pancreatojejunostomy

above the anastomosis using 3–0 chromic suture so that the actual anastomosis rests in the infracolic compartment 1 cm below the mesocolon (Fig. 5).

Comment

The definition of DGE which we use is derived from Wente et al.[4] and includes any of the following:

1. Nasogastric (NG) tube removed later than the morning of postoperative day 5
2. NG tube reinserted on postoperative day 4 or later.
3. Inability to tolerate liquid diet by postoperative day 7

When the third criterion is the basis for diagnosis, it is confirmed by upper gastrointestinal series. If normal emptying of the stomach is observed and oral intake is satisfactory within 24 h with use of antiemetics and reduction in narcotics, then the criterion is considered not satisfied.

The technique has been used in 25 patients having a standard Whipple procedure. No patient fulfilled criteria 1 or 2. Three patients had poor oral intake and were evaluated by upper gastrointestinal series. The study confirmed DGE in one of the three patients in the study group. Figures 6 and 7 are pictures from the studies in the other two patients showing no or minimal problems with gastric emptying. These patients successfully resumed oral intake within 24 h after treatment with reduction in narcotics and scheduled antiemetics and were not considered to have DGE.

In summary, a new technique of gastroenterostomy, which is associated with a low incidence of DGE, is described.

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REVIEW PAPER

SSAT Maintenance of Certification: Literature Review on Gastroesophageal Reflux Disease and Hiatal Hernia

Nathaniel J. Soper

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Abstract
Background This article reviews the current literature pertaining to the diagnosis and management of gastroesophageal reflux disease (GERD) and hiatal hernia.
Discussion GERD is one of the most common gastrointestinal disorders in the USA. For effective management, a conclusive diagnosis must be made. Most patients are effectively managed by acid suppression therapy, whereas others require procedural treatment. Endoluminal treatment of GERD is an option, but long-term results of this therapy are unknown. The "gold standard" surgical treatment of GERD is laparoscopic Nissen fundoplication. Large hiatal hernias are difficult to manage with a relatively high rate of recurrent hiatal hernia.
Conclusion Whether or not to use mesh at the hiatus to decrease this occurrence is currently debatable.

Keywords Gastroesophageal reflux disease · GERD · Endoluminal treatment · Nissen fundoplication · Hiatal hernia

GERD—Definition

Gastroesophageal reflux disease, or GERD, is one of the most common gastrointestinal diseases among adults in the USA. It is estimated that several billion dollars per year are spent by Americans on over the counter antacids, histamine receptor blockers, and proton pump inhibitors (PPI), which is reflected in the frequency of direct-to-patient marketing programs by the pharmaceutical industry. A recent consensus conference (the Montreal Consensus) defined GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications".[1] Symptoms were considered to be "troublesome" if they adversely affected an individual's well-being. The consensus panel recognized GERD as an entity consisting of at least two of these three characteristics: recognized etiologic agent(s), consistent anatomic alterations, and identifiable group of signs and symptoms.

GERD can lead to both esophageal and non-esophageal symptoms. The most common typical symptoms of GERD are heartburn and regurgitation. Heartburn is defined as a burning sensation in the retrosternal area, and regurgitation is defined as the perception of flow of gastric content into the pharynx or mouth. Non-esophageal GERD symptoms include chronic aspiration with cough and laryngitis. At its core, GERD is the failure of the anti-reflux barrier, allowing abnormal amounts of reflux of gastric contents into the esophagus (it must be acknowledged that small amounts of reflux are normal). GERD ultimately is a mechanical disorder caused by a defective anti-reflux barrier, but failed esophageal peristalsis or defective gastric emptying can also contribute to the problem.[2] Although the anti-reflux barrier is incompletely understood, contributions are made by the lower esophageal sphincter, the diaphragmatic crura, and phrenoesophageal ligament.[3] When the anti-reflux barrier fails, allowing stomach contents to reflux into the esophagus, it can lead to a spectrum of disease ranging from symptoms alone to significant esophageal tissue damage, including ultimately the development of adenocarcinoma. The refluxate may be primarily acidic or non-acidic (associated with high concentrations of bile acids). Non-acidic reflux may be an important cause of chronic

N. J. Soper (✉)
Department of Surgery, Northwestern University Feinberg School of Medicine,
251 E Huron St, Galter 3-150,
Chicago, IL 60611, USA
e-mail: nsoper@nmh.org

cough and may be an important agent in the development of metaplastic transformation.[4]

GERD—Diagnosis

The diagnosis of GERD can be made by endoscopy or by direct measurement of gastric contents entering the esophagus. Endoscopic evidence of GERD includes development of a "mucosal break," defined as an area of slough or erythema clearly demarcated from adjacent normal-appearing mucosa,[5] by a peptic stricture in the absence of malignancy, and/or by histologic proof of Barrett's esophagus.[6,7] However, and especially in the era of widespread PPI use, many patients with GERD have no visible esophageal lesions, so-called nonerosive reflux disease. Direct measurement of gastric content refluxing into the esophagus can be done using either a catheter-based pH-measuring system,[8] a wireless pH-measuring device,[9] or by a multichannel intralumenal esophageal impedance study,[10] which also assesses for non-acidic reflux by demonstrating oral movement of non-acidic liquid.

GERD—Treatment

Treatment of GERD is almost always initiated with medical therapy. Various lifestyle changes may favorably affect GERD symptoms, including weight loss and elevation of the head of the bed.[1] However, acid suppression therapy is the primary treatment modality for GERD. There is generally an efficacious hierarchy of medical treatments for GERD, with antacids being less effective than histamine receptor blockers, which are, in turn, inferior to the use of PPIs. Thus, when a definitive diagnosis of GERD has been made, the most effective initial treatment will be with PPIs. Although uncommon, some patients experience side effects from the use of these drugs, including headaches, nausea, or constipation.

Consideration should be given to procedural treatment of GERD—either an endolumenal approach or an operation—if the following indications exist:

1. Complications of GERD (such as peptic stricture or Barrett's esophagus)[11,12]
2. Extraesophageal manifestations (chest pain, pulmonary symptoms)[13,14]
3. Failed medical management (side effects or inadequate symptom control), or
4. Desire to discontinue medical treatment despite adequate symptomatic control.

The preoperative evaluation of patients being considered for anti-reflux procedures should be directed at proving the presence of GERD and to selecting the appropriate procedure in order to optimize outcomes. All patients should undergo upper GI endoscopy to help make the diagnosis and to rule out other significant mucosal abnormalities, such as Barrett's esophagus. Physiologic studies confirming reflux, using either pH probes or impedance studies, should be performed when the diagnosis is not confirmed by endoscopy. Esophageal manometry to assess the motility characteristics of the esophagus is recommended prior to procedural treatment by most experts, but there are few hard data in the literature mandating preoperative manometry.[15,16] Esophageal manometry may be valuable in ruling out named motility disorders such as achalasia and as a diagnostic aid in those patients who subsequently experience severe dysphagia post-fundoplication. Barium swallow X-rays may be of value in assessing the size of hiatal hernias, and gastric emptying tests may be useful in patients who have significant bloating or early satiety as a dominant symptom.[17]

Several prospective, randomized, controlled trials have compared the outcomes of surgical therapy with medical therapy for GERD.[18–22] As a group, these studies document surgery to provide an effective alternative to medical treatment from a symptomatic standpoint, but also resulting in significantly less acid exposure and augmented lower esophageal sphincter pressure.[23–25] Although it is true that many studies report up to a fifth of post-fundoplication patients resume proton pump inhibitor therapy, most of these patients have no objective evidence for GERD recurrence on 24-h pH studies.[26]

The "open" Nissen fundoplication was first described in the mid-1950s and was the primary operation performed for GERD until the early 1990s. Since then, the laparoscopic Nissen fundoplication has rapidly become the procedure of choice. Multiple prospective randomized trials have been performed comparing laparoscopic and open fundoplication for GERD. In a recent meta-analysis of these trials, the laparoscopic approach has been shown to be associated with a shorter hospital stay and recovery time compared to the open operations.[27]

There were no deaths in either group, and perioperative morbidity was found to be lower after the laparoscopic compared to the open fundoplication. The long-term control of reflux was similar in the two groups, but there was a significantly higher rate of reoperations following laparoscopic fundoplication.

The technique of fundoplication requires additional comment. The Nissen fundoplication is a 360° wrap of the fundus behind the esophagus. However, many technical details differ between surgeons. As part of a multicenter randomized trial, an effort was undertaken to standardize the surgical technique of the "short, floppy" Nissen fundoplication.[28] The essential technical steps included: (1) opening of the phrenoesophageal

ligament, (2) preservation of the hepatic branch of the vagus nerve, (3) dissection of both crura, (4) transhiatal mobilization to allow at least 3 cm of intra-abdominal esophagus, (5) division of the short gastric vessels to ensure a tension-free fundoplication, (6) closure of the crura posterior to the esophagus with nonabsorbable sutures, (7) creation of a 1.5- to 2.0-cm wrap with at least one suture incorporating the anterior wall of the esophagus, and (8) bougie dilator placement at the time of wrap construction.

However, many alternative fundoplications have been described, with a wrap of the fundus incorporating less than 360° of the esophagus and positioned either anterior or posterior to the esophagus. Many of these partial fundoplications were initially advocated for patients with poor esophageal motility determined by esophageal manometry. Current evidence suggests that tailoring the fundoplication on the basis of preoperative motility studies does not correlate particularly well with postoperative clinical symptoms in patients with esophageal dysmotility.[29,30]

There have been many prospective randomized trials comparing the Nissen fundoplication to various partial fundoplications. A recent meta-analysis reviewed 11 prospective randomized trials comparing total with partial (both anterior and posterior) fundoplications.[31] Total fundoplication had a greater incidence of postoperative dysphagia and patients requiring redo operations. "Wind"-related symptoms—bloating, flatulence, and inability to belch—were also more common in total fundoplication patients. However, overall relief of symptoms and quality of life were similar following both types of fundoplication. It should be noted that the duration of follow-up in most of these trials was generally short term, and the relative length of the fundoplications was not standardized. In the American literature, several retrospective studies have shown inferior long-term control of GERD in patients undergoing partial fundoplications compared to total fundoplications.[32,33] The location of practice and standards of training seem to have a large impact on the type of fundoplication performed. In general, the laparoscopic Nissen fundoplication is the most common operation performed in the USA, whereas partial fundoplications are more frequently performed in Europe and Australia.

Endolumenal Anti-reflux Therapy

For the last decade, numerous devices have been designed to control GERD using endolumenally applied strategies. The concept is very appealing: insert a device through the mouth down to the lower esophagus and perform a procedure that reduces reflux without requiring incisions traversing the abdominal wall. The devices have included modalities that narrow the esophageal lumen with suturing techniques, by delivering radiofrequency energy to the area of the lower esophageal sphincter, by injecting bulking agents into this region, or with plications at the gastroesophageal junction. However, most of these devices are no longer on the market as a result of lack of efficacy, safety considerations, or failed business models.[34] At the current time, the only endolumenal anti-reflux device being used in the USA is the EsophyX instrument that is employed to construct a transoral incisionless fundoplication using endoscopically placed plastic fashioners. This device has undergone several modifications, and the technique itself has evolved over time. Relatively small series with short follow-up have been reported showing a good safety profile and the ability to stop PPI therapy in the majority of patients.[35]

Reoperative Fundoplications

Regardless of the technique of anti-reflux surgery, symptomatic "failure" of the procedure is seen in up to 20% of patients. This failure can take the form of untoward symptoms despite normal postoperative anatomy and physiology, which likely represents poor patient selection.[36] Anatomic and physiologic failures occur in at least 10% of patients in the long term. Anatomic fundoplication failure includes the following: disruption of the wrap, migration of the gastroesophageal junction with recurrent hiatal hernia (with or without the wrap also migrating into the chest), dysphagia caused by a "too tight" or a twisted fundoplication, or a fundoplication which slips down onto the body of the stomach. The symptoms caused by these anatomic failures may be severe enough to lead to reoperation in up to 5% of patients.[37] Reoperation may be performed laparoscopically or using open techniques, either transabdominal or transthoracic. Several retrospective studies have evaluated outcomes of attempted laparoscopic redo anti-reflux surgery. Revisional surgery requires longer operative times and is associated with higher conversion rates and more complications than primary operations.[38–40] Thus, although laparoscopic approaches to redo operations are feasible with reasonable postoperative outcomes, they come at the price of more perioperative complications and should only be performed by experienced surgeons.

Paraesophageal Hiatal Hernias

Hiatal hernias occur as the result of enlargement of the esophageal hiatus, allowing portions of the stomach, and sometimes other organs, to herniate into the mediastinum.

The vast majority of hiatal hernias are type I or "sliding" hiatal hernias where there is axial migration of the esophagogastric junction and portions of the stomach into the chest. A type II hiatal hernia is an isolated paraesophageal hiatal hernia in which the esophagogastric junction remains within the abdomen, but a portion of the stomach herniates alongside the esophagus into the mediastinum. These hiatal hernias are quite rare. Another form of paraesophageal hernia, type III, occurs when there is both migration of the esophagogastric junction into the chest as well as stomach herniating superiorly alongside the distal esophagus. Finally, a type IV includes herniation of other organs into the thoracic cavity, usually the omentum and/or colon, or left lateral segments of the liver. Paraesophageal hiatal hernias make up approximately 10% of all hiatal hernias and tend to occur in elderly patients.

Surgical dogma for many years was that the presence of a paraesophageal hiatal hernia demanded operative repair due to the perceived high risk of strangulation. This dictum has recently been challenged by Stylopoulos et al.[41] Using a Markov Monte Carlo model incorporating data from the surgical literature and a large administrative patient data base, they determined that the morbidity and mortality estimates for both emergency and elective repair of these hernias were much less than previously thought. The conclusion of the study was that watchful waiting was appropriate for patients with asymptomatic or minimally symptomatic paraesophageal hiatal hernias.

When operation is indicated, it can generally be performed using laparoscopic techniques. Several large series have been reported with laparoscopic reduction and repair of the hiatal hernia. The vast majority of surgeons advocate combining a fundoplication with this repair.[42–44] The mortality rate for repair of paraesophageal hernias is generally less than 2% with a morbidity rate of 5%. Anatomic evidence of recurrent hiatal hernia will be manifest in up to 40% of patients, but most such hernias are small and asymptomatic.[45]

This high rate of hernia recurrence may be attributable to shortening of the esophagus, tension at the hernia repair, or ultrastructural defects in the intrinsic crural musculature.[46] Some authors advocate frequent use of esophageal lengthening procedures at the time of hiatal hernia repair.[43] Others have advocated for the use of prosthetic material at the hiatus. The use of PTFE and polypropylene mesh has been shown to result in a lower rate of hernia recurrence than primary closure.[47,48] However, the use of prosthetic material at the hiatus may lead to the incorporation of the esophageal or gastric wall into the mesh with significant complications, even requiring gastrectomy or esophagectomy.[49,50]

These findings have led to the search for a bioprosthetic mesh that can be used to decrease the hiatal hernia recurrence rate without such complications. A multicenter, prospective randomized trial compared the use of a crural buttress using a mesh constructed from porcine small intestinal submucosa compared to primary repair.[51] This study utilized barium swallow X-rays performed at 6 months postoperatively that demonstrated anatomic hiatal hernia recurrence in 24% of patients undergoing primary repair compared to only 9% of patients receiving the bioprosthetic buttress. However, in an update at 5 years postoperatively, the recurrence rate was nearly identical between the two groups, and in excess of 50%.[52] It should be noted that the majority of recurrent hiatal hernias were small type I hernias resulting in few symptoms. Thus, at the current time, although the rationale for the use of mesh at the esophageal hiatus to decrease tension and thus minimize hernia recurrence is cogent, it is unclear if mesh should be used, and if so, what type.

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CASE REPORT

Preoperative Diagnosis of Early Cystic Duct Cancer Using Endoscopic Ultrasonography and Endocholangioscopy: Report of a Case

Hiroaki Shiba · Takeyuki Misawa · Ryusuke Ito · Hiroo Imazu · Masafumi Suzuki · Katsuhiko Yanaga

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Abstract Primary cystic duct carcinoma is a rare condition, for which preoperative diagnosis is difficult. We herein report a case of early primary carcinoma of the cystic duct, which was diagnosed preoperatively using endoscopic ultrasonography and endocholangioscopy. A 76-year-old man was admitted to our hospital with epigastric pain and liver dysfunction. Endoscopic ultrasonography revealed a cystic duct tumor, in diameter of 2.2 cm, which extended to the common bile duct. Endocholangioscopy revealed a well movable papillary tumor at the origin of the cystic duct. The patient underwent cholecystectomy and excision of the extrahepatic bile duct and lymph node. Histological findings confirmed the diagnosis of early papillary adenocarcinoma of the cystic duct.

Keywords Endoscopic ultrasonography · Cystic duct cancer · Diagnosis

Introduction

Primary carcinoma of the cystic duct is a rare condition, was reported with an incidence of 0.03–0.05% of autopsy examples,[1] and was identified in only 2.6% of all carcinomas of the bile duct[2] and 1.5% of all carcinomas of the gallbladder.[3] Preoperative diagnosis of primary carcinoma of the cystic duct is difficult and is often confirmed at histological findings of the excised tumor.[4] We herein report a case of early primary cystic duct carcinoma, which was successfully diagnosed preoperatively.

H. Shiba (✉) · T. Misawa · R. Ito · K. Yanaga
Department of Surgery, Jikei University School of Medicine,
3-25-8, Nishi-Shinbashi, Minato-ku,
Tokyo 105-8461, Japan
e-mail: hs0817@jikei.ac.jp

H. Imazu
Department of Endoscopy, Jikei University School of Medicine,
3-25-8, Nishi-Shinbashi, Minato-ku,
Tokyo 105-8461, Japan

M. Suzuki
Department of Pathology, Jikei University School of Medicine,
3-25-8, Nishi-Shinbashi, Minato-ku,
Tokyo 105-8461, Japan

Case Report

A 76-year-old man was admitted to our hospital with epigastric pain and liver dysfunction. The patient had no significant past medical history nor any hospitalization. On physical examination, the abdomen was flat, and neither tumor nor enlarged gallbladder was palpable. Enhanced computed tomography (CT) revealed a hypervascular tumor at the cystic duct bifurcation and dilated common hepatic duct. Magnetic resonance cholangiopancreatography (MRCP) revealed focal loss of high intensity, and endoscopic retrograde cholangiopancreatography (ERCP; Fig. 1) revealed a filling defect at the cystic duct bifurcation. Endoscopic ultrasonography (EUS) revealed a cystic duct tumor, in diameter of 2.2 cm, which extended into the extrahepatic bile duct without invasion to circumference structure (Fig. 2). Endocholangioscopy revealed a well movable papillary tumor with a distinct stalk, originating from the cystic duct bifurcation and propounding into the extrahepatic bile duct, and without superficial spreading such as advanced stage cancer, which was suggested to be a noninvasive and an early-stage tumor (Fig. 3). Laboratory

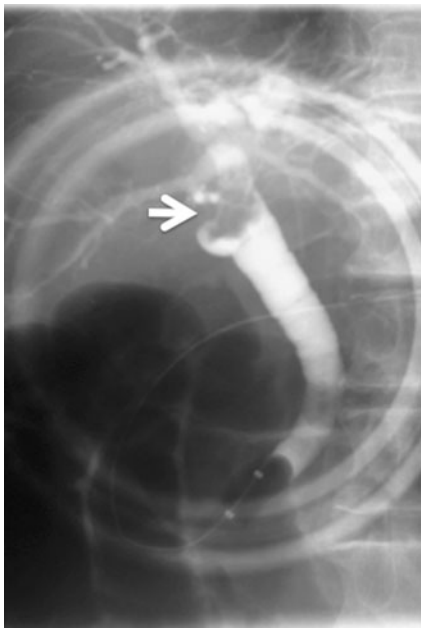

Fig. 1 Endoscopic retrograde cholangiopancreatography revealed a filling defect at the cystic duct bifurcation

investigations included carcinoembryonic antigen of 2.4 ng/ml and carbohydrate antigen 19-9 of 20 U/ml. With a preoperative diagnosis of primary papillary adenocarcinoma of the cystic duct, cholecystectomy, extrahepatic bile duct resection, and adjacent lymph node dissection followed by biliary reconstruction with hepaticojejunostomy were performed. Intraoperative frozen section of both the proximal and the distal resection stumps were cancer free. The tumor had a distinct stalk and was diagnosed macroscopically as mucosal papillary carcinoma. Therefore, we decided that more radical resection such as pancreaticoduodenectomy was not necessary for curative treatment of the tumor.

The excited specimen showed a papillary tumor with the diameter of 25×22×15 mm in the cystic duct (Fig. 4). Histological findings revealed well-differentiated mucosal papillary adenocarcinoma of the cystic duct without lymph node metastasis (pT_{1a}, pN_0, Stage IA). The patient made a satisfactory recovery without a complication and was discharged on the 14th postoperative day.

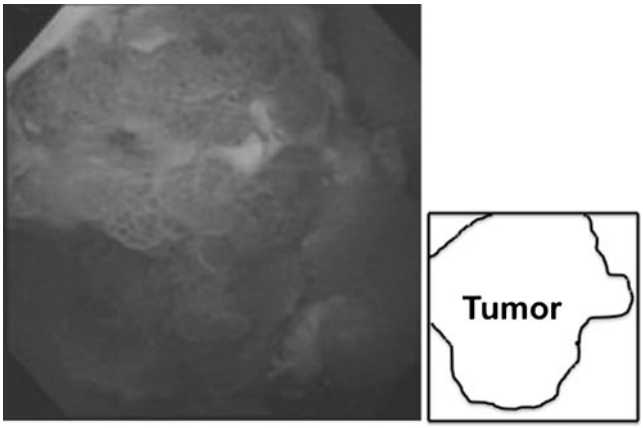

Fig. 3 Cholangioscopy revealed a papillary tumor at the cystic duct bifurcation in the common bile duct

Discussion

In 1951, Farrar's criteria for diagnosis of primary cystic duct carcinoma was reported as follows: the growth must be restricted to the cystic duct, there must be no neoplastic process in the gall bladder, hepatic, or common bile ducts, and a histological examination of the growth must confirm the presence of carcinoma cells.[5] However, there were only few cases that satisfy Farrar's criteria because the majority of the advanced carcinoma originating from cystic duct were excluded.[6] Because of anatomical characteristics, a cystic duct carcinoma has few pathognomonic clinical manifestations, and identification of a primary site is difficult. Therefore, the cases of primary cystic duct carcinoma diagnosed preoperatively in early stage were extremely rare. Recent improvements in imaging and endoscopic modalities, including CT, MRCP, ERCP, and EUS allowed preoperative acquisition of detailed information of cystic duct. In our case, the cystic duct and the tumor were identified by EUS and endocholangioscopy, and the primary cystic duct carcinoma could be diagnosed in early stage. The clinical symptoms of primary cystic duct carcinoma are associated with cystic duct or bile duct obstruction, such as pain in the right hypochondrium, palpitating of dilated gallbladder, jaundice, and liver dysfunction.[5,7]

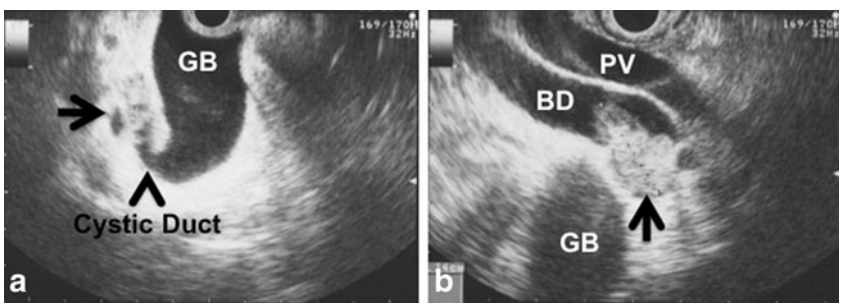

Fig. 2 Endoscopic ultrasonography revealed a tumor (**a**; *arrow*) originating from the cystic duct (**a**; *arrow head*), which extended into the common bile duct (**b**; *arrow*)

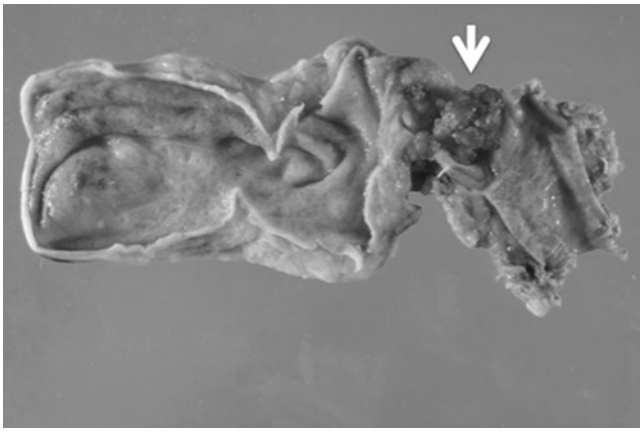

Fig. 4 Excited specimen showed a papillary tumor with the diameter of 25×22×15 mm in the cystic duct (*arrow*)

Endocholangioscopy with duodenoscopic assistance directly visualize the bile duct. Several studies reported the usefulness of endocholangioscopy on management of various bile duct lesions, such as diagnosis of biliary malignant tumors[8] and treatment of difficult-to-treat bile duct stones.[9] The fragility of equipments still remains as the problem for development of endocholangioscopic techniques, and further improvements of endocholangioscope and other equipments are required.[10]

Advanced primary cystic duct carcinoma invades the hepatic hilum and/or involves the confluence of the cystic duct[6,11] and shows a high frequency of perineural infiltration.[12] Radical resection is necessary for potentially curative treatment of cystic duct carcinoma. Fortunately, the present case was diagnosed as noninvasive early cystic duct carcinoma by EUS, endocholangioscopy, and intraoperative findings. Then, the patient underwent cholecystectomy, extrahepatic bile duct resection, and adjacent lymph node dissection as curative treatment with enough surgical margins and without lymph node metastasis, and therefore, radical resection such as pancreaticoduodenectomy could be avoided.

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GI IMAGE

Endoscopical En Bloc Resection of a Large Duodenal Adenoma with Focal High Dysplasia

Hydroxypropyl Methylcellulose as a Safe Lifting Agent in a Large Duodenal Adenoma EMR

Cinzia Quondamcarlo · Stefano Pontone · Alessandra Panarese · Daniele Pironi · Paolo Pontone · Angelo Filippini

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Abstract Endoscopic mucosal resection is a potential alternative to surgery when submucosal invasion and lymph node involvement are excluded. We describe an en bloc resection of a large, focal, high-grade tubulovillous nonampullary adenoma of duodenal wall using hydroxypropyl methylcellulose as a lifting agent.

Keywords Duodenal adenoma · EMR · En bloc resection · Hydroxypropyl methylcellulose

A 68-year-old woman was referred to our surgical department for a large duodenal adenoma. Upper endoscopy showed a 30-mm diameter sessile lesion of anterolateral duodenal wall with central depression (Fig. 1) and biopsy specimens revealed a tubulovillous adenoma (TVA). Adenocarcinoma was suspected basing on the size of the lesion and anamnestic data. Indeed, she

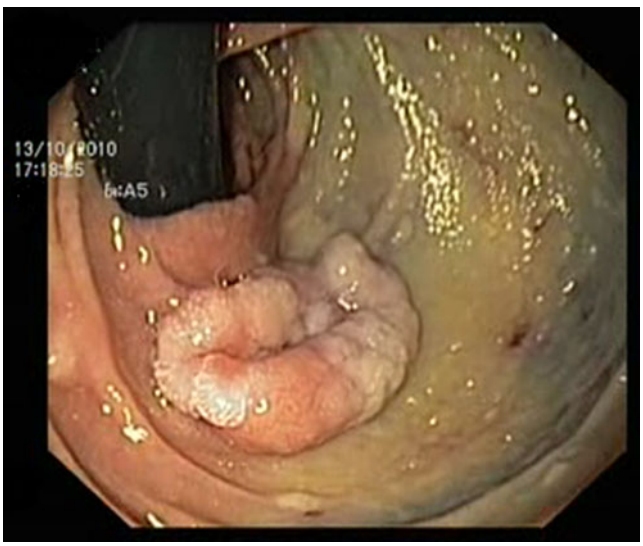

Fig. 1 Gastroscopic retro-vision image (GIF-Q180; Olympus Europe GmbH, Hamburg) of a 30-mm diameter sessile lesion of anterolateral duodenal wall with central depression

C. Quondamcarlo · S. Pontone (✉) · A. Panarese · D. Pironi · P. Pontone · A. Filippini
Department of Surgical Sciences, "Sapienza" University of Rome, V. le Regina Elena 324, 00161 Rome, Italy
e-mail: stefano.pontone@uniroma1.it

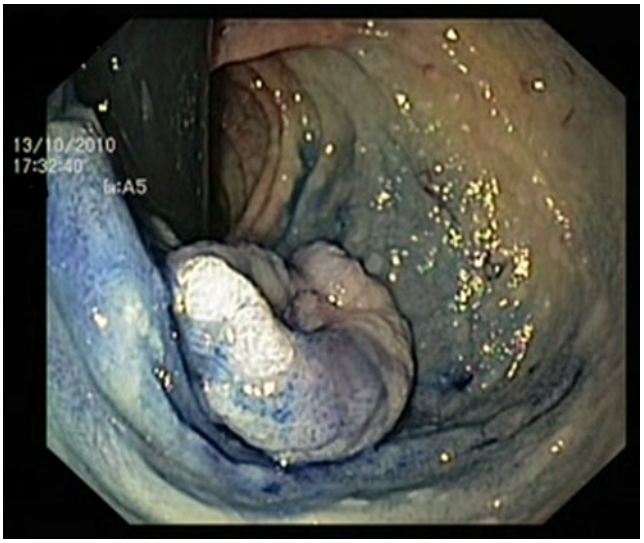

Fig. 2 The lesion after lifting by a submucosal injection of hydroxypropylmethylcellulose mixed with normal saline, epinephrine, and indigo carmine

had undergone several abdominal surgeries for endometrial cancer (bilateral ovariohysterectomy), colon cancer (right emicolectomy), and subsequent tumor recurrence that require the transverse colon resection and subtotal gastrectomy. No specific mutation was demonstrated at the genetic testing. The endoscopic ultrasonography was negative for submucosal invasion and lymph node involvement. Thus, the endoscopic mucosal resection (EMR) was considered a potential alternative to surgery.[1,2]

In order to obstacle the rapid dissipation of the lifting agent, to evidence the correct plane resection and obtain an effective sclerotherapy, the lesion was elevated by a large volume (>20 mL) submucosal injection of hydroxypropylmethylcellulose (HPMC; GEL 4000®; Bruschettini srl, Italy) mixed with normal saline (HPMC and normal saline, 1:2), epinephrine, and indigo carmine (Fig. 2). A forward-viewing standard endoscope was used and en bloc resection was performed in retro vision (Fig. 3a). There was no perforation or clinically significant bleeding after resection (Fig. 3b). Histologic assessment after resection revealed focal high-grade TVA. Endoscopic surveillance was scheduled to detect and treat recurrence.

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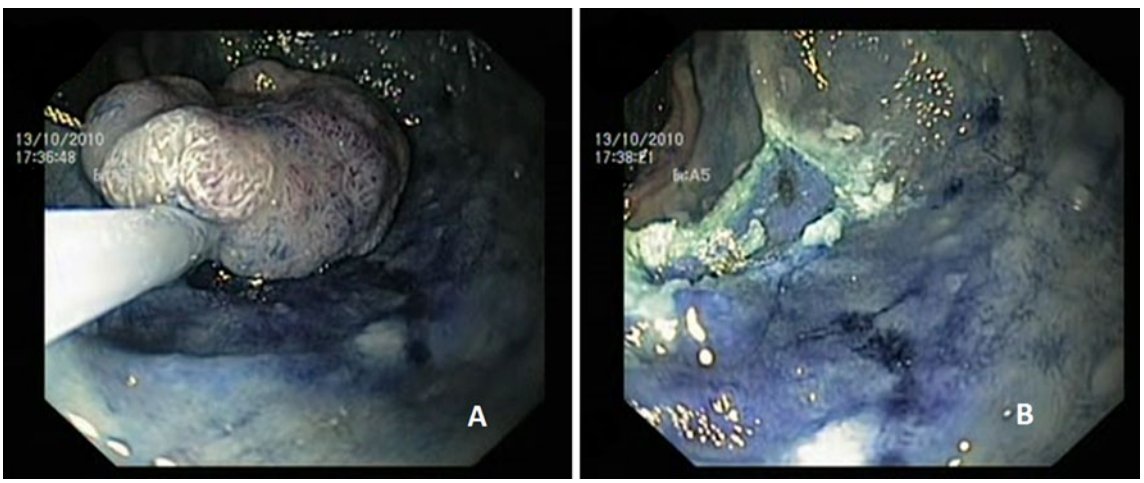

Fig. 3 **a** En bloc EMR performed by oval snare, **b** duodenal wall after resection

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GI IMAGE

Acute Appendicitis Secondary to a Granular Cell Tumor of the Appendix in a 19-Year-Old Male

Marco Zoccali · Nicole Cipriani · Alessandro Fichera · Jerrold R. Turner · Mukta Krane

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Abstract
Introduction Granular cell tumors are rare, usually benign, neoplasms presenting as solitary small nodules in the skin or subcutaneous tissue. Involvement of the gastrointestinal tract is unusual, particularly of the appendix, and it is characterized by indolent, submucosal lesions usually diagnosed as an incidental finding.
Case report We describe the rare case of acute appendicitis secondary to a granular cell tumor of the appendix in a 19-year-old male.

Keywords Granular cell tumor · Appendicitis · Laparoscopic appendectomy

Introduction

Granular cell tumor (GCT) or Abrikosoff's tumor is a rare, usually benign, neural neoplasm hypothesized to originate from Schwann cells, occurring most frequently in women of middle age, with a higher incidence in the black race.[1] It usually presents as a solitary, small nodule in the tongue, skin, or subcutaneous tissue but can arise in other areas. Localization in the gastrointestinal (GI) tract is rare (5%), with the esophagus being the most common site.[2] The diagnosis of GI GCT is often incidental during endoscopy or surgical resection, appearing as a submucosal nodule.[3] The involvement of the appendix is extremely rare, with only 11 cases reported in the literature.[4–14]

M. Zoccali · A. Fichera · M. Krane
Department of Surgery, University of Chicago Medical Center,
5841 S. Maryland Ave, MC 5095,
Chicago, IL 60637, USA

M. Zoccali (✉)
First General Surgery Unit, Department of Surgery,
Catholic University of Rome,
Rome, Italy
e-mail: mzoccal@surgery.bsd.uchicago.edu

N. Cipriani · J. R. Turner
Department of Pathology, University of Chicago Medical Center,
Chicago, IL, USA

Case Report

A 19-year-old Hispanic male presented to the emergency department with a complaint of right lower quadrant (RLQ) pain for 2 days. He was tender in the RLQ, without peritonitis, fever, or elevated white count. He was on antibiotics as previously prescribed by his primary care physician. Past medical history was unremarkable. Abdominal CT scan showed an inflammatory mass in the right lower quadrant consistent with a dilated appendix, with a round structure adjacent to the tip of the appendix suggesting a developing abscess (Fig. 1a, b).

Due to the clinical presentation and radiological findings, the patient underwent a diagnostic laparoscopy. A 13-cm-long appendix was noted adherent to the anterior abdominal wall, with clear sign of inflammation more evident at the distal aspect. The mid appendix was thickened (transverse diameter about 3.5 cm), with a possible intraluminal mass (Fig. 1c). The appendix was completely mobilized, without violation of the lumen. A laparoscopic appendectomy was performed, with wide margins between the section line and the suspected mass. Gross examination of the specimen in the pathology department demonstrated a well-circumscribed, firm, tan 3.5-cm mass extending into the lumen at the center of the appendix (Fig. 1d).

The final pathological diagnosis was granular cell tumor (GCT) of the appendix with concomitant acute appendicitis (Fig. 2).The absence of necrosis, hypercellularity, mitotic figures, or involvement of the muscularis propria, along

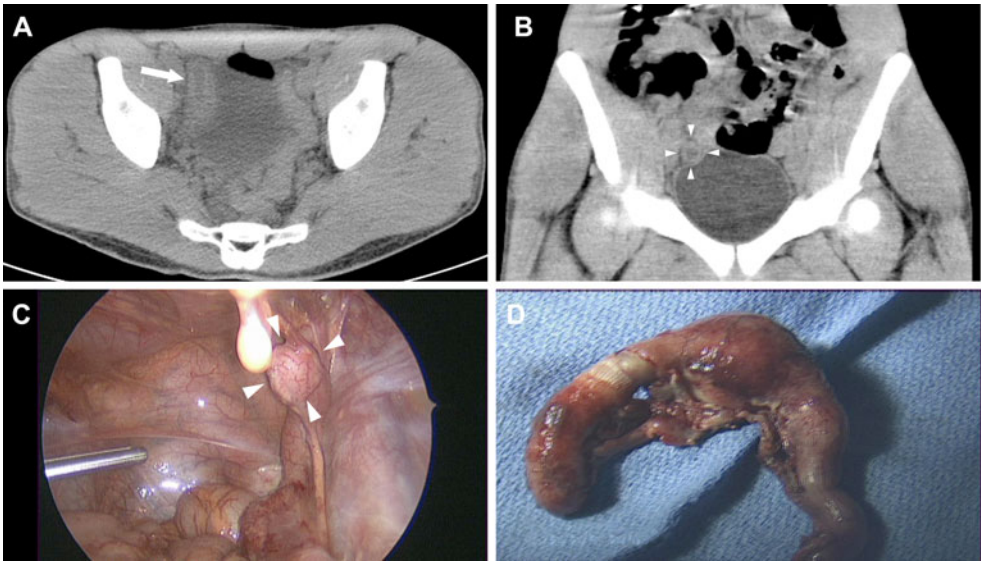

Fig. 1 a, b CT scan without oral and IV contrast showing a thickened tubular structure (*arrows*) extending from the cecum with approximate diameter of 1.8 cm, consistent with an inflamed appendix. A round structure is identified adjacent to the tip of the appendix (arrowheads). **c** Intraoperative findings. A long appendix adherent to the anterior abdominal wall is visualized, with a >3-cm mass in its midportion (*arrowheads*). **d** Gross appearance of the resected appendix, with a well-circumscribed 35-mm firm mass in the middle third

with the small size (<4 cm) suggests a benign behavior of the tumor.

The postoperative course was unremarkable, with the patient tolerating a solid diet on the first postoperative day. The patient was discharged on postoperative day 2. His early postoperative follow-up was uneventful, and a clinical and radiological follow-up has been planned.

Discussion

GCT, a rare and typically benign tumor, was first described by Weber in 1854 and characterized as clusters of large cells with granular eosinophilic cytoplasm.[15] In 1926, Abrikosoff reported a series of five GCTs originating from the tongue, and hypothesizing a striated muscle origin named these lesions granular cell myoblastomas.[16] Subsequently, Feyrter renamed these tumors granular cell neuromas, assuming a perineural origin according to the tendency of the lesions to occur in proximity to the peripheral nerves.[17] Currently, it is hypothesized that GCTs originate from Schwann cells, a hypothesis supported by recent ultrastructural and histochemical studies, showing a characteristic positivity for both nuclear and cytoplasmic S-100.[18–23]

It has been estimated that GCT accounts for approximately 0.03% of all human neoplasms and is reported as a pathological finding in 0.017% to 0.029% of all resected specimens.[24–26] GCT occurs more frequently in women in the fourth to sixth decades of life and is three times more prevalent in the black race.[1,2] Although these tumors can arise from any organ, they occur most often in the tongue (40%), skin and subcutaneous tissues (30%), and breast, presenting as a single, firm nodule less than 3 cm in size (15%).[2,27–29] The reported incidence of multiple GCT varies in the literature between 7% and 29%.[14,30–32]

The gastrointestinal localization accounts for only 2.7% to 8.1% of all GCT. The esophagus is the most frequently involved site in the GI tract accounting for about 30% of cases, and GCT is most often found in the distal third of the esophagus. The colon is the second most common site in the GI tract.[3,33] Usually the diagnosis of GI GCT is incidental during endoscopy or surgical resection, appearing as a submucosal nodule covered by intact mucosa. Differential

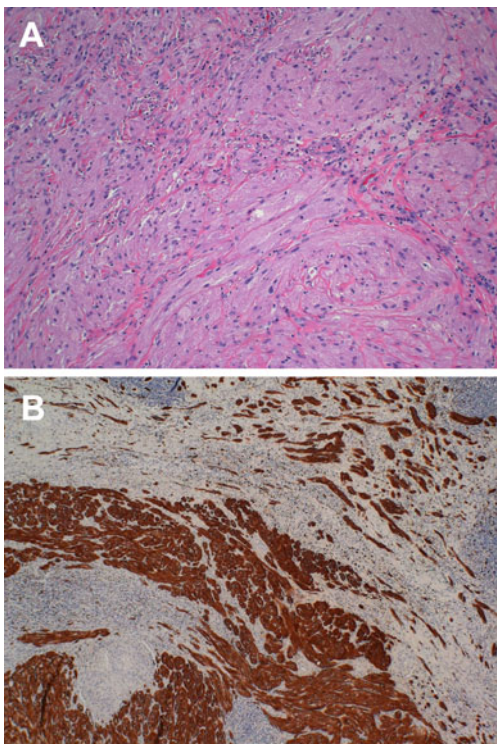

Fig. 2 **a** Neoplasm consisting of nests and chords of plump to spindle cells with granular amphophilic cytoplasm, ill-defined cell borders, and oval to elongate nuclei (H&E, ×100). **b** Immunohistochemical stain for S-100 showing a diffuse, strong positivity (×40)

diagnosis consists of polyps and other submucosal lesions including lipomas, leiomyomas, and gastrointestinal stromal tumors.[3,34,35] Endoscopic ultrasonography can be helpful in defining the submucosal origin of the lesion, but clinical and radiologic diagnostic criteria are lacking.[33,36,37] The final diagnosis depends on pathological findings including nests of plump polygonal and fusiform cells, with abundant granular eosinophilic cytoplasm containing lysosomal granules, and immunohistochemically staining positive for S-100.[2]

A GCT of the vermiform appendix is an extremely rare occurrence. From a review of the English literature, we found only 11 documented case of appendiceal GCT. The patients' age at diagnosis was between 32 and 62 years, with the majority of patients over the age of 40.[4,7,9–12].The cases are equally distributed between the sexes, with a higher prevalence in the black race when ethnicity is specified.[4,6,7,13,14] In most cases, it was a single neoplasm with two studies reporting appendiceal lesions in the context of multiple GCTs of the GI tract.[10,14] Because of their small size and the indolent behavior, GI GCTs are usually asymptomatic. However, when occurring at the appendix, the neoplasm may obstruct the lumen resulting in secondary appendicitis, as described in five cases.[7,8,11–13] To our knowledge, this is the first case described in the literature of a GCT of the appendix occurring in a symptomatic, young non-black male.

A malignant GCT is uncommon (1–3%) and is suggested by size >4 cm, necrosis, spindling of tumor cells, high mitotic activity and nuclear-to-cytoplasm ratio, and a strong positivity for p53 and Ki67 proteins.[38] The most effective treatment is a complete resection with negative margins, achieved either endoscopically or surgically, with a reported overall recurrence rate of 2–8%.[3,34,36,39,40]

Conclusions

A granular cell tumor of the appendix is a rare entity, often diagnosed incidentally during surgery for acute appendicitis or other non-related reasons. Nevertheless, this possibility needs to be taken in account when a mass is recognized in the context of the appendix, in order to provide a complete resection with wide margins. Although considered benign, an appropriate follow-up should be warranted, especially in the presence of features suggestive for a more aggressive behavior.

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GI IMAGE

The Rapunzel Syndrome: A Hard-To-Swallow Tale

Thierry Bège · Ariadne Desjeux · Benjamin Coquet-Reinier · Stéphane V. Berdah · Jean-Charles Grimaud · Christian Brunet

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Abstract
Introduction Rapunzel syndrome is a rare entity comprising of a large gastroduodenal trichobezoar due to trichotillomania. Its treatment is often surgical.
Case Report A 27-year-old patient was investigated after an upper gastro-intestinal tract obstruction. Computed tomography and endoscopy showed a large gastric trichobezoar with a duodenojejunal tail. Conservative treatments failed to remove the bezoar. We performed a short laparotomy which allowed the removal of the bezoar through a longitudinal gastrotomy. Postoperative course was uneventful.

Keywords Gastric trichobezoar · Rapunzel syndrome · Longitudinal gastrotomy

A 27-year-old patient presented with a recurrent epigastric pain, associated with vomiting and 5 kg weight loss. Her past medical history included a laparoscopic cholecystectomy a month ago, with uneventful postoperative course. Blood tests and abdominal ultrasound showed no abnormality. Abdominal computed tomography revealed a proximal jejunal intussusception associated with gastric and duodenojejunal bezoar (Fig. 1). Endoscopy confirmed the diagnosis of trichobezoar, but failed to extract it. Chemical dissolution with papaïne also failed. Laparotomy was performed through a short longitudinal epigastric incision. Longitudinal gastrotomy was performed, allowing the extraction of the gastric and duodenojejunal-shaped hair ball (Figs. 2 and 3). Postoperative course was uneventful, and the patient

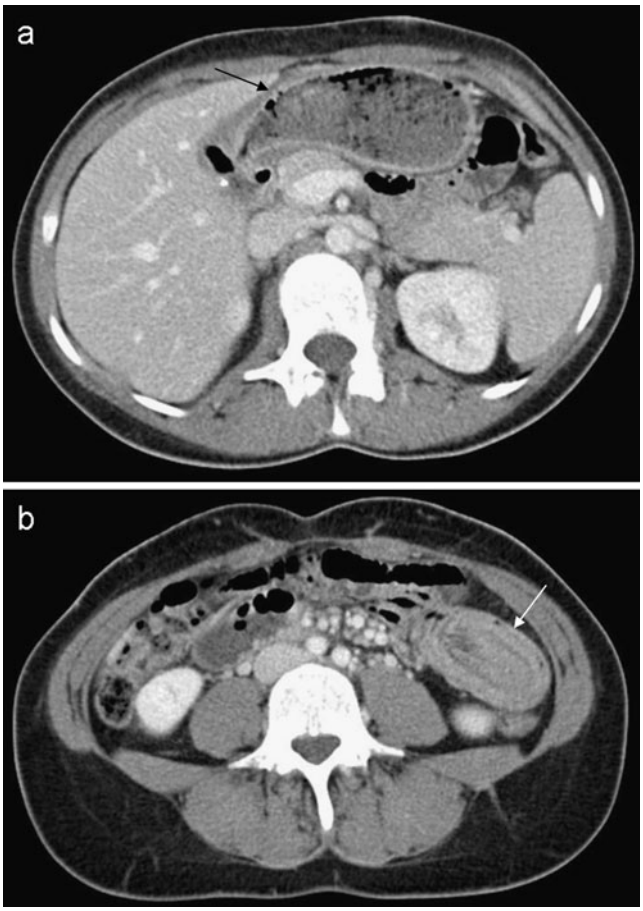

Fig. 1 CT abdomen demonstrating **a** duodenojejunal trichobezoar (*black arrow*) and **b** small bowel intussusception (*white arrow*)

T. Bège (✉) · B. Coquet-Reinier · S. V. Berdah · C. Brunet
Department of Digestive Surgery, Hôpital Nord,
Chemin des Bourrely,
13915 Marseille cedex 20, France
e-mail: thierry.bege@ap-hm.fr

A. Desjeux · J.-C. Grimaud
Department of Gastro-enterology, Hôpital Nord,
Chemin des Bourrely,
13915 Marseille cedex 20, France

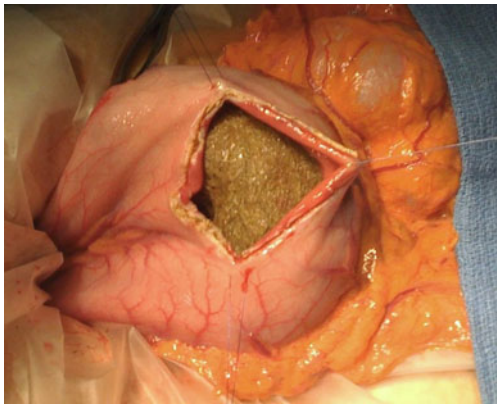

Fig. 2 A trichobezoar occupying the whole stomach

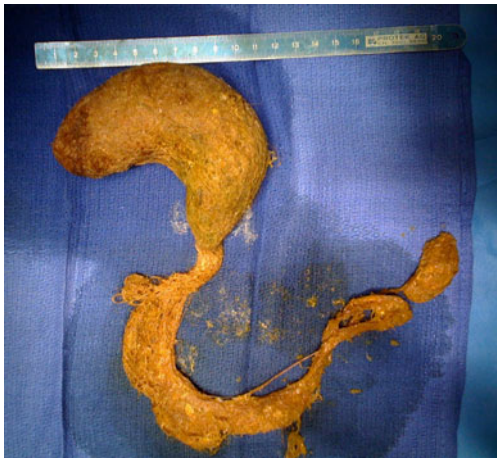

Fig. 3 Post-surgical specimen

regained her normal weight. She accepted psychiatric follow-up, though denying hair ingestion (trichotillomania).

Gastric trichobezoar with a duodenal or duodenojejunal tail is named Rapunzel syndrome after the 1812 German tale written by Grimm brothers (recently adapted into an animated musical film by Walt Disney Studios), where a girl with a long-braided hair used it to help her lover climb the tower where she was imprisoned. It often results in anorexia with vomiting and the whole range of resulting complications (e.g. anemia and hypoalbuminemia), with proximal intestine intussusception, pancreatic or biliary obstruction, hemorrhage and perforation.[1] Conservative treatment fails most of the time, and open or laparoscopic gastrotomy is the treatment usually advocated.[2]

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MULTIMEDIA ARTICLE

Laparo-Endoscopic Single-Site (LESS) with Transanal Natural Orifice Specimen Extraction (NOSE) Sigmoidectomy: A New Step before Pure Colorectal Natural Orifices Transluminal Endoscopic Surgery (NOTES®)

Joel Leroy · Michele Diana · James Wall · Federico Costantino · Jacopo D'Agostino · Jacques Marescaux

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Abstract
Introduction We present the first human case of laparo-endoscopic single-site sigmoidectomy with transanal natural orifice specimen extraction.
Discussion This technical achievement is a new step toward pure colorectal Natural Orifices Transluminal Endoscopic Surgery. It is the product of a gradual development with critical steps being conceived and standardised in years of experimental and clinical procedures.

Keywords NOTES® · NOSE · Single port · LESS · Laparoscopic colorectal surgery

Introduction

Benefits of a minimal invasive surgical approach in complex surgical procedures including colorectal resections have been demonstrated in prospective clinical trials.[1–4] Decreased pain and better quality of life[5] combined with equivalent oncologic outcomes have driven laparoscopic colorectal surgery; however, the global penetration remains low,[6] due in part to inadequate training of surgeons.[7]

Laparo-endoscopic single-site surgery (LESS) and Natural Orifice Transluminal Endoscopic Surgery (NOTES®) are evolving techniques that are pushing the technical limits of minimally invasive surgery. With less incisions, there is a renewed interest in a classically described technique of natural orifice specimen extraction (NOSE) originally proposed by Morris Franklin.[8]

The common focus of these concepts is to minimize abdominal wall trauma in gaining access to the peritoneal cavity and/or extracting the surgical specimen. The goal is ultimately reduce incisional complications of pain, infections and hernia.[9]

During colorectal procedures, there are two critical steps that are challenging in minimal invasive approaches. The first is the construction of the anastomosis, and the second is the extraction of the specimen.

Solutions to obviate the need to enlarge a port incision or to perform a mini-laparotomy are the intracorporeal anastomosis and the use of NOSE. We have taken a stepwise experimental and clinical approach to developing minimally invasive techniques to address these challenges.

After a preparatory experimental phase,[10] we published the first case of LESS sigmoidectomy for diverticulitis.[11] Furthermore, as a preparatory step toward NOTES® colorectal procedures, we conceived a technical trick to achieve a percutaneous endoluminal control position of the anvil in virtually all the segments of the colon (PECAC).[12] We used this technique to perform a single port sigmoidec-

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J. Leroy (✉) · M. Diana · J. Wall · F. Costantino · J. D'Agostino · J. Marescaux
Department of General, Digestive and Endocrine Surgery, IRCAD/EITS Institute, University Hospital of Strasbourg, 1 Place de l'Hôpital, 67091 Strasbourg Cedex, France
e-mail: joel.leroy@ircad.fr

tomy with transabdominal specimen extraction and a triport sigmoidectomy with transanal specimen extraction.

The PECAC technique offers the possibility of precisely positioning the anvil proximally colon, but is not suitable to pass an anvil in oncologic cases and in the presence of significant inflammatory stenosis. A prospective study on sigmoidectomy with transanal extraction of the specimen is currently ongoing at our Surgical Department.

The logical next step for us was to perform a full-laparoscopic single port sigmoidectomy with transanal NOSE that is presented here. At the time the article was written there were no published reports of a LESS sigmoidectomy with transanal NOSE.

Patients and Methods

Patient

A 51-year-old woman, BMI 23 kg/m^2, without previous abdominal surgery, presented with recurrent acute diverticulitis 10 years after an initial episode. CT scan revealed uncomplicated sigmoid diverticulitis, and she was treated conservatively with antibiotics. Eight weeks after the acute phase of her second attack, she was scheduled for sigmoid colectomy. Preoperative endoscopic evaluation revealed a significant inflammatory stenosis of the sigmoid. Both single port laparoscopic approach and transanal specimen extraction are routinely used in our University Hospital.

Informed consent for a single port NOSE approach sigmoid colectomy was discussed with the patient who agreed to proceed. A low-fibre diet was started 5 days before surgery, and a bowel preparation by high volume enema with 2 l of polyethilene glycol solution was performed the day before surgery.

Procedure

The patient was placed in the lithotomy position. Antibiotic prophylaxis (2 g of Cefazolin and 1 g of Metronidazol i.v.) was administered during the induction phase, 15 min before the incision.

Clip 1

Pneumoperitoneum was achieved through a 12-mm Versastep™ trocar (Covidien) inserted into the umbilical region using a mini-open technique. Once the abdominal cavity had been insufflated with 4 l of CO_2, explorative laparoscopy confirmed the feasibility of the planned procedure by ruling out dense adhesions and persistent inflammation. The incision was then enlarged to 3.5 cm, and the Versastep™ port was replaced by the Single Incision Laparoscopic Surgery port (SILS™, Covidien, Westbury, MA). Two rigid (5 mm or 12 mm) and one flexible trocar (Karl Storz®, Tuttlingen, Germany) were inserted through the SILS™ port. Next, the patient was positioned in a Trendelenburg right side down position to enhance the exposure of the pelvis and the sigmoid colon. The uterus was suspended to the abdominal wall with transparietal stitches passed with a straight needle around the round ligaments of both sides. A 5-mm endoscope with a 30° optic and an extra-long (50 cm) shaft (Karl Storz®), a double-curved grasper (S-Portal Series Leroy's design, Karl Storz®) and the new 5-mm Ligasure™ blunt tip long probe (Covidien, Norwalk, Connecticut) were inserted in the SILS™. Suction was connected to the valve on the shaft of the curved grasper (S-Portal Series Leroy's design, Karl Storz®) providing a continuous evacuation of smoking with very low negative pressure applied. This trick creates a "chimneys effect" which is important to maintain a clear operating field with only a single port. Smoke arising from dissected tissues forms a column of clouding directly in the operating field when the sole escape point is the SILS™ port. However, aspiration through the hollow tip of the instrument draws smoke away from the optic and maintains excellent visualization

A medial-to-lateral approach was used to dissect the sigmoid colon. Mesenteric dissection and branch vessel sealing were done close to the colon using the 5-mm Ligasure™ blunt tip long probe (Covidien, Boulder, Colorado). Next, lateral dissection was begun, and once freed, the distal sigmoid was closed with an intracorporeal suture to avoid faecal spillage.

Clip 2

The high rectum was then transected with the 5-mm Ligasure™ blunt tip long probe after transanal cleaning just below the ligature. A transparietal stitch was passed on the anterior aspect of the rectal stump to keep it open. An Endoloop™ (Endo Suture System™; Ethicon, Somerville, NJ) was tied around the distal sigmoid, and the extremity of the loop kept long was grasped with a transanally passed forceps and sigmoid was gently pulled out through the anus maintaining the rectum open.

Clip 3

A 30-cm long, decimal 2 Polysorb™ (Covidien, Boulder, Colorado) suture was attached at the tip of the anvil of a circular stapler (PCEEA™ 28 DST Series Autosuture™ EEA™ Covidien) that is subsequently be used to create the colorectal anastomosis. At this point, a longitudinal enterotomy was made above the inflammatory and stenotic segment of the sigmoid, and the anvil was pushed into the

descending colon cephalad to the proximal resection site leaving the suture outside. Next, the proximal resection site was laparoscopically identified and transection made with linear cutting roticulating stapler (EndoGIA™ 60 blue cartridge, Covidien) taking care that Polysorb™ (Covidien, Boulder, Colorado) suture attached to the anvil got entrapped in the staple line. The specimen was then extracted through the open rectal stump, under laparoscopic visualization. No wound protector was used at the extraction site. The rectal stump was closed by two staple loads with the EndoGIA™.

With a coagulating hook, a small enterotomy was made close to the staple line on the antimesenteric side of the proximal colon and, using a "fishing technique", the Polysorb™ suture was captured inside the lumen by the hook. The suture was then pulled through the enterotomy, enabling a snug delivery of the anvil through the colotomy.

Position of the anvil was secured by tightening an Endoloop (Endo Suture System; Ethicon, Somerville, New Jersey) around the colotomy cuff. The head of the circular stapler (28Fr, DST series PCEEA; Covidien) was passed transanally and mated with the anvil pike as in a standard end-to-end anastomosis. The stapler was engaged under full-laparoscopic visualization.

After removal of the stapler, the tissue rings were closely inspected to ensure completeness. The anastomosis was inspected laparoscopically to ensure it was well oriented without tension. Peritoneal fluid samples were collected and sent for bacteriological analysis.

The fascia was closed with interrupted 1-0 Polysorb™, and the skin was reapproximated with a running 3-0 Monocryl™.

Results

Operative Outcomes

Skin-to-skin operating time was 105 min, and no intra-operative complications occurred. The operative field was clear and smokeless during all the intervention due to "chimney effect". The umbilical skin incision length was 3 cm, and the specimen length was 25 cm.

Postoperative Outcomes

The postoperative course was uneventful. Time to first flatus and to first stool passage was 2 and 3 days, respectively. Time to resume normal diet was 5 days, and the patient went home on postoperative day 6. Overall visual analogic scale (VAS) was 7, 5, 4, 3, 2 and 0 from POD 1 to POD 6, respectively. The patient complained mainly of shoulder pain while surgical site pain was considerably less; however, the VAS captured only overall pain. Sphincter tonus was normal on postoperative physical exam.

The gram stain of the peritoneal fluid sample was negative; however, the culture was positive for three bacterial strains (*Streptococcus salivaris*, *Citrobacter koserii* and *Enterococcus durans*). The bacterial load was classified as "low" in a semi-quantitative estimation for all bacteria grown in culture. Pathology confirmed the presence of sigmoid diverticulitis. At the short-term follow-up, the patient was fully ambulatory without pain and had full control of both stool and flatus. The cosmetic results were excellent (Fig. 1).

Discussion

The ultimate aim of NOTES® is to offer less invasive, incision-less surgery that may even be performed on an outpatient basis. This revolutionary concept is partially driven by the public demand,[13] and has benefited from industry investment in new surgical tools design. NOSE is a NOTES®-related concept in which natural orifices are looked mainly as "a way out" to spare further trauma to the abdominal wall.

Pros and Cons of LESS

Theoretical benefits of LESS are: reduced postoperative pain and use of narcotics, reduced morbidity with faster recovery time and possibly lower costs due to shorter length of hospital stay, reduced incidence of port-site infections and herniation[9] and enhanced cosmetic results. LESS procedures are highly demanding due to conflict between operating instruments and optic system coming from the single port, lack of triangulation, in-line view and difficult exposure. These shortcomings have been partially addressed by technological improvements, but surgeon's laparoscopic training and skill remain the major point for a successful LESS surgery.

To reduce conflicts and enhance triangulation, we used a curved grasper and an extra-long scope to avoid external conflicts between the surgeon's and the assistant's hands (Fig. 2). SILS™ expanded foam port (Covidien), thanks to its softness, allows good freedom of movements into the abdominal cavity.

Pros and Cons of NOSE

NOSE in colorectal surgery has been the subject of many recent publications and is a non-standardised procedure with several different techniques. Expected benefits of NOSE in laparoscopic surgery, especially in procedures

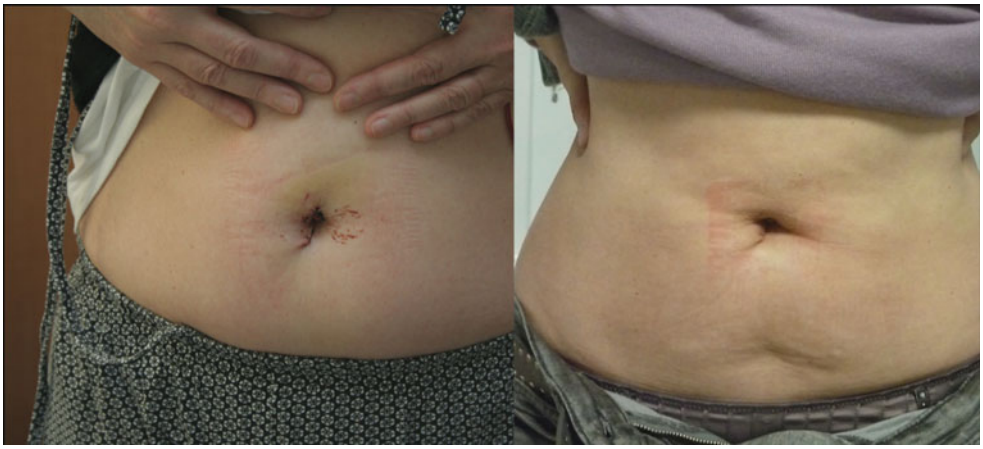

Fig. 1 Postoperative follow-up of the surgical site. Excellent cosmetic results of the umbilical incision at day 3 and day 30

with a large specimen, is to prevent the need for an enlarged port site or mini-laparotomy. Furthermore, transanal placement of the anvil in the NOSE procedure is a good solution to avoid exteriorisation of healthy bowel to perform the anastomosis. In fact, it has been reported that intracorporeal anastomosis construction is superior in terms of return of bowel function, postoperative narcotic use and length of stay and morbidity in comparison to the extracorporeal technique.[14] This issue is expected to be even more important in LESS procedures in which the bowel to be resected would have to be exteriorised through the single-site wound with the meso-colon under tension and the bowel beneath the abdominal wall at risk for ischemia. Another advantage of NOSE in colorectal resection is that the natural orifice opening to introduce the anvil of the circular stapler will be included in the resected specimen. Worldwide experience with this technical adjunct in colorectal is still very limited to support the potential advantages.

In reviewing the current state of the art of single port in colorectal surgery[15], incisions of up to 6–8 cm have been reported to construct the anastomosis extracorporeally and to extract the specimen. This leads to increased risk of parietal morbidity such hernia, pain and infection. Our aim is to keep the incision size at the minimum. The SILS™ port is admittedly bulky and needs a skin incision of 3.5 cm and an even bigger fascia incision. Through such fascia incision, the anastomosis is possible to perform and to extract the specimen with no additional risk. Indeed, our effort was to show the feasibility of NOSE during a single port sigmoidectomy.

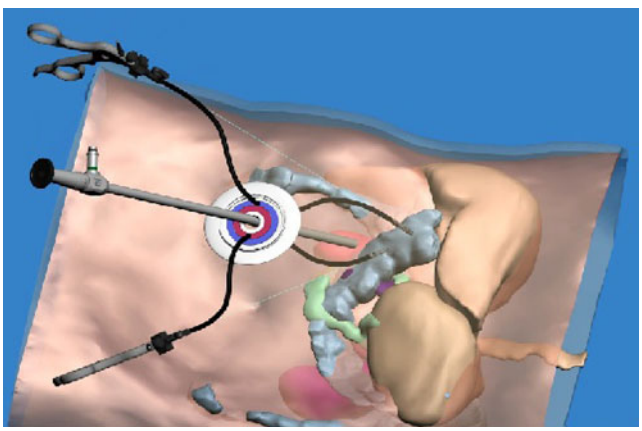

Fig. 2 The S-Portal Series Leroy's design, Karl Storz® double-curved instruments reduce external conflicts between the surgeon's and the assistant's hands and offer a good triangulation

Smaller single port devices or mini-laparoscopic instruments passed in multiple fascia incisions, as per Curcillo's Single Port Access technique,[16] could enhance the interest of transanal NOSE. Furthermore, the transanal route could be used to perform a part of the dissection in a hybrid NOTES® procedure.

LESS with transanal NOSE sigmoidectomy is clearly not suitable for all the cases and thus a careful patient selection is mandatory. Obesity, American Society of Anaesthesiology (ASA) score of 3 or 4 and surgeon's experience have been recognized as independent risk factors of conversion from laparoscopic to open surgery in a large patient series.[17] Furthermore, while in an acute non-complicated diverticulitis inflammation tends to remain more localized, a past episode of acute sigmoiditis results more commonly in a thickened bowel wall and mesentery with significant adhesions. With no prior abdominal surgery, a low BMI and mild, localized acute sigmoid diverticulitis, our patient was an ideal candidate for the procedure.

NOSE carries also a number of potential risks that warrant consideration. The first concern is peritoneal contamination risk secondary to the opening of the rectal stump to retrieve the specimen. Contamination of peritoneal cavity in colorectal surgery is frequent even in conventional non-NOSE procedures.[18]

In our experience on transanal NOSE sigmoidectomies, 100% of culture was positive; however, no patients developed significant intra-abdominal infections. To fully assess this issue, a prospective study comparing peritoneal contamination in NOSE and non-NOSE colorectal procedures would be needed.

Similarly, the extension of NOSE to oncologic cases will demand a strict evaluation from ethical committees, and in our opinion, it should not be performed without careful protection (plastic wound protector and specimen bag retrieval) to reduce the possibility of neoplastic seeding at the extraction site.

Furthermore, transanal route allows the extraction of specimen that seems quite bulky almost without resistance, but one may speculate about a possible impairment of the sphincter function. Although, our experience with several transanal extraction no incontinence was reported, it would be worthy to assess this issue with a prospective functional anal manometry evaluation.

Conclusion

A LESS sigmoidectomy with transanal NOSE for diverticular sigmoiditis was feasible with an excellent outcome. This achievement is not simply the result of combining two independent concepts (LESS and NOSE), but rather the natural evolution towards the most minimally invasive approach conceivable to perform colorectal procedure with a surgical specimen to retrieve. The key steps of the present procedure have been carefully validated through a stepwise standardisation in both the experimental and clinical settings. We are now ready to prospectively evaluate reproducibility and benefits of this approach.

Conflicts of Interest Authors declare that they no conflicts of interests.

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LETTER TO THE EDITOR

Caval Clamping During Total Hepatectomy with Caval Preservation in Liver Transplantation

Cuneyt Kayaalp · Sezai Yilmaz

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Dear Sir,

We read with interest the article entitled "An Alternative Surgical Technique for Caval Preservation in Liver Transplantation" by Doria[1] in 2010 of the *Journal of Gastrointestinal Surgery*. We needed to make some comments about this technique.

Hanging of the liver particularly hepatic veins over the vena cava inferior without separation of short hepatic veins is a challenging method. Doria and colleagues reported that all three hepatic veins can be hanged and clamped transversally in cases of difficult total hepatectomies with caval preservation for liver transplantation (Fig. 1a). We agree with the authors that total hepatectomies with caval preservation can sometimes be difficult and caval clamping can be required. We performed almost 450 liver transplantations with caval preservation (90% living donor) during the last 3 years and sometimes we needed total caval clamping. However, we preferred suprahepatic caval clamping (Fig. 1b) and according to our opinion, the proposed technique by Doria and his colleagues can be difficult and even dangerous. The liver tissue covering the hepatocaval ligament and the caudate lobe surrounding the vena cava in patients with cirrhosis does not allow the transverse hanging of the hepatic veins (Fig. 2a). There is

C. Kayaalp (✉) · S. Yilmaz
Department of General Surgery, Inonu University, Turgut Ozal Medical Center,
Malatya, Turkey
e-mail: cuneytkayaalp@hotmail.com

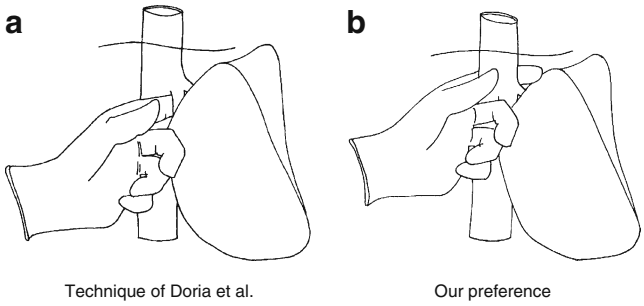

Fig. 1 **a** Technique of Doria et al. **b** Our preference

no safe avascular area for the transverse hanging between the hepatic veins and the retrohepatic vena cava (Fig. 2b). The well-known safe area for liver hanging on the retrohepatic vena cava is not transversal but vertical.[2] In addition, continuing caval blood flow in that technique does not reduce the risk of bleeding during dissection between the liver and the vena cava.

The authors applied this technique to only four patients and did they experience any difficulty in handling the hepatic veins? Was there any bleeding during hanging?

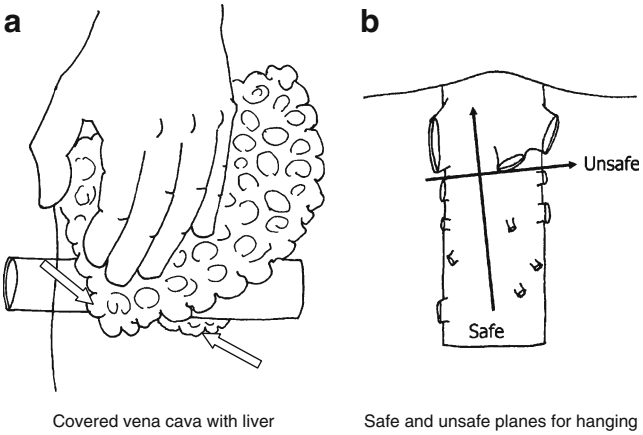

Fig. 2 **a** Covered vena cava with liver. **b** Safe and unsafe planes for hanging

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DOI 10.1007/s11605-011-1532-8

LETTER TO THE EDITOR

Author's Reply to Letter "An Alternative Surgical Technique for Caval Preservation in Liver Transplantation"

Cataldo Doria · Adam S. Bodzin · Adam M. Frank · Warren R. Maley · Carlo B. Ramirez

Received: 18 January 2011 / Accepted: 1 April 2011 / Published online: 6 May 2011

Dear Editor:

Thank you for the opportunity to reply to the letter that you recently received from Drs. Kayaalp and Yilmaz. We appreciate and agree with the comments of Drs. Kayaalp and Yilmaz; however, we think it is important to clarify a few issues.

1. In their letter Drs. Kayaalp and Yilmaz indicated that the hanging maneuver of the "hepatic veins over the vena cava inferior without separation of short hepatic veins is a challenging method." We agree with that statement, however, we are unaware of a described hanging maneuver of the hepatic veins over the inferior vena cava (IVC), nor was it our intention to define such a maneuver. With our technique, we create a dissection area between the IVC and the three hepatic veins that is sufficiently large enough to place a surgical clamp across the three hepatic veins.
2. The cumulative experience of the five authors of the paper titled "An alternative surgical technique for caval preservation in liver transplantation" is over 1,200 liver transplants. These include live donor as well as cadaver donor liver transplants performed with an array of techniques that vary from the "standard" to the piggy-back technique in its various forms. Based on our cumulative experience the drawing numbered 1b provided by Drs. Kayaalp and Yilmaz is a beautiful representation of one very important step of the "standard" or "bi-caval" technique for orthotopic liver transplantation: the encirclement of the supra-hepatic IVC before it is clamped in the very last portion of the hepatectomy—a technique that is different from the one we described in our paper. Thank you for the picture.
3. We agree with Drs. Kayaalp and Yilmaz that our proposed alternative surgical technique for caval preservation is challenging. That is the reason why in the last paragraph of the discussion section of our paper we indicated that this technique should only be performed by "experienced transplant surgeons."
4. Furthermore, the anatomy of the retro-hepatic veins is variable and not standard. This is the reason why the described surgical technique should be used in cases of favorable anatomical variation of the retro-hepatic veins which allow an easy blunt dissection of the plane between the hepatic veins and the IVC.
5. Since the paper was published, one more patient has been transplanted using this technique at our institution. Finally, as an answer to the questions posed by Drs. Kayaalp and Yilmaz in their last paragraph, when properly used in the right candidate, the handling of the hepatic veins in this technique does pose an extra-challenge that can be overcome by experienced transplant surgeons. As far as the question as to the amount of bleeding observed during the use of this technique, the answer is that the anatomy of the retro-hepatic veins was favorable enough to allow a bloodless finger dissection of the plane between the hepatic veins and the IVC.

C. Doria (✉) · A. S. Bodzin · A. M. Frank · W. R. Maley · C. B. Ramirez
Division of Transplantation, Department of Surgery, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA
e-mail: cataldo.doria@jefferson.edu