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SSAT CONTROVERSY IN GI SURGERY DEBATE

Intramucosal Esophageal Cancer and High-Grade Dysplasia: Which Treatment Frame the Debate

Brant K. Oelschlager

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Keywords Intramucosal esophageal cancer · Dysplasia

Surgical therapy or endoscopic therapy: which is best for the treatment of high-grade dysplasia (HGD) and intramucosal (IM) adenocarcinoma of the esophagus? This is a reasonably recent debate, one that did not exist 5–10 years ago. Even today, surgical textbooks suggest esophageal resection as the appropriate treatment for this disease.[1] Debating this question is important yet difficult because the treatments are so different with different risk and benefit profiles. As with any therapy, every treatment has a risk/benefit ratio that must be taken into account when deciding the appropriate therapy. An example of this is shown in Fig. 1, suggesting a theoretical risk–benefit plot today versus 10 years ago. With improvements in staging, morbidity associated with esophageal resection and the rapid increase in available endoscopic ablative and resection techniques both have a role and we need to understand their current and ever-changing place in the armamentarium of treatment. So how does the debate lay out?

Dilemmas in Treatment

There are several dilemmas in the treatment of intramucosal cancer and high-grade dysplasia of the esophagus that are relevant to our discussion. It is helpful to think of each of these when treating patients.

B. K. Oelschlager (✉)
University of Washington,
Seattle, WA, USA
e-mail: brant@u.washington.edu

Diagnostic

How confident can we be with a diagnosis of HGD? Occasionally, the first time diagnosis of HGD represents overstaging, with subsequent biopsies (or resection) revealing low-grade dysplasia or non-dysplastic Barrett's. Conversely, the difference between intramucosal and submucosal cancers is small and often subtle. Since a submucosal lesion has a nearly 45% chance of lymphovascular invasion or frank nodal metastases, the diagnostic uncertainty must be considered when deciding treatment.[2]

Malignant Risk of the Lesion

Is everyone's risk the same? Of course not. The length of involvement in patients with Barrett's, whether it is unifocal or multifocal, nodular, molecular markers, and other risk factors clearly play a role. The riskier the lesion, the more surgical resection should be considered.

Completeness of Resection/Ablation

How confident can we be that all the disease is gone? This is a big question for endoscopic therapy and not only affects the long-term outcomes of the disease but also affects the patient's psyche and their worry about the future. Surgical therapy is obviously the most definitive way to completely resect esophageal lesions, but even this does not assure eradication. Although the exact risk is debatable, some patients with intramucosal cancer will die of extra-esophageal disease despite esophagectomy. Moreover, perhaps as many as 50% of patients will redevelop Barrett's in their residual esophagus after resection, so neither

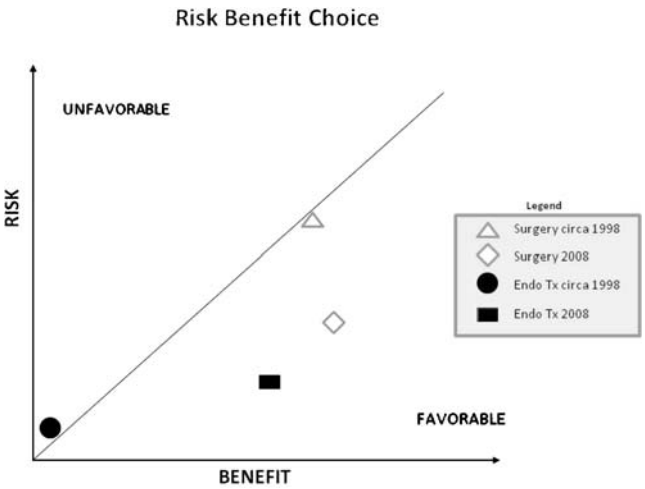

Figure 1 A theoretical risk–benefit for treatment of HGM/IM cancer plot: 1998 vs. 2008.

treatment can claim to completely eradicate dysplasia/cancer.[3]

Morbidity and Mortality of Treatment

The morbidity and mortality of both treatments is going down with time. Obviously, endoscopic therapy holds the lowest risk of complication, but even surgical therapy is getting safer. Standard protocols for perioperative care, centralized care in high volume centers, and minimally invasive surgical techniques are all responsible for esophagectomy being much safer now. This is a moving target (with current outcomes often better than published results) and is provider-specific. This means that the right procedure for a given patient will likely change with time and vary depending on local expertise and institutional volume.

Eradication of Disease

Eradication of disease is always an important consideration in patients with dysplasia or cancer. However, this is a disease that starts with gastroesophageal reflux disease (GERD), progresses to Barrett's, then dysplasia, and ultimately cancer. So is it important to eradicate cancer, dysplasia, Barrett's, and GERD or all of the above? Obviously, the treatment may be different depending on the answer to this question.

What We Learned from Surveillance?

The first proposed alternative to surgery, which does not get much press any more, is surveillance; but it still has a role and we have learned a lot from this experience. The accuracy of defining dysplasia and cancer continue to improve with improvements in imaging, better biopsy techniques, and better and more consistent pathologic recognition and differentiation. With this, the incidence of progression of HGD to cancer goes down, since fewer cancers are misidentified as HGD. As a result, these improvements in disease surveillance affect the decision of therapy. When there is less uncertainty about a patient with HGD harboring a cancer, the motivation to proceed with a radical extirpation of the esophagus goes down as well.

Prerequisites for Endoscopic and Surgical Therapy

If endoscopic therapy is to have a primary role in the therapy of HGD and IM cancers, there are certain features that are necessary. There must be no under-staging of disease; there should be a low failure rate, and if there are failures, there should be a way to accurately assess them; the complication rate should be low; the functional results superior to resection; there should be a way of dealing with the underlying disease (GERD) to prevent the same cycle of progression; and there should be consistency amongst practitioners.

Likewise, if surgical treatment is to remain as a viable option, it must have: a low complication rate; a reasonable functional result; and have consistent results amongst surgeons. Obviously, endoscopic techniques, as well as surgical ones, are a moving target and have variable results amongst those performing them. This makes comparing these two options all the more difficult.

Problems with the Literature

As a result, this becomes a comparison of apples and oranges, with the strengths of one approach compared to the weakness of the other, which makes it very difficult to come to the right answer when there are essentially no well-controlled direct comparison trials. My co-authors, Drs. Peters and Schembre, are going to discuss the literature from each side, but it is important when digesting this that one be aware of the general problems with the literature from both camps.

The surgical literature is obviously more extensive, but one must be careful not to use older results to reflect current outcomes. The surgical literature tends to include series with all patients, even those with unfavorable disease or tumor characteristics. There are few studies on long-term quality of life. Finally, there is a lack of consistent approach, with many different methods of performing esophageal resection used today.

The endoscopic literature is newer, and is a faster moving target, than surgery. Many case series are likely to be selective ones including lesions with favorable features, with the other patients referred for surgery. There are, for obvious reasons, shorter follow-up, so the long-term control

of esophageal cancer is still somewhat unknown. Finally, endoscopic therapy for HGD and IM cancer is being done by only a select few, with all the data coming from the experts and innovators and none from the "community standard".

Does One Shoe Fit All?

The answer is probably no. The correct answer will probably depend on whether the patient is young or old, has long vs. short segment Barrett's, unifocal versus multifocal disease, well-differentiated vs. poorly differentiated tumor, a nodular vs. flat lesion, and even symptomatic versus asymptomatic GERD. It is a complex problem with much to consider, so fortunately, there is more than one treatment available.

Conclusion

The truth is that in 2008, both endoscopic and surgical resection play a role in the treatment of IM cancer and HGD, so a critical look at the role of each is important. As one decides what is right for the individual patient, pay close attention to: (1) patient characteristics, (2) disease characteristics, (3) extent of disease, and (4) local or treating physician expertise. Finally, count on this debate to continue to change rapidly, as endoscopic, as well as, surgical therapy continue to improve and change, with advances in technology and experience.

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Endotherapy for Barrett's Esophagus with High-Grade Dysplasia and Intramucosal Carcinoma

Drew B. Schembre

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Introduction

The incidence of adenocarcinoma of the esophagus in the USA appears to be rising rapidly.[1,2] The prevalence of Barrett's esophagus (BE) appears to be increasing as well.[3] The vast majority of adenocarcinoma of the esophagus arises within Barrett's esophagus, and the identification of the immediate histologic precursor to cancer, high-grade dysplasia (HGD), is the endpoint of current Barrett's surveillance programs.[4] Once HGD has been found, management has included close endoscopic surveillance, esophagectomy, and, more recently, endoscopic ablative therapies (ET). ET has included photodynamic therapy (PDT), endoscopic mucosal resection (EMR), endoscopic submucosal dissection, radiofrequency ablation (RFA) and cryotherapy, as well as a variety of thermal treatments such as argon plasma coagulation (APC).[5–9]

In theory, surveillance identifies those individuals who progress to cancer early, allowing intervention while it may still be curative and sparing those who never progress the risks of therapy. However, early cancers may be difficult to recognize endoscopically and may even be missed by standard biopsy protocols.[10] Further, the rate of progression of HGD to cancer can vary widely, with patients with multifocal HGD and aneuploidy at particularly high risk for malignant progression.[11]

D. B. Schembre (✉)
Virginia Mason Medical Center,
Seattle, WA, USA
e-mail: drew.schembre@vmmc.org

For these reasons, surveillance protocols have fallen out of favor. At the same time, awareness of BE and the connection between gastroesophageal reflux (GERD) and esophageal cancer is rising, both among primary care physicians and the lay public. Endoscopy to detect BE has been recommended for patients who experience regular heartburn symptoms or who require frequent acid suppressant medication to control symptoms.[12] Newer, less expensive methods for detecting BE in patients with GERD such as unsedated, transnasal endoscopy[13] and wireless capsule endoscopy[14] have been proposed. These techniques have even been cited as tools for BE screening in patients without GERD, as up to 40% of patients with BE do not experience classic GERD symptoms.[15]

The questions of whether to treat patients with BE and dysplasia surgically or by ET—or which patients may be more appropriate for either modality—remain pivotal in many tertiary care centers in industrial countries. In many centers, esophagectomy remains the standard intervention for these patients, provided they are fit for surgery. However, ET has become more popular as experience with the techniques and evidence of efficacy has accumulated. Public demand for less invasive therapies has also spurred a growth in these treatments. This paper will look at the available evidence and show why ET should stand as the first line for most patients with BE and HGD or intramucosal carcinoma (IMC).

Background

HGD and IMC are, by definition, mucosal processes. It follows then that if the diseased mucosa can be removed or destroyed and replaced by normal or non-dysplastic mucosa, the progression from dysplasia to invasive cancer

will be prevented. HGD has no ability to metastasize or invade. IMC—cancer that does not invade beyond the muscularis mucosa—while technically a cancer with the potential to metastasize, rarely does. In large series, the incidence of lymph node metastases among esophagi resected for IMC ranges from 0% to 3%.[16–18]

In 1993, two landmark papers were published showing that if the mucosa in Barrett's esophagus is destroyed endoscopically—in these papers by Nd:YAG laser—and intra-esophageal acid is controlled by high-dose proton pump inhibiters, non-dysplastic squamous tissue tends to regrow in the treatment area.[19,20] Over the intervening 15 years, ablation and endoscopic resection techniques have evolved dramatically to the point where large areas of diseased mucosa and submucosa can be removed safely and even the longest segments of BE can be ablated to the submucosa. Briefly, these techniques include:

1. EMR: A variety of techniques have been described to create a pseudo-polyp of mucosa and submucosa, usually after injecting saline into the submucosa to create a buffer between the muscularis propria and the diseased mucosa. The upper layers are then lifted either with a grasping forceps (through a double-channel endoscope) or with suction via a clear plastic cap attached to the tip of the endoscope. A snare is then dropped around the pseudo-polyp and the tissue is resected with electrocautery. The Duette™ system (Cook Medical, Bloomington, IN, USA) creates pseudo-polyps with a clear cap, but provides six elastic bands which can be deployed at the base of the pseudo-polyps, after which a snare can be passed through the system to cut the pseudo-polyp off either above or just below the band. Multiple defects from these resected pseudo-polyps can be overlapped to create a broad mucosal resection area. Mucosa and much of the submucosa are often removed. This not only removes diseased tissue but allows a more accurate histologic assessment of the degree of dysplasia and depth of invasion. Series have shown that EMR after pinch biopsy frequently changes the level of dysplasia or tumor stage and usually upstages it.[21,22] Scarring and luminal narrowing following EMR has limited its application to very large areas and to one-step circumferential procedures, although new protocols for circumferential EMR have been utilized successfully.[23]
2. PDT: This deep mucosal ablation technique has been around for many years and has employed a variety of photosensitizers. Successful ablation of BE has largely relied on the deep burns created with porfimer sodium as a sensitizer (Photofrin™, Axcan Pharma, Chateau St. Hilaire, Quebec) rather than the more superficial burns generated with amino leuvulinic acid and others. The procedure begins with an infusion of the photosensitizer, followed 48 h later by illumination with intense mono-frequency light (620 μm for porfimer sodium) of the BE by a radial diffusing fiber passed through an endoscope. Dosimetry is dependent upon the amount of photosensitizer infused, intensity of light and duration of light exposure, as well as oxygen content in the treated tissue, since tissue destruction depends upon free radical generation from activated photosensitizer molecules. A photochemical burn develops in light-exposed tissue after 6–24 h and may be up to 4 mm deep, depending on dosimetry. Downsides to PDT include prolonged cutaneous photosensitivity of up to a month or more, post-procedure pain, and stricture formation.[24]
3. Radiofrequency ablation: RFA (Barrx Medical, Sunnyvale, CA, USA) is a relative newcomer and uses an array of bipolar electrodes distributed on a size-specific balloon that is inflated within the diseased section of the esophagus and activated. An energy generator delivers up to 12 J/cm^2 over a 3-cm area. A smaller, hinged "thumbnail" applicator can be used to ablate smaller areas. Tissue ablation is usually restricted to the mucosal layer and stricture formation appears to be less common than with PDT.
4. Cryotherapy: Cryotherapy provides tissue destruction via freeze–thaw cycles in the mucosa, either with the direct application of liquid nitrogen (CSA™, CSA Medical Inc., Baltimore, MD, USA) or as a result of rapidly expanding CO_2 gas (Polar Wand™, GI Supply, Wayne, PA, USA). Tissue ablation tends to be more superficial than PDT and may result in fewer strictures or post-procedure pain. The large amount of gas released in the stomach poses a risk of bloating or even perforation.

Efficacy of Endoscopic Therapy

Numerous studies and case series over the last decade have demonstrated the effectiveness of a variety of endoscopic therapies for BE with dysplasia.[25–32] A representative, but by no means complete synopsis, of recent studies is contained in Table 1. Many earlier reports described treatment with PDT, while subsequent reports include EMR with PDT or even EMR alone. The most recent series describe results with RFA and cryotherapy. ET studies have been criticized for a lack of consistency regarding protocols, outcome measures and randomization, as well as small numbers and short follow-up periods. However, several series now report patients followed out over 5 years, and a cumulative experience of over 600 ET patients exists in the literature. Unfortunately, given the great differences between ET and surgery, it appears very unlikely that a randomized trial of the two therapies will occur.

Table 1 Studies of Endoscopic Therapies for Barrett's Esophagus with Early neoplasia

Author (year)	Treatment	Patients	CR (%)	F/U (months)	Recurrence (%)
Buttar et al.[25]	EMR/PDT	17	94	13 (3–48)	6
Pacifico et al.[26]	EMR/PDT	24	83	12 (10–14)	0
Peters et al.[23]	EMR	39	89	11 (5–18)	0
Overholt et al. [51]	PDT	138	77	60+	13
Ell et al.[28]	EMR	100	99	37 (2–83)	11[a]
Schembre et al.[29]	EMR/PDT	61	77	20 (6–84)	7
Ganz et al.[30]	RFA	92	90	12 (8–15)	10[a]
Gondrie et al. [52]	EMR/RFA	12	100	14	0
Pouw et al.[31] (AB)	EMR/RFA	44	98	12 (5–17)	0
Dumont et al.[32] (AB)	Cryo	14	86	Not stated	N/A

CR complete response, *EMR* endoscopic mucosal resection, *PDT* photodynamic therapy, *RFA* radiofrequency ablation, *Cryo* cryotherapy

[a] Recurrences were treated endoscopically in all instances

In published series (not including early reports using amino leuvulinic acid PDT or thermal ablation with contact probes or argon plasma coagulation), ET has resulted in complete eradication of dysplastic tissue in the setting of BE at an average rate of 87%, ranging from 77% to 100%. Further, recurrence of HGD or cancer occurred rarely, from a high of 13% (in a PDT only series designed to look at the efficacy of PDT versus acid suppression alone) to 0% in several other studies, for an average recurrence rate of 8% over 2 years. In most cases, recurrences were treated successfully by ET.

ET was compared with esophagectomy in two medium-sized retrospective series from US medical centers.[33,29] In the Mayo study, 129 patients with BE and HGD who had been treated with PDT with or without EMR were compared to 70 patients with similar histology who had undergone esophagectomy over a 10-year period. Groups were comparable, although the ET group was older and less healthy than the surgical group. Both groups were followed for a median of 60 months. Outcomes in terms of cancer-free survival were similar at 5 years, and overall survival was virtually identical. No patient in either group died of esophageal cancer. Similar results were seen at our own institution where 61 patients underwent ET and 32 had esophagectomy for BE with HGD or IMC over a 7-year period. In this series, ET patients were 6 years older on average than surgical patients and had slightly higher ASA scores. Overall survival was similar, with no patient in either group succumbing to esophageal cancer.

Safety of Endoscopic Therapy

Reviewing the same studies of ET reveals that the procedures are safe, with only one mortality reported among 541 patients treated (<0.2%). Major complications, such as perforation, bleeding, or prolonged hospitalization, occurred in about 4% of patients (range 0–12%). In contrast, although mortality among surgical series was far less than the 4–17% commonly cited for esophagectomy series,[34] surgical deaths still occurred, at an average rate of 1.5% (range 0–3%), and the incidence of serious morbidity, including anastomotic leak, pulmonary embolus, and wound infection, was 36% (range 11–57%). Further, surgery appears to cost up to 50% more than ET, at least for initial treatment.[29]

Despite some common post-surgical changes in eating and digestion, quality of life after esophagectomy has been reported in a number of studies using the SF.36 survey to equal or even surpass that of age- and sex-matched controls.[35,36] In a recent study from our own institution, this also appears to be true. Quality of life measures from SF.36 surveys as well as from the gastrointestinal quality of life index (GIQOLI) were similar among a group of 27 ET patients and 13 surgical patients who filled out surveys a year or more after treatment. However, after correcting for age differences, SF.36 scores trended higher in the ET group but did not reach significance, while GIQOLI scores were on average over 16% higher ($p<0.05$) among younger ET patients.[37]

Dispelling Misconceptions

As with any new therapy, complications and failures of treatment have occurred with ET as the tools and techniques have evolved. Further, because the esophagus remains in place, some level of risk remains that dysplastic tissue will persist or recur over the patient's lifetime. This must be explained to and accepted by the patient. Patients must also agree to close follow-up and probably surveillance endoscopy at regular intervals, even after complete ablation of BE has been accomplished. It is therefore inevitable that some insecurity will accompany ET. Unfortunately, misperceptions have circulated about what exactly that risk is. Further, even though it has not been reported since the early days of PDT,[38] fear persists that undetected cancer will develop following ET, perhaps growing beneath a layer

Table 2 Complications Associated with Endotherapy for Barrett's Early Neoplasia

Author (year)	Treatment	30-Day mortality (%)	Major complications (%)	Minor complications (%)
Buttar et al.[25]	EMR/PDT	0	6	48
Pacifico et al.[26]	EMR/PDT	0	0	16
Peters et al.[23]	EMR	0	2	26
Overholt et al. [51]	PDT	0	12	94
Ell et al.[28]	EMR	0	0	11
Schembre et al.[29]	EMR/PDT	2	7	33
Ganz et al.[30]	RFA	0	0	1
Gondrie et al. [52]	EMR/RFA	0	0	8
Pouw et al.[31] (AB)	EMR/RFA	0	10	10
Greenwald et al. [53] (AB)	Cryo	0	2	5

of neo-squamous epithelium and that ET will actually hinder the detection of the cancer. It is time to view these concerns through the lens of published experience (Tables 2 and 3).

While no one disputes the reported rates in the surgical literature of "undiscovered" cancer that were ultimately identified at final pathology after esophagectomy for HGD, it is important to review those series from the perspective of an endotherapist. This is exactly what Konda et al.[39] did recently. They reviewed 23 articles describing esophagectomy for BE with HGD and concluded that the actual incidence of invasive cancer in surgical series was 12.7%. Much of this discrepancy centers around the definition of "invasive" cancer. Many series included IMC along with submucosal and deeper cancers, even though IMC rarely if ever metastasizes[40] and can be treated by ET as effectively as HGD. Further, in many of these series, once a superficial pinch biopsy had been obtained showing HGD (often noted by pathologists as "at least HGD"), no additional effort was made to reveal deeper invasion preoperatively because the anticipated treatment for HGD and invasive cancer was the same—esophagectomy. The majority of patients in these series did not undergo preoperative endoscopic ultrasound, much less high-definition endoscopy, chromoendoscopy, or EMR. In multiple series, when EMR is performed following pinch biopsy diagnosis of HGD, the disease is upstaged to IMC or invasive cancer in up to 30% of cases.[41] Finally, in the Kunda review, the incidence of invasive cancer among patients with no visible nodules or ulcerations (lesions that would likely be targeted for EMR during ET) was only 3%.

Reports of buried glands began showing up soon after ET was introduced. This usually occurred following shallow ablative therapies such as aminoleuvulinic acid PDT and thermal, "pinpoint" ablative therapies such as heater probe and APC.[42,43] In rare cases, cancer did appear to develop beneath neo-squamous epithelium, but even these were readily detectable at endoscopy.[44] Buried glands are seen much less commonly after deeper ablative therapies such as EMR and PDT, or even after the more superficial ablation by RFA, perhaps due to the more uniform burn created by a distending balloon at the time of ablation. In a recent review of over 4,300 biopsy specimens obtained after RFA for ablation of BE, no buried glands were detected.[45] In other series, when buried glands were detected, they were often in close proximity to islands of persistent BE, indicating incomplete ablation, and the buried glands were subsequently eradicated.[46]

The natural history of buried glands is largely unknown. Buried glands are frequently identified in patients on proton-pump inhibitor (PPI) therapy who have never undergone ablation, and there is even data to suggest that

Table 3 Complications Associated with Esophagectomy for Barrett's Early Neoplasia[54–59]

Author	Patients	Operative mortality (%)	Morbidity (%)
Heitmiller et al.[54]	30	3.3	20
Zaninotto et al.[55]	15	0	80
Headrick et al.[56]	54	1.8	57
Luketich et al.[57]	35	1.4	32
Tseng et al.[58]	60	1.7	29
Moraca and Low[36]	36	0	11
Williams et al.[59]	38	0	37

buried glands atrophy over time and disappear.[47] Finally, among the major published series of ET, there are no reports of unseen cancer developing under neo-squamous mucosa.

There is a perception that once a patient undergoes a successful esophagectomy for BE with dysplasia, he or she will be free from the possibility of developing recurrent BE or cancer: No esophagus equals no risk for esophageal cancer. Of course, some esophagus remains even after a high anastomosis and this tissue may be subjected to the same environmental and genetic factors that led to the development of BE in the native esophagus. Franchimont et al.[48] reported that 47 of 66 (71%) patients who had undergone esophagectomy developed significant esophagitis in the esophageal remnant. Nine of these patients (13%) developed BE at a median of 489 days after surgery, even though none had residual BE seen on endoscopy immediately post-op. In fact, two patients did not have BE prior to esophagectomy. Additionally, PPI therapy did not appear to influence development of BE, suggesting that other environmental factors such as fermenting stomach contents or refluxed bile may play a role in the development of BE.

Wolfsen et al.[49] reviewed 36 patients who underwent endoscopy after esophagectomy for BE with dysplasia or localized cancer. All patients had squamous mucosa at the proximal extent of the resected esophagus; however, at intervals ranging from 7 to 88 months, eight individuals (25%) developed recurrent BE. Seven of these patients were found to have significant esophagitis, suggesting ongoing GERD after esophagectomy. Four patients had some degree of dysplasia and two had already developed early cancers.

While these numbers seem high, the real incidence of recurrent BE after esophagectomy remains poorly understood because unless there are symptoms, most patients who undergo esophagectomy are not subjected to surveillance endoscopy. It is therefore unclear whether recurrent BE among patients who have undergone successful ET is any higher or lower than among esophagectomy patients.

Who Should Get What?

At our institution, all patients referred with BE and HGD or IMC get both a surgical and a GI consultation. All patients undergo endoscopy with endoscopic ultrasound and, if no obvious invasive disease is detected, EMR of any nodular or ulcerated areas or particularly dark areas seen on narrow band imaging. An attempt is made to present all patients at Thoracic Tumor Board to discuss findings and treatment options. The results of tumor board discussions are then shared with the patient and his or her family, as well as with the referring physician. We often recommend ET for patients with short segment BE, a single nodule of IMC, those at high surgical risk, and to those who express a preference for ET. We reserve esophagectomy as a first-line treatment for those with long segment BE, generally over 10 cm, those with multifocal high-grade or nodular disease, those at high risk for non-compliance or an inability to submit to frequent endoscopic follow-up at our institution, those with a heightened level of anxiety, and those with a preference for up-front surgical therapy.

Conclusion

The point of this discussion is not to try to show that ET is always preferable to esophagectomy for patients with BE and dysplasia. Clearly, both esophagectomy and endotherapy are effective. However, that endotherapy may be better for some patients than esophagectomy. And rather than the traditional view that ET should be reserved for older, sicker patients, ET may be preferable for young, healthy patients as well.

Other Considerations

It is important for surgeons to understand and discuss ET with patients before esophagectomy. Patients want to know about alternatives even if they opt for surgery, and it is better to discuss those options before they are no longer options. Endotherapy does not preclude surgery for progressive disease, and there is no evidence that esophagectomy is more difficult among those who have had endotherapy. In fact, operative times and complications have been shown to be identical with and without prior extensive EMR.[50] Endotherapies are improving all the time, which implies that patients who recur or fail initial ET may be candidates for superior non-surgical therapies in the future. Finally, medical centers that offer both ET and esophagectomy in a collaborative manner will probably see patient satisfaction and referrals rise.

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SSAT Controversies Intramucosal Esophageal Cancer and High-Grade Dysplasia: Which Treatment?

Surgical Therapy: Improved Outcomes and Piece of Mind

Jeffrey H. Peters

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Keywords Barett's · Esophagus · High-grade dysplasia · GERD

Introduction

At the outset, it should be noted that endoscopic therapy for Barrett's associated high-grade dysplasia (HGD) is a significant advance in our ability to treat early esophageal neoplasia, is here to stay, and should be embraced by the surgical community. Esophagectomy is, and should remain, a very viable treatment option. The rationale for esophagectomy includes the following:

1. Most, if not all, patients with high-grade dysplasia will develop invasive carcinoma
2. Endoscopic treatments require careful patient selection and intense follow-up
3. There is a subset of patients with risk factors associated with failure of endoscopic therapy
4. The morbidity, mortality, and quality of life following esophageal resection are steadily improving.

These are important caveats which make the decision regarding the ideal therapy for esophageal high-grade dysplasia increasingly difficult.

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J. H. Peters (✉)
Department of Surgery,
University of Rochester School of Medicine & Dentistry,
601 Elmwood Ave, Box Surg,
Rochester, NY 14642, USA
e-mail: jeffrey_peters@urmc.rochester.edu

The Natural History of High-Grade Dysplasia

While we have experienced an era where treating high-grade dysplasia with watchful waiting was advocated, the advent of safe and efficacious endoscopic therapies is moving the mindset increasingly toward early treatment. Several prospective studies, three of the best, from the University of Washington[1,2] and the University of Kansas[3] have documented that in most patients with high-grade dysplasia, cancer will be identified if the patient is followed long term. Recognizing a 15–20% histologic interpretation discordance, these data show that up to 80% of patients will be identified with invasive adenocarcinoma when followed out to 8 years or more. Given an appropriate candidate for therapy, most centers would not advocate watching high-grade dysplasia in the present era.

Intensity of Follow-Up Required with Endoscopic Treatment of Barrett's HGD

Achieving published outcomes with endoscopic therapy requires a commitment to resources and follow-up that may be difficult or impossible for many centers. This can be illustrated by a careful review of the intensity of follow-up post-treatment in the widely quoted report of the Wiesbaden group.[4] Ell at al. showed that endoscopic mucosal resection (EMR) was associated with low morbidity and no mortality and eliminated the neoplastic focus over a 3-year time span. This study, from one of the leading centers in the world, highly experienced in endoscopic treatment of early esophageal cancer, helped solidify the role of EMR in the spectrum of treatment options for early esophageal neoplasia. The

context in which endoscopic therapy is used and the outcomes achieved is critical, however, and it is important that the data not be extrapolated in the treatment of patients beyond those described in the various studies. In the Wiesbaden experience, 100 patients were selected out of 667 possible candidates over 7 years. All patients underwent very intensive staging, including endoscopic ultrasound and radiographic procedures, high resolution videoendoscopy with methylene blue chromoendoscopy, detailed morphologic assessment of the lesions according to the Japanese classification for early gastric cancer, an intense biopsy protocol (four quadrants, every 1 cm), routine histologic assessment by two different pathologists, and high frequency (20 mHz) ultrasound. Equally intense follow-up was required, with follow-up endoscopy at 1, 2, 3, 6, 9, 12, 16, 24, 30, and 36 months with repeated high resolution and chromoendoscopy, a routine rigorous biopsy protocol, endoscopic and abdominal ultrasound, and computed tomography, all at each time point. The rigor of the patient selection and follow-up should be evident, as well as the difficulty most of us would have in reproducing it.

Choosing this intensive endoscopic course versus a 10-day hospitalization following esophagectomy which, in the setting of HGD, has a mortality approaching zero, can be a difficult decision for both the surgeon and patient. The intensity of follow-up and anxiety required following a decision for endotherapy is arguably the key factor driving a decision toward resection. Careful follow-up is required due to a significant incidence of metachronous cancer. Although most such lesions can also be effectively treated endoscopically, studies to date indicate a 15–25% prevalence of a metachronous cancer over 5 years which must be detected at a curable stage and successfully treated, a paradigm that is practically difficult to do in many practices. Further, the compliance with such an intensive follow-up regimen is also a concern. Surveys would suggest that only 50–55% of patients come back for their 2- or 3-year surveillance biopsies for quiescent Barrett's esophagus. We may be fooling ourselves to expect that 100% of patients would comply with the regimen described above.

Individual Variability in the "Severity" of Barrett's HGD and Outcomes Following Endoscopic Ablation

Multiple studies suggest that all high-grade dysplasia is not the same and that both the treatment success and the risk of invasive adenocarcinoma vary considerably. Consequently, there is likely a subset of patients in which resection should be the treatment of choice. The Barrett's segment length, the multi-focality of dysplasia or neoplasia, the presence of absence of a visible lesion, and in some reports, genetic and cell cycle abnormalities have been shown to affect the efficacy of endoscopic treatments. Each of these can and should guide treatment decisions. In one of the few comparisons of the outcomes in patients following endoscopic mucosal resection and photodynamic therapy (EMR/PDT) and surgical resection, investigators from the Mayo Clinic reported that patients in which endoscopic therapy incompletely eradicated the columnar lined segment and/or dysplasia had longer segments of Barrett's.[5] Other studies have also shown that longer segments of Barrett's are more difficult to completely treat with endotherapy.[6]

Multifocal neoplasia correlates with the risk of cancer in a resection specimen and the risk of failure of endotherapy.[7,8] Both US and Japanese data show that as the number of neoplastic lesions increases, the chances of a cancer and/or failure of EMR and endotherapy increases. Portale et al. have shown that the presence of a visible lesion, the number of levels at which a biopsy reveals high-grade dysplasia, and the number of biopsies at any particular level with HGD have relevance to the presence or absence of invasive cancer in the surgical specimen.[9] Each of these factors should be taken into account when undertaking treatment decisions in patients with high-grade dysplasia or early cancer. Further, a visible nodule or ulcer has a high change of harboring invasive submucosal cancer. Under these circumstances, EMR to determine the depth of penetration may be the ideal means to stage the lesion prior to a decision for endoscopic therapy versus or resection.

Morbidity, Mortality, and Functional Outcome of Esophagectomy is Continuously Improving

The risk–benefit ratio for treatment decisions rests very heavily on the potential complications and functional outcome of each treatment option. Mortality following esophagectomy in the setting of high-grade dysplasia is very different (much lower) than in the setting of established cancer. Tseng et al. recently reported zero mortality in patients undergoing esophagectomy for HGD.[10] In fact, Williams et al. outlined 22 studies over nearly 20 years in which the cumulative reported mortality was 0.94%.[11] There have been only five deaths reported in patients resected for high-grade dysplasia. This is in contrast to the commonly quoted esophagectomy mortality rates of 8–25% in reports touting endoscopic treatment.

For all practical purposes, esophagectomy cures Barrett's esophagus. Although columnar lining and intestinal metaplasia have been described in the cervical esophageal remnant following esophagectomy, it uncommonly presents a clinical problem. There is no recommendation for surveillance post esophagectomy and reports of a second cancer developing in the cervical esophageal remnant harboring Barrett's are rare.[12–14]

Alterations in functional outcome after esophagectomy may also be overemphasized. Williams et al. in a careful functional analysis of patients following transhiatal esophagectomy for HGD found that the vast majority are doing quite well. Seventy-five percent of the patients had no dietary restrictions, and 82% of them had normal numbers of bowel movements.[11] Outcomes may be even better following vagal sparing esophagectomy.[15]

So where do we stand? Endoscopic therapy can and should be embraced with enthusiasm. Current techniques of EMR and radiofrequency ablation[16] represent a significant step forward. A significant role for esophagectomy remains however. Select patients, particularly the young in which the intense follow-up and anxiety over the course of 10–20 years is not practical, should be considered for resection. Esophagectomy should also be entertained in patients at high risk of endoscopic failure and/or concurrent invasive adenocarcinoma including those with long segment Barrett's with multifocal dysplasia, a visible lesion, those with identified genetic and cell cycle abnormalities and those that do not want to undergo more intensive follow-up.

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SSAT/SAGES JOINT SYMPOSIUM

The Pancreatic Anastomosis: The Danger of a Leak, Which Anastomotic Technique is Better?

David B. Adams

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Keywords Pancreaticojejunostomy · Pancreatic anastomosis

Every pancreatic surgeon has a favorite way to construct a pancreatic anastomosis after pancreatoduodenectomy. All represent variations on three fundamental techniques: the end-to-side pancreatic duct to jejunal mucosa anastomosis, the end-to-end invaginating pancreaticojejunostomy, and the end-to-side pancreaticogastrostomy.[1] In the pancreatic anastomotic leak study group report of 1,507 patients, pancreaticojejunostomy was utilized in the majority of patients (87.6%) and pancreaticogastrostomy was utilized in 12.4%.[2] An internal stent was placed across the anastomosis in about half of the patients. A duct to mucosa anastomosis was constructed in two thirds of patients, and a third of the patients had a dunking type of anastomosis. In a PubMed search for "pancreatic anastomosis," over 1,700 publications are listed over the past five decades. The titles are notable for adjectives such as new, modified, simpler, reliable, secure, safe, novel, and best of all, easier. The Nobel physicist Ernest Rutherford's remark that "all science is either physics or stamp collecting," is substantiated by the many published individual reports of successful pancreatic anastomotic techniques.

The Achilles heel of the Whipple operation is the pancreatic anastomosis. Anastomotic leaks are the source of major morbidity and mortality due to the intraperitoneal release of enterokinase and activation of pancreatic enzymes with subsequent septic and hemorrhagic complications. The modern morbidity of the Whipple procedure ranges from 6% to 57%, with fistula rates of 0% to 20% and mortality rates of 0% to 13%. The postoperative pancreatic fistula rate is the standard to measure the success of the pancreatic anastomosis. The International Study Group on Pancreatic Fistula defines a fistula as a volume of drainage on or after postoperative day 3 with a drain amylase greater than three times normal. Most fistulas are clinically insignificant but those that result in sepsis, percutaneous catheter drainage, reoperation, and death are graded as clinically significant. The at-risk pancreas is one that is soft, fatty, noncalcific, and nonfibrotic with a small duct. Leak rates are increased in patients who have a hemoglobin A1-c greater than 6% and those with an abnormal magnetic resonance imaging time signal intensity curve. Neoplasms of the duodenum, terminal bile duct, and ampulla of Vater are disorders where leak rates are increased.[3]

Randomized controlled trials providing evidence for the best way to do a pancreatic anastomosis are few.[4] A systematic review and meta-analysis comparing pancreaticojejunostomy with pancreaticogastrostomy reviewed three randomized controlled trials that showed no difference in leak rates between the pancreaticojejunostomy and pancreaticogastrostomy.[5] This was distinctly different from 13 nonrandomized observational clinical studies which showed a significant result in favor of pancreaticogastrostomy, with reduction of fistula and mortality rates. This analysis high-

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D. B. Adams (✉)
Division of Gastrointestinal & Laparoscopic Surgery,
Medical University of South Carolina,
Ashley River Tower, 25 Courtenay Drive,
Charleston, SC 29403, USA
e-mail: adamsdav@musc.edu

lights the problems presented by uncontrolled studies due to sample size, selection bias, confirmation bias, missing outcomes, and confounders such as surgeon preference, experience, and ability. Observational clinical studies frequently differ from well-done randomized controlled trials due to the role that surgeon experience and preference play in operative outcomes.

If the leak rate is the best means of assessing short-term success, anastomotic patency may be the best measure of long-term success of the pancreatic anastomosis. Similar to the data on short-term outcomes, substantial evidence on long-term outcomes is hard to find. In an animal model, the pancreatic duct was completely closed in half of the animals with invaginating end-to-end anastomosis 8 weeks after surgery and was patent in all with a duct to mucosa end-to-side anastomosis. Another animal study showed that pancreatic juice flow rates were better in the end-to-side duct to mucosa anastomosis than the end-to-end invaginating anastomosis 8 weeks after surgery. In the duct to mucosa anastomosis, the pancreatogram was normal in all animals; and in all the invaginating anastomosis, the duct was dilated. In an attempt to examine this question clinically, the Mayo Clinic studied 122 patients who underwent pancreatoduodenectomy for benign disease from 1993 to 2002 and were able to identify four patients with strictures of the pancreaticojejunostomy.

What are some of the published recommendations? Ranson in 1995 recommended an end-to-side anastomosis for the low-risk pancreas and an end-to-end invagination for the high-risk pancreases. John Howard in 1997 concluded that the end-to-side mucosa-to-mucosa stented pancreaticojejunal anastomosis was the best. Buchler in 2002 recommended a two-layer single-stitch technique with absorbable monofilament sutures and a duct to mucosa anastomosis done end-to-side without stents.

What becomes clear in modern literature is that experience appears to trump evidence in the selection of the anastomotic technique. The Japan Pancreatic Surgery Questionnaire Survey data indicated that the selection of a pancreatic reconstruction technique was related to higher incidences of morbidity and was significantly higher in low-volume hospitals that used multiple pancreatic resection techniques. High-volume hospitals had better outcomes attributed to expert pancreatic reconstruction skills that could be mastered only through frequent repetition. In an analysis of surgeon age and operative mortality in the United States, pancreatectomy was a procedure where the surgeon over 60 at high-volume centers had the lowest pancreatoduodenectomy complication rate. What Justice Holmes said about the legal profession applies to the surgical profession and the pancreatic anastomosis. “The merit of the common law,” Holmes wrote, “is that it decides the case first and then determines the principles afterwards. The life of the law has not been logic; it has been experience.” The life of the pancreatic anastomosis likewise appears to be based on experience not evidence. The pancreatic surgeon who believes his thinking is guided by scientific principles, even those who think their reasoning is deductive and their operative decision making is evidence-based, thinks the way everyone else does. First they decide, then they deduce.

What is the best pancreatic anastomosis technique? Duct to mucosa end-to-side pancreaticojejunostomy? Invaginating pancreaticogastrostomy? End-to-side pancreaticogastrostomy? Open pancreaticogastrostomy? One layer? Two layers? Three layers? Stented? Drained? Binding? Inkwell? Polypropylene mesh-reinforced? Round ligament-reinforced? Surgical microscope? Absorbable sutures? Monofilament permanent sutures? The answers are not clear, but the recommendations grounded on well-known surgical principles are sound. The choice of pancreatic anastomotic technique should be based on individual experience. Adherence to basic principles of the pancreatic anastomosis is more important than any one particular method. These principles include: good exposure and visualization; fine, nonstrangulating suture placement to produce a water-tight patent anastomosis; blood supply preservation; tension-free fixation of the gastrointestinal tract to the pancreas; and coverage of the cut pancreas.

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SSAT/SAGES JOINT SYMPOSIUM

Stents, Glue, Etc.: Is Anything Proven to Help Prevent Pancreatic Leaks/Fistulae?

Richard D. Schulick · Kiyoshi Yoshimura

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Keywords Stents · Glue · Pancreatic leaks/fistulae

Of the three anastomoses performed with pancreaticoduodenectomy, the "Achilles heal" is the pancreatic anastomosis. When Allen O. Whipple, M.D. reported his series of three patients who underwent pancreaticoduodenectomy at the American Surgical Association in 1935, he described a two-stage operation in which the first stage included a cholecystogastrostomy and a gastrojejunostomy to resolve jaundice and gastric outlet obstruction.[1] In the second operation, the patient underwent resection of the pancreatic head and duodenum. The distal bile duct was ligated and the first portion of the duodenum oversewn (biliary and gastrointestinal continuity was established with the first operation). The pancreatic remnant was oversewn and left to fistulize through a surgically placed drain. Towards the end of his career, he reported his one-stage procedure in which the pancreatic remnant was anastomosed to the jejunum.[2] The high morbidity and mortality rates associated with this operation are principally due to pancreatic leaks. Since the 1980s, multiple institutions reported considerably lower mortality rates, but pancreatic leak remained a considerable source of morbidity.[3–5]

The scope of this section is to summarize the effect of three specific interventions: (1) use of octreotide; (2) use of pancreatic duct stents (internal and external); and (3) use of fibrin glue on pancreatic fistula rates and intra-abdominal complications. The clinical studies examined include only randomized controlled trials (level one evidence) and are limited to those focusing on pancreaticoduodenectomy.

Octreotide

Octreotide is a synthetic octapeptide that mimics natural somatostatin. Use of octreotide decreases splanchnic blood flow and pancreatic fluid secretion, and theoretically, it potentially has the ability to decrease pancreatic fistula rates. Six randomized controlled trials have been completed studying the use of octreotide in patients undergoing pancreatectomy (Table 1).[6–11] Three of these trials also included patients who underwent distal pancreatectomy, but the majority in these patients underwent pancreaticoduodenectomy. The other three trials included only patients undergoing pancreaticoduodenectomy. These trials varied in terms of the dose of octreotide used (ranging from 100 to 250 μg) and the duration of treatment. Only one trial[8] demonstrated a statistically significantly lower pancreatic fistula rate (20% vs. 9%) associated with the use of octreotide. This same trial did

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R. D. Schulick (✉)
Johns Hopkins University,
600 N Wolfe St., Blalock 685,
Baltimore, MD 21287, USA
e-mail: rschulick@jhmi.edu

K. Yoshimura
Johns Hopkins University,
1650 Orleans St., 442,
Baltimore, MD 21231, USA

Table 1 Trials with use of octreotide in patients undergoing pancreatectomy

Author (year)	PD rate (%)	Treatment group	Number of patients	Dose (μg SC)	Mortality rate (%)	Fistula rate (%)
Buchler (1992)	81	Octreotide	68	100	3	24
		Control	71		10	41
Pederzoli (1994)	60	Octreotide	76	100	NA	12
		Control	86		NA	23
Montorsi (1996)	66	Octreotide	111	100	8	9*
		Control	107		6	20
Lowy (1997)	100	Octreotide	57	150	1	12
		Control	53		0	6
Yeo (2000)	100	Octreotide	104	250	0	9
		Control	107		1	11
Barnett (2004)	100	Octreotide	205	150–250	2	13
		Control	61		0	8

*$p<0.05$

not demonstrate a difference in the mortality rate between the two groups.

Pancreatic Duct Stent

A pancreatic duct stent is a plastic tube that can be operatively placed through a pancreaticojejunostomy (or gastrostomy) and into the pancreatic duct. These stents can be totally internal (typically shorter), or they can be externally drained (typically longer). Theoretically, they have the potential to: (1) facilitate the precise placement of sutures intraoperatively, to prevent accidental suture closure of the pancreatic duct; (2) "protect" the pancreaticojejunal anastomosis against activated pancreatic enzymes; and (3) in the case of externally vented stents, divert pancreatic juice from the anastomosis.

A randomized controlled trial of internal pancreatic duct stenting with pancreaticoduodenectomy from the Johns Hopkins Medical Institutions has been reported.[12] In this trial, 258 patients were randomized to receive a 6-cm length of a plastic stent with diameters of 3.5, 5, or 8 french (depending on duct diameter) during creation of the pancreatic anstomosis or no stent. No statistically significant differences in mortality, complication, pancreatic fistula, or intra-abdominal abscess rates were found.

Another randomized controlled trial of external pancreatic duct stenting with pancreaticoduodenectomy from the Queen Mary Hospital has been reported.[13] In this trial, 120 patients were randomized to receive an external pancreatic duct stent or no stent. This was a positive trial in that they reported lower pancreatic fistula rates, days in the intensive-care unit, and days with parenteral nutrition in the group that was stented. It must be noted, however, the norms of practice were widely disparate from many Western centers in terms of use of intensive care, hospital length of stay, number of days until regular diet, and use of parenteral nutrition. Overall morbidity and mortality rates were no different between the two groups. It also must be noted that a pancreatic fistula (albeit controlled and through an operatively placed stent) was technically created in every patient that received a stent.

Fibrin Glue

Fibrin glue is a tissue adhesive composed of human fibrinogen and thrombin. Theoretically, it has the potential to decrease pancreatic leakage by mechanically sealing the anastomosis.

A randomized controlled trial of topical fibrin glue with pancreaticoduodenectomy from the Johns Hopkins Medical Institutions has been reported.[14] In this trial, 125 patients were randomized to receive 8 ml of fibrin glue applied cirucumferentially around the pancreatic anastomosis or no glue. There were no statistically different rates of mortality, morbidity, pancreatic fistula, or intra-abdominal abscess between the two groups.

Another randomized controlled trial of intraductal fibrin blue with pancreaticoduodenectomy was reported by a consortion of 15 hospitals in France.[15] In this trial, 182 patients who underwent pancreaticoduodenectomy (77%) or distal pancreatectomy (23%) were randomized to received 3 to 5 ml of intraductal fibrin glue or none. There were no statistically different rates of mortality, pancreatic fistula, or intra-abdominal complication between the two groups.

Summary

Although mortality from pancreaticoduodenectomy has improved dramatically over the past three decades, morbidity from this operation remains high. A significant contributor to postoperative morbidity is pancreatic leak and fistula. Level one evidence does not support the use of octreotide to prevent pancreatic fistula (in five of six trials). Nor does it support the use of internal pancreatic duct stents. A randomized controlled trial from Hong Kong did demonstrate improvement in pancreatic fistula rate, decreased use of intensive care, and decreased use of parenteral nutrition when an external pancreatic duct stent was used. However, the impact is difficult to interpret in the context of common practices in many Western centers. Level one evidence does not support the use of topical or intraductal fibrin glue to decrease pancreatic fistula or intra-abdominal complications.

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Defining, Controlling, and Treating a Pancreatic Fistula

David Mahvi

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Keywords Pancreatic fistula diagnosis · Pancreatic fistula treatment

The Achilles heel of pancreatic surgery is the pancreas. After resection of the pancreatic head, the residual pancreas must be drained into the gastrointestinal tract. This connection is among the most tenuous in surgery. Hundreds if not thousands of publications have been devoted to pancreatic surgical technique based on the hope that some technical innovation will prevent this complication. To summarize this vast literature: as long as an experienced pancreatic surgeon performs the procedure, no method of anastomosis is less likely to result in a pancreatic leak than another. This review will focus on complications of pancreatoduodenectomy. The treatment of a postoperative leak or fistula after distal pancreatectomy is less of a clinical issue but can be diagnosed and treated using similar methods. The diagnosis of a leak will first be defined and then the treatment of both an acute leak and a chronic controlled fistula will be discussed. The difference between a leak and a fistula is control and chronicity. When a leak is controlled and persists, it becomes a fistula. Though leak and fistula are different aspects of the same disease process, the treatment of an acute leak is very different than the treatment of a chronic fistula.

The pancreatic anastomosis will leak 15% to 25% of the time.[1] The consequences of a leak have improved over time, but the leak rate has not changed. A leak, thus, cannot be avoided and is best anticipated both by the surgeon and the patient. The failure to recognize this common complication of pancreatic resection leads to delay in treatment and the potential of a fatal outcome. Any change in the clinical course of a patient after pancreatic resection should raise the thought of a pancreatic leak.

The Diagnosis of a Leak The literature is difficult to interpret without some standardized method of reporting. Two expert groups have approached the task of defining a leak. They each developed both a biochemical and a clinical definition. The general theme of both consensus statements is similar. When amylase-rich fluid is detected in a drain, it may represent a leak; but in the early postoperative period, the amylase content of a drain can vary. Sarr and coauthors recommended that in addition to amylase rich fluid (they defined amylase rich as five times the normal serum level), the drainage should occur five or more days post-resection, and the drain volume should be greater than 30 cm^3/day.[1] Three years later, a second group (the International Study Group for Pancreatic Fistula (ISGPF)) suggested a slightly different definition of leak.[2] The ISGPF included many members of the first group including Dr. Sarr. The definition of a leak was liberalized by the second group. Their rationale was that the stringent definitions proposed by the original group missed some clinically relevant leaks. The concentration of amylase in the fluid was changed from five- to threefold greater than the serum level. The requirement for 30 cm^3/day was omitted, and the timing was altered to 3 days post-resection rather than 5 days. These efforts resulted in a clinically meaningful method to compare complication rates after pancreatic resection.

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D. Mahvi (✉)
Feinberg School of Medicine, Northwestern University,
Chicago, IL, USA
e-mail: dmahvi@nmh.org

The impact of a biochemical leak on an individual patient varies and has no relationship to the biochemical parameters which define a leak. Clinical classification systems have been validated that stratify patients into groups based on the systemic impact of the leak and the need for further therapy.[3,4] A grade 1 leak had no clinical sequel. A grade 2 leak necessitated percutaneous drain placement for intra-abdominal abscess, resulted in delayed gastric emptying, or required hospital readmission. A grade 3 leak required reoperation or resulted in death. The Sarr classification system and the ISGPF classification system were equally good at detecting grade 3 leaks. The ISGPF criteria demonstrated a higher total leak rate than the Sarr criteria (27% vs. 14%), but the majority of the leaks noted with the less stringent ISGPF system were grade 1. As a means to contrast disparate reports, the ISGPF definitions will detect more leaks but miss very few clinically relevant leaks and, thus, has become the standard.

The Treatment of a Leak The treatment of a leak is dependent on the clinical grade and thus the systemic impact of the leak. A grade 1 leak requires no treatment. The patient with a grade 1 leak should be offered a normal diet and discharged with the drain in place. Octreotide has no role in the patient with a grade 1 leak. A grade 3 leak is rare (9% of leaks) and requires urgent control of sepsis in a desperately ill patient. The treatment of a grade 2 leak is the art rather than the science of pancreatic surgery. This is a rare event with a variable presentation and no real data comparing treatments. The key elements of therapy are aggressive drainage of intra-abdominal fluid collections and adequate nutritional support.

The Treatment of a Fistula A subset of patients with a leak will ultimately develop a chronic fistula. There is broad consensus that early operative intervention results in poor outcome in patients with fistula. Most of these fistulas will close spontaneously with observation alone, but at some point, there is little hope that a fistula will close. Precisely when a chronic fistula will not resolve is unknown. We have not noted healing of a fistula that persists for more than 2 months after the resolution of sepsis despite gravity (rather than suction) drainage. A fistulogram with water soluble contrast will both secure the diagnosis and confirm that an enteric (non-pancreatic) fistula is not present.

A leak persists because the resistance to flow in the fistula is less than the resistance to flow in the pancreatic–enteric anastomosis. Treatment has focused on methods to decrease flow (such as octreotide), increase resistance (drain removal or fibrin glue), or convert the fistula tract to an enteric anastomosis. Several groups have evaluated octreotide to treat fistula after pancreatoduodenectomy. The key endpoint in these studies was resolution of the fistula. The general consensus was that a decrease in fistula output with octreotide had no impact on fistula resolution. We do not use octreotide in the treatment of pancreatic leaks or fistulas.

Methods to increase resistance in the fistula tract, in contrast, have been successful (though in small series). Over time, the resistance to flow will increase in the fistula. The removal (or advancement out) of a long-standing drain increases the resistance in the fistula tract both by removal of the stenting effect of the drain and by the fibrosis of the drain tract. We have removed long standing drains in four patients without subsequent cutaneous fistula formation. Fibrin glue injected into the fistula tract after drain removal has also resulted in fistula resolution, especially in the patient group with low output fistulas.[5]

Late operative intervention has also been successful in a small selected series.[6] In this report, a Roux limb of jejunum was anastomosed to the fibrotic fistula tract. This resulted in resolution of the fistula in all the treated patients.

Summary Pancreatic leak after pancreatoduodenectomy occurs in 14–25 % of cases. The current grading systems for both biochemical and clinical leak effectively identify significant leaks and allow comparison between clinical studies. When a chronic fistula develops, observation is the initial treatment in all patients and fails in only a small subset. Octreotide does not aid in the resolution of a fistula. The options for treatment of a persistent chronic fistula include removal of the drain and injection of the fistula tract with fibrin glue or fistula tract–enteric anastomosis. All of these options have resulted in fistula closure in the majority of patients.

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ORIGINAL ARTICLE

Preoperative Lower Esophageal Sphincter Manometry Data *Neither* Impact Manifestations of GERD *nor* Outcome After Laparoscopic Nissen Fundoplication

Otto Riedl · Michael Gadenstätter · Wolfgang Lechner · Gerhard Schwab · Martina Marker · Ruxandra Ciovica

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Abstract
Background Experience with laparoscopic antireflux surgery (LARS) in patients with gastroesophageal reflux disease (GERD) and manometrically intact lower esophageal sphincter (LES) is limited. The disease pattern may be different and LARS may fail to control reflux or result in higher rates of dysphagia. This is the first study investigating the impact of preoperative LES manometry data not only on manifestations of GERD and subjective outcome alone but also on objective outcomes 1 year after LARS.
Methods Three hundred fifty-one GERD patients underwent LARS and had subjective symptom and quality of life assessment, upper gastrointestinal endoscopy, barium swallow esophagogram, 24-h esophageal pH monitoring, and manometry pre- and 1 year postoperatively. Patients were divided into those with a preoperatively intact versus defective LES based on intraabdominal length and resting pressure. Baseline and 1-year postoperative follow-up data were compared.
Results Preoperative manifestations of GERD were similar in each group. Postoperatively, all symptoms except flatulence, quality of life scores, and objective manifestations improved significantly in each group.
Conclusions The preoperative manometric character of the LES *neither* impacts the manifestations of GERD *nor* subjective and objective outcomes after LARS. Patients with GERD and manometrically intact LES have no higher risk for postoperative dysphagia.

Keywords Lower esophageal sphincter · Manometry · Gastroesophageal reflux disease · Laparoscopic Antireflux Surgery · Fundoplication · Outcome

Introduction

Gastroesophageal reflux disease (GERD) has emerged as one of the most common gastrointestinal disorders in modern civilization.[1] It is a multifactorial disorder with the central pathogenetic problem of an insufficient antireflux barrier allowing too much aggressive gastric and duodenal juice to reflux into the esophagus and damage the esophageal mucosa.[2–6] The lower esophageal sphincter (LES) represents this antireflux barrier, wherein clinical and in vitro studies have shown that the sphincter's competence primarily depends on the mechanical effect of the lower esophageal sphincter pressure (LES P) and the intraabdominal length (LES IAL) exposed to the positive environmental pressure of the abdomen.[7,8] Esophageal manometry of most GERD patients shows mechanically impaired LES competence,[8–11] and the occurrence of pathologic gastroesophageal reflux therein is easily explained. In the remaining minor proportion of patients with manometrically intact LES, several other mechanisms have been proposed to explain the impaired competence of the LES and, therefore, the occurrence of pathologic gastroesophageal reflux. These include transient relaxations of the LES,[2,9,12,13] impaired esophageal peristalsis,[6,14,15] impaired gastric emptying, increased

O. Riedl · M. Gadenstätter · W. Lechner · G. Schwab · M. Marker · R. Ciovica
Department of Surgery, General Hospital of Krems, Krems, Austria

O. Riedl (✉)
Pfarrplatz 4,
3484 Grafenwoerth, Austria
e-mail: otto.riedl@gmx.at

M. Gadenstätter
Karl Landsteiner Institute, St. Poelten, Austria

intragastric or intraabdominal pressure,[2,9,11,16,17] increased body mass index, smoking, medications, alcohol, caffeine, and a host of other factors.[9,17]

Since antireflux surgery provides mechanical restoration and augmentation of the LES,[3,5,18–24] concern has been raised about laparoscopic antireflux surgery (LARS) in patients with mechanically intact LES manometry. The disease pattern may be different and LARS may fail to control reflux or result in higher rates of dysphagia. A careful and extended review of the international literature has revealed that experience is limited. The few studies specifically addressing these questions lack adequate numbers of patients, use different definitions of "LES competence," and evaluate GERD manifestations and outcomes based merely on subjective symptoms.[9–11] We have conducted this retrospective review of a prospectively collected data set with detailed and complete pre- and postoperative follow-up to figure out whether preoperative LES manometry data impact (a) the manifestations of GERD, (b) patients' subjective, and (c) objective outcomes assessed 1 year after LARS.

Material and Methods

From January 2003 to December 2006, 395 GERD patients underwent laparoscopic Nissen fundoplication in a single specialized center (Foregut Laboratories of the Department of Surgery, Hospital Krems, Austria). This is a retrospective review of a prospectively collected data set including 351 GERD patients with complete pre- and 1-year postoperative (median 55 weeks) follow-up data.

Before referral to hospital, 92% of all patients were receiving medical care; 8% had no medication or contact to a physician prior to presentation. However, before surgery, all patients had been receiving long-term proton pump inhibitor therapy with a standard daily dose (40 mg Esomeprazole). A higher dose was prescribed if patients still suffered from GERD symptoms. LARS was indicated and performed in patients who had a long history of persistent or recurrent GERD symptoms, complications of GERD, and impaired quality of life despite medical therapy. Surgery was also performed if patients had a relapse of GERD symptoms after medical therapy was stopped and if patients preferred surgery to life-long medical therapy. All study patients were treated with standardized laparoscopic Nissen fundoplication as described previously,[25] performed by two experienced surgeons.

Evaluation of GERD Symptoms

The frequency and severity of acid reflux (S1), epigastric pain (S2), regurgitation (S3), respiratory symptoms (S4), globus sensation (S5), dysphagia (S6), and flatulence (S7) were assessed using standardized symptom questionnaires. Symptom severity was scored between 0 (none) and 6 (extremely severe, Table 3). In addition, psychological consultation and quality of life assessment were obtained from each patient. The disease-related quality of life was evaluated using the gastrointestinal quality of life index (GIQLI).[26] This questionnaire is well established, validated, and recommended by the European Study Group for antireflux surgery. In addition, the health-related quality of life (HRQL) questionnaire was used to evaluate the efficacy of therapy.[27] The scores of both questionnaires were calculated as previously described.[26,27]

Evaluation of *Objective* GERD Manifestations

To evaluate *objective* GERD manifestations, all patients underwent upper gastrointestinal endoscopy, a barium swallow esophagogram, esophageal manometry, and 24-h esophageal pH monitoring.

Upper gastrointestinal endoscopy was performed under sedation. The location of the gastroesophageal junction (GEJ) was defined as the site where the proximal extent of the gastric rugal folds meets the tubular esophagus. Hiatal hernia was diagnosed when the difference between the position of the crural impression and the GEJ was 2 cm or more. Combined with findings from barium esophagogram, the presence and dimensions of hiatal hernias were evaluated carefully. Esophagitis was either graded using the Savary–Miller,[28] or the Los Angeles[29] classification system. However, this study focused on the presence of erosive esophagitis.

A preoperative barium esophagogram was performed to help in identifying and determining the size of hiatal hernia, to confirm gastroesophageal reflux of barium, and to exclude esophageal stricture.

Esophageal manometry was performed using a stationary pull-through technique with a five-channel water-perfused catheter consisting of a 5-cm spacing between the channels.[8] Medications that might interfere with esophageal motor function (i.e., metoclopramide, cisapride, nitrates, β-agonists, and calcium-channel-blocking agents) were discontinued 7 days before the study. The catheter was withdrawn across the cardia to identify the higher pressure zone of the LES. At the respiratory inversion point, the amplitude of the LES pressure (LES P) and length of the sphincter exposed to abdominal pressure (LES IAL) were measured and documented. The LES was considered to be incompetent if the resting pressure was below 8 mmHg and/or the intraabdominal sphincter length was below 1 cm.[8]

The esophageal pH was monitored for 24 h as previously described by positioning the pH measurement electrode 5 cm above the manometrically measured upper border of the LES.[30] Acid-suppressing medications (e.g., H2-blocking agents and proton pump inhibitors) were discon-

tinued 7 days before the study. A DeMeester reflux score≥ 14.72 indicated abnormal acid reflux.

Clinical assessment, quality of life evaluation, upper gastrointestinal endoscopy, barium esophagogram, esophageal manometry, and 24-h esophageal pH monitoring were routinely performed preoperatively and approximately 1 year after surgery (median 55 weeks). Preoperative and postoperative data were collected prospectively by a research assistant and entered in a Microsoft Excel® database. Patients with complete pre- and 1-year postoperative follow-up data were included into this retrospective study.

In order to analyze the impact of preoperative LES manometry data on GERD manifestations and LARS outcome, patients were grouped based on the main variables representing LES competence in esophageal manometry,[8] the LES IAL and LES P: group I (LES IAL pathological, <1 cm; LES P pathological, <8 mmHg), group II (LES P pathological), group III (LES IAL pathological), and group IV (LES IAL normal, ≥1 cm; LES P normal, ≥8 mmHg). Preoperative and 1-year follow-up data were then compared for the entire population and each group.

Statistical Analysis

Variables were described by frequencies, mean±SD, and median and interquartile range. The chi-square test was used to test the significance of frequencies. The Kruskal–Wallis test and *U* test were used when appropriate to test for statistical significance between groups. The Wilcoxon test was used to test for differences between pre- and postoperative values, wherein a p value<0.05 was considered to be statistically significant. Statistical analysis was performed in SPSS 14.0 for Microsoft Windows (SPSS Inc., 1989–2005).

Results

Preoperative Descriptive Statistics

Preoperative descriptive data for each group are listed in Table 1. We found no significant differences among the groups concerning the frequency (Table 2) and severity (Table 3) of GERD symptoms. Objective GERD parameters were distributed evenly among the groups as well (Table 1). Although pathologically high in each group, patients with short LES IAL and low LES P (group I) had significantly higher DeMeester scores (p=0.025). Quality of life scores (GIQLI and HRQL) did not differ significantly among the four groups (Table 4). Altogether, the subjective and objective manifestations of GERD were the same in each group, independent of preoperative LES manometry data.

Table 1 Pre- and Postoperative Descriptive Data for the Entire Population (Total)/Per Group

	Total	Group I	Group II	Group III	Group IV	p value
Number of patients, n (%)	351 (100%)	131 (37.3%)	130 (37.0%)	22 (6.3%)	68 (19.4%)	
Gender (males), n (%)	217 (61.8%)	89 (67.9%)	82 (63.1%)	14 (63.6%)	42 (61.8%)	NS
Age (years)	50.3±11.5	51.3±12.0	49.2±11.5	49.5±10.1	50.4±11.1	NS
Reflux esophagitis, n (%)						
Preoperative	198 (56.4%)	82 (62.6%)	70 (53.8%)	16 (72.7%)	30 (44.1%)	NS
Postoperative	22 (6.3%)	13 (9.9%)	5 (3.8%)	1 (4.5%)	3 (4.4%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
Hiatal hernia, n (%)						
Preoperative	332 (94.6%)	126 (96.2%)	124 (95.4%)	21 (95.5%)	61 (89.7%)	NS
Postoperative	16 (4.5%)	7 (5.3%)	6 (4.6%)	0 (0.0%)	3 (4.4%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
Barium-esophagogram: reflux, n (%)						
Preoperative	194 (55.3%)	81 (61.8%)	66 (50.8%)	15 (68.2%)	33 (48.5%)	NS
Postoperative	16 (4.5%)	8 (6.1%)	2 (1.5%)	2 (9.1%)	3 (4.4%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
pH monitoring: DeMeester score, n (%)						
Preoperative	35.02±28.56	38.99±27.78	34.98±30.62	29.42±21.05	31.78±29.93	0.025
Postoperative	9.24±13.12	9.94±14.14	8.5±11.73	8.59±12.23	9.60±16.20	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	

I: LES IAL and LES P pathological; II: only LES P pathological; III: only LES IAL pathological; IV: LES IAL and LES P normal

NS = p>0.05

Table 2 Pre- and Postoperative GERD Symptoms: Frequency; Entire Population (Total)/Per Group

	Total, *n* (%)	Group I, *n* (%)	Group II, *n* (%)	Group III, *n* (%)	Group IV, *n* (%)	*p* value
S1: Acid reflux						
Preoperative	340 (96.9%)	129 (98.5%)	126 (96.9%)	21 (95.5%)	64 (94.1%)	NS
Postoperative	36 (10.2%)	12 (9.2%)	10 (7.7%)	3 (13.6%)	11 (16.2%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
S2: Epigastric pain						
Preoperative	292 (83.2%)	108 (82.4%)	105 (80.8%)	20 (90.9%)	59 (86.8%)	NS
Postoperative	32 (9.1%)	11 (8.4%)	10 (7.7%)	1 (4.5%)	10 (14.7%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
S3: Regurgitation						
Preoperative	238 (67.8%)	93 (71.0%)	85 (65.4%)	13 (59.1%)	47 (69.1%)	NS
Postoperative	12 (3.4%)	2 (1.5%)	6 (4.6%)	1 (4.5%)	3 (4.4%)	NS
p value	<0.001	<0.001	<0.001	<0.001	<0.001	
S4: Respiratory symptoms						
Preoperative	194 (55.3%)	70 (53.4%)	74 (56.9%)	12 (54.5%)	38 (55.9%)	NS
Postoperative	76 (21.7%)	21 (16.0%)	33 (25.4%)	5 (22.7%)	17 (25.0%)	NS
p value	<0.001	<0.001	<0.001	0.020	<0.001	
S5: Globus sensation						
Preoperative	43 (12.3%)	19 (14.5%)	18 (13.8%)	0 (0.0%)	6 (8.8%)	NS
Postoperative	29 (8.3%)	8 (6.1%)	11 (8.5%)	0 (0.0%)	10 (14.7%)	NS
p value	NS	0.016	NS	NS	NS	
S6: Dysphagia						
Preoperative	47 (13.4%)	17 (13.0%)	14 (10.8%)	1 (4.5%)	6 (8.8%)	NS
Postoperative	34 (9.7%)	10 (7.6%)	10 (7.7%)	1 (4.5%)	6 (8.8%)	NS
p value	NS	NS	NS	NS	NS	
S7: Flatulence/bloating						
Preoperative	103 (29.3%)	30 (22.9%)	46 (35.4%)	4 (18.2%)	23 (33.8%)	NS
Postoperative	132 (37.6%)	42 (32.1%)	58 (44.6%)	5 (22.7%)	27 (39.7%)	NS
p value	0.005	0.040	NS	NS	NS	

I: LES IAL and LES P pathological; II: only LES P pathological; III: only LES IAL pathological; IV: LES IAL and LES P normal
NS = $p>0.05$

Postoperative Outcome—Entire Study Population

Most GERD symptoms (frequency and severity) improved postoperatively (Tables 2 and 3). The frequencies of acid reflux (S1), epigastric pain (S2), regurgitation (S3), and respiratory symptoms (S4) were reduced significantly, whereas the rate of flatulence (S7) was significantly higher 1 year after LARS (Table 2). Similarly, the severity scores of all symptoms except flatulence were significantly improved (Table 3). Postoperatively, neither frequency nor severity of dysphagia worsened (Tables 2 and 3). Furthermore, there was a significant relief of each objective GERD parameter (Table 1) and improvement of quality of life (Table 4) as well.

Postoperative Outcome—Groups I–IV

Subjective outcome (symptom frequency and severity) of each group was similar to the entire study population. However, only patients with pathologically short LES IAL and low LES P (group I) had significantly lower rates of globus sensation (S5) and significantly higher rates of flatulence (S7) 1 year after LARS (Table 2). Apart from that, we observed a significant relief of all objective GERD parameters (Table 1) and improvement of quality of life (Table 4 and Fig. 1) in each group, as shown for the entire population.

Postoperative patient characteristics were the same in each group independent of preoperative LES manometry data (Tables 1, 2, 3, and 4).

Table 3 Pre- and Postoperative GERD Symptoms: Severity Scores (Median); Entire Population (Total)/Per Group

	Total	Group I	Group II	Group III	Group IV	*p* value
S1: Acid reflux						
Preop	4	5	4	4	4	NS
Postop	1	0	1	0	0	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S2: Epigastric pain						
Preop	4	5	5	4	4	NS
Postop	0	0	1	0	1	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S3: Regurgitation						
Preop	4	4	4	3	4	NS
Postop	1	0	1	1	0	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S4: Respiratory Symptoms						
Preop	2	2	1	2	1	NS
Postop	0	0	0	1	0	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S5: Globus sensation						
Preop	3	3	2	3	3	NS
Postop	1	1	1	1	2	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S6: Dysphagia						
Preop	3	3	2	3	3	NS
Postop	1	0	0	1	0	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	
S7: Flatulence/bloating						
Preop	2	2	2	2	2	NS
Postop	3	4	3	3	3	NS
p value	<0.05	<0.05	<0.05	<0.05	<0.05	

I: LES IAL and LES P pathological; II: only LES P pathological; III: only LES IAL pathological; IV: LES IAL and LES P normal

Severity scoring: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=very severe, 6=extremely severe

NS = $p>0.05$

Discussion

Prior to LARS, most surgeons routinely obtain esophageal manometry studies and thereby observe the LES to be *intact* in some GERD patients.[9] Since the proportion of these patients is relatively small, experience is limited: the disease pattern may be different and it is unclear whether augmentation of a manometrically intact LES by fundoplication[3,5,18–24] will control reflux and result in higher rates of postoperative dysphagia, respectively. Despite an extensive

Table 4 Pre- and Postoperative Quality of Life Scores (GIQLI, HRQL); Entire Population (Total)/Per Group

Quality of Life	Total	Group I	Group II	Group III	Group IV	*p* value	
GIQLI	Preoperative	92.91±18.92	94.22±18.33	94.45±19.77	95.69±15.59	89.51±19.82	NS
	Postoperative	117.89±15.33	119.14±15.14	118.38±15.14	123.81±12.93	113.58±16.89	NS
	p value	<0.001	<0.001	<0.001	0.002	<0.001	
HRQL	Preoperative	19.94±9.85	21.47±9.42	18.42±9.72	18.92±13.51	20.88±9.18	NS
	Postoperative	2.97±4.76	2.62±3.81	2.58±4.05	2.44±4.98	4.27±6.83	NS
	p value	<0.001	<0.001	<0.001	0.002	<0.001	

I: LES IAL and LES P pathological; II: only LES P pathological; III: only LES IAL pathological; IV: LES IAL and LES P normal

NS = $p>0.05$

Medline® and Pubmed® literature research, we have only found three publications specifically addressing these questions,[9–11] and to the best of our knowledge, this single institutional outcome study of 351 patients is the largest to date.

The design of previous studies is similar.[9–11] *None* of these studies explicitly defined LES competence and, thus, characterized their groups differently, hindering comparability. According to Cowgill et al.,[9] impaired LES competence refers to pathologically low LES P combined with short LES IAL, found in 51% of their study population. Patti et al.[10] only focused on the impact of the preoperative LES P, and in 86% of their study population impaired LES competence was diagnosed. Ritter et al.[11] regarded the LES competence as impaired in 71% of patients if LES P, LES IAL, overall length, or any combination of these variables was pathological. Using the same, most detailed definition, Zaninotto et al.[8] diagnosed impaired LES competence in 60% of GERD patients, with low LES P and short LES IAL as the most common mechanical defects. Based on this evidence, our study population was grouped. In this context, it shall be emphasized that unlike each previous report,[9–11] we did not just differentiate between intact and impaired LES but considered LES manometry data in more detail; we found pathological LES IAL in 6.3%, pathological LES P in 37.0%, and a combination of pathological LES IAL and LES P in 37.3% of GERD patients. Despite the different definitions of LES competence and varying percentages reported previously, it is without controversy and consistent to our findings that preoperative manometry shows LES competence in a minority of GERD patients.[8–11]

The question whether the manifestations of GERD are the same in this minority of patients could be elucidated in our study. Frequency and severity of subjective symptoms were similar in each group, confirming data of previous reports.[9,11] The only objectively evaluated GERD parameters previously reported were the results of preoperative 24-h pH monitoring showing elevated DeMeester scores independent of preoperative LES manometry data,[9,10] consistent with our findings. We found a significantly higher median DeMeester score in group I (p=0.025), which was not surprising considering the fact that this group represents patients with the most defective LES. Our study is the *first* that also analyzed several other objective manifestations of GERD and possible relations to preoperative LES manometry data (Table 1). Distributed evenly among each group, current data show that manifestations of GERD are independent of the manometric character of the LES. This finding is confirmed by the even distribution of quality of life scores among the groups (Table 4 and Fig. 1). To the best of our knowledge, no previous study has analyzed the impact of LES manometry data on quality of life in GERD patients.[9–11]

Reviewing the international literature analyzing the impact of LES manometry data on the outcome of LARS revealed that each previous report addresses this question based upon subjective symptom assessment and patients' information *only*.[9–11] Confirming previous findings,[9–11] we observed that most GERD symptoms were significantly reduced (frequency) and relieved (severity) after LARS, independent of preoperative LES manometry. However, we

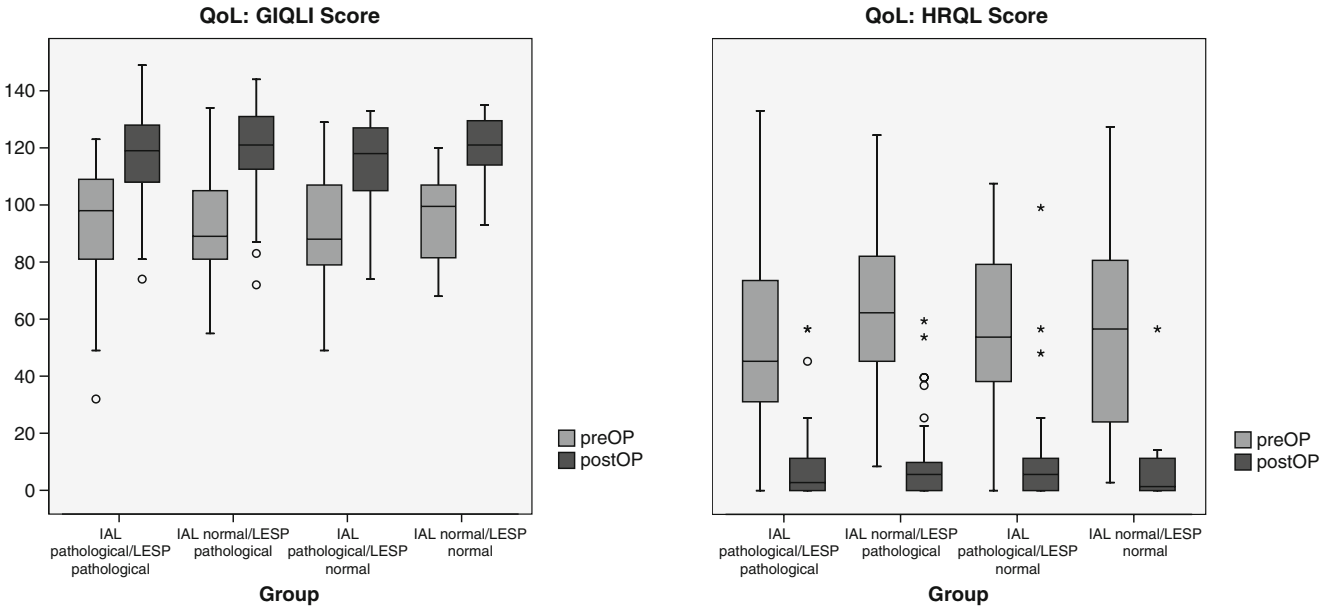

Figure 1 Pre- and postoperative quality of life (GIQLI, HRQL); per group: (I: LES IAL and LES P pathological; II: only LES P pathological; III: only LES IAL pathological; IV: LES IAL and LES P normal).

found patients with pathologically short LES IAL and low LES P (group I) to have significantly lower rates of globus sensation (S5) and significantly higher rates of flatulence (S7) 1 year after LARS (Table 2). Similarly, Cowgill et al.[9] reported that the frequency and severity of "choking" significantly improved in this very group of patients, whereas, interestingly, the postoperative rates of "gas/bloating" showed a statistically insignificant decrease,[9] directly contrasting our findings. We have found *no* other study specifically investigating this. However, Galvani et al.[31] indicate that symptoms may generally provide an unreliable index of postoperative abnormal reflux and failure of LARS. The strength of *our* study is the fact that unlike each previous study, postoperative outcome was not only evaluated on the basis of subjective symptoms alone but also on the basis of objective GERD manifestations in a large study population (n=351). Moreover, this is the *first* study specifically evaluating the impact of LES manometry data on pre- versus postoperative quality of life using validated and well-established QOL questionnaires.[26,27] Both objective GERD manifestations (Table 1) and quality of life improved significantly in each group and scores were distributed evenly among the groups (Table 4 and Fig. 1). Hence, these data show that GERD patients benefit from LARS and have similar outcomes 1 year postoperatively, independent of preoperative LES manometry data.

Patients with GERD and manometrically intact LES might be expected to have a higher risk for postoperative dysphagia.[9] The reported incidence of dysphagia varies between 70% within 6 weeks and 1% after a mean follow-up of 33 months postoperatively.[32–37] In a systematic review of studies reporting outcomes following LARS in 2,453 patients, the early postoperative dysphagia rate was 20% and persisted in 5.5% of patients beyond 6 months postoperatively.[37] Due to this time-dependent variability, it is important to consider the follow-up period before comparing dysphagia rates. Therefore, as a standard, each of our patients was followed up 1 year (median 55 weeks) after LARS. Another important factor for adequate comparability is the fact that all patients of this study were treated using the same standardized surgical procedure,[25] since different techniques and modifications have been described as means to impact postoperative dysphagia rates.[18,38,39] Accordant to previous studies,[9–11] we found a median postoperative dysphagia rate of 7.8% independent of preoperative LES manometry data. One year after LARS, neither the rate of nor the risk for dysphagia was significant in each group. Severity scores were similar among the groups as well. Even though Blom et al.[40] reported that postoperative dysphagia was six times more common in patients with normal to high mean preoperative LES P, the vast majority of reports supports our finding.[32,38,41,42]

Like many non-randomized studies, ours has some limitations. First, the distribution of the different groups is not equal. However, several statistical tests have been applied to adjust imbalances and warrant reliable results. Moreover, even when patients were grouped in a different way to analyze LES IAL or LES P pathology independently (i.e., LESIAL: groups I and III combined versus groups II and IV or LESP: groups I and II combined versus groups III and IV), no significant differences became evident, confirming our conclusions. Second, aiming for maximal validity, only patients with complete pre- and postoperative data have been included in this retrospective study. This might have caused a selection bias. Third, similar to previous studies,[9–11] our follow-up review extends to median 55 weeks after LARS and symptom improvement can possibly deteriorate over a longer period of time. Although no such trend has been apparent over the time period of our study, long-term follow-up of our patients is continuing to demonstrate the durability of these improvements.

Conclusion

Preoperative LES manometry data have no impact on disease pattern and manifestations of GERD. Laparoscopic antireflux surgery is effective in GERD patients *regardless* of their preoperative LES manometry data. Even in patients with manometrically intact LES, it controls reflux and is not associated with an increased incidence of postoperative dysphagia.

Prospective randomized trials analyzing the impact of LES manometry data with long-term follow-up are important to confirm findings presented in this study and to facilitate recommendations whether or not LES manometry should be performed routinely prior to LARS.

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2008 SSAT PLENERY PRESENTATION

Probiotics Improve Outcomes After Roux-en-Y Gastric Bypass Surgery: A Prospective Randomized Trial

Gavitt A. Woodard · Betsy Encarnacion · John R. Downey · Joseph Peraza · Karen Chong · Tina Hernandez-Boussard · John M. Morton

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Abstract
Introduction Roux-en-Y gastric bypass (RNYGB) surgery offers an effective and enduring treatment for morbid obesity. Gastric bypass may alter gastrointestinal (GI) flora possibly resulting in bacterial overgrowth and dysmotility. Our hypothesis was that daily use of probiotics would improve GI outcomes after RNYGB.
Methods Forty-four patients undergoing RNYGB were randomized to either a probiotic or control group; 2.4 billion colonies of *Lactobacillus* were administered daily postoperatively to the probiotic group. The outcomes of H_2 levels indicative of bacterial overgrowth, GI-related quality of life (GIQoL), serologies, and weight loss were measured preoperatively and at 3 and 6 months postoperatively. Categorical variables were analyzed by χ^2 test and continuous variables were analyzed by *t* test with a $p<0.05$ for significance.
Results At 6 months, a statistically significant reduction in bacterial overgrowth was achieved in the probiotic group with a preoperative to postoperative change of sum H_2 part per million (probiotics=−32.13, controls=0.80). Surprisingly, the probiotic group attained significantly greater percent excess weight loss than that of control group at 6 weeks (controls=25.5%, probiotic=29.9%) and 3 months (38.55%, 47.68%). This trend also continued but was not significant at 6 months (60.78%, 67.15%). The probiotic group had significantly higher postoperative vitamin B12 levels than the control group. Both probiotic and control groups significantly improved their GIQoL.
Conclusion In this novel study, probiotic administration improves bacterial overgrowth, vitamin B12 availability, and weight loss after RNYGB. These data may provide further evidence that altering the GI microbiota can influence weight loss.

Keywords Microbiota · Bacteria · Bacterial overgrowth · Weight loss · Morbid obesity · Gastric bypass · Probiotics

Introduction

Obesity is the leading public health crisis in the developed world.[1] Despite public health initiatives, obesity rates in the US continue to increase, growing from 15% in 1980 to 33.3% of men and 35.3% of women in 2006.[2] Bariatric surgery remains the only proven effective and enduring treatment for morbid obesity.[3,4] Roux-en-Y gastric bypass (RNYGB) is a highly effective surgery which uses both restriction and malabsorption to achieve weight loss. However, RNYGB may alter enteric microflora resulting in "Roux Syndrome" and bacterial overgrowth (BO).[5] This limb may be a blind pouch in which bacteria flourish due to stasis of digestive material. Patients with BO experience nonspecific digestive symptoms including abdominal pain, bloating, increased flatulence, and diarrhea.[6,7]

The number and type of bacteria in the intestine are regulated in part by gastric acid secretion and by intestinal motility. BO risk factors include a decrease in gastric acid secretion or a decline in intestinal motility both of which may occur after RNYGB.[8] BO in the small intestine can

G. A. Woodard · B. Encarnacion · J. R. Downey · J. Peraza · K. Chong · T. Hernandez-Boussard · J. M. Morton
Department of Surgery,
Surgery Center for Outcomes Research and Evaluation (SCORE),
Stanford University School of Medicine,
Stanford, CA, USA

J. M. Morton (✉)
300 Pasteur Drive, H3680,
Stanford, CA 94025, USA
e-mail: morton@stanford.edu

lead to vitamin deficiencies, fat malabsorption, and malnutrition.[6,9,10] In addition, vitamin B12 is catabolized by intestinal bacteria unless it is bound to intrinsic factor from the gastric parietal cells.[11] Consequently, gastric bypass patients lack available intrinsic factor and may have bacterial overgrowth with subsequent increased risk of vitamin B12 deficiency.[12,13]

Another impact of enteric microflora is its effect upon weight loss. The human gut contains over ten[13] microorganisms known as the microbiota which perform symbiotic digestive and metabolic functions within the human gastrointestinal (GI) tract acting as digestive factories.[14] Bacteroidetes and Firmicutes are the two main bacterial divisions which make up the microbiota in the human gut and their relative abundance differs between obese and lean individuals. Obese mice have an increase in Firmicutes and a decrease in Bacteroidetes compared to their lean littermates, leading to the theory that certain GI microbiota extract more energy from food.[15]

Potential mediators to the gut microbiota are probiotics which are considered to be safe therapy because the microorganisms they contain are found naturally in human microflora. Clinically, probiotics such as *Lactobacillus* species have acted as "enteric bacteria transplants" proving to be an effective treatment for infective gastroenteritis, antibiotic-associated diarrhea, pouchitis, decreasing levels of *Helicobacter pylori* in the stomach, irritable bowel syndrome, ulcerative colitis, general inflammation, preventing and treating acute respiratory infections, urogenital infection, acute otitis media, allergy, pancreatitis, Crohn's disease, and inflammatory bowel syndrome.[16–22]

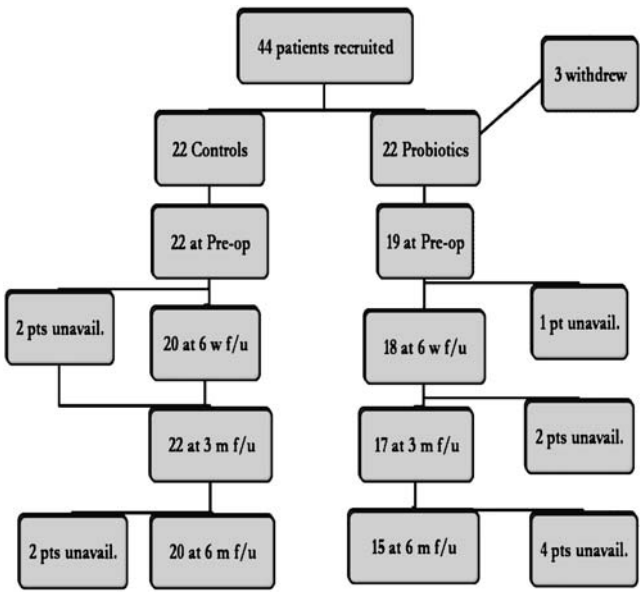

Figure 1 Randomization and follow-up flow chart.

Table 1 Study Demographics

	Controls	Probiotics	*p* value
Number	22	19	–
Age (years)	41.2	48.6	0.026
% Female	90.9	84.2	0.649
% White	68.2	63.2	0.859
% DM	18.2	52.6	0.026
% HTN	59.1	57.9	0.939
% PPI use	13.6	21.1	0.534
H. pylori+ (%)	37.5	21.4	0.350
Preoperative BMI (kg/m^2)	49.6	45.7	0.0946
Preoperative weight (lb)	306.4	276.6	0.0512
Height (in.)	66.0	65.4	0.5654
Ideal body weight (lb)	160.2	157.8	0.5450
Excess body weight (lb)	146.3	118.8	0.0524

Patients in the control group (n=22) and the probiotic group (n=19) had no statistically significant difference for 38 of 40 variables. The only significant differences were the probiotic group was significantly older and had a higher rate of preoperative diabetes mellitus with a $p<0.05$ significance using a two-sample t test with equal variances

Our study hypothesis was whether probiotic administration after RNYGB influenced GI quality of life (GIQoL), BO, and weight loss following RNYGB.

Methods

Forty-four morbidly obese patients undergoing RNYGB at a single academic institution from 2006 to 2007 were prospectively enrolled in the trial at the initial consult clinic visit. All RNYGB procedures were performed laparoscopically by a single surgeon, with a standard 15–30-cm gastric pouch and 100-cm Roux limb. Patients were randomized at the time of the initial consult to a probiotic or control group

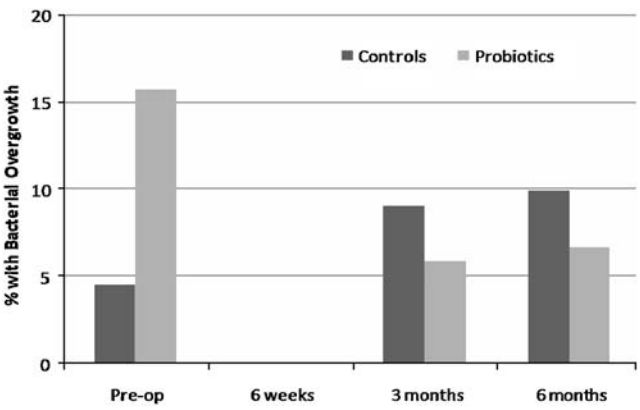

Figure 2 Prevalence of bacterial overgrowth. Overgrowth defined by H_2 breath measurements in probiotic and control groups preoperatively and at 6 weeks and 3 and 6 months postoperatively (nonsignificant).

Table 2 Preoperative H_2 Breath Measurements

H_2 measure	Controls	Probiotics	*p* value
Sum	29.3	38.9	0.359
Mean	3.8	4.1	0.718
Peak	5.2	6.3	0.408

using a computerized random number generator. Bariatric surgeon and medical staff involved in patient care were blinded and only the research coordinators were aware of which group patients had been assigned. Both study groups received the same standard bariatric medical care, nutritional counseling, and weight loss support groups. Both groups were allowed to consume yogurt, a natural source of probiotics, given that the amount of probiotic in yogurt is negligible compared to our supplement. Patients were aware that they had a random chance of taking probiotics. This study was approved by the Stanford School of Medicine Administrative Panels on Human Subjects in Medical Research and all patients were consented to participate in the study.

Per standard protocol, all patients were given preoperative 2 g cefazolin and were instructed to take daily multivitamins, B12, 20 mg AcipHex to prevent ulcer formation, and ursodeoxycholic acid to prevent cholelithiasis. All patients

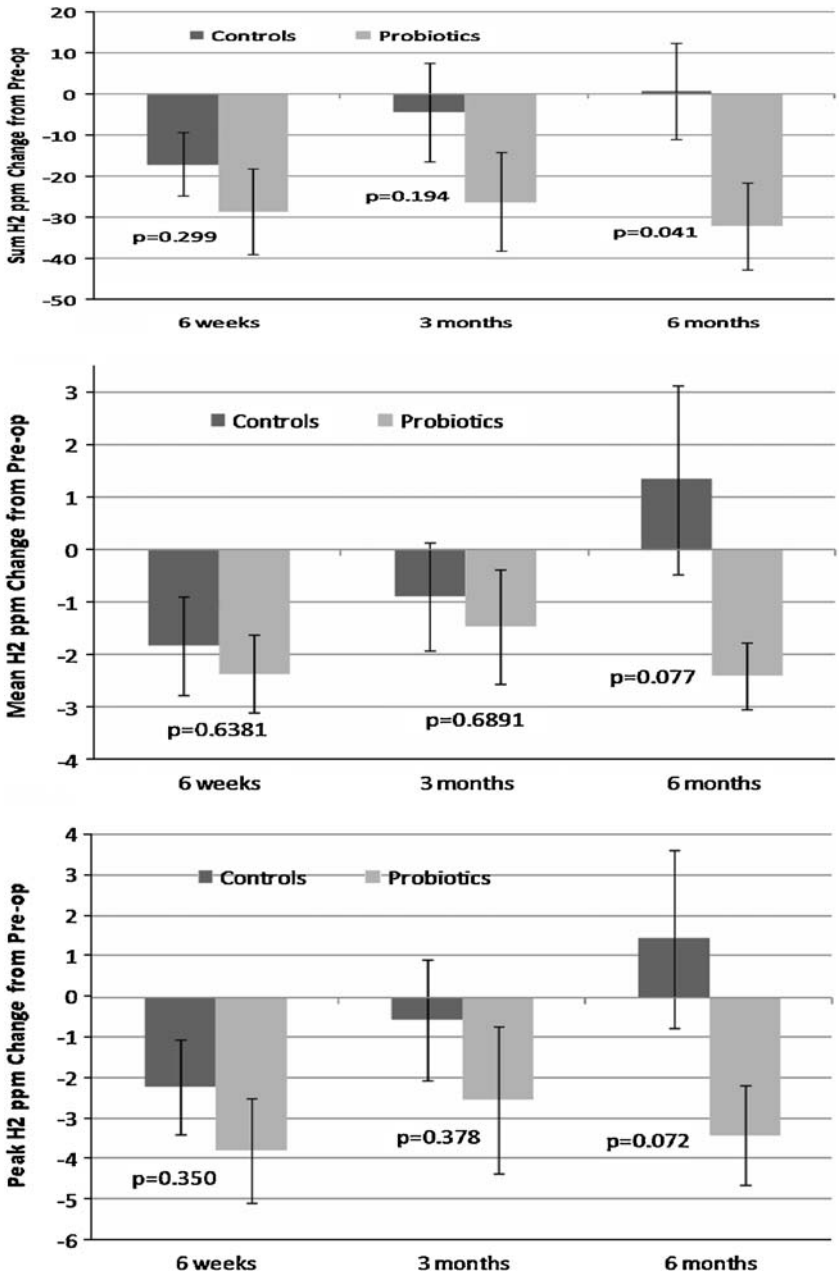

Figure 3 Postoperative H_2 ppm changes. H_2 breath levels were significantly lower than preoperative values at 6 weeks postoperatively in both groups. However, at 3 and 6 months postoperatively, only the probiotic group maintained the reduction in H_2 part per million levels. The same pattern was observed in total sum H_2 part per million, mean H_2 part per million per breath, and peak H_2 part per million measurements.

were seen at 2 and 6 weeks and 3 and 6 months postoperatively per standard practice. The following serologies were obtained preoperatively and at 3 and 6 months postoperatively: total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), triglyceride to HDL ratio, lipoprotein A, high-sensitivity C-reactive protein, homocysteine, hemoglobin A1C, total bilirubin, aspartate transminase, alanine aminotransferase, alkaline phosphatase, thyroid-stimulating hormone, fasting insulin, vitamin B12, and folate.

Patients in the probiotic group were given a 6-month supply of Puritan's Pride® probiotic supplement with each pill containing 2.4 billion live cells of *Lactobacillus* species. Patients were instructed to take one probiotic pill each day and to refrigerate the unused pills. Compliance was monitored with weekly phone calls from the research team with patients reporting 100% compliance. After initial randomization into two groups of 22 each, three patients were excluded from the probiotic group. One patient did not undergo RNYGB and two patients voluntarily withdrew from the study prior to their preoperative appointment citing breath testing time restraints (Fig. 1).

Weight, GIQoL, and bacterial overgrowth were measured preoperatively and at 3 and 6 months postoperatively. Patient's gastrointestinal quality of life was measured with the gastrointestinal-related quality-of-life index which is scored from 30 to 120 with higher scores indicative of better GIQoL.

BO measurement was determined by hydrogen (H_2) breath testing using the HBT Sleuth® which measures H_2 gas in parts per million. Patients were NPO for at least 8 h and a baseline fasting H_2 measurement was taken. Patients were then given 8 oz of skim milk, containing 13 g of carbohydrates, and H_2 measurements were taken every 15 min for ≥120 min. BO is defined by the H_2 Sleuth® manufacturer as having a baseline level of ≥12 H_2 parts per million or having an increase of ≥12 H_2 parts per million over the baseline value. In the process of breaking down carbohydrates in the lumen of the intestine, GI bacteria produce gas by-products, one of which is H_2. This H_2 diffuses into the bloodstream and is expired in exhaled breath. H_2 in exhaled breath can be used to detect abnormal breakdown or malabsorption of carbohydrates in the intestine.

Comparative analyses between the two groups, probiotics and controls, were performed using STATA 10.0 (Statacorp LP). Categorical and continuous variables were compared by Pearson's chi-squared test, Fisher's exact test, or *t* test as appropriate. Variables examined included age, gender, race, insurance status, serologic results, preoperative body mass index (BMI), and excess weight loss at 6 weeks and 3 and 6 months. Excess weight loss is defined by weight loss relative to ideal weight expressed as a percentage. Significance was achieved if $p \leq 0.05$.

Results

The overall demographics of patients in this study are representative of the general bariatric patient population. In comparing demographics between the two groups, the probiotic group was older (probiotics=48.6 years vs. controls=41.2 years) and had a higher rate of preoperative diabetes mellitus (18.2%, 52.6%). However, there was no significant difference for 38 of the 40 measured preoperative variables including sex, race, preoperative hypertension, preoperative proton pump inhibitor use, *H. pylori* status, preoperative BMI, height, and ideal body weight between the two groups (Table 1). The overall complication rate between the two groups was similar and there were no probiotic-related complications.

In examining the outcomes of BO, the probiotic group demonstrated significantly fewer signs of bacterial overgrowth than did the control group with a $p<0.05$ significance using a two-sample *t* test with equal variances. The probiotic group had a higher prevalence of BO than the control group preoperatively, while the control group had a higher prevalence of BO postoperatively (Fig. 2). BO is a rare event so H_2 breath levels were used as a surrogate marker for the number of hydrogen-producing enteric bacteria. Preoperatively, there were no significant differences in the total sum of measured H_2 values, mean, and peak H_2 parts per million between the control and probiotic groups (Table 2). Postoperatively, the probiotic group underwent greater reductions in all H_2 measures (Fig. 3). H_2 breath levels were significantly lower than preoperative values at 6 weeks postoperatively in both groups; however, at 3 and 6 months postoperatively, only the probiotic group

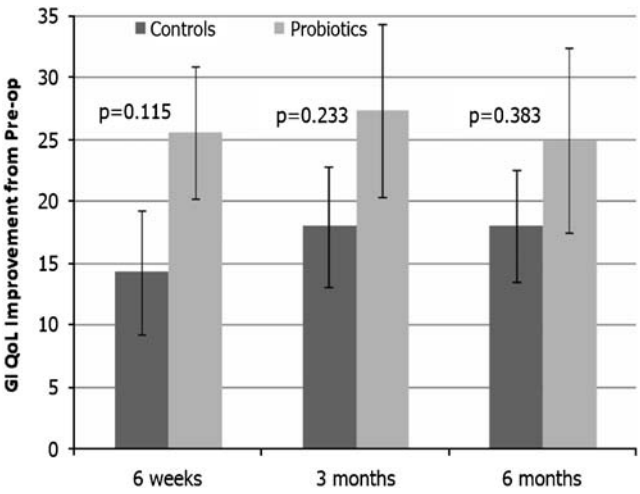

Figure 4 Percent improvement in GI quality of life postoperatively. GI QoL scores were significantly improved from preoperative in both groups. The probiotic group underwent a greater relative increase in GI QoL scores but these results were not statistically significant by two-sample *t* test with equal variances.

Table 3 Levels of Vitamin B12

	Controls (pg/ml)	Probiotics (pg/ml)	*p* value
Preoperative	619	668	0.5591
3 months	811	1,214	0.0410
6 months	714	975	0.0586

Control group compared to probiotic group preoperatively and at 3 and 6 months postoperatively with a two-sample *t* test with equal variances with $p \leq 0.05$ for significance

maintained the reduction in H_2 part per million levels from preoperative. The same pattern was replicated in total sum H_2 parts per million, mean H_2 parts per million per breath, and peak H_2 parts per million measurements. The differences were significant at 6 months by two-sample *t* test with equal variances $p<0.05$ for H_2 reductions total sum (probiotics= 32.13 H_2 part per million reduction vs. controls=0.80 increase). At 6 months, there was a similar trend in mean H_2 parts per million per breath (probiotics=2.41 H_2 part per million reduction vs. controls=1.34 increase) and peak H_2 part per million breath levels (probiotics=3.40 H_2 part per million reduction vs. controls=1.45 increase).

Both the probiotic and control groups had significant improvement in their GIQoL score after RNYGB surgery from their preoperative scores with $p<0.01$ for both groups at all time points. The probiotic group had a greater relative increase in GIQoL score at all time points, but this difference was not statistically significant (Fig. 4).

The probiotic group had significantly higher B12 levels from the control group at 3 and 6 months (Table 3). The probiotic group had higher vitamin B12 levels at 3 months (controls=811, probiotics=1,214) and at 6 months (714, 975). All other laboratory values examined were not significant (not shown).

Of note, the probiotic group lost significantly more weight than the control group (Table 3). At 6 weeks postoperatively, the probiotic group had achieved more percent excess weight loss (probiotics=29.90% vs. controls=25.50%, $p=0.0577$) and these differences were significant at 3 months (probiotics=47.68% vs. controls=38.55%, *p* value 0.0222). At 6 months postoperatively, this trend continued and neared statistical significance (probiotics=67.15% vs. controls= 60.78%, $p=0.2730$).

Conclusion

In this novel prospective randomized trial, the use of probiotics after gastric bypass trended towards reduced H_2 breath levels, further improved GIQoL, increased vitamin B12 levels, and increased weight loss. The trend towards reduction in H_2 breath values was not significant at 6 weeks and 3 months in any group, suggesting that changes in GI microbiota from probiotic use occurs gradually. The initial reduction in all H_2 breath indicators in both groups was probably a result of the 2 g Cefazolin preoperatively given to prevent wound infection. This antibiotic administration may explain early postoperative similarities between the control and probiotic groups; however, it is also possible that the early similarities were a result of the major anatomic GI changes from RNYGB surgery. These data may suggest that the preoperative antibiotics affect GI bacteria for months after a single dose and that probiotic use requires time to exert and effect on GI microbiota (Table 4).

Higher H_2 breath test values and more bacterial overgrowth would have been expected in the probiotic group given that it was older. Older patients are at a higher risk of developing BO because they have less gastric acid production.[23, 24] Instead, the patients taking probiotics had significantly greater decreases in H_2 breath testing levels and a lower postoperative prevalence of BO.

There was not a significant difference in GIQoL between the probiotic and control groups because they both underwent drastic increases from preoperative baseline to postoperative. This is likely because RNYGB exerts such a powerful effect on GI quality of life that it is difficult to discern any difference between the two groups.

Patients taking probiotics had significantly higher levels of B12 at 3 and 6 months postoperatively. These higher B12 levels might reflect a lower number of intestinal bacteria catabolizing B12 in the probiotic group. This is an important finding for post-RNYGB or duodenal-switch patients who may be at increased risk of B12 deficiency.

Table 4 Effects of Probiotic Use on Weight Loss

		Controls (95% CI)	Probiotics (95% CI)	*p* value
6 weeks	*N*	20	18	
	% EWL	25.50 (22.01, 28.98)	29.90 (26.79, 33.03)	0.0577
3 months	*N*	22	17	
	% EWL	38.55 (33.24, 43.87)	47.68 (41.70, 53.65)	0.0222
6 months	*N*	20	15	
	% EWL	60.78 (53.08, 68.45)	67.15 (57.67, 76.64)	0.2730

Groups were compared preoperatively and at 6 weeks and 3 and 6 months by two-sample *t* test with equal variances

The study was limited by not employing a placebo for the control arm. However, the additional case crossover design of the study where patients acted as their own control before and after surgery within each arm helps to mitigate this concern. Furthermore, most equivalently sized placebo pills contained sugar which was felt to be contra-indicated in the post-gastric-bypass patient.

The increased weight loss in the probiotic group is interesting because they were older and had more preoperative diabetes which both decrease weight loss after bariatric surgery which suggests that the control group should have lost more weight.[23]

It should be noted that this study was originally designed to detect differences in H_2 breath values with additional weight loss an unexpected benefit of probiotic use. This study may have been underpowered to detect a statistically significant difference in weight loss which was seen nevertheless at 6 weeks and 3 months. Further studies will be powered towards long-term differences in weight loss.

The changes in weight loss were significant at 3 months but not at 6 months. This is possibly due to decreasing compliance over time. Bariatric patients must take a regimen of daily pills including a multivitamin, vitamin B12, AcipHex, and ursodeoxycholic acid. A high volume of pills makes patients less likely to comply with medications particularly refrigerated ones like the probiotics.[25,26] In addition, patients become less compliant with long-term medications over time so worse compliance is expected at 6 months postoperatively.[27] The increased weight loss in the probiotic group is potentially due to altering GI microbiota to decrease energy extraction from food. However, it is also possible that patients taking probiotics experience better GI motility and quality of life allowing better toleration of healthy foods high in protein as opposed to easy-to-digest comfort foods like bread.

These results suggest the use of a daily probiotic for all patients undergoing RNYGB in order to reduce postoperative morbidity and maximize weight loss. Our findings may benefit patients at post-duodenal switch surgery also at increased risk for malabsorption. It is possible that the morbidly obese have a different set of microbiota that enables them to be extraordinarily efficient at extracting calories from food. The feasibility of altering the gut microbiota is supported by the results of this study and by research in mice.[28]

A recent *New England Journal of Medicine* article demonstrated that having obese acquaintances lead to obesity.[29] The possible infectious spread of obesity has been established in animals and humans with many proposed mechanisms including canine distemper virus, Rous-associated virus-7, *Chlamydia pneumoniae*, scrapie agent, Borna disease virus, GI microbiota, and adenoviruses SMAM-1, Ad-36, Ad-37, and Ad-5.[30,31–34] While obesity is clearly related to health behaviors, there is increasing evidence that differences in GI energy extraction may differ between individuals. While these effects are relatively minor, studies have shown that even a small increase in caloric consumption can lead to weight gain over a year.[35]

Bacteroidetes to Firmicutes ratios have been documented between obese and lean humans, but much further study in humans are necessary to fully characterize the relationship between microflora and energy extraction.[36] In addition, studies of GI microbiota of patients taking probiotics will reveal if the changes in weight and GI quality of life are species specific and how plastic the ratios of Bacteroidetes to Firmicutes can be. Gastric bypass patients are an ideal platform in which to study the effect of probiotics on the microbiota because the neutral environment of the gastric pouch will not destroy probiotics as a normally acidic undivided stomach might.

This study examined the effects of probiotics quantitatively and qualitatively. This study represents the only study to date to quantify the rarity of bacterial overgrowth or the effects of probiotic use in a bariatric patient population. This is the first study to suggest that probiotic administration may influence weight loss by changing the enteric bacterial composition. In summary, probiotics may safely improve GI outcomes after RNYGB surgery including potentially weight loss and micronutrient levels.

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2008 SSAT POSTER PRESENTATION

Changes in Inflammatory Biomarkers Across Weight Classes in a Representative US Population: A Link Between Obesity and Inflammation

Xuan-Mai T. Nguyen · John Lane · Brian R. Smith · Ninh T. Nguyen

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Abstract
Background Obesity has been linked with a chronic state of inflammation which may be involved in the development of metabolic syndrome, cardiovascular disease, non-alcoholic steatohepatitis, and even cancer. The objective of this study was to examine the association between obesity class and levels of inflammatory biomarkers from men and women who participated in the 1999–2004 National Health and Nutrition Examination Survey (NHANES).
Methods Serum concentrations of C-reactive protein (CRP) and fibrinogen were measured among US participants of the 1999–2004 NHANES. We examined biomarker levels across different weight classes with *normal* weight, *overweight*, and *obesity classes 1, 2, and 3* were defined as BMI of <25.0, 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0, respectively.
Results With CRP levels for normal weight individuals as a reference, CRP levels nearly doubled with each increase in weight class: +0.11 mg/dl (95% CI, 0.06–0.16) for overweight, +0.21 mg/dl (95% CI, 0.16–0.27) for obesity class 1, +0.43 mg/dl (95% CI, 0.26–0.61) for obesity class 2, and +0.73 mg/dl (95% CI, 0.55–0.90) for obesity class 3. With normal weight individuals as a reference, fibrinogen levels increase with increasing weight class and were highest for obesity class 3 individuals, +93.5 mg/dl (95% CI, 72.9–114.1). Individuals with hypertension or diabetes have higher levels of CRP and fibrinogen levels compared to individuals without hypertension or diabetes, even when stratified according to BMI.
Conclusions There is a direct association between increasing obesity class and the presence of obesity-related comorbidities such as diabetes and hypertension with high levels of inflammatory biomarkers.

Keywords Inflammation · C-reactive protein · Fibrinogen · Obesity · Biomarker · Hypertension · Diabetes · NHANES

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X.-M. T. Nguyen · J. Lane · B. R. Smith · N. T. Nguyen
Department of Surgery,
University of California, Irvine Medical Center,
Orange, CA, USA

N. T. Nguyen (✉)
Division of Gastrointestinal Surgery,
University of California, Irvine Medical Center,
333 City Blvd West, Suite 850,
Orange, CA 92868, USA
e-mail: Ninhn@uci.edu

Introduction

The prevalence of obesity in the United States is reaching epidemic proportions with one-third of the population being obese (BMI>30 kg/m^2) and two-thirds being overweight.[1] Health conditions associated with excess weight include increased risk for type II diabetes, hypertension, dyslipidemia, metabolic syndrome, atherosclerosis, degenerative joint disorders, obstructive sleep apnea, and certain cancers.[2–8] Obesity is also associated with cardiovascular disease which is the leading cause of mortality in the United States.[9] While the mechanistic relationship between obesity and the development of obesity-related conditions are not clearly understood, there is growing evidence to support the role of inflammation as a possible link.[10–13]

C-reactive protein (CRP) and fibrinogen are biomarkers representing increased risk for cardiovascular morbidity and mortality.[14,15] CRP, the most extensively studied inflam-

matory biomarker, is a protein produced by hepatocytes in the presence of inflammation due to factors such as infection, injury, or conditions such as obesity.[16] Elevated levels of CRP have been associated with increased inflammation in the coronary arteries, and thus a marker for increased risk for atherosclerosis and cardiovascular disease.[17,18] A meta-analysis of seven studies comparing individuals within the top third with those within the bottom third at study baseline showed that higher CRP levels were associated with a risk ratio of 1.7 (95% CI 1.4–2.1) for coronary heart disease (CHD).[19] Additionally, studies using older NHANES III (1988–1994) data have shown that levels of CRP are elevated in individuals with high BMI.[20,21] Another inflammatory biomarker that plays a direct role in coronary artery thrombosis is fibrinogen.[22] Fibrinogen, a major coagulation protein and the precursor to fibrin, is a major determinant of platelet aggregation and plasma viscosity.[23,24] To our knowledge, no studies to date have examined the relationship between fibrinogen levels and body weight, but a meta-analysis of 18 studies examining the association between fibrinogen and CHD found that individuals with fibrinogen values within the top third compared to individuals within the bottom third of the study distribution had a high risk ratio of 1.8 (95% CI 1.6–2.0) for development of CHD.[18] Since the relationship between obesity and cardiovascular disease, as well as the relationship between inflammation and cardiovascular disease, had been established, this study aimed to examine the association between obesity class and levels of inflammatory biomarkers (CRP and fibrinogen) utilizing more recent data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. We hypothesized that there is a direct relationship between the levels of inflammatory biomarkers with increasing degree of obesity and there is an interaction between level of biomarkers and diabetes and hypertension.

Subjects and Methods

Study Population

The NHANES is conducted by the National Center for Health Statistics which is part of the Centers for Disease Control and Prevention. The NHANES provides cross-sectional health and nutrition data for the US population. The survey examines a nationally representative complex, multistage probability sample of about 5,000 US civilians each year, located within 15 counties across the country. The NHANES survey consists of an extensive health information interview, a complete physical examination, and extensive laboratory testing. The physical examinations were performed in a mobile examination center and all subjects signed a consent form approved by the Human Subjects Committee in the US Department of Health and Human Services.[25–27] The three latest, continuous NHANES dataset were collected between 1999–2000, 2001–2002, and 2003–2004. Prior to 1999, the NHANES were performed in cluster as NHES I (1960–1962), NHANES I (1971–1974), NHANES II (1976–1980), and NHANES III (1988–1994).

Additional information from each participant was collected during an in-home interview and subsequent medical evaluation at a mobile examination center. During the in-home interview, information on age (limited to participants ≥20 years), sex, race/ethnicity, smoking history, alcohol consumption, history of diabetes mellitus, history of arthritis, and medication usage was obtained. Participants currently smoking a cigarette, pipe and/or cigar were classified as smokers while alcohol consumption was defined as having at least one drink per week in the past 12 months. The prevalence of arthritis was self-reported and defined as ever being told by a doctor or health professional. At the mobile examination center, blood pressure measurements were taken by trained interviewers and physicians using standardized measurement protocols recommended by the American Heart Association.[28] Height, weight, and lipid profile measurements were determined using standard protocols. More details are provided in the NHANES Laboratory/Medical Technologists Procedures Manual.[29]

Participants were considered to have hypertension if their mean systolic blood pressure, measured at the mobile examination center, was greater than 140 mmHg or mean diastolic blood pressure was greater than 90 mmHg, if they were told by their doctor that they have high blood pressure or hypertension, or if they were taking antihypertensive medications. Diabetes mellitus was self-reported and defined to include subjects who were told by their doctor they have diabetes and subjects who stated that they were currently using antidiabetic medication(s) such as insulin or oral hypoglycemic agents.

Definition of Obesity

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The National Heart, Lung, and Blood Institute's definition for overweight and obesity were used to categorize the degree of obesity. A BMI <18.5 was categorized as *underweight*; a BMI between 18.5 and 24.9 was categorized as *normal weight* class; a BMI between 25.0 and 29.9 was categorized as *overweight*; a BMI between 30.0 and 34.9 was categorized as *obesity class 1*; a BMI between 35.0 and 39.9 was categorized as *obesity class 2*; and a BMI ≥40.0 was categorized as *obesity class 3*. In this study, we did not differentiate between *normal weight* and *underweight* class.

Biomarkers

CRP concentrations were available for participants aged 3 years and older and fibrinogen concentrations were taken for individuals aged 40 years and older. Using blood samples collected from participants, CRP concentrations were determined using latex-enhanced nephelometry. Plasma fibrinogen levels were quantified using the Clauss clotting method and were only available for NHANES 1999–2002.[30] We analyzed the levels of CRP and fibrinogen across the classes of obesity.

Statistical Analysis

All statistical analyses were conducted in SAS 9.1 (SAS Institute Inc., Cary, NC, USA). Due to the NHANES' complex probability sampling of the US population, sample weights, stratification, and clustering of the sampling design were incorporated into all SAS survey procedures to ensure the correct estimation of standard errors, confidence intervals and p values. A 6-year sample weight was used for CRP analyses and a 4-year weight was used for the fibrinogen analysis. Two different sample weights were needed because CRP measurements were available for 1999–2004 surveys while fibrinogen was only measured between 1999 and 2002. These specific sample weights were created according to the National Center for Health Statistics guidelines to account for oversampling of certain age, sex, race/ethnicity domains and differential non-response or undercoverage.[31]

The initial study sample included 29,402 individuals with only 24,157 participants having CRP measurements. Since this study was limited to adult age 20 years or older, a total of 10,796 persons were excluded from the CRP analysis, yielding a total of 13,361 individuals for the final CRP analyses. Fibrinogen data was only publicly available for a subset of participants aged 40 years or older in the NHANES 1999–2002 giving a total of 5,690 persons for the analyses of fibrinogen levels. We limited our study sample to those age 20 years or older because only individuals with complete data for additional variables adjusted for in our analyses (i.e., smoking) were considered.

Unadjusted and adjusted linear regression models were designed to assess the association between obesity class (with normal weight [BMI<25.0 kg/m^2] as the reference point) with CRP and fibrinogen levels. Adjusted models accounted for the possible effects of sex, age, race, smoking status, alcohol usage, arthritis status, blood pressure, and triglyceride levels. Analysis of variance was used to compare mean biomarker concentrations between all groups. To determine if mean biomarker concentrations differed between participants with hypertension and diabetes compared to participants without hypertension and diabetes according to obesity class, a multiplicative interaction term was created between the BMI variable and the dichotomous disease variable for inclusion in additional regression analyses. A similar strategy was applied to test for differences in biomarker marker levels by weight class and ethnicity. Unless otherwise noted, data are presented as mean±standard error (SE) and statistical significance was set at p values <0.05.

Results

Table 1 lists the demographics of the study population according to obesity class. The majority of the study individuals were categorized as *normal* or *overweight*; 3,262 of the study participants were categorized as *obesity class 1*; 1,335 of the study population were categorized as *obesity class 2*; and 827 individuals were categorized as *obesity class 3* (BMI≥40). Estimates for the presence of diabetes and hypertension within each of the weight classes shows that those in the normal weight group had the lowest prevalence of diabetes at 1.3% and hypertension at 6.8% while those in obesity class 3 had the highest prevalence for diabetes at 11.5% and hypertension at 45.2% (Table 1).

Association between CRP Levels and Obesity Class

The association between CRP and obesity class was initially examined using linear regression without adjustments and results were similar to those from adjusted linear regression (data not shown). Table 2 presents the change in CRP levels across weight classes after adjusting the regression model for age, gender, race/ethnicity, systolic blood pressure, diastolic blood pressure, triglyceride level, presence of arthritis, smoking status, and alcohol consumption. There was a positive association between CRP concentration and each of the BMI levels (p<0.01). The mean CRP level for the reference group, which consisted of non-smoking, white males with a BMI <25 kg/m^2, was 0.05 mg/dl. With each increase in weight category, the mean CRP level increased by 0.11±0.03 mg/dl for the overweight group, 0.21±0.03 mg/dl for obesity class 1 individuals, 0.43±0.09 mg/dl for obesity class 2 individuals, and 0.73±0.09 mg/dl for obesity class 3 individuals. The largest increase in CRP concentration was among individuals in obesity class 3. A test for trend showed that the overall increasing change in CRP concentrations was statistically significant (p=0.04). Analysis on the relationship between BMI and CRP concentration persists when further stratified by ethnicity (Table 3).

Association between Fibrinogen Levels and Obesity Class

The association between fibrinogen and obesity class was initially examined using linear regression without adjust-

Table 1 NHANES Population Characteristics by Body Mass Index Categories, 1999–2004

	Body mass index categories, kg/m^2				
	Normal (<25.0) n=17,571	Overweight (25.0–29.9) n=6,407	Obesity class 1 (30.0–34.9) n=3,262	Obesity class 2 (35.0–39.9) n=1,335	Obesity class 3 (≥40.0) n=827
Characteristics					
Age, %[a]					
20.0–29.9 years	1,173 (44.4)	774 (29.3)	402 (15.2)	161 (6.1)	133 (5.0)
30.0–39.9 years	880 (36.3)	795 (32.8)	434 (17.9)	178 (7.3)	138 (5.7)
40.0–49.9 years	693 (29.3)	838 (35.4)	479 (20.2)	213 (9.0)	146 (6.2)
50.0–59.9 years	504 (28.1)	646 (36.0)	369 (20.6)	165 (9.2)	108 (6.0)
≥60 years	1,649 (33.0)	1,869 (37.5)	939 (18.9)	366 (7.3)	161 (3.2)
Gender, %[a]					
Male	8,696 (60.4)	3,431 (23.8)	1,512 (10.5)	504 (3.5)	248 (1.7)
Female	8,875 (59.1)	2,976 (19.8)	1,750 (11.7)	831 (5.5)	579 (3.9)
Race/ethnicity, %[a]					
Non-Hispanic White	6,301 (56.0)	2,752 (24.5)	1,382 (12.3)	522 (4.6)	293 (2.6)
Non-Hispanic Black	4,524 (62.3)	1,293 (17.8)	743 (10.2)	390 (5.4)	312 (4.3)
Mexican American	5,064 (60.8)	1,840 (22.1)	905 (10.9)	345 (4.1)	170 (2.0)
Other[b]	1,682 (65.5)	522 (20.3)	232 (9.0)	78 (3.0)	52 (2.0)
Current smoker, %[a]	1,368 (41.5)	1,045 (31.7)	553 (16.8)	198 (6.0)	130 (3.9)
Systolic BP (mmHg)[c]	119.3±0.4	124.1±0.5	125.5±0.5	126.8±0.7	128.0±1.0
Diastolic BP (mmHg)[c]	70.2±0.3	72.5±0.3	73.7±0.4	74.3±0.4	75.0±0.6
Triglycerides (mg/dl)[c]	118.0±3.7	159.7±4.4	177.8±7.2	175.2±7.4	170.5±6.8
Total cholesterol (mg/dl)[c]	195.3±0.9	207.7±1.0	207.5±1.2	206.6±1.7	197.7±1.8
HDL cholesterol (mg/dl)[c]	58.1±0.4	50.9±0.3	46.8±0.4	46.6±0.5	46.2±0.6
LDL cholesterol (mg/dl)[c]	114.4±1.1	125.2±1.0	126.3±1.4	122.8±2.2	118.8±2.5
Alcohol (drinks/day)[c]	2.0±0.1	2.1±0.1	1.9±0.1	1.9±0.2	1.4±0.1
C-reactive protein (mg/dl)[c]	0.3±0.01	0.4±0.01	0.5±0.01	0.7±0.04	1.1±0.06
Fibrinogen (mg/dl)[c,d]	354.3±4.4	361.4±2.7	376.6±3.2	387.7±5.1	436.9±7.2
Diabetic, %[a]	235 (1.3)	318 (5.0)	228 (7.0)	132 (9.9)	95 (11.5)
Hypertensive, %[a]	1,194 (6.8)	1,624 (25.3)	1,089 (33.4)	533 (39.9)	374 (45.2)

[a] Values depicted as n (%) of each row

[b] Includes respondents indicating multiracial or an ethnicity other than Mexican American, Non-Hispanic White, or Non-Hispanic Black

[c] Mean value±standard error

[d] Fibrinogen measurements only available for individuals age 40 years and older participating in the NHANES 1999–2002 surveys

Table 2 Adjusted Linear Regression Analysis for the Association between Biomarker Levels and Obesity Class, NHANES 1999–2004

Obesity class (body mass index, kg/m^2)	Change in CRP level (mg/dl)±SE	Change in fibrinogen level (mg/dl)±SE
Normal (<25.0)	Reference[a]	Reference[b]
Overweight (25.0–29.9)	0.11±0.03*	11.5±3.9*
Obesity class 1 (30.0–34.9)	0.21±0.03*	25.6±5.0*
Obesity class II (35.0–39.9)	0.43±0.09*	40.0±7.6*
Obesity class III (≥40.0)	0.73±0.09*	93.5±10.1*

Regression model adjusted for age, gender, race/ethnicity, systolic blood pressure, diastolic blood pressure, triglyceride level, smoking, arthritis status, and alcohol

*p<0.01, compared to reference value

[a] CRP reference value: 0.05 mg/dl

[b] Fibrinogen reference value: 287.28 mg/dl

Table 3 CRP Levels According to Ethnicity, NHANES 1999–2004

Obesity class (body mass index, kg/m^2)	Mean CRP level (mg/dl)±standard error			
	Non-Hispanic White	Non-Hispanic Black	Mexican American	Other
Normal (<25.0)	0.11±0.01 *n*=2,295	0.12±0.01 *n*=2,657	0.15±0.01 *n*=2,820	0.13±0.01 *n*=725
Overweight (25.0–29.9)	0.24±0.03 *n*=301	0.24±0.03 *n*=411	0.31±0.02 *n*=548	0.20±0.03 *n*=99
Obesity class 1 (30.0–34.9)	0.41±0.04 *n*=131	0.54±0.08 *n*=189	0.38±0.03 *n*=214	0.30±0.05 *n*=53
Obesity class II (35.0–39.9)	0.63±0.12 *n*=44	0.42±0.06 *n*=83	0.41±0.05 *n*=87	0.66±0.34 *n*=12
Obesity class III (≥40.0)	0.89±0.17 *n*=15	0.69±0.06 *n*=70	0.78±0.15 *n*=34	0.71±0.16 *n*=8

Within each obesity class, mean CRP concentration was significantly different across the ethnicity groups; p value <0.01 for the interaction term for BMI and ethnicity

ments (data not shown), and results were similar to those found in the model that adjusted for age, gender, race/ethnicity, systolic blood pressure, diastolic blood pressure, triglyceride level, presence of arthritis, smoking status, and alcohol consumption. An upward trend was observed for mean fibrinogen levels across weight classes where concentrations ranged from 287.28 mg/dl for normal weight individuals to 380.78 mg/dl for obesity class 3 individuals (p=0.04). With normal weight individuals as a reference, the mean fibrinogen levels for those in the overweight category increased by 11.5± 0.01 mg/dl, 25.6±5.0 mg/dl for obesity class 1 individuals, 40.0±7.6 mg/dl for obesity class 2 individuals, and 93.5± 10.1 mg/dl for obesity class 3 individuals (Table 2). Changes in fibrinogen levels across all weight classes compared to fibrinogen levels in the normal weight group were statistically significant (p<0.01). The greatest increase in mean fibrinogen level was among the obesity class 3 group where mean fibrinogen levels increased by 32.5% compared to fibrinogen levels in the normal weight group. Analysis on the relationship between BMI and fibrinogen levels persists when further stratified by ethnicity (Table 4).

Association between Inflammatory Biomarkers with Diabetes and Hypertension

Results from regression analysis confirmed that a synergistic relationship exists between levels of inflammatory biomarkers with diabetes and hypertension, even when stratified by BMI. Within each BMI category, additional subgroups were created based on the presence or absence of diabetes or hypertension and the mean CRP and fibrinogen concentrations were determined. Individuals with diabetes had higher mean CRP and higher mean fibrinogen concentrations than individuals without diabetes even when stratified according to BMI (Tables 5 and 6). Similarly, individuals with hypertension had higher mean CRP and higher mean fibrinogen concentrations than individuals without hypertension even when stratified according to BMI (Tables 5 and 6).

Discussion

In this cross-sectional analysis of US men and women, the lowest concentrations of CRP and fibrinogen were found among normal weight individuals. As BMI ranges increased from overweight to obesity classes 1, 2, and 3, CRP concentration increased by 0.11±0.03 mg/dl, 0.21± 0.03 mg/dl, 0.43±0.09 mg/dl, and 0.73±0.09 mg/dl, respectively, and fibrinogen levels increased by 11.5± 3.9 mg/dl, 25.6±5.0 mg/dl, 40.0±7.6 mg/dl and 93.5± 10.1 mg/dl, respectively. The strongest association between obesity and change in biomarker concentration was observed among those in obesity class 3.

Table 4 Fibrinogen Levels According to Ethnicity, NHANES 1999–2002

Obesity class (body mass index, kg/m^2)	Mean fibrinogen level (mg/dl)±standard error			
	Non-Hispanic White	Non-Hispanic Black	Mexican American	Other
Normal (<25.0)	352.41±5.21 *n*=1,045	372.31±6.95 *n*=289	360.94±9.09 *n*=304	353.32±9.38 *n*=141
Overweight (25.0–29.9)	357.89±3.33 *n*=1,057	380.96±5.52 *n*=347	353.16±3.68 *n*=525	374.17±7.32 *n*=162
Obesity class 1 (30.0–34.9)	373.94±3.77 *n*=557	406.48±7.04 *n*=196	364.60±5.62 *n*=272	375.50±9.25 *n*=74
Obesity class II (35.0–39.9)	381.54±5.99 *n*=208	418.82±10.74 *n*=118	375.20±10.06 *n*=114	403.49±16.54 *n*=23
Obesity class III (≥40.0)	439.52±8.64 *n*=111	432.99±9.78 *n*=82	412.87±13.42 *n*=54	436.15±31.49 *n*=11

Within each obesity class, mean fibrinogen concentration was significantly different across the ethnicity groups; p value=0.02 for the interaction term for BMI and ethnicity

Table 5 CRP Levels According to Diabetes and Hypertension Status, NHANES 1999–2004

Obesity class (body mass index, kg/m^2)	Mean CRP level (mg/dl)±standard error			
	No diabetes	Diabetes*	No hypertension	Hypertension**
Normal (<25.0)	0.30±0.02 n=2,960	0.63±0.11 n=196	0.26±0.01 n=3,471	0.48±0.04 n=1,039
Overweight (25.0–29.9)	0.36±0.01 n=2,940	0.46±0.06 n=298	0.35±0.01 n=3,179	0.45±0.03 n=1,507
Obesity class 1 (30.0–34.9)	0.49±0.18 n=1,494	0.55±0.04 n=214	0.48±0.02 n=1,488	0.54±0.02 n=1,009
Obesity class II (35.0–39.9)	0.70±0.04 n=543	0.95±0.23 n=125	0.68±0.05 n=529	0.75±0.07 n=494
Obesity class III (≥40.0)	1.01±0.06 n=358	1.05±0.13 n=85	0.99±0.08 n=303	1.20±0.07 n=333

*p value<0.01, CRP levels and diabetes interaction using 2-way ANOVA, **p value=0.06, CRP levels and hypertension interaction using two-way ANOVA

We observed a strong association between increasing weight class and increasing CRP concentrations. Compared to normal weight individuals, there was a 2-fold increase in mean CRP levels in overweight individuals; a 4-fold increase in obesity class 1 individuals; and an 8-fold and 14-fold increase among obesity class 2 and obesity class 3 individuals, respectively. Using data from NHANES III (1988–1994), Ford similarly found that CRP concentrations increased across six weight categories (BMI<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m^2). Ford also found that the odds ratio for elevated CRP levels above the 85th percentile for BMI of 25 to<30 was 1.51 (95% CI 1.23, 3.86); 3.19 (95% CI 2.60, 3.91) for BMI of 30 to <35; 6.11 (95% CI 4.67, 7.98) for BMI 35 to <40; and 9.30 (95% CI 6.43–13.46) for those with BMI ≥40 compared to those with BMI <25 kg/m^2.[19] Similarly, Visser and colleagues found that, with increasing BMI, the presence of elevated CRP levels, defined as CRP≥0.22 mg/dl, increases for both overweight and obese (≥30 kg/m^2) groups. Visser and colleagues also found that overweight men and overweight women were 1.41 (95% CI 1.09, 1.81) and 2.23 (95% CI 1.86, 2.67) times more likely to have elevated CRP levels compared to normal-weight counterparts.[20]

The normal range for fibrinogen is between 200 and 400 mg/dl.[32,33] In our adjusted regression analysis between fibrinogen levels and weight class, being in the overweight, obesity class 1, obesity class 2, and obesity class 3 groups placed individuals increasingly near the upper limit of normal fibrinogen levels. Elevated fibrinogen levels have been previously shown to associate with insulin resistance and atherosclerosis.[34] We also examined fibrinogen concentrations across weight class according to diabetes status. Our findings suggest that increasing severity of obesity is associated with increased risk for diabetes. The results also support the idea that inflammation may play a role in the development of insulin resistance,[35] underlying the importance of having a normal BMI to prevent the disease onset.

In addition to what has been presented in past studies, this study quantifies the estimated change in biomarker concentrations across different weight classes. As anticipated, those individuals in the highest weight class, obesity class 3, had significantly higher CRP and fibrinogen concentrations relative to the normal BMI group as well as the other weight groups. This trend did not change with adjustments for age, gender, arthritis status, race/ethnicity, or smoking, suggesting that the observed CRP–obesity relationship is not due to other factors possibly affecting CRP levels and/or weight status. When we stratified by diabetes status, we also found that individuals in obesity class 3 had higher biomarker levels than those in obesity classes 1 and 2. This was also observed when we compared

Table 6 Fibrinogen Levels According to Diabetes and Hypertension Status, NHANES 1999–2002

Obesity class (body mass index, kg/m^2)	Mean fibrinogen level (mg/dl)±standard error			
	No diabetes	Diabetes*	No hypertension	Hypertension**
Normal (<25.0)	357.5±6.3 n=890	413.4±15.4 n=100	343.8±4.9 n=1,160	381.4±5.5 n=618
Overweight (25.0–29.9)	364.3±3.8 n=964	380.7±15.8 n=139	353.2±2.7 n=1,239	375.9±3.9 n=851
Obesity class 1 (30.0–34.9)	375.2±5.3 n=469	402.1±7.5 n=85	372.8±4.4 n=535	380.5±4.9 n=564
Obesity class II (35.0–39.9)	400.6±7.2 n=178	410.9±11.6 n=50	383.1±8.0 n=206	392.1±7.5 n=257
Obesity class III (≥40.0)	441.7±9.6 n=102	444.1±15.8 n=33	438.9±12.9 n=90	435.8±7.7 n=168

*p value=0.09, fibrinogen levels and diabetes interaction using two-way ANOVA, **p value<0.01, fibrinogen levels and hypertension interaction using two-way ANOVA

CRP levels between diabetics and non-diabetics in obesity class 3 to those in the overweight and normal weight categories. Extending our analyses, we also stratified by hypertension status, reporting the mean biomarker concentrations within each weight class for a representative US population. The general trend supports our primary hypothesis that inflammation severity, indicated by elevated biomarker levels, directly correlates to weight class.

Inflammation in the presence of obesity is thought to arise primarily in adipose tissue as a result of chronic disruption of metabolic homeostasis, which leads to increased cytokine production and the activation of inflammatory signaling pathways in the body.[12,13,36] A recent clinical study by Madsen and colleagues investigated the effects of short-term and long-term weight loss on levels of CRP and fibrinogen among obese subjects and found that long-term weight loss was associated with decreased CRP and fibrinogen concentrations.[37] A systematic review found that for each 1 kg of weight loss, mean CRP levels were reduced by 0.13 mg/l.[38] Moderate, short-term weight loss, however, was shown to have no effect on fibrinogen levels,[23] suggesting that long-term weight loss solutions through lifestyle changes or surgical intervention may be more useful for reducing inflammation and related disease risks.

Limitations of this study include the lack of repeated measurements of biomarker levels as well as the absence of information regarding any previous medical or surgical treatment for obesity. Additionally, the extent of our study on inflammatory biomarkers was limited by the availability of biomarker measurements in the NHANES dataset; we did not have the opportunity to access other markers of inflammation such as interleukin-6 or TNF-alpha. The population used for our CRP analyses also differed from the population used for the fibrinogen analysis because fibrinogen data was only collected among those who were 40 years of age and older between 1999 and 2002 while CRP measurements were taken among those who were 20 years of age and older between 1999 and 2004. There is also the possibility for information and recall bias in this study because data on hypertension, arthritis, and diabetic status were collected by means of self-report. However, in this study, possible information and recall biases were minimized by taking into account additional data collected on hypertension and diabetes medication usage as well as any relevant examination or laboratory data. Additionally, the under- or over-reporting of hypertension and diabetes should be similar across BMI categories. Despite these limitations, this study utilizes a large, comprehensive data set that serves as a representative sample of the US population, allowing for greater generalizability of the study results. Multiple markers of inflammation were also assessed, which increased the possibility of capturing a more complete description of inflammatory status among individuals. Future studies are needed to determine if the changes in inflammatory markers further differ among obese individuals, and whether inflammatory biomarker levels decrease at a different rate and by different amounts in obesity class 1 vs. obesity class 2 or 3. If trends from this current study are persistent in such future studies, we anticipate that changes in levels of inflammatory biomarkers will differ according to weight class. Thus, the current findings of an association of CRP and fibrinogen and body weight, if causal, would imply that weight reduction leads to reduced prevalence of inflammation with attendant public health benefits.

Conclusions

This study demonstrates that levels of inflammatory biomarkers vary across weight classes, and that this difference in CRP and fibrinogen concentration is persistent when patients are subgrouped by ethnicity and by the presence or absence of diabetes and hypertension. As shown in our analyses, an increase in severity of obesity corresponded to higher CRP and fibrinogen levels. Such elevated biomarker concentrations based on a 6-year period (1999–2004) suggest that the optimal weight class should be within normal range of having a BMI less than 25.0 to possibly reduce the burden of obesity-related comorbidities in the US.

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ORIGINAL ARTICLE

Surgery for Gastrointestinal Stromal Tumors of the Stomach

Gerd R. Silberhumer · Martin Hufschmid · Fritz Wrba · Georg Gyoeri · Sebastian Schoppmann · Barbara Tribl · Etienne Wenzl · Gerhard Prager · Friedrich Laengle · Johannes Zacherl

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Abstract
Background Gastrointestinal stromal tumors (GISTs) are the main mesenchymal neoplasms in the gastrointestinal tract. Tumor size, mitotic rate, and location correlate with potential malignancy and recurrence rate. Results of surgical treatment of gastric GIST are analyzed with emphasis on recurrence of disease after intermediate follow-up.
Methods From 1998 to 2006, a total of 63 patients (median age 62.1±14.1) underwent gastric resection for GIST. Fifty-five patients (93.6%) returned for follow-up investigations, which included computed tomography in 45, gastroscopy in 32, and endosonography in 29. Positron emission tomography was done in five patients.
Results Mean tumor size was 5.3±3.8 cm. Open atypical gastric resection was done in 32, distal gastric resection in five, and remnant gastrectomy in four patients. Laparoscopic gastric resection was initiated in 22 patients; the conversion rate was four of 22 (18.2%). Overall, R0 resection was reached in 61/63 patients (96.8%). According to the Fletcher criteria, 33 tumors (52.4%) were classified as intermediate or high risk GIST. Six patients (9.5%) died of unrelated causes before follow-up. After a median follow-up of 2.5 years, overall recurrence rate was 7.0% after R0 resection.
Conclusion Histologically proven complete resection is an effective treatment for gastric GIST. Laparoscopic procedures were carried out successfully in selected patients.

Keywords Gastric GIST · Endosonography · Malignant behavior · Laparoscopic surgery

Introduction

Gastrointestinal stromal tumors (GISTs) are considered to be the most common mesenchymal tumors of the gastrointestinal (GI) tract.[1] There has been considerable discussion on the definition of GIST for decades. Due to their

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G. R. Silberhumer · G. Gyoeri · S. Schoppmann · G. Prager · F. Laengle · J. Zacherl
Department of General Surgery, University Clinic of Surgery, Medical University Vienna, Vienna, Austria

M. Hufschmid · E. Wenzl
Department of Surgery, Landeskrankenhaus Feldkirch, Feldkirch, Austria

F. Wrba
Department of Pathology, Medical University Vienna, Vienna, Austria

B. Tribl
Department of Gastroenterology and Hepatology, University Clinic of Internal Medicine III, Medical University Vienna, Vienna, Austria

J. Zacherl (✉)
University Clinic of Surgery, Medical University Vienna, AKH 21.A, Waehringer Guertel 18-20, A-1090 Vienna, Austria
e-mail: johannes.zacherl@meduniwien.ac.at

appearance, GISTs were previously classified as smooth muscle tumors, such as leiomyomas, leiomyoblastomas, and leiomyosarcomas.[2] Clinical, molecular-biologic, and histopathologic investigations confirmed that GISTs are completely different tumors from leiomyomas.[3] Mazur et al. used the term *GIST* for the first time in 1983 to describe a non-epithelial neoplasm of the GI tract that lacks immunohistochemical characteristics of Schwann cells and smooth muscle cells.[4]

It has recently been proposed that GIST tumors originate from stem cells that differentiate to the interstitial cell of Cajal, an intestinal pacemaker cell staining for the myeloid stem cell antigen CD34 and frequently marked by the presence of the c-kit protooncogene.[5–8] Discovering gain-of-function mutations in the c-kit proto-oncogene was of crucial importance concerning the genesis and classification of these tumors. The kit protein is often detected by immunohistochemical assays for CD117 antigen.[9,10] Almost all GISTs have constitutive ligand-independent activation of the mutated kit protein, resulting in a shift of balance between cell survival and proliferation, away from apoptosis.[11,12]

Most GISTs are found in the stomach (up to 70%) and the small intestine (up to 30%), but can also occur in the colon and rectum (up to 15%).[1,13,14] GISTs rarely develop in the omentum, mesentery, or retroperitoneum. Over 95% of patients present with a solitary primary tumor that grows in an endophytic way and many are well confined by a thin surrounding pseudocapsula.[15] Up to 60% of GISTs recur despite histopathologically complete resection; the most common sites of metastases are the peritoneum and the liver.[16] Regional lymph node metastases are rare (around 6%).[1,16,17] The site of origin within the GI tract has also been identified as a prognostic factor.[13] Gastric GISTs tend to a more favorable clinical course compared with those from the small intestine. In 2002, Fletcher et al. published a paper on the risk of the aggressive behavior of GISTs. The degree of risk depends on tumor size and mitotic count.[9]

Although GISTs have been reported in patients of all ages, a peak with a median age of approximately 60 years has been found.[1,16,18] In most patients, the diagnosis is sporadic, and the tumors can grow very large before producing symptoms as they tend to displace adjacent structures without invasion. Some unspecific symptoms include abdominal discomfort, bloating, pain, increased abdominal girth, and GI bleeding.

Surgical treatment is the only chance of cure for patients with primary localized GIST. There is no surgical consensus about laparoscopic or open surgical treatment. The tumor must be resected en bloc without opening it to prevent subsequent peritoneal seeding.[16,19] There is no apparent benefit in obtaining wide resection margins.[19,20] Lymphadenectomy is generally not indicated because metastases to the lymph nodes are rare.[20] Laparoscopic resection can be done easily in most locations by wedge resection or tumorectomy and gastric suture. Controversy surrounds the maximum diameter of GIST for laparoscopic resection. Since respective reports are limited, we evaluated the results of gastric GISTs treated at our institutions.[21–24]

Patients and Methods

Study Population

The study cohort consisted of 63 patients suffering from GIST in the stomach were treated by surgery at the Department of Surgery, Hospital Feldkirch, Vorarlberg (11 patients; 17.5%) and at the University Clinic of Surgery, Medical University Vienna (52 patients; 82.5%) from 1998 to 2006. Histologic diagnosis of all tumors was confirmed by pathologists of the Department of Pathology of the Medical University Vienna.

Histologic Classification

Diagnosis of GIST was made according to the recommendations of Fletcher et al. outlined in a consensus approach concerning histomorphology, immunohistochemistry, and definition of risk of this neoplasm.[9] Histologically, the tumors were classified in three type categories: spindle cell, epitheloid, or mixed. Immunhistochemically, the tumors were analyzed for expression of CD117 (the c-kit proto-oncogene product), CD34, desmin, smooth muscle actin (SMA), and S100. Immunohistochemistry was done using Vectastain Elite PK6100 Standard (Vector Laboratories, Burlingame, CA), based on the avidin–biotin peroxidase complex system and diaminobenzidine as the chromogen. The antibodies used are listed in Table 1.

For estimating the risk of aggressive behavior, tumors were classified in four categories based on size and mitotic count as very low risk, low risk, intermediate risk, and high risk neoplasms.[9] Resection was classified as incomplete when gross residual disease was present at surgery or when resection margins were involved histologically.

Follow-up

All patients who received surgical treatment for gastric GIST were invited for follow-up investigations between October 2006 and March 2007. These consisted of gastroscopy, contrast-enhanced multislice computed tomography (CT) with gastric filling, endosonographic ultrasound (EUS), or positron emission tomography (PET).

Table 1 Primary Antibodies Used in This Study

Antigen	Clone	Final protein concentration (mg/L)	Pretreatment	Source
CD117	Polyclonal A4502	25.65	HIER	Dako, Glostrup, Denmark
CD34	Monoclonal QBEnd/10	50.00	None	Novocastra, New Castle, UK
Desmin	Monoclonal D33	1.00	None	Monosan, Uden, Netherlands
SMA	Monoclonal 1A4	19.50	MWE	Dako, Glostrup, Denmark
S100	Polyclonal Z0311	2.25	None	Dako, Glostrup. Denmark

HIER heat-induced epitope retrieval in citrate buffer, pH 6.0; *MEW* microwave epitope retrieval in citrate buffer, pH 6.0

Statistical Analysis

Statistical analysis was done using independent samples *t* test, chi-square test, and Kaplan Meier survival analysis. All data were calculated using SPSS version 11.0.4 (SPSS Inc., Chicago, IL).

Results

The cohort consisted of 63 patients (23 female, 36.5%; 40 male, 63.5%); mean age was 62.3±14.4 years. In 29 patients (46.0%), the tumor was diagnosed by chance, 15 patients (23.8%) were symptomatic because of GI bleeding, 12 patients (19.1%) appeared with uncharacteristic abdominal pain, and seven (11.1%) presented with other symptoms.

Tumor Characteristics

Twenty-nine tumors (46.0%) were located in the corpus, 18 (28.6%) in the antrum, ten (15.9%) in the fundus region, and six (9.5%) at the esophagogastric junction. Mean tumor size was 5.3±3.8 cm and mean mitotic count was 5.2±6.1 per 50 high-power fields. According to the Fletcher criteria five tumors (7.9%) were classified as very low risk, 25 (39.7%) low risk, 15 (23.8%) intermediate risk, and 18 (28.6%) high risk (see Table 1). In nine patients (14.3%), immunohistochemical staining was negative for c-kit. Immunhistochemical analysis was positive for CD117 in 58 patients (92.1%) and positive for CD34 in 39 (61.9%). Histologically, 44 tumors (69.9%) were characterized as spindle cell type, 14 tumors (22.2%) as epitheloid type, and five tumors (7.9%) as mixed type.

Surgical Aspects

Laparoscopic tumor resection was initiated in 22 patients (34.9%). It was necessary to convert to an open approach in four (18.2%). Reasons for conversion were inappropriate tumor location (three patients, 13.6%) and size (one patient, 4.6%). Additionally, two Toupet and two anterior fundoplasty procedures were carried out laparoscopically due to gastroesophageal reflux disease or tumor localization in the fundus.

Open procedures consisted of atypical stomach resection in 32 patients (50.8%), five (7.9%) distal gastric resections, and remnant gastrectomy in four (6.4%). Additionally, three splenectomies, two partial colectomies, and one cholecystectomy were carried out. Tumor and patient characteristics are shown in Table 2.

R0 resection was achieved in 61 patients (96.8%) and R2 resection in two patients (3.2%). In one of the two R2-resected patients, only tumor debulking was possible; the other patient had synchronous metastatic disease in the peritoneum and liver that was not resectable. No hospital mortality was encountered. One patient suffered from catheter sepsis, one from postoperative ileus, which was treated conservatively, and one patient developed a gastrocutaneous fistula. The mean time of hospitalization was significantly lower after laparoscopic procedures (7.8 vs. 12.2 days; $p<0.01$). Two patients (3.2%) received imatinib as adjuvant chemotherapy. In both cases with R2 resection imatinib was administered with palliative intention.

Follow-up

Follow up was completed in 59 patients (93.6%), since four patients (6.4%) were lost to follow-up. Of these, six patients (9.5%) died of unrelated causes before follow-up investigations after R0 resection (Table 3). Follow-up investigations consisted of CT (45 patients, 71.4%), gastroscopy (32 patients, 54.2%), EUS (29 patients, 49.2%), and PET (five patients, 8.5%). Mean follow-up time was 37.0±27.9 months (median 30.1 months).

Recurrence after histologically complete resection was observed in four of 57 patients (7.0%). Local recurrence was seen in two patients: one patient developed liver metastasis and the other showed multiple recurrent lesions. Three patients with GIST recurrence were treated with imatinib: one patient showed stable disease, one showed partial response, and the third received imatinib in a neoadjuvant setting before liver resection. One patient died

Table 2 Patient Characteristics and Results in Open and Laparoscopic Tumor Resection Groups

		Open	Laparoscopic[a]
Patients (*n*)		41	22
Age (year)		62.5±16.1	61.3±9.3
Tumor size (cm)		5.8±4.0	3.5±1.4
Surgical treatment (n)	Tumorectomy	30	19
	Wedge resection	–	3
	Distal resection	5	–
	Gastrectomy	4	–
	Debulking	2	—
R Status (n)	R0	39	22
	R2	2	0
Fletcher classification (n)	very low	1	4
	Low	13	12
	Intermediate	11	4
	High	16	2
Complications (*n*)		3	0
Hospitalization (days)		12.8±5.0	7.8±3.1
Recurrence		4	0
Follow-up (months; range)		41±31	30±20

[a] Includes conversion

2 months after R2 resection because of cardiac insufficiency. The other patient with an R2 situation showed no tumor progression under imatinib therapy. Kaplan Meier curves for overall survival are shown in Fig. 1.

Discussion

In this study, we focused on gastric GISTs treated by resection. The stomach is the predominant location for GISTs, comprising 45% to 70% of all GISTs.[13] In the literature, the definitions of "benign" and "malignant" GIST are still controversial; the main focus is identification of lesions with high potential for metastasis. Increasingly, long-term follow-up reports tend to outline the malignant potential of this kind of tumor. Considering recurrence rates around 20% and more, the malignant behavior of this kind of tumor should be recognized.[1,25,26] Five-year survival rates vary between 28% and 65% dependent on the possibility of complete resection.[1,3,19,27,28] In recent reports, tumor size and mitotic count are identified as prognostic markers among patients who underwent GIST resection.[1,9,14,29] No apparent benefit was achieved by extended resection margins or lymphadenectomy.[19,20] According to Fletcher, R0 resection combined with low-risk profile are predictive for long-term survival.[1,9]

In the present report, recurrence rate after complete resection of GIST is below 10% within a mean follow-up period of 30 months. In contrast, other centers reported recurrence rates up to 50%.[1,21,30] Various circumstances may be considered to explain this discrepancy.

Table 3 Distribution of Follow-Up Investigations

	PET	EUS	Gastro	CT
PET	5	1	1	4
EUS	1	29	29	20
Gastro	1	29	32	25
CT	4	20	25	45

CT computed tomography; *EUS* endoscopic ultrasonography; *Gastro* gastroscopy; *PET* positron emission tomography

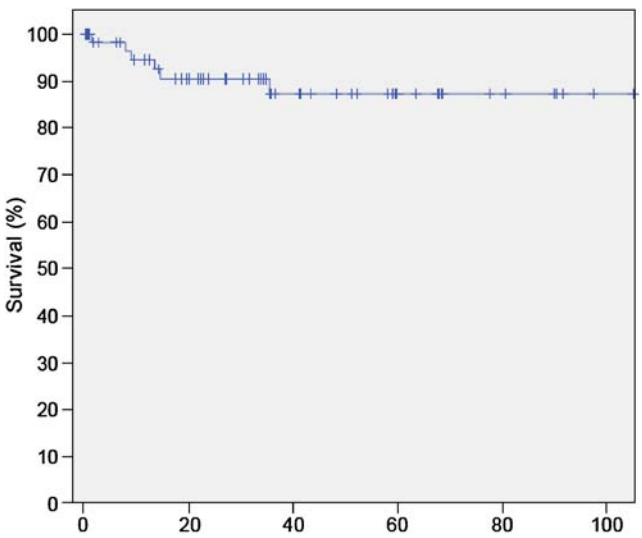

Figure 1 Overall survival.

First, one may argue that follow-up investigations were insufficient in our study. However, in comparison with previous reports, patients were reevaluated very carefully in our study by extensive methods such as multidetector gastric hydro-CT, upper GI endoscopy, and/or endosonography. This report is the first presenting EUS as follow-up examination after GIST resection. Most of the patients underwent at least two reevaluation methods; some also had additional PET scanning. Thus, follow-up methodology in our population compares favorably with other series and fulfills the currently established standards.[9,24]

EUS is well established as a preoperative diagnostic tool but was previously used only in selected patients or case studies for follow-up investigations.[16] Aside from allowing inspection of the gastric cavity/mucosa, this method enables the investigator to visualize the gastric wall below the scar after surgical treatment. Thus, the implementation of EUS may help to detect recurrence of disease within the stomach. As a disincentive, EUS is more invasive, and patient compliance is limited in the follow-up setting when compared with CT. In our study, 24 of 53 patients (45.3%) refused EUS for follow-up. EUS can increase follow-up sensitivity in scientific trials, but it might not be appropriate in general practice follow-up, as there is no evidence that presymptomatic detection of recurrence is beneficial for the individual patient. As mentioned by other authors, PET scan has proven highly sensitive but is still costly and limited in availability.[24]

Secondly, the observation time may influence recurrence rate. However, the duration of follow-up in the presented cohort is within the range of previous papers.

Size and risk category distribution have been shown earlier to have prognostic potential. Again, tumors were homogenously distributed according to the Fletcher classification in this series. More than 50% of tumors were estimated as intermediate or high risk GISTs. We conclude that risk distribution resembles the pattern of other reports. It is worth mentioning that all patients who experienced recurrence were treated for high-risk GISTs.

Previous large series generally included GIST of the entire GI tract. Reports exclusively presenting results of gastric GIST are rare and are hampered by small study populations and/or short follow-up intervals.[21–23] On the other hand, as has been observed earlier, GISTs arising in the stomach have a more favorable outcome compared with tumors of the intestine.[9,13] In other words, authors exclusively reporting on gastric GIST encountered recurrence rates of about 10%, which correlates well with our observation.[21,31,32] It is our impression that inclusion of GIST of the entire GI tract may be the main reason for the discrepancy regarding recurrence rates between the earlier large series (including gastric and intestinal GIST) and our population (exclusively gastric GIST).

The use of adjuvant chemotherapy has been kept very restrictive in our institutions because of the absence of scientific evidence of benefit of multimodal treatment for resectable gastric GIST. Nevertheless, the trend in the literature points toward a combined treatment or strategy consisting of chemotherapy after surgery for intermediate and high risk GIST.[16,33] However, prospective long-term studies have to evaluate the benefit of combined therapy in cases of gastric GIST.[33,34]

Besides evaluating disease recurrence, we focused on the laparoscopic treatment approach in this report. Initially, gastric GIST was predominantly approached by an open technique to ensure negative resection margins and to avoid tumor rupture.[16,24] During a GIST consensus meeting in 2004, a maximum diameter of 2 cm was considered the limit for a laparoscopic approach.[24] Nevertheless, some centers tend to enlarge laparoscopic resection to GISTs with a maximum diameter of up to 5 cm and more.[21–23]

Certain tumor localizations may limit laparoscopic resection. In the literature, conversion to an open approach is more likely in patients with tumor proximity to the gastroesophageal junction.[20,35] In our opinion, surgeons should carefully evaluate laparoscopic stapled resection of tumors located near the esophagogastric junction and the gastric outlet to avoid functional stenosis.[35] By laparoscopic tumor excision and suturing of the defect, as opposed to laparoscopic stapled wedge resection, the extent of loss of gastric wall may be limited to the absolutely necessary amount. If gastric outlet obstruction is likely after resection of large prepyloric tumors, laparoscopic distal gastric resection and reconstruction may be performed in experienced centers. Locally advanced GIST directly located at the esophagogastric junction may require open cardiac resection and jejunal interposition.

In our experience, the laparoscopic approach may be favored in experienced hands because of reduced access trauma, shorter hospitalization, and preserved abdominal wall integrity.[23] Large tumors (up to 6 cm) can be retrieved safely in a bag by functional muscle preserving minilaparotomy. We did not observe any case of tumor rupture or any recurrence in the laparoscopic group. All patients with recurrence of disease were originally treated by open access. Of course, we are aware that this observation may be subject to a selection bias.

Exophytic tumor growth and the observed rarity of lymphatic involvement, which facilitate surgical treatment and laparoscopic access, could turn laparoscopic resection into the standard procedure in tumors smaller than 7 to 10 cm.[19,20] In this study, we were able to show that laparoscopic treatment is a safe procedure even in patients with tumors up to 6 cm. The increasing indication for laparoscopic tumor resection may result in reduced costs for the healthcare system because of benefits like reduced

hospitalization and back to work time and in reduced surgical morbidity, if experience in various laparoscopic gastric resection techniques is warranted.

Conclusion

In conclusion, radical surgery for gastric GIST is a safe treatment and offers a high likelihood for cure. Recurrence of gastric GIST after R0 resection is rare after both open and laparoscopic resection. In our opinion, laparoscopic treatment for GIST can be offered even in tumors larger than 2 cm if complete resection and retrieval of the intact tumor is warranted. Depending on the location of the tumor, the indication for laparoscopic resection can safely be expanded to tumors even larger than 5 cm. Regarding multimodal treatment, further studies are needed to prove the benefit of adjuvant chemotherapy for histologically completely resected gastric GISTs.

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ORIGINAL ARTICLE

Surgical Therapy for Gastrointestinal Stromal Tumours of the Upper Gastrointestinal Tract

Amitabha Das · Robert Wilson · Andrew V. Biankin · Neil D. Merrett

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Abstract
Aim This study aimed to examine clinicopathological features and outcomes after primary resection of gastrointestinal stromal tumours (GIST) of the upper gastrointestinal tract
Method Fifty consecutive patients were identified as having a mesenchymal tumour of the upper gastrointestinal tract resected at our institution, of which 47 were GISTs. The influence of clinicopathological variables on disease-free survival was evaluated using Kaplan–Meier estimates and Cox hazard model.
Results The median age was 62.8 (21.3–94.7). The commonest presenting symptoms were anaemia (43%) and pain (34%). Tumours were located in the stomach (64%), small bowel (34%) and oesophagus (2%). Median follow-up was 20.4 (2–106) months. Fletcher low/intermediate-risk tumours had a significantly better (p=0.0008) 2- and 5-year actuarial survival of 100% compared with 88% and 58% for high-risk group. Recurrence-free survival at 2 and 5 years was 100% for low/intermediate-risk group compared with 68% and 45% for the high-risk group (p=0.0008). Univariate analysis of predictors of recurrence identified male sex, high mitotic rate and tumour size as significant. Multivariate analysis showed high mitotic rate as the only poor prognosticator (Hazard ratio=16.7, p=0.02).
Conclusion Surgical excision of low- and intermediate-grade GIST has an excellent prognosis. Surgery remains the mainstay of treatments, and high-grade tumours carry a significantly worse prognosis. High mitotic rates are an independent poor prognosticator.

Keywords Gastrointestinal stromal tumours · Surgery · Outcomes · Prognostic factors

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A. Das · A. V. Biankin · N. D. Merrett
Departments of Surgery and Gastroenterology,
Bankstown Hospital, University of New South Wales,
Eldridge Rd,
Bankstown, New South Wales 2200, Australia

R. Wilson · N. D. Merrett
Department of Surgery, Liverpool Hospital,
Elizabeth St Liverpool,
Sydney, New South Wales 2170, Australia

A. V. Biankin · N. D. Merrett
Cancer Research Programme,
Garvan Institute of Medical Research,
384 Victoria St. Darlinghurst,
Sydney, New South Wales 2010, Australia

N. D. Merrett (✉)
Upper GI Surgery, Sydney Southwest Area Health Service,
Bankstown Hospital,
Eldridge Rd,
Bankstown, New South Wales 2200, Australia
e-mail: neil.merrett@sswahs.nsw.gov.au

Introduction

Gastrointestinal stromal tumour (GIST) is the commonest mesenchymal tumour of the gastrointestinal tract. GISTs have only relatively recently been recognised as a distinct entity and in the past were often classified variously as leiomyoma, leiomyosarcoma, leiomyoblastoma or schwannoma.[1,2] GISTs are thought to arise from the interstitial cell of cajal.[3] A key mutation in the development of GIST involves a tyrosine kinase receptor function gain, which becomes constitutionally active resulting in proliferation of cells. The Ckit or CD117 is the commonest mutated protein involved, followed by PDGFRA mutations.[4] Improved understanding of these mutations has enabled the development and application of targeted therapy using tyrosine kinase inhibitors.[5] Targeted therapy has demonstrated efficacy in the treatment of metastatic or inoperable GIST, but currently definitive surgical resection offers the only possibility of cure. This study's aim was to evaluate the outcome and determine prognostic factors after surgical treatment of a primary GIST in our series of patients.

Material and Methods

A retrospective review of a prospectively collected database was searched for the last 50 consecutive patients at our institution to have undergone primary resection of upper gastrointestinal mesenchymal tumours. Of the 50 patients, 47 had excision of a GIST. The resections were performed between Dec 1999 and July 2008.

Patient demographics, symptoms at presentation, site of tumour and operation performed were recorded. The histological features of the tumour recorded included size, mitotic rate, presence of ckit or CD34 marker and necrosis or ulceration of the tumour. Tumour recurrence and mortality were used to evaluate outcome. The Fletcher[6] classification was used to stratify patients into low, intermediate and high risk for disease progression. Kaplan–Meier analysis with log rank test for significance was used to evaluate, in a univariate model, factors that affected recurrence-free survival. A multivariate Cox proportional hazard model was used to further examine prognostic factors identified in the univariate model.

Data analysis was performed using StatView v4.5 (Abacus Concepts Inc., Berkeley, CA, USA) for PC.

Results

Between Dec 1999 and July 2008, 47 patients had a primary excision for GIST. There were 26 males (55%) and 21 females (45%). Median age was 63 (see Table 1).

Table 1 Patient Characteristics

Number of patients	47
Male:female	26:21
Median age (range)	62.8 (21.3–94.7)
Presentation (%)	
Haematemesis/melaena	10 (21.3)
Anaemia	20 (42.6)
Obstruction	6 (12.7)
Pain	16 (34.0)

The commonest symptom at presentation was pain (34%), then haematemesis or melaena (21%), followed by obstructive symptoms (13%). Anaemia was present in 42% of patients.

The commonest site for GIST was the stomach, followed by duodenum, jejunum, ileum and oesophagus (see Table 2).

Resections performed included gastro-oesophagectomy for lower oesophageal and cardio-oesophageal tumours and total gastrectomy for large and/or proximal gastric tumours. Distal gastrectomy was performed for larger tumours of the antrum. For smaller body or fundal lesions, a laparoscopic wedge excision was carried out. Lesions in the second part of the duodenum were treated with a pancreaticoduodenectomy. Small bowel tumours were treated by segmental excision (Table 3).

The Fletcher[6] classification was used to stratify tumours as low, intermediate or high grade. Briefly, low-grade tumours are those with size <5 cm, mitotic count <5/50 high-power field (HPF). Intermediate grade are those with size between 5 and 10 cm with mitotic count <5 or size <5 cm and mitotic count of 6–10. High-grade lesions are those with size >10 cm or mitotic count >10 or size >5 cm with mitotic count>5.

Table 2 Tumour Location

Location of tumour	Number (% total)
Stomach	30 (64%)
Gastro-oesophageal jct	1 (2%)
Cardia	4 (9%)
Fundus	8 (17%)
Body	10 (21%)
Antrum	7 (15%)
Duodenum	7 (15%)
D2	4 (9%)
D4	3 (6%)
Jejunum	6 (13%)
Ileum	3 (6%)
Oesophagus, distal	1 (2%)

Table 3 Operations Performed

Surgical procedure	Number (% total)
Distal/partial gastrectomy	21 (45%)
Small bowel resection	12 (26)
Laparoscopic wedge excision	5 (11%)
Whipple's operation	4 (9%)
Total gastrectomy	3 (6%)
Oesophagectomy	2 (4%)

There were 20 low-risk tumours, 13 intermediate and 14 high-grade tumours (see Table 4). The overall median follow-up was 20.4 months (2–106 months). No deaths or recurrences occurred in the low-risk group. One distant recurrence but no deaths occurred in the intermediate group. Four patients in the high-risk group had distant recurrence and one other patient had metastatic disease at initial presentation. There were four deaths in this group. Tyrosine kinase inhibitors were not used in an adjuvant setting, with therapy only being instituted in the presence of proven recurrence. Imatinib was the preferred agent used in this setting. Sunitinib was used in two patients who developed resistance to imatinib.

Tumours classified as Fletcher low or intermediate risk had a significantly better (p=0.0008 chi-squared test) 2- and 5-year actuarial survival of 100% compared with 88% and 58% for the high-risk group. Recurrence-free survival at 2 and 5 years was 100% for the low- and intermediate-risk group compared with 68% and 45% for the high-risk group (p=0.0008 log rank test). The median time to death following recurrence was 32 months, ranging from 20 to 49 months. The Kaplan–Meier plot for recurrence-free survival according to tumour risk is shown in Fig. 1a.

Clinicopathological variables were further examined using a univariate model to determine significant predictors of recurrence (Table 5). Kaplan–Meier estimates with a log rank test for significance was used. Clinical variables examined included age >62.8 (median age of the group), gender, presence of anaemia or symptoms of pain. Pathological variables examined included presence of necrosis, ulceration, ckit or CD34 expression, tumour size >10 cm, a mitosis count >10 per 50 HPF. A p value <0.2 was considered significant in the univariate model. Female sex, a mitotic count >10 and tumour size >10 cm were found to be significant (see Fig. 1b–d). When these three variables were analysed in a Cox proportional hazard model, the only independent predictor of risk found was the mitotic count of the tumour (p=0.02).

Discussion

GISTs were once thought to be rare, but it is now appreciated that, while these tumours are not common, the incidence is several fold higher[7] than initially thought, possibly due to increased use of upper gastrointestinal endoscopy.[8]

The nearly even sex distribution of tumours and median age of 63 in our series of patients is consistent with published reports. We however found a broader age range (21–94 years) to that reported (40–80 years).[9–11]

Bleeding and anaemia are a common presentation (42%) and the development of symptoms is related to the size of the tumour. Larger tumours may also present with pain and obstruction.[6,12,13] Asymptomatic GISTs are usually found incidentally at endoscopy or laparotomy.

Surgery is the mainstay of treatment for primary localised GIST, its aim being to remove the tumour with clear margins

Table 4 Clinicopathological Features vs Fletcher Risk of Tumours

	Low	Intermediate	High
Number of patients (Male:female)	20 (9:11)	13 (6:7)	14 (11:3)
Median age (years)	65.1	65.7	60.9
Mean size tumour in millimeter (range)	33.5 (5–50)	72.2 (56–100)	97.6 (35–220)
Ckit positive (%)	95	92	100
CD34 positive (%)	50	69	57
Necrosis (%)	5	38	71
Ulceration (%)	20	62	93
Necrosis and ulceration (%)	0	23	71
Lymph node metastasis	0	0	0
Pain (%)	35	38	35
Anaemia (%)	55	54	79
Tumour recurrence (n, %)	0	1 (7.7%)	4 (28.6%)
Death (n, %)	0	0	4 (28.6%)

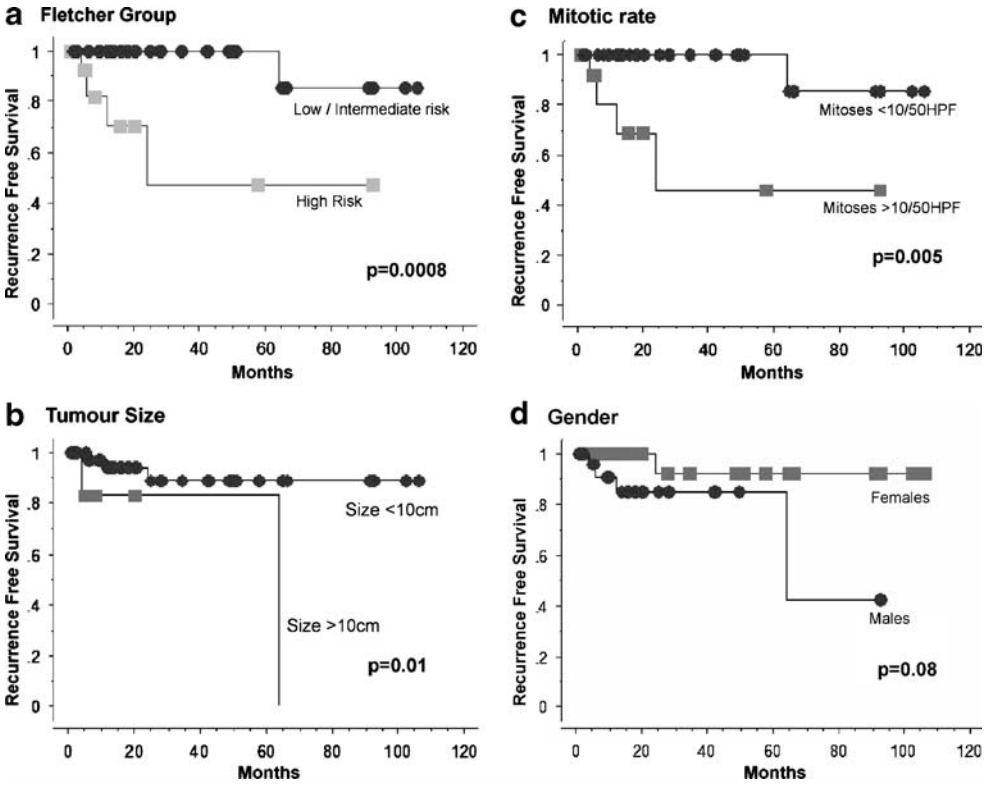

Figure 1 Kaplan–Meier plots according to **a** Fletcher risk, **b** tumour size, **c** mitotic rate and **d** gender.

(R0). This may necessitate removal of the entire organ afflicted such as the stomach for larger lesions, though more limited resections can be used with smaller lesions if the principle of a R0 resection is not compromised.

Minimally invasive approaches are being increasingly utilised, especially for tumours requiring limited resections.[14] Tumours most amenable to a laparoscopic approach are those located in the gastric body or fundus. In our series, 17% of patients with gastric GISTs had a minimally invasive resection. None of these patients had compromise of the resection margins. Endoscopic tattooing of the tumour margins either pre- or intra-operatively is a useful technique to help safeguard the resection margins in laparoscopic resections.

Tumour seeding from rupture of a GIST[15] is a potential complication which would render the patient incurable and is a risk at open and particularly during minimally invasive surgical approaches. Careful tumour handling is imperative at all times, and minimal manipulation of the tumour by graspers during laparoscopic surgery is advisable and the tumour should be enclosed in a bag in removal through the skin incision.

Table 5 Univariate and Multivariate Analysis of Predictors for Recurrence

	Number at risk	Univariate analysis	Multivariate analysis hazard ratio (95% CI)	*P* value
Age>62.8	23	p=0.81		
Female sex	21	p=0.08*	0.617 (0.046–8.20)	0.71
Ulceration	25	p=0.21		
Necrosis	16	p=NS		
CD34 positive	27	p=0.99		
Ckit positive	45	p=NS		
Mitosis >10/50	13	p=0.005*	16.7 (1.49–186.7)	0.02*
Size >10 cm	6	p=0.015*	5.76 (0.661–50.1)	0.11
Location in Stomach	30	p=0.68		
Presence of anaemia	29	p=0.26		
Pain symptoms	17	p=0.58		

Asterisks refer to p value reaching statistical significance

Lymphadenectomy is not usually required when a pre-operative diagnosis of a GIST has been made unless there is evidence of nodal spread either by pre-operative staging with computed tomography scanning, positron emission tomography scan or endoscopic ultrasound or if nodes appear to be involved at the time of surgery.[16] Lymph node involvement is a late event in the evolutionary progression of the tumour and is often preceded by haematogenous spread with a described risk of less than 2%.[17,18] Nodal disease was not identified in any of the cases in our series either with pre-operative investigations or at final histology, even in the high-risk group.

The biological behaviour of GISTs is uncertain, and it is difficult to classify a tumour into a definite benign or malignant category. Instead, risk stratification is used to predict risk of recurrence. The Fletcher[6] classification is one such approach; it is widely used and is based on tumour size and mitotic rate. Various other risk factors have been assessed in the literature, including age, sex, location of tumour and ckit and CD34 markers. In general, consensus for variables other than size and mitotic rate is lacking. While males have been reported[19] to have a worse outcome and higher rates of high-risk tumours,[20] this has not been supported by other studies[21,22] including ours ($p=0.08$)

Small bowel GISTs have been reported as having a worse prognosis compared to gastric tumours[20,22,23,24] but this has been challenged by other studies.[1,19,25]. Our series found no worse outcome being associated with small bowel tumours.

We confirmed the significance of tumour size and mitotic rate for predicting recurrence. However, on multivariate analysis, the only independent variable was mitotic rate ($p=0.02$).

Tumour size was not an independent predictor ($p=0.11$). Wu in a series of 100 GIST resections[26] and Singers' series of 48 patients[27] similarly found mitotic rate but not size to be an independent prognosticator. Larger series, however, have found both size and mitotic rate to be independent predictors.[19,28] This discrepancy may be explained by review of the hazard ratio as the hazard ratio for mitotic count >10/50HPF is high (HR 14.6–45.9) and is typically several fold larger than that for size >10 cm (HR 2.5–20.9).[19,29]

Achieving R0 resection is vital as recurrent disease fails to be indefinitely controlled with tyrosine kinase inhibitors. However, negative margins may not be sufficient to prevent recurrence particularly in high-risk patients. The 5-year recurrence rate of 45% for high-risk tumours underlines the need to better manage this group of patients to reduce their risk of future disease.[29] The ACOSOG Z9001[30] of imatinib versus placebo for intermediate- and high-risk tumours in the adjuvant setting was stopped early when preliminary analysis showed an improved survival-free advantage for imatinib. To further refine those patients who will benefit from adjuvant therapy, studies to investigate the promise shown by mutational analysis[25,29] are needed.

Down-staging therapy with imatinib for locally advanced GIST, where surgery alone is unlikely to achieve negative resection margin or do so with high morbidity, has been explored. In a series with 11 cases[31] of locally advanced tumours treated pre-operatively with imatinib for a median duration of 11.9 months, complete resection was possible in all cases. However, the pre-operative length of treatment and long-term outcomes have yet to be determined. Complete resection of recurrent or metastatic disease after imatinib therapy is associated with significantly improved outcome compared with an incomplete resection.[31,32] Similarly, the place of debulking surgery in patients with distant metastatic disease at the time of presentation compared to the use of targeted therapy alone has yet to be determined but it is possible that debulking of tumour may benefit patients with tyrosine-kinase-responsive disease as reduced tumour volume may translate into a delay in the development of resistance to chemotherapy.

Conclusion

GISTs of the upper GI tract commonly present with bleeding and anaemia, with the stomach being the most frequent site of involvement. Complete surgical excision of the primary tumour is necessary without the need for routine lymphadenectomy. The laparoscopic approach is feasible for tumours of the gastric body or fundus. Fletcher low/intermediate-risk tumours carry an excellent prognosis after resection. High-grade tumours are more likely to recur, and a high mitotic count is an independent predictor of recurrence.

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ORIGINAL ARTICLE

Modified Devine Exclusion with Vertical Stomach Reconstruction for Gastric Outlet Obstruction: A Novel Technique

Takatsugu Oida · Kenji Mimatsu · Atsushi Kawasaki · Hisao Kano · Youichi Kuboi · Sadao Amano

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Abstract
Background A gastroenterostomy is the most commonly performed palliative procedure in patients with gastroduodenal outflow obstruction (GOO) caused by unresectable advanced gastric and pancreatic cancer. We developed a new technique—modified Devine exclusion with vertical stomach reconstruction—and evaluated the efficacy of this procedure.
Methods We retrospectively studied 60 patients who underwent gastrojejunostomy for GOO caused by unresectable advanced gastric and pancreatic cancer. These patients were divided into two groups, the conventional gastrojejunostomy group (CGJ group) and the modified Devine exclusion with vertical stomach reconstruction group (MDVSR group).
Results The mean duration of the required nasogastric suction, the number of days after which diet could be initiated and after which oral ingestion of solid food could by safely resumed, and the duration of hospitalization after the surgery were significantly shorter in the MDVSR group. The patients in the MDVSR group had a significantly longer duration of stay at home and survival after the surgery. Moreover, in the MDVSR group, GOO did not recur in any of the patients until the time of death.
Conclusion We consider that our procedure of modified Devine exclusion with vertical stomach reconstruction is an easy and feasible technique for GOO.

Keywords Unresectable gastric and pancreatic cancer · Laparoscopic gastrojejunostomy · Devine exclusion · Gastroduodenal outflow obstruction · Vertical stomach reconstruction

Introduction

Gastroenterostomy is the most commonly performed palliative procedure in patients with unresectable obstructing carcinomas of the gastric antrum and pancreas.[1,2] The aim of this conventional procedure is to enable the resumption of sufficient oral intake, which has, however, been associated with significantly delayed return of gastric emptying (DRGE) in 10% to 21% of patients on whom it is performed.[3,4] Exclusional gastrojejunostomy was originally developed by Devine[5] in 1925 as a method for antral exclusion and complete stomach division in the management of difficult duodenal ulcers. However, Devine exclusion carries the risk of a blowout of the distal gastric remnants. Therefore, we developed a modified Devine exclusional gastrojejunostomy; moreover, to ensure that the gastric contents easily reach the jejunum vertically, we performed horizontal side-to-side gastrojejunostomy. This procedure provided a good quality of life the patients with gastroduodenal outflow obstruction (GOO) caused by unresectable advanced gastric and pancreatic cancer. Previously, we have reported the case of a long-term surviving patient who underwent S-1 chemotherapy after this procedure.[6] In this study, we evaluate the efficacy of our procedure in the prevention of the blowout of the distal gastric remnant and DRGE for GOO caused by unresectable advanced gastric

T. Oida (✉) · K. Mimatsu · A. Kawasaki · H. Kano · Y. Kuboi
Department of Surgery,
Social Insurance Yokohama Central Hospital,
268 Yamashita-cho, Naka-ku, Yokohama,
231–8553 Yokohama, Japan
e-mail: ooida.takatsugu@yokochu.jp

S. Amano
Department of Surgery, Nihon University School of Medicine,
0–1 Kami-cho, Oyaguchi,
Itabashi-ku 173–1123, Tokyo, Japan

and pancreatic cancer. Moreover, considering the benefit of laparoscopic surgery, we developed a technique—laparoscopic modified Devine exclusion with vertical stomach reconstruction—as a palliative procedure for GOO to prevent DRGE and the blowout of the distal gastric remnant.

Patients and Methods

Patients

We retrospectively studied 60 patients (43 men and 17 women, aged 47–85 years; mean age, 69.9 years) who underwent gastrojejunostomy for GOO caused by unresectable advanced gastric and pancreatic cancer, between September 2000 and April 2008 at the Department of Surgery, Social Insurance Yokohama Central Hospital, Yokohama, Japan. The patients were divided into two groups: the conventional gastrojejunostomy group (CGJ group) and the modified Devine exclusion with vertical stomach reconstruction group (MDVSR group). Considering the benefits of laparoscopic surgery in recent time, we performed MDVSR via the laparoscopic approach—laparoscopic modified Devine exclusion with vertical stomach reconstruction (LMDVSR)—in five of the 30 patients in the MDVSR group.

Surgical Technique

The procedures were performed with the patients in the supine position and under general anesthesia. An upper midline incision was made in the CGJ and MDVSR patients. Abdominal drain was not used in any of the patients.

Conventional Gastrojejunostomy

An ultrasonically activated device was used to divide the gastrocolic ligament in order to facilitate entry into the greater sac. The proximal jejunum at approximately 40 cm from the ligament of Treitz was brought to the stomach in the antecolic position. An Endo-GIA 45-mm stapler (Ethicon, Endo-Surgery, Cincinnati, OH, USA) was used to perform gastrojejunostomy at the dependent part of the stomach, 3 cm proximal to the obstructing antral tumor. Braun anastomosis was performed with the stapler 20 cm below the anastomotic site of the gastrojejunostomy (Fig. 1).

Modified Devine Exclusion with Vertical Stomach Reconstruction (MDVSR)

An ultrasonically activated device was used to divide the gastrocolic ligament in order to facilitate entry into the greater sac. Initially, hemitransection was performed at the dependent part of the stomach, 3 cm proximal to the obstructing antral tumor, with an Endo-GIA 45-mm stapler (Ethicon, Endo-Surgery): a 2-cm-wide segment near the lesser curvature, which served as a drainage route for contents on the oral side of the gastroduodenal constriction, was not resected. The distal site of the hemitransection was buried into the remnant distal stomach, and a seroserosal suture was made (Figs. 2 and 3).

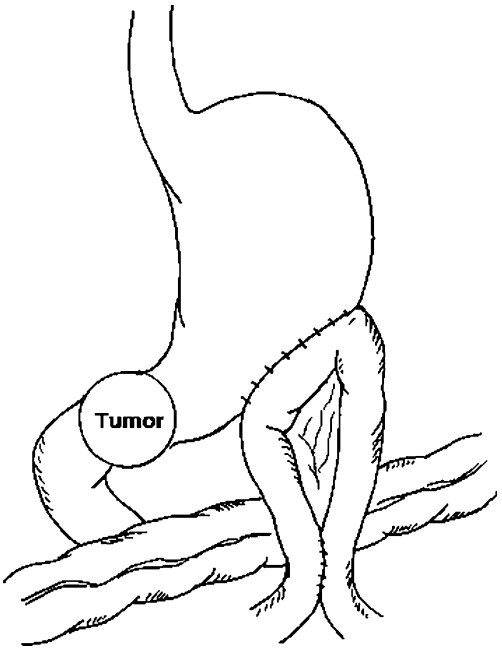

Figure 1 Conventional gastrojejunostomy. The proximal jejunum at approximately 40 cm from the ligament of Treitz was brought to the stomach in the antecolic position. Gastrojejunostomy was performed at the dependent part of the stomach, 3 cm proximal to the obstructing antral tumor. Braun anastomosis was performed 20 cm below the anastomotic site of the gastrojejunostomy.

Subsequently, the proximal site of the hemitransected stomach was vertically stretched, and the proximal stomach was re-resected horizontally with the stapler. The resected part was small and triangular (Fig. 2). In our reconstruction, the proximal jejunum at approximately 40 cm from the ligament of Treitz was brought to the stomach in the antecolic position. Then, a horizontal side-to-side gastrojejunostomy was performed using a stapler. The opening created for the insertion of the stapler was closed with a continuous suture. Finally, a stapler was used to perform Braun anastomosis 20 cm below the anastomotic site of the gastrojejunostomy. The opening created for the insertion of the stapler was sutured (Fig. 3).

In LMDVSR, five ports (one 10-mm, two 12-mm, and two-5 mm ports) were placed. A 10-mm trocar was inserted into the upper region of the umbilicus, and a pneumoperitoneum was created at a pressure of 10 mmHg. A 12-mm port was then placed on the right and left subcostal margins along the midclavicular line, and two additional 5-mm ports

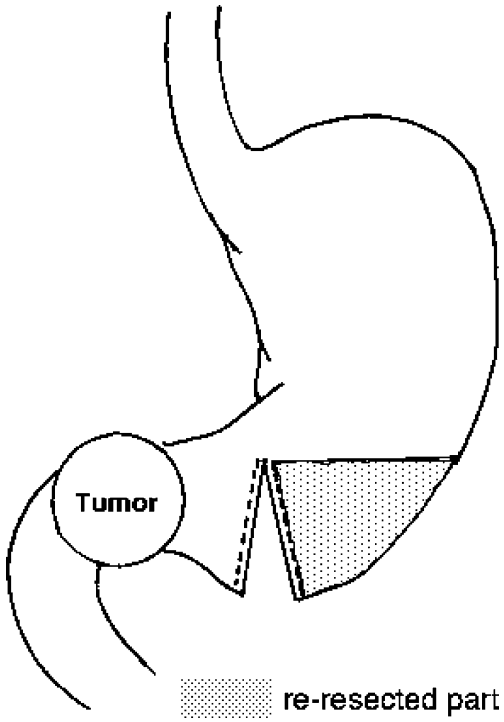

Figure 2 Our modification of Devine exclusion. A "hemitransection" was made at the dependent part of the stomach, 3 cm proximal to the obstructing antral tumor, with the use of a stapler: a 2-cm-wide segment near the lesser curvature was not transected. The distal site of the hemitransection was buried into the remnant distal stomach and a seroserosal suture was made.

were placed in the right and left upper quadrants. The procedures following this one were the same as those for MDVSR.

Definition of Delayed Gastric Emptying

Delayed gastric emptying (DGE) was considered to be present in patients in whom oral ingestion of solid food could safely be resumed ten or more days after the operation and in whom there was no prompt response to pharmacologic therapy with metoclopramide, cisapride, mosapride citrate, itopride hydrochloride, domperidone, or erythromycin, as reported previously.[7] The nasogastric tube was removed when the amount of gastric contents was lower than 300 ml/day.

Operative mortality was defined as any death occurring within 30 days of the procedure.

Statistical Analysis

Univariate analysis was performed using the Student's *t* test for continuous variables and the Fisher's exact test and chi-square test for categorical variables. A *p* value of less than 0.05 was considered to indicate significance.

Results

CGJ was performed in 30 patients and MDVSR in 30. Five of the 30 patients in the MDVSR group underwent LMDVSR without requiring conversion to open surgery. Table 1 shows the patient characteristics and preoperative variables. No differences were observed in the mean age, sex ratio, and preoperative clinical data. The indications for gastrojejunostomy were similar between the two groups. Table 2 shows the intra- and postoperative variables. No significant differences were observed in the mean operative time or blood loss between the two groups. None of the patients in either group required blood transfusion. No deaths occurred in either group. The mean time during which nasogastric suction was required was 3.0±1.9 days in the MDVSR group and 4.3±1.8 days in the CGJ group; thus, the MDVSR patients were initiated on the diets significantly faster than the CGJ patients ($p<0.011$). The mean time before initiation of the diet after surgery was significantly lesser in MDVSR group (4.7±1.2 days) than

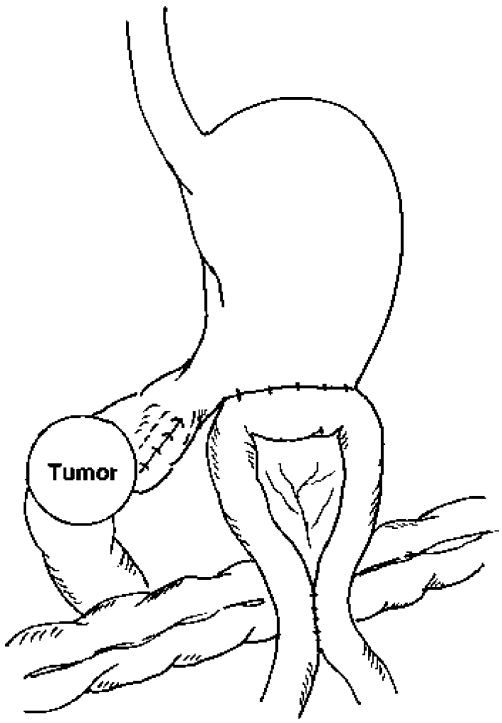

Figure 3 Re-resection of the proximal stomach and vertical stomach reconstruction. The distal site of the hemitransection was buried in the remnant distal stomach by seroserosal sutures. The proximal site of the hemitransected stomach was vertically stretched and was re-resected horizontally. The resected part was small and triangular. The proximal jejunum at approximately 40 cm from the ligament of Treitz was brought to the stomach in the antecolic position. Then, a horizontal side-to-side gastrojejunostomy was performed using the stapler. Braun anastomosis was performed 20 cm below the anastomotic site of the gastrojejunostomy.

Table 1 Characteristics of the Patients (CGJ vs MDVSR)

	CMJ (n=30)	MDVSR (n=30)	P value
Age	69±8	71±8	0.529
Sex ratio (M/F)	22:8	21:9	0.774
Diagnosis			
Gastric cancer	23 (77%)	24 (80%)	0.754
Pancreatic cancer	7 (23%)	6 (20%)	1
Reasons for unresectability			
Multiple liver metastases	14 (47%)	15 (50%)	0.796
Peritoneal dissemination	16 (53%)	13 (43%)	0.438
Direct invasion into neighboring organs	3 (10%)	3 (10%)	1

in the CGJ group (6.4±12.8 days; $p<0.00007$). Moreover, the mean time after which oral ingestion of solid food could be safely resumed was significantly lesser in the MDVSR group (7.0±1.5 days) than in the CGJ group (10±2.8 days; $p<0.0000013$). The incidence of DGE was significantly lower in the MDVSR group (6.7%) than in the CGJ group (46.7%; $p<0.009$). The duration of hospitalization after surgery was significantly shorter in the MDVSR group (11±3.3 days) than in the CGJ group (17±7.7 days; $p<0.00028$). The duration of stay at home after surgery was significantly longer in the MDVSR group (163± 129 days) than in the in the CGJ group (82±61 days; $p<0.00289$). Moreover, the survival period after surgery was significantly longer in the MDVSR group (192± 138 days) than in the CGJ group (103±60 days; $p<0.0019$). Postoperative complications such as pneumonia and wound infection were observed in 6.7% and 3.3% patients in the CGJ group and 3.3% and 3.3% patients in the MDVSR group, respectively, which were not significantly different between the two groups ($p<0.554$, $p=1$). In the MDVSR group, GOO did not recur in any of the patients until the time of death. In contrast, GOO was observed in five (16.7%) patients of the CGJ group ($p<0.02$). Table 3 shows the intra- and postoperative variables compared CGJ group and LMDVSR group. The mean operative time was significantly longer in LMDVSR group (113±52 min) than in the CGJ group (83±18 min; $p<0.029$); however, blood loss was lesser in the LMDVSR group (31± 8.2 ml) than in the CGJ group (80±73 ml) without significant difference ($p<0.146$). The mean time during which nasogastric suction was required was 1.0±0.0 days in the LMDVSR group and 4.3±1.8 days in the CGJ group; thus, the LMDVSR patients were initiated on the diets significantly faster than the CGJ patients ($p<0.00037$). The mean time before initiation of the diet after surgery was significantly lesser in LMDVSR group (3.8±0.4 days) than in the CGJ group (6.4±1.8 days; $p<0.0041$). Moreover, the mean time after which oral ingestion of solid food could be safely resumed was significantly lesser in the LMDVSR group (6.2±0.4 days) than in the CGJ group (10±2.8 days; $p<0.0042$). DGE was not observed in the LMDVSR group. The duration of hospitalization after surgery was significantly shorter in the LMDVSR group (11±1.9 days) than in the CGJ group (17±7.7 days; $p<0.0113$). The duration of stay at

Table 2 Outcomes (CGJ vs MDVSR)

	CGJ (n=30)	MDVSR (n=30)	P value
Operative time (min)	83±18	87±29	0.464
Blood loss (ml)	80±73	61±23	0.167
N-G removal	4.3±1.8	3.0±1.9	0.011[a]
Initial diet	6.4±1.8	4.7±1.2	0.00007[a]
Days after which solid diet could be resumed (days)	10.2±2.8	7.0±1.5	0.0000013[a]
Complications			
Pneumonia	2 (6.7%)	1 (3.3%)	0.554
Wound infection	1 (3.3%)	1 (3.3%)	1
DGE	14 (46.7%)	2 (6.7%)	0.009[a]
Recurrence of OGG	5 (17%)	0 (0%)	0.02[a]
Duration of hospitalization (days)	17±7.7	11±3.3	0.00028[a]
Duration of stay at home (days)	82±61	163±129	0.00289[a]
Survival (days)	103±60	192±138	0.0019[a]

N-G nasogastric tube

[a] significant difference

Table 3 Outcomes (CGJ vs LMDVSR)

	CGJ (n=30)	LMDVSR (n=5)	P value
Operative time (min)	83±18	113±62	0.029[a]
Blood loss (ml)	80±73	31±8	0.146
N-G removal	4.3±1.8	1.0±0.0	0.00037[a]
Initial diet	6.4±1.8	3.8±0.4	0.0041[a]
Days after which solid diet could be resumed (days)	10.2±2.8	6.2±0.4	0.0042[a]
Complications			
Pneumonia	2 (6.7%)	0 (0%)	1.000
Wound infection	1 (3.3%)	1 (20%)	0.269
DGE	14 (46.7%)	0 (0%)	0.069
Recurrence of OGG	5 (17%)	0 (0%)	1.000
Duration of hospitalization (days)	17±7.7	11±1.9	0.0113[a]
Duration of stay at home (days)	82±61	186±82	0.0020[a]
Survival (days)	103±60	212±80	0.0010[a]

N-G nasogastric tube

[a] significant difference

home after surgery was significantly longer in the LMDVSR group (186±82 days) than in the in the CGJ group (82± 61 days; $p<0.0020$). Moreover, the survival period after surgery was significantly longer in the LMDVSR group (212±80 days) than in the CGJ group (103±60 days; $p<0.0010$). Postoperative complications such as wound infection were observed in a patient (20%) in the LMDVSR group, respectively, although, GOO did not recur in any of the patients until the time of death.

Discussion

Loop gastroenterostomy is the most commonly applied palliative procedure in patients with unresectable obstructing carcinomas of the gastric antrum and pancreas.[1,2] However, this procedure has been associated with a significant DRGE in 10%–21% of all cases.[3,4] Exclusional gastrojejunostomy was originally developed by Devine[5] in 1925 as a method of antral exclusion and complete stomach division in the management of difficult duodenal ulcers. However, Devine exclusion bears the risk of a blowout of the distal gastric remnant.

We performed the modified Devine gastrojejunostomy with hemitransection by open laparotomy in patients with unresectable gastric and pancreatic cancer to prevent a blowout of the distal gastric remnant. Moreover, we improved the reconstructive procedure, MDVSR, in order to ensure that the gastric contents easily reach the jejunum vertically after performing modified Devine exclusion. Recently, laparoscopic gastric bypass for the treatment of GOO has been reported to be a feasible and safe surgical technique.[8–10] Laparoscopic Devine's procedure for the palliation of GOO has also been reported.[11–13] Therefore, considering the benefits of laparoscopic approach as a minimally invasive surgery, we also performed LMDVSR recently.

Kaminishi's procedure involves stomach partitioning gastrojejunostomy in which the stomach is partially partitioned into the proximal and distal parts. The proximal part of the stomach is anastomosed to the proximal part of the jejunum, and Braun's anastomosis is not performed.[11] Ammori's procedure is an antecolic loop gastrojejunostomy performed after transection of the stomach 5 cm proximal to the obstructing antral tumor with the use of a stapler, and Braun's anastomosis is not performed.[12] Suzuki's procedure is an antecolic side-to-side Roux-en-Y gastrojejunostomy after hemitransection (a 3-cm-wide segment near the lesser curvature is not transected), with side-to-side jejunojejunostomy.[13] However, transection of the stomach may prevent postoperative DRGE and hemorrhage of the tumor. Devine exclusion has some disadvantages. If there is no drainage route from the distal remnant stomach, gastric secretion and bleeding from the lesion may lead to rupture of the transected site of the distal remnant stomach. Devine exclusion carries the risk of a blowout of the distal gastric remnant. To prevent this, Kato et al.[14] and Suzuki et al.[13] performed hemitransection wherein they used a 2- to 3-cm-wide segment near the lesser curvature as a drainage route for the remaining gastric contents. We also performed hemitransection with the use of a 2-cm-wide segment near the lesser curvature as a drainage route.

Ensuring that the gastric contents easily reach the jejunum and preventing blowout of the distal gastric remnants and DRGE are important to palliative gastrojejunostomy. Side-to-side anastomosis at the anastomotic sites of gastrojejunostomy provides a larger diameter than end-to-side anastomosis dose; moreover, horizontal side-to-side gastrojejunostomy enables gastric contents to easily reach the jejunum vertically. In horizontal side-to-side gastrojejunostomy, the stapler was inserted horizontally into the stomach and jejunum and fired. This facilitated

the formation of an anastomotic site with a large diameter and a straight dietary route from the stomach to the jejunum.

With regard to the position of the gastrojejunostomy, the hemitransection was made at the dependent part of the stomach, and a horizontal side-to-side gastrojejunostomy was performed after re-resection of the proximal stomach. With this procedure, we were able to retain a large volume of the remnant stomach so that the patient was tolerant to food ingestion, and we were able to ensure a straight dietary route to the jejunum.

In our procedure, we combined the modified Devine exclusion with vertical stomach reconstruction and Braun's anastomosis. This procedure ensured a straight dietary route to the jejunum, thereby ensuring that the gastric contents easily reach the jejunum and preventing DRGE. Choi[10] reported that DRGE was observed in two patients (20%) who underwent open gastrojejunostomy and in one patient (10%) who underwent laparoscopic gastrojejunostomy. Kazanjian et al.[15] reported DRGE in one patient (11%) who underwent laparoscopic gastrojejunostomy; this patient could not tolerate oral intake. The sample size used in our study is small; nevertheless, DRGE was not observed in the MDVSR group and DGE was observed in only 6.7% of them, which is a significantly lower rate in comparison to that of the CGJ group.

Doberneck and Berndt[16] reported that no significant differences attributable to the antecolic or retrocolic route were observed in the postoperative course. We used the antecolic route because of the ease in pulling up the jejunum and the decreased risk of decompression in the gastrojejunostomy caused by tumor growth. Choi[10] reported that GOO recurred in two patients (20%) who underwent open and laparoscopic gastrojejunostomy. However, in the MDVSR group in our study, GOO recurrence was not observed in any patient until death.

Recently, the novel oral fluoropyrimidine anticancer drug S-1 has been introduced for the treatment of advanced gastric cancer because of its excellent response rate acceptable toxicity and the convenience of administering it orally.[17] If the patients can resume sufficient oral intake after the surgery, they can be discharged from the hospital and receive chemotherapy such as S-1 in the outpatients clinic. In fact, in our study, 32 of the 60 patients (53%), i.e., 19 of the 30 patients (63%) in the MDVSR group and 13 of the 30 patients (43%) in the CGJ group, underwent S-1 chemotherapy after the surgery. It is important for patients to achieve an adequate nutritional state in order to increase their chance of receiving adjuvant chemotherapy, which may also prolong the patients' survival. In unresectable and recurrent gastric cancer, the prognosis with best supportive care is poor, with a survival period of 3–4 months.[18]

In our study, the mean survival time was 192±138 days in the MDVSR group, which is rather longer than the mean survival time of 3 months reported by Kwok et al.[19]

Conclusion

Our technique of gastrojejunostomy—modified Devine exclusion combined with vertical stomach reconstruction—is an easy and feasible palliative procedure for preventing the blowout of the distal gastric remnant and DRGE for GOO caused by unresectable advanced gastric and pancreatic cancer. Moreover, laparoscopic modified Devine exclusion combined with vertical stomach reconstruction is useful as a minimally invasive surgical procedure.

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ORIGINAL ARTICLE

Factors Influencing Lymph Node Recovery from the Operative Specimen after Gastrectomy for Gastric Adenocarcinoma

Scott J. Schoenleber · Thomas Schnelldorfer · Christina M. Wood · Rui Qin · Michael G. Sarr · John H. Donohue

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Abstract
Background Regional lymph node metastases are an important predictor of survival for patients with resectable adenocarcinoma of the stomach. Currently, the number of lymph nodes examined is frequently less than requirements for accurate staging. Clinical factors associated with lymph node recovery are understood poorly.
Methods We performed a retrospective chart review of 99 consecutive patients who underwent gastrectomy for gastric adenocarcinoma distal to the gastroesophageal junction to determine clinical variables associated lymph node recovery.
Results Ninety-nine patients underwent gastrectomy for gastric adenocarcinoma at our two hospitals. More than 15 lymph nodes were examined in 64% of specimens. Univariate analysis showed an association between the number of lymph nodes recovered and the number of positive nodes, lymphadenectomy extent, hospital, surgeon, and pathology technician ($p<$ 0.001). Multivariate analysis identified the pathology technician as the most important healthcare-related variable contributing to the variation of lymph node recovery, using fixed- ($p<0.001$) and random-effects models.
Conclusions This study suggests that the pathology technician is an important healthcare-related factor influencing lymph node recovery after gastrectomy. In identifying potential areas benefiting from a systems improvements approach, focus on the technical aspects of specimen processing may be of benefit in maximizing the number of lymph nodes recovered.

Keywords Gastric cancer · Lymph nodes · Human factors · Neoplasm staging

Introduction

Regional lymph node metastases are considered one of the most important predictors of survival for patients with resectable gastric adenocarcinoma.[1,2] Prior studies have shown that at least 15 lymph nodes should be examined in order to reduce the chance of missed metastatic lymph nodes to an acceptable low level.[3,4] In 1997, the American Joint Committee on Cancer/Union Internationale Contre le Cancer staging system for gastric cancer was adjusted to reflect the importance of adequate lymph node sampling.[5,6] Currently, the TNM system suggests that greater than 15 nodes be examined in order to determine the N category accurately.[5,6] Despite the importance of the need for accurate staging, recent studies suggest that lymph node assessment for staging in gastric adenocarcinoma is inadequate in 62% to 71% of patients.[7–9] In addition to the potential for inadequate patient education concerning prognosis, this deficiency in lymph node assessment also has potentially important implications for appropriate adjuvant treatment and affects comparisons between studies on the various treatments of gastric cancer. Some patients with a small primary neoplasm might not receive adjuvant

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S. J. Schoenleber · T. Schnelldorfer · M. G. Sarr · J. H. Donohue (✉)
Division of Gastroenterologic and General Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: donohue.john@mayo.edu

C. M. Wood · R. Qin
Division of Biostatistics, Mayo Clinic, Rochester, MA, USA

treatment in the false belief that the neoplasm was without regional metastasis. The effect on survival of this shift in stage with potential undertreatment is not well elucidated.

Clinical factors correlating with the number of lymph nodes examined are poorly understood. To date, studies have suggested that the patient's age, sex, race, tumor pathology, and gastrectomy type, among others, are associated with the number of lymph nodes examined in the operative specimen.[8,9] Further study is indicated to determine methodologic and human variables involved to potentially delineate areas which need systematic improvement. The current study examines clinical variables that correlate with the number of lymph nodes examined in operative specimens after gastrectomy for gastric adenocarcinoma.

Material and Methods

This was a retrospective, observational study of 99 patients who underwent gastrectomy for adenocarcinoma or carcinoma in situ of the stomach at Mayo Clinic Rochester from November 2002 through August 2006. Only patients with primary malignancy distal to the gastroesophageal junction were included. Patients were excluded from the study if they had undergone prior gastric operation or prior perigastric lymphadenectomy. The patients' clinical records were analyzed for demographic information, clinical and operative data, pathologic assessment of the specimen, and multiple aspects of human factors involved in processing the specimen (primary surgeon, pathologist, pathology technician). All patients had given consent to have their records included in research at Mayo Clinic. This study was approved by the Institutional Review Board.

For data analysis, surgeons, pathology technicians, and pathologists were grouped according to volume of operations performed or specimen processed. High-volume surgeons defined as having performed greater than ten gastrectomies for adenocarcinoma during the study period were handled individually. The low-volume surgeons were pooled for analysis according to hospital. Similarly, pathology technicians and pathologists who had processed greater than eight specimens during the study period were handled individually. The low-volume pathology technicians and pathologists were grouped with their peers.

Data are reported as percentage or mean ± standard deviation (range) unless otherwise specified. Linear regression models were constructed for univariate analysis. p values <0.05 were considered statistically significant. Prespecified variables believed to be clinically important and statistically significant variables were included in the multiple-variable model. Healthcare-related variables were considered in both fixed- and random-effects models. Normality was investigated using residual plots. All analyses were performed using SAS version 9.1 software (SAS Institute Inc, Cary, NC, USA).

Results

Patient Demographics

The study group was comprised of 99 patients (57% males) with a mean age of 67±17 (range 27–94) years. The ethnic breakdown consisted of 69% Caucasians, 4% Asian–Americans, 1% African–American, and 26% of other or unknown ethnicity. The mean body mass index (BMI) of the patients was 26±5 (range 17–41). Approximately half (48%) of the study population had undergone a major abdominal operation in the past. Only a small percentage of the study group had undergone neoadjuvant chemotherapy and/or radiation therapy (4% and 1%, respectively).

Operative Details

All patients underwent gastrectomy at one of the two Mayo Clinic Rochester tertiary care hospitals (hospitals A and B), but more patients (72%) received care at hospital A. Between these two hospitals, a total of 15 different surgeons operated on 99 patients. Four of the 15 surgeons had each performed more than ten gastrectomies for adenocarcinoma during the study period. Of these four, three were located at hospital A and one at hospital B. The remaining 11 surgeons were split between the two institutions. Sixteen percent of patients underwent partial gastrectomy; 36% underwent subtotal gastrectomy, and 47% underwent total gastrectomy, while D1 and D2 lymphadenectomy was performed in 57% and 43% of patients, respectively. In 7% of patients, the operation was performed laparoscopically. In 90% of patients, the procedure was performed with a curative intent, while distant metastases were evident in 10% of patients who required a gastrectomy for palliative purposes.

Histopathologic Findings

Pathology reports from each patient were reviewed. These data are based on reports prepared by 24 senior pathologists and 31 pathology technicians who evaluated the 99 specimens. All specimens were processed in the standard fashion without the use of defatting agents. For practical purposes, we defined the pathology technician as the person who actually performed the pathologic lymph node recovery. This group includes nonphysician technicians and resident physicians. Location of the cancer in the stomach was as follows: body (28%), antrum (28%), fundus (11%), cardia (4%), and pylorus (4%); 16% of specimens were of the linitis plastica type and had diffuse involvement while a

location was not specified in the pathology report in the other 8% of specimens. Nearly all specimens (96%) were histologically poorly differentiated or undifferentiated. The average size of the neoplasm was 7.1±5.0 cm in largest dimension (range 0.3–22 cm). Tumor stage was most frequently T2 and T3 (Tis 2%, T1 17%, T2 33%, T3 38%, T4 9%). Greater than 15 lymph nodes were recovered in 63 patients (64%). Of those 63 patients, 32% were stage N0, 22% stage N1, 26% stage N2, and 20% stage N3. Operative margin was positive in 9% of patients.

Univariate Analysis

Factors that could impact lymph node recovery were analyzed individually against the number of lymph nodes recovered from operative specimens (Table 1). Patients with more advanced disease determined by T stage were found to have had more extensive lymph node recovery (mean number of lymph node (LN) by T stage: Tis 22±17; T1 18±14; T2 18±10; T3 31±22; T4 28±15; p=0.01). Similarly, patients with a greater number of lymph nodes recovered were more likely to have positive lymph nodes identified (mean number of LN retrieved: N0 20±18; N1 20±11; N2 27±18; N3 37±20; p=0.01). Extent of lymphadenectomy also correlated with lymph node recovery. Predictably, patients who underwent D1 lymphadenectomy had fewer nodes examined than those patients who underwent D2 resection (D1 19±14; D2 31±20; p<0.001). Of the seven patients in our study who underwent laparoscopic resection, there was no difference in the number of lymph nodes examined when compared to open surgical resection (laparoscopic LN 19±12; open LN 25±18; p=0.41).

Systems-based factors were also assessed in the univariate analysis. Notably, patients who underwent gastrectomy at hospital A had 18±12 LN examined, while those at hospital B had 38±22 nodes examined, an average difference of 20 LN (p<0.001). The surgeon performing the operation also correlated with lymph node recovery (p<0.001). On average, surgeon 1 resected a greater number of LN (42±17) than any other surgeon (surgeon 2 20±13; surgeon 3 22±11; surgeon 4 11±7; others at hospital A 20±12; others at hospital B 27±31). Pathology technicians were also associated with variation in lymph node recovery. Tech 1 retrieved 50±21 LN, while tech 2 recovered 13±9 nodes and other technicians recovered 21±12 nodes (p<0.001). Senior pathologists, however, were not correlated with lymph node recovery (pathologist 1 24±16; pathologist 2 17±9; pathologist 3 24±13; other pathologists 26±19; p=0.59).

There was no association between lymph node recovery and BMI, prior operation, neoadjuvant chemotherapy or radiation therapy, type of gastrectomy, open versus laparoscopic operation, curative or palliative operation, metastatic disease, or margins of tumor resection.

Table 1 Univariate Analysis Identifying Factors Associated with Lymph Node (LN) Recovery after Gastrectomy for Gastric Adenocarcinoma (n=99)

		Number	LN retrieved	p value
T stage	TIs	2	22±17	0.01
	T1	17	18±14	
	T2	33	18±10	
	T3	38	31±22	
	T4	9	28±15	
N stage[a]	N0	39	20±18	0.01
	N1	22	20±11	
	N2	25	27±18	
	N3	13	37±20	
Lymphadenectomy	D1	56	19±14	<0.001
	D2	43	31±20	
Hospital	A	71	18±12	<0.001
	B	28	38±22	
Surgeon	1	21	42±17	<0.001
	2	19	20±13	
	3	11	22±11	
	4	14	11±7	
	Others, hospital A	27	20±12	
	Others, hospital A	7	27±31	
Pathology technician	1	16	50±21	<0.001
	2	22	13±19	
	Others	15	21±12	

[a] As determined in all 99 patients independent of total number of lymph nodes retrieved.

Multivariate Analysis

A multivariate analysis was performed using both fixed- and random-effects models to determine the relative healthcare-related contributions to observed variation in LN recovery. Once again, number of positive lymph nodes ($p=0.003$) and extent of lymphadenectomy ($p<0.001$) remained significant using this model. Interestingly, when evaluating the staff-related factors, neither the surgeon ($p=0.16$) nor the senior pathologist ($p=0.03$) contributed to lymph node recovery as much as the pathology technician ($p<0.001$). To verify these findings, a random-effects analysis was performed. This analysis confirmed that the pathology technician introduced the most variation into the process of lymph node recovery as compared to the other healthcare-related factors (random error (reference)=133; surgeon=3; senior pathologist=10; pathology technician=281).

Discussion

Cancer staging is of importance in clinical practice because it provides important information to the patient and guides the clinician toward specific therapies. In gastric adenocarcinoma, TNM staging is complicated frequently by the fact that lymph node recovery and thus histologic analysis for metastases in gastrectomy specimens is often inadequate.[7–9] This retrospective study of 99 patients attempted to determine systems-based factors influencing lymph node recovery.

Factors affecting lymph node recovery in gastric cancer occur at multiple levels: patient/cancer pathology, operative technique, and tissue processing. Previous studies examining the roles of variables related to the patient and cancer pathology have shown that lymph node recovery is more likely to be adequate in the following groups: females, younger patients, patients with higher stage disease, and in patients undergoing a more extensive operation, among others.[8,9] While understanding the variables inherent to the patient is necessary, it is also of importance to identify factors which could potentially be modified for an improvement in systems-based practice. Therefore, we focused our study on the technical aspects of operative resection and pathologic preparation as it pertains to the final staging of gastric cancer.

The surgeon has the obvious potential to introduce variations in lymph node removal. Indeed, when we performed a univariate analysis, there was an association between the surgeon and the number of nodes recovered. In contrast, when the technical factors of operative resection, surgeon, pathologist, and pathology technician were all taken into account in the multiple-variable model, the surgeon was no longer associated with lymph node recovery. This observation led us to conclude that surgeons at our academic institution are performing fairly similar and appropriate operations on all patients and are not a major contributor to the variation of lymph node recovery. This finding highlights the key limitation of this study: it was performed at a large tertiary care center with surgeons experienced in oncologic and gastrointestinal surgery. Because of extensive experience with gastrectomy and extended lymphadenectomy, the impact of the surgeon on nodal retrieval at our institution may appear to be artificially less than might be expected at institutions less experienced in gastric cancer.

Our attention was then turned to the technical aspects of tissue processing, specifically the role of the pathology technician and senior pathologist handling the specimen. While two high-volume technicians processed 38% of our specimens (tech 1 16%, tech 2 22%), the majority of the 31 technicians each processed only a small number of gastrectomy specimens during the study period. Along with the fact that the average lymph node recovery by technician 1 was well above the required 15 nodes for staging and that of technician 2 was just below that threshold, we realize that the person processing the specimen is a primary contributor to variation in lymph node recovery from the operative specimen. Indeed, the variation in node recovery was associated with the pathology technician in both the univariate and multiple-variable analyses. When we then evaluated the role of the senior pathologist, we found it to be associated only weakly with lymph node retrieval in the multivariate analysis. As demonstrated by the random-effects analysis, the senior pathologist did not introduce nearly as much variation into the process of lymph node recovery as the pathology technician, leading us to conclude that the senior pathologist is associated with lymph node recovery mainly because of strong working relationships with certain pathology technicians.

Our institution relies heavily on the skill of the pathology technicians to process carefully the resection specimens immediately postoperatively. This method has its limitations, however. Consequently, a variety of techniques have been developed to aid in the recovery of lymph nodes in cancer specimens. For example, in Japan, the surgeon will often do much of the initial processing of the specimen personally.[10] Other institutions have evaluated fat-clearing protocols to reveal lymph nodes in cancer specimens.[11,12] The premise behind each of these processes is to make it easier for the person ultimately responsible for tissue processing to identify and thereby recover as many lymph nodes as possible. One particular area of focus has been the use of techniques of sentinel lymph node biopsy in gastric cancer. While employed widely in other neoplasms, various sentinel node techniques have begun to show promise in the detection of micrometastases in gastric cancer.[13,14] The

precise role of these techniques in clinical practice, however, remains an area of active investigation.

These special techniques are not performed in the routine processing of gastrectomy specimens at our institution. Nonetheless, this study would suggest that, in many cases, adequate numbers of lymph nodes can be recovered even without special methods. This study raises the question of why some technicians in our institution are able to routinely recover more lymph nodes than other technicians. The answer to this question is not entirely clear but is likely dependent on a number of factors. One possible explanation is that nodal recovery is linked with the years of experience of each pathology technician. Although data for the years of experience were not available for all the technicians, the two high-volume technicians, technicians 1 and 2, have worked in pathology for a total of 14 and 5 years, respectively. Aside from this difference in years of experience, these two individuals have otherwise had similar training. Neither of these technicians has received formal education as pathology assistants. Both received on-site occupational training at the time of hire. This training was not standardized and may have led to differences in technique. In comparison, all new pathology technicians at our institution are required to have completed a 2-year pathology assistant training program. Such a program may result in more overall consistency in lymph node recovery. In addition to formal training, it seems likely that some technicians may be more motivated than others to find as many lymph nodes as possible. This possibility would likely be influenced by a combination of factors, including personality, time of day, number of specimens evaluated in a day, and whether or not the technician realizes the clinical importance of nodal recovery.

Regardless of how lymph nodes are recovered, the ultimate goal is accurate pathologic staging of the cancer through evaluation of at least 15 lymph nodes recovered from the specimen. In addition to evaluation of the special methods for detection of lymph nodes, focus on basic elements of tissue processing, such as prospectively evaluating exactly why some technicians recover more lymph nodes from a specimen than others may be of clinical benefit. The long-term outcome of such a project could be the development of an optimal, efficient, and reliable protocol for tissue processing.

Conclusion

This study indicates that the most important factor of the healthcare-related factors examined in our center influencing lymph node recovery after gastrectomy for gastric adenocarcinoma is the pathology technician. In identifying potential areas benefiting from a systems improvement approach, focus on the technical aspects of processing the specimen appears to be of greatest benefit.

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ORIGINAL ARTICLE

Risk Factors for Morbidity and Mortality Following Gastroenterostomy

Martin Poulsen · Mauro Trezza · Ghayyath H. Atimash · Lars T. Sorensen · Finn Kallehave · Ulla Hemmingsen · Lars N. Jorgensen

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Abstract
Background Morbidity and mortality following traditional surgical treatment of gastric outlet obstruction is high. The aim of this work was to identify risk factors predictive of postoperative complications and mortality following gastroenterostomy.
Methods One-hundred sixty-five consecutive patients subjected to open gastroenterostomy from January 1996 through July 2003 were included. Data on vital signs and operative variables were retrieved from medical records and recorded retrospectively. Risk factors for postoperative complications and mortality within 30 days after operation were analyzed with multiple logistic regression.
Results The 30-day complication and death rates were higher after emergency operations (80% and 60%) than after elective operations (32% and 25%). A multivariate analysis disclosed that hypoalbuminemia (≤32 g/l), comorbidity, high age, and hyponatremia (<135 μmol/l) were significantly associated with postoperative death, whereas hypoalbuminemia, comorbidity, high age, and emergency operation were predictors of postoperative complications.
Conclusions Complications and mortality after gastroenterostomy due to gastric outlet obstruction are associated with modifiable and non-modifiable risk factors. Prior to surgery means should be taken to correct low albumin and sodium levels to prevent complications. In addition, the surgeon should consider alternative treatment modalities including laparoscopic gastroenterostomy, self-expanding metallic stents, or tube gastrostomy to relieve or palliate gastric outlet obstruction.

Keywords Gastric outlet obstruction · Gastroenterostomy · Morbidity · Mortality · Risk factors · Surgery

M. Poulsen · G. H. Atimash · L. T. Sorensen · U. Hemmingsen · L. N. Jorgensen
Department of Surgery, Bispebjerg Hospital,
Bispebjerg Bakke 23,
DK-2400 Copenhagen NV, Denmark

M. Trezza · F. Kallehave
Department of Surgery, Aalborg Hospital,
Hobrovej 18-22,
DK-9100 Aalborg, Denmark

M. Poulsen (✉)
Department of Surgery, Roskilde Hospital,
Koegevej 7-13,
DK-4000 Roskilde, Denmark
e-mail: martinp@dadlnet.dk

Introduction

Gastric outlet obstruction causes nausea and vomiting due to gastric retention and, consequently, malnourishment. Open gastroenterostomy is the traditional operative technique to bypass a benign or malignant obstruction in the lower gastric region or duodenum. It has been our clinical impression that this procedure is associated with a considerable rate of postoperative complications and mortality.

Methods of palliation and the use of prophylactic gastroenterostomy in the treatment of unresectable malignant gastric outlet obstruction remain controversial. Gastroenterostomy is advocated by some groups as a prophylactic procedure in patients undergoing hepaticojejunostomy for obstructive jaundice due to unresectable pancreatic cancer but without signs or symptoms of gastric retention because 8–20% of these patients will later experience gastroduodenal obstruction,[1–4] especially patients with a better prognosis.[5] An identical conclusion was obtained in a randomized

study.[6] Other groups argue that patients with unresectable pancreatic cancer generally experience an unfavorable rapid progression with a too short survival to obstruct[7–9] and advocate a gastroenterostomy only in patients with present or impending gastroduodenal obstruction.[10–12]

New methods including endoscopic stent treatment or laparoscopic gastroenterostomy have been reported to provide acceptable gastroduodenal transit and a reduction of morbidity and mortality.[9,11,12] The aim of the present paper was to identify predictive risk factors for postoperative mortality and complications following open gastroenterostomy to optimize selection of patients that may benefit from treatment with less invasive surgical procedures.

Materials and Methods

All consecutive patients undergoing open gastroenterostomy (ICD 10 code: JDE 00) as either a primary or secondary procedure from January 1996 through July 2003 at the departments of surgery of two major Danish hospitals (Bispebjerg and Aalborg) were included. The patients' medical records were retrospectively searched by two investigators from each center (MP, MT, GHA, and FK) for data on demography, comorbidity, indication for surgery, pathology, postoperative course, and selected preoperative biochemical variables (Table 1).

The data were analyzed by use of SPSS for Windows (version 8.0.2, SPSS Inc., Chicago, IL, USA). Separate explorative analyses were conducted for elective and emergency operations using the chi-square test for dichotomous variables and the Mann–Whitney test for continuous variables, respectively. A p value of 0.05 or less was considered statistically significant. Then, two sets of multivariate analyses were carried out with postoperative complications and mortality as dependent variables. In both cases, univariate analyses were performed first and the odds ratio of each variable was estimated. Subsequently, a forward

Table 1 Baseline Characteristics

	Elective operation (n=140)		Emergency operation[a] (n=25)		P
Demographic characteristics					
Age (median, 90% interpercentile range)	70	46–86	75	49–91	n.s.
BMI (median, 90% interpercentile range)	23	16–32	23	18–32	n.s.
Alcohol consumption, drinks per week (median, 90% interpercentile range)	0	0–21	0	0–16	n.s.
Male gender	75	53.6%	6	24.0%	<0.05
Smoker	52	37.1%	7	28.0%	n.s.
Comorbidity					
Cardiovascular	31	22.1%	12	48.0%	< 0.05
Pulmonary	7	5.0%	2	8.0%	n.s.
Diabetes or thyroid diseases	15	10.7%	1	4.0%	n.s.
Gastrointestinal	15	10.7%	4	16.0%	n.s.
Biochemical variables					
Anemia (<7.0 mmol/l for women and <8.0 mmol/l for men)	80	57.1%	14	56.0%	n.s.
Hypopotassemia (<3.5 μmol/l)	40	28.6%	14	56.0%	< 0.05
Hyponatremia (<135 μmol/l)	38	27.1%	12	48.0%	n.s.
Hyper-p-creatinemia (>110 μmol/l for women and >130 μmol/l for men)	5	3.6%	6	24.0%	< 0.01
Hypo-p-albuminemia (≤32 g/l)	95	67.9%	21	84.0%	n.s.
Malignant obstruction, n=120					
Pancreatic cancer	66	47.1%	4	16.0%	<0.01
Gastric cancer	23	16.4%	0	0.0%	<0.05
Other type of cancer	25	17.9%	2	8.0%	n.s.
Benign obstruction, n=45					
Ulcer related	12	8.6%	12	48.0%	<0.001
Crohn's disease	2	1.4%	0	0.0%	n.s.
Other non-defined obstructions	12	8.6%	7	28.0%	<0.05

Number of patients and percentages (unless otherwise indicated in parentheses)

[a] Perforated gastric ulcer, bleeding peptic ulcer, or mechanical bowel obstruction

selection procedure was carried out where variables likely to be associated with the dependent variable ($p \leq 0.2$) were included in a multivariate model. Before establishing the final model, all variables not being significant ($p > 0.05$) were discarded by a backward elimination procedure. Finally, tests for linearity and interaction terms between variables were examined. All results were described with odds ratio and 95% confidence interval.

Because this was a retrospective descriptive study with anonymous presentation of the data, no approval from the local Ethics Committee was required.

Results

During the study period, open gastroenterostomy was performed in 165 patients, of whom 84.8% were operated on electively. The median postoperative length of hospital stay for patients discharged alive from hospital was 11 days (90% interpercentile range, 5–40 days) after elective surgery and 16 days (3–45 days) after emergency procedures. Table 1 summarizes the clinical and pathological characteristics of the patients. Male gender and cancer causing the gastric outlet obstruction were factors that were significantly more frequent in the group of patients who had elective operation, whereas benign obstruction, cardiovascular comorbidity, and preoperative electrolyte derangement were found significantly more often in the group that underwent emergency operation.

Complications

Seventy-nine postoperative complications were recorded in 65 patients (39.4%; Table 2). Patients undergoing emergency operations experienced significantly higher rates of postoperative heart failure and wound problems including burst abdomen. Furthermore, emergency operation as compared with elective procedures was associated with a higher number of postoperative complications (80.0% vs. 32.1%). The multivariate analysis identified high age, hypoalbuminemia, comorbidity, and emergency operation as factors independently associated with an increased risk of postoperative complications (Table 3).

Mortality

The 30-day mortality rate was 30.3% (Table 2). Mortality was higher in patients with postoperative complications (58.5% vs. 12.0%) and following emergency operation (60.0% vs. 25.0%).

Thirty-five patients (29.2%) with a malignant disease and 15 patients (33.3%) with a benign disease died within the first 30 days after gastroenterostomy. High age, hypoalbuminemia, comorbidity, and hyponatremia were the independent risk factors statistically significantly associated with an increased 30-day mortality rate in this population (Table 4).

Discussion

This study demonstrates that preoperative hypoalbuminemia, comorbidity, and high age are predictors for both postoperative morbidity and mortality. Emergency operation and preoperative hyponatremia are additional risk factors for postoperative morbidity and mortality, respectively.

Table 2 Postoperative Complications, Reoperation Rates, and Mortality within the first 30 days After Gastroenterostomy

	Elective operation ($n=140$)		Emergency operation ($n=25$)		P
	Number	Percentage	Number	Percentage	
Wound related problems	6	4.3	6	24.0	<0.01
Respiratory insufficiency[a]	21	15.0	6	24.0	n.s.
Heart failure	3	2.1	8	32.0	<0.001
Thromboembolism	3	2.1	1	4.0	n.s.
Systemic complications[b]	13	9.3	4	16.0	n.s.
Anastomotic problems	2	1.4	1	4.0	n.s.
Other complications	3	2.1	2	8.0	n.s.
Patients with one or more postoperative complications	45	32.1	20	80.0	<0.001
Reoperation	14	10.0	5	20.0	n.s.
Fatal outcome	35	25.0	15	60.0	<0.01

[a] Pneumonia, pulmonary edema or atelectasis

[b] Hypovolemia, renal failure, stroke, sepsis, or anemia

Regardless of benign or malignant pathology, we find that hypoalbuminemia was associated with an increased rate of postoperative complications and mortality. Low serum albumin is a marker for malnutrition and disease, and it is well recognized that hypoalbuminemia is associated with a poor postsurgical outcome with regard to both complications[13–18] and mortality.[14,16] Improvement of the patient's perioperative nutritional status with enteral or parenteral nutritional support has been suggested to decrease this risk.[19–21] At least 7–15 days nutritional therapy is necessary to reduce the risk of postoperative complications[19] excluding the possibility to correct albumin levels before emergency operations. Enteral nutritional support should receive high priority in the postoperative period for these patients.[20,21] There are data to support that immune enhancing enteral nutrition in particular has a protective effect against postoperative infectious complications.[15] The retrospective design of the present trial precludes a registration of the nutritional support provided to the individual patients in this study.

It is well documented that surgical patients with high age or comorbidity are at an increased risk of both postoperative complications and death. Especially, cardiopulmonary disease, renal failure, or surgery in an emergency setting have been identified as major risk factors.[22] However, the literature is scarce on whether preoperative plasma levels of sodium predict postoperative complications and mortality. Hyponatremia is the most common encountered electrolyte imbalance reported in critical disease[23] and is associated with an increased 30-day postoperative mortality in the present study. Pathophysiologic mechanisms in the development of hyponatremia include congestive heart failure, liver insufficiency, thiazide medication, inappropriate hydration therapy, and postoperative stress-related-syndrome of antidiuretic hormone secretion.[23,24] It has been reported that lack of correction of severe hyponatremia in hospitalized patients is associated with an increased mortality rate.[25] In the present investigation, preoperative hyponatremia was associated with postoperative mortality despite the fact that we did not differentiate between severity levels of hyponatremia.

Palliative surgical bypass in patients with unresectable periampullary carcinoma is associated with a 3–30% perioperative mortality rate[2,4,8,9,26,27] and a 30–70% morbidity rate.[1,3,4,6–9,11,28] A frequent complication is delayed gastric emptying.[26] The 29% mortality rate among the patients with a malignant disease in this study is equivalent with other series, but the 33% mortality rate reported in the present study for patients with a benign obstruction is higher compared to other studies.[29,30]

Table 3 Variables Significantly Associated with Postoperative Complications after Gastroenterostomy

	Univariate			Multivariate[a]		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (increment per year)	1.04	1.02–1.07	0.004	1.03	1.01–1.07	0.027
Plasma albumin						
Normo-albuminemia	1	–		1	–	
Hypo-albuminemia	3.01	1.40–6.46	0.014	2.49	1.08–5.73	0.032
Comorbidity						
No	1	–		1	–	
Yes	2.95	1.47–5.95	0.004	2.31	1.08–4.94	0.030
Type of operation						
Elective	1	–		1	–	
Emergency	8.44	2.98–23.94	<0.001	6.36	2.13–18.97	<0.001
Natrium (plasma level)						
Normo-natremia	1	–				
Hypo-natremia	2.11	1.07–4.15	0.048			
Potassium (plasma level)						
Normo-potassemia	1	–				
Hypo-potassemia	2.42	1.24–4.71	0.017			
Pre- and perioperative packed red blood cell units						
No	1	–				
Yes	2.03	1.05–3.93	0.010			
Gender						
Male	1	–				
Female	1.83	0.97–3.45	0.289			

[a] Analyzed by logistic regression. Hosmer and Lemeshow goodness-of-fit test, 0.31

Table 4 Variables Significantly Associated with a Fatal Outcome Within 30 Days After Gastroenterostomy

	Univariate			Multivariate[a]		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.07	1.03–1.10	<0.001	1.05	1.02–1.09	0.003
Albumin (plasma level)						
Normo-albuminemia	1	–		1	–	
Hypo-albuminemia	7.39	2.49–21.95	0.001	5.54	1.26–7.21	0.004
Comorbidity						
No	1	–		1	–	
Yes	3.27	1.49–7.18	0.011	3.02	1.27–7.21	0.017
Natrium (plasma level)						
Normo-natremia	1	–		1	–	
Hypo-natremia	4.11	2.01–8.39	0.001	2.78	1.25–6.21	0.023
Postoperative complications						
No	1	–				
Yes	10.32	4.74–22.50	<0.001			
Creatinine						
Normo-creatinemia	1	–	0			
Hyper-creatinemia	12.40	2.57–59.80	0.004			
Potassium						
Normo-potassemia	1	–				
Hypo-potassemia	2.31	1.16–4.61	0.045			
Type of operation						
Elective	1	–				
Emergency	4.50	1.85–10.92	0.003			
Sex						
Male	1	–				
Female	1.69	0.86–3.32	0.162			

[a] Analyzed by logistic regression. Hosmer and Lemeshow goodness-of-fit test, 0.85

This study suggests that other temporary or permanent types of treatment should be considered for patients with one or more of the defined risk factors. Laparoscopic gastroenterostomy result in less immune suppression, lower morbidity, earlier gastric emptying, and shorter hospital stay than open gastroenterostomy.[29,31] The endoscopic application of self-expanding metallic stents (SEMS) for gastroduodenal malignancies has been associated with shorter hospitalization,[32–35] earlier resumption of food intake,[33,35,36] lower rates of morbidity,[32] mortality,[32,35] and cost-effectiveness[34] compared to open gastroenterostomy. Furthermore, SEMS is an effective and safe treatment in patients with a short remaining lifespan,[37,38] but controlled trials comparing SEMS with laparoscopic gastroenterostomy are still needed before one or the other procedure is finally preferred.

Quality of life is often a neglected factor during treatment of terminally ill patients, but since many of the patients with gastric outlet obstruction have a short life expectancy, it is an important factor to consider.[6,35,36] Ouchi et al.[27] concluded that gastric resection and gastroenterostomy as a palliative measure in patients with advanced gastric cancer had no effect on prolongation of survival or improvement of quality of life, thus favoring minimally invasive alternative treatment modalities such as SEMS[39] or jejunal feeding obtained by a direct percutaneous endoscopic jejunostomy technique.[40] Antrectomy as part of a palliative Billroth-2 procedure in patients with unresectable pancreatic cancer has appeared safe, but toleration of an oral diet did not occur before an average of 11 days after surgery.[41] There is no high level evidence that this procedure is associated with less morbidity or mortality compared with simple gastroenterostomy in patients with gastric outlet obstruction due to unresectable malignancy.

In conclusion, gastroenterostomy due to gastric outlet obstruction is associated with certain risk factors that should be taken into consideration before operation. In order to minimize postoperative mortality and morbidity, the surgeon should correct nutritional and electrolyte imbalance and otherwise carefully select those patients who are offered an open gastroenterostomy. Laparoscopic

gastroenterostomy or SEMS may appear as better alternatives if the patient is old or suffer from one or more concurrent medical diseases.

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ORIGINAL ARTICLE

Mesenteric Venous Thrombosis and Factors Associated with Mortality: A Statistical Analysis with Five-Year Follow-Up

S. Abu-Daff · N. Abu-Daff · M. Al-Shahed

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Abstract
Objective The objective was to study the factors associated with mortality in mesenteric venous thrombosis (MVT).
Methods We reviewed all cases of bowel ischemia at our institute from 1984 to 2004 and identified 31 cases of MVT and compiled data concerning their demographics, risk factors, investigations, management, surgical procedures, and outcomes. Survival was analyzed for both 30-day and 5-year periods.
Results Analysis of factors associated with mortality in our 31 case series revealed that 30-day mortality was strongly associated with colonic involvement in ischemia (p=.008) as well as short bowel syndrome (p=.028) and possibly failure to anti-coagulate the patient (p=.07). While 5-year mortality was strongly associated with "short bowel syndrome" as defined by small bowel remaining less than 100 cm (p=.031). Further study using a multivariate Cox proportional hazard analysis showed that mortality within the 30-day period was mainly related to colon ischemia with p value of.014 and an odds ratio of 17.4, while short-bowel syndrome was the predominated factor in the 5-year mortality analysis with a p value of.029 and an odds ratio of 5.
Conclusion Thirty-day mortality for MVT is strongly associated with colonic involvement as well as "short-bowel" syndrome, while anticoagulation may be protective. Five-year survival was found to be strongly associated with "short-bowel "syndrome.

Keywords MVT · Mesenteric · Venous · Thrombosis · Mortality · Ischemia

Introduction

Mesenteric venous thrombosis (MVT) is a rare but lethal form of mesenteric ischemia representing about 5% of all cases of bowel ischemia.

Its clinical presentation varies greatly, and it is difficult to achieve a clinical diagnosis in these patients, leading to a delay in treatment.

Advances in imaging techniques and increased awareness of the condition have enabled earlier recognition and not uncommonly MVT can now be treated without surgical intervention.[1]

Mortality rates, although better than other causes of intestinal ischemia, remains high.[2,3] In this study, we attempt to elaborate on the factors that are associated with mortality in MVT.

Methods

We retrospectively followed the clinical course of 31 cases of acute MVT. These cases represent less than 5% (31/638) of the cases that were diagnosed as intestinal ischemia during the last 20 years in our hospital.

S. Abu-Daff · N. Abu-Daff · M. Al-Shahed
Department of Surgery, Riyadh Military Hospital,
Riyadh, Saudi Arabia

S. Abu-Daff (✉)
Riyadh Military Hospital, A12,
P.O. Box 7897, Riyadh 11159, Saudi Arabia
e-mail: sabudaff@rmh.gov.sa

Extraction of the data was performed using a standardized form. The basis of identification was either radiological or surgical. IV contrast computed axial tomography (CT) was the radiological test we relied on in our study, with diagnosis achieved when there was a documented filling defect within the superior mesenteric vein, omental thickening, mesenteric fat stranding, bowel wall thickening, and dilatation of the superior mesenteric vein or ascites. In the cases where the CT was initially reported as "normal," they were reviewed again by a radiologist not involved with the cases or our study and not informed of the initial report for further confirmation. Intraoperative findings of patent arteries, thrombosed veins with congested and hemorrhagic bowel, achieved surgical diagnosis.

Clinical data, particularly history of risk factors, previous thrombosis, as well as the presentation, clinical findings, initial laboratory results, radiological results, anticoagulation, operative findings, and mortality data were all retrieved from the patient's medical records.

Laboratory investigations that were taken into account included hemoglobin, white blood cell count, platelets, and the coagulation profile taken at the presentation of symptoms.

Management of our patients was either surgical or conservative, based largely on their clinical presentation and hospital course.

Mortality in our study is defined as death within 30 days of presentation to our service or within 5 years after discharge. Patients with no long-term clinic follow-up records were contacted by telephone for further information.

Analysis and Results

Eighty-percent of our cases (25/31) presented at the emergency department, with the remaining 20% (6/31) being in-hospital consultations from other departments most notably gastroenterology and cardiology. The male to female ratio was 3:1, and the age ranged from 24 to 75 years with a mean age of 53.5 years.

The most frequent symptom was pain, which was present in all of our patients, followed by vomiting 24/31 (77%), distention 20/31 (65%), constipation 13/31 (42%), diarrhea 5/31 (16%), and fever 1/31 (3.2%; Fig. 1).

Due to the disease's subacute nature and variation in symptoms, many of our patients presented late particularly when their initial symptom would be constipation or nausea; once the condition becomes ischemic and, therefore, painful, presentation to the emergency department is usually within 3 days. In our study, duration of symptoms ranged from 1 to 40 days with a mean of 11.7 days.

The pain was generalized in most of our patients 17/31 (56%), and epigastric 8/31 (26%,), central, and right upper-quadrant were equally represented 2/31 (6%), and only a

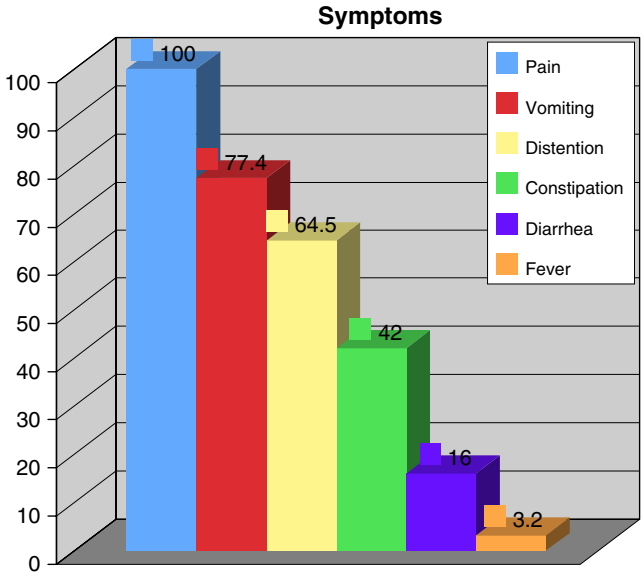

Figure 1 Symptoms in 31 patients with MVT represented as percentage.

single case each of left upper quadrant and pelvic pain were noted (3%). Local signs of peritonitis occurred in 18/31 (58%) of our patients.

Many combined risk factors were present as evident from their medical histories. The most prominent was liver disease, "21/31" 68% of patients had some form of liver disease. Liver cirrhosis accounted for 15 of these cases, most of which were due to chronic viral hepatitis while three were due to schistosomiasis, a single case each of cavernous hemangioma, hydatid cyst of the liver, and acute fulminant hepatitis causing mesenteric venous thrombosis MVT; there were also two cases of hepatocellular carcinoma.

Previous history of abdominal surgery was present in 10/31 (32%) patients, splenectomy being the most notably recorded operative procedure of these (6/10).

MVT was associated with malignancy in 5/31 (16%) of our patients: two patients had hepatocellular carcinoma and a single case each of prostatic, pancreatic, and colon cancer.

Six of 31 (20%) of our patients had a history of heart disease, and five were labeled as heart failure with a documented ejection fraction less than 30%. Six of 31 patients were diabetic, and two patients had previous history of MVT. Other risk factors that were present in our survey were polycythemia, Crohn's disease, oral contraceptive pill usage, and acute pancreatitis representing a single case each.

Only one patient was labeled initially as idiopathic MVT; however, after further evaluation, he was found to have factor V "Leiden" deficiency (Fig. 2).

Laboratory investigations that were analyzed included the initial values on presentation; the mean hemoglobin was 13.3 g/dl (SD 2.5), white cell count of 13.7×10^3 (SD 6.6),

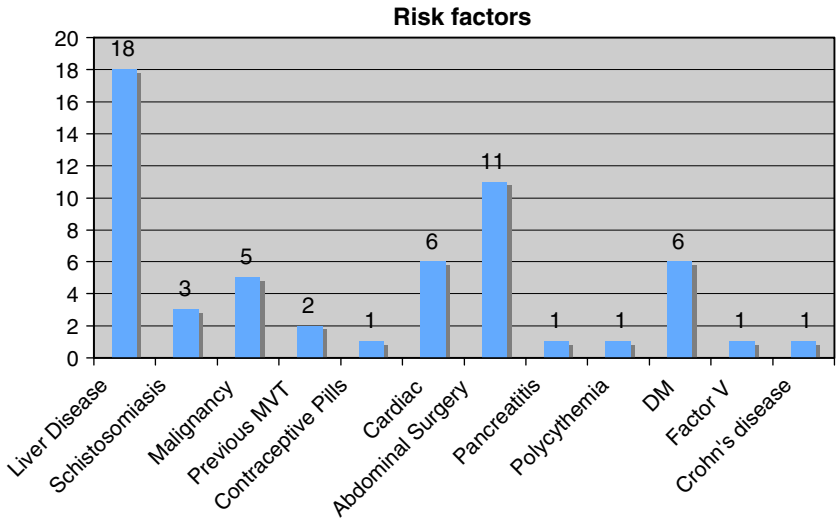

Figure 2 Risk factors, represented as number of cases. Note that some patients had more than one risk factor.

platelets of 333×10^3 (SD180), PT was 17.7 s (SD 7.7), PTT of 39 s (SD 17), and INR of 1.3 (SD 0.4).

All of our patients had abdominal X-rays performed, 51% showed moderately dilated small bowel loops, 10% showed multiple air fluid levels, and the remaining 39% were normal. U/S abdomen was performed in 14/31 (46%) patients. Duplex ultrasound was diagnostic for MVT in 7/14 (50%) of patients, in 3/14 (21.4%) was undiagnostic due to poor visualization secondary to gas interference, while 4/14 (28.6%) of cases were inconclusive.

Contrast-enhanced CT scan of the abdomen was performed in 18/31 of the cases and was diagnostic in approximately 90% of the cases by showing a clear thrombus within the SMV in 13/18 cases (72.2%) or suggestive findings of ischemia in 3/18 cases (16.6%). A normal CT was reported in 2/18 cases (11%) and was reviewed for further confirmation.

Achieving diagnosis "in-hospital" had an average duration of less than 24 h, with the exception of two cases; a case that was initially diagnosed by ultrasound as a case of cholycystitis, 4 days later was shown to be MVT and a case of liver cirrhosis in which diagnosis was delayed for 7 days.

Management of these cases depended greatly on the clinical and radiological findings on patients that presented with signs of peritonitis, or free air in the abdomen were taken for operative management. Overall, 24/31 cases underwent surgery. All patients who underwent a laparotomy underwent resection of the affected bowel segment. The ileum was the most frequent segment affected 8/24 (32%), followed by the jejunum and ileum 8/24 (32%), jejunum (12%) 3/24, colon 5/24 (20%), and duodenum 3/24 (12%; Fig. 3).

A second-look procedure was performed in 6/18 (30%) of the operated cases; one patient had a colostomy formed, another had an ileostomy formed, one patient had a washout for an intra-abdominal hematoma, two patients had further resection of small bowel, while the last patient had a second- and third-look procedure necessitating resection of almost his entire small bowel.

Most of the patients received postoperative heparin followed by long-term warfarin anticoagulation (29/31; 95%) ,and one patient underwent successful thrombolytic therapy.[4]

All of our patients received IV antibiotics, a regimen of third generation cephalosporin, and metronidazole. Postoperative resuscitation was with crystalloids and blood products, TPN was started if the patient was kept NPO for more than 1 week.

Mortality that occurred in our study included four cases that died within a 30-day period, one patient died on the 11th day, two died on the 12th day, and one died on the 27th day. These deaths occurred due to sepsis and multiorgan failure.

Five-year follow-up revealed six more mortalities, at 3, 4, 6, 11, 30, and 36 months.

Two patients died due to pleural effusion and pulmonary edema secondary to their malignancies, three patients who suffered from postoperative short-bowel syndrome died of severe malnutrition and overwhelming sepsis, and one patient died of heart failure.

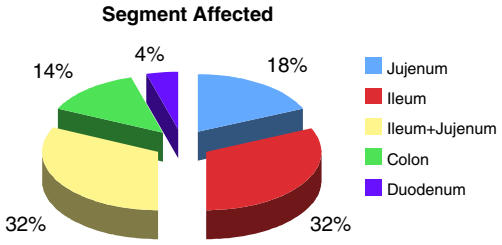

Figure 3 Intraoperative findings of 24 cases that underwent surgery and bowel resection. Note that cases of colonic and duodenal ischemia also had associated small bowel ischemia and resection.

We analyzed our cases looking for any associated risk factors predictive of mortality; we defined two categories of mortality, 30-day mortality "short-term" and 5-year survival "long term." The covariates that were analyzed were; age >60 years, heart failure, liver cirrhosis, malignancy, associated portal vein thrombosis, surgery, second-look surgery, postoperative anticoagulation, ischemia of the colon, and length of small bowel remaining less than 100 cm "short bowel syndrome." The Fisher's exact test was used to assess association of the factors with mortality for both periods, followed by a multivariate Cox proportional hazard analysis of the significant factors (Table 1).

The data strongly implicate two factors that affect mortality within a 30-day period, and those are involvement of the colon (p=.008) and small bowel remaining less than 100 cm (p=.028). Failure to anticoagulate the patient at p=.07 may also prove a contributing factor, but this study had insufficient power to demonstrate significance. The Cox proportional hazard analysis with forward stepwise regression of these factors showed that the primary predictor of mortality was the colon with a p value of .014 and an odds ratio of 17.4 (95% CI).

As for 5-year survival, we performed the Fisher's exact test on the surviving patients, blinding the 30-day mortality cases and found that short bowel syndrome was predictive of mortality. With a p value of.031, the Cox proportional hazard analysis revealed a p value of.029 and an odds ratio of 5 (95% CI; Fig. 4).

Power testing showed our study to be underpowered, particularly for malignancy, which requires >108 patients for proper testing. Other covariates such as age and heart failure were also underpowered. Statistical analysis was performed using the SPSS program (SPSS Corporation, Chicago IL, USA).

Table 1 Risk Factors and Mortality

Risk factor "p value"	30-day	5-year
Age>60	NS	NS
Heart failure	NS	NS
Colon ischemia	.008	NS
SB<100 cm	.028	.031
Surgery	NS	NS
Second-look surgery	NS	NS
Malignancy	NS	NS
PVT	NS	NS
Failure of anticoagulation	.07[a]	NS
Liver disease	NS	NS

P values were calculated using the Fisher exact test and are two-tailed
NS not statistically significant, *PVT* portal vein thrombosis, *SB< 100 cm* small bowel remaining less than 100 cm, "short-bowel syndrome"

[a] Considered as significant due to lack of power in this covariate.

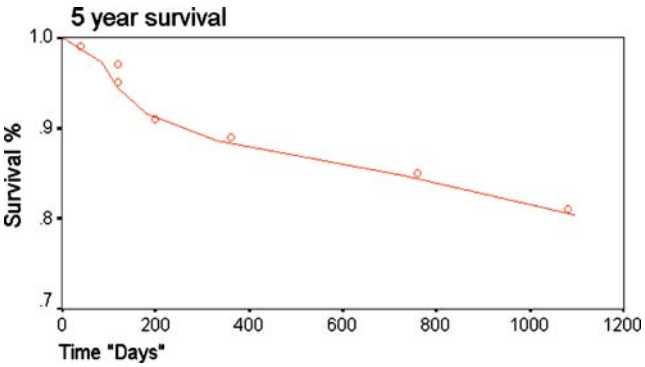

Figure 4 Five-year mortality Cox-proportional hazard curve.

Discussion

MVT was seen in less than 5% of the cases of mesenteric ischemia in our hospital during a 20-year period and presented as 31 cases. It is likely that this is an underestimation of the true incidence, as there were many cases that were excluded due to our rigorous criteria, such as cases in which there was no conclusive radiological or intraoperative evidence, or in which the patient was thought to be suffering from ischemic colitis or nonocclusive ischemia.

Most of the affected patients in our study as well as others were male;[5] this remains unusual, as the realm of venous thrombosis is usually of a female predominance. The mean age was 54 years, notably younger than bowel ischemia due to arterial causes.[5] In fact, on closer examination of our data, we could identify two groups of patients, the younger age group, which usually had a hypercoaguable state or a local abdominal cause, and the older age group where the risk factors were mainly liver disease, malignancies, and heart failure.

The overwhelming risk factor in our study was liver disease (21/31), and this ranged from chronic liver cirrhosis to acute fulminant hepatitis and including three cases of active schistosomiasis. Portal hypertension prior to diagnosis was noted in two of our patients and was documented by abdominal Doppler ultrasound.

Local causes such as previous abdominal surgeries were seen in 11 of our patients, with a strong predominance for splenectomy. Many studies have cited splenectomy as being the most common abdominal surgery to cause MVT;[6] this is probably due to migration of the thrombus from the ligated splenic vein to the superior mesenteric vein. A more recent prospective study of the portal venous system and thrombosis occurring after laparoscopic splenectomy has shown that the occurrence of portal system thrombosis is frequent although rarely symptomatic, clearly a complication of the pneumo-peritoneum that is induced during the procedure adding to the migration of the splenic vein thrombus.[7] Hyper-coaguable states, such as polycythemia,

Factor V "Leiden" mutations, and being on oral contraceptive pills was seen as a single case each in our study. Although polycythemia was reported as the commonest hypercoaguable state to cause MVT by Rhee and Gloviczki,[8] it is now recognized that factor V "Leiden" mutation, and protein S, C deficiencies are the most common hypercoaguable states and is strongly implicated in many cases of MVT.[1,9] Overall the term "idiopathic" is being used less frequently in this condition.

Presentation in our cases had the universal symptom of abdominal pain, although this varied greatly by site, severity, and duration in each patient, reflecting the location as well as the severity of the ischemia. Other symptoms were less frequent but abdominal distention and vomiting predominated. Clinically, most patients had generalized abdominal or epigastric tenderness with abdominal distention; peritonitis was a frequent finding and reflects a delay in diagnosis and prompted an immediate surgical intervention.

Laboratory values taken from our patients at presentation included a complete blood count and coagulation profile and were usually within the normal range for most if not all of our patients. Only five of our patients who were treated conservatively had serum lactate performed, and these patients also had normal or near normal results. One of our patients presented with massive ascites, and a peritoneal tap revealed it to be hemorrhagic; unfortunately, the patient's presentation and laboratory investigations were rarely, if ever, helpful in achieving diagnosis.

Regarding radiological investigations, conventional abdominal radiographs were performed in all our patients, and the most predominant finding was distention of the small bowel loops with occasional air fluid levels. However, a large proportion of patients (39%) had a completely normal abdominal X-ray. Duplex ultrasound of the abdomen was more informative and was able to detect MVT in half of the patients and also had the ability to provide important information about the liver and portal vein status of the patient. However, there is a serious limitation in these cases as they usually present with abdominal distention, obscuring the ultrasound view as well as a limitation in detecting proximal MVT. CT abdomen remains the investigation of choice, with a sensitivity nearing 90%.[10] However, owing to the limits in spatial resolution, evaluation of the smaller distal mesenteric branches remain a challenge and difficult to detect. Furthermore, a thrombosed SMV did not always necessitate a surgical intervention. Grisham et al.[9] have also demonstrated in their study of 23 patients that even cases with multiple segments, MVT were not associated with an increase in mortality making even this "Gold-standard" investigation difficult to interpret in terms of achieving a clinical decision on management. New work on intestinal fatty acid binding protein[11] that is released into the bloodstream during ischemia is extremely promising, the day that bowel ischemia can be diagnosed by a simple blood or urine test may not be very far.

Management was dictated by the clinical presentation of the patient and the attending surgeon's decision, overall diagnosis was achieved operatively in most of our patients due to their late presentations. Resection and primary anastomosis was the most commonly performed procedure with a 24-h second-look laparotomy performed when this was not feasible. Rhee and Gloviczki have suggested using fluorescein-assisted evaluation in marginally viable bowel.[8] Their study as well as ours showed that conservative management is feasible in many instances of MVT, although this depends on how early diagnosis is achieved.

Almost all of our patients were anticoagulated with heparin followed by long-term warfarin treatment whether treated surgically or conservatively; Anticoagulation was shown to have a survival benefit in MVT.[1,8]

One of our patients successfully underwent thrombolytic therapy; although this treatment option has been successful in some case reports, it is fraught with serious complications. Grisham et al. have shown an increase of mortality in cases treated with thrombolytics.[9]

Mortality of the disease in the literature varies from 11% 30%; [3,6,12] however, it has been shown, thanks to the monumental systematic review of Schoots et al. that mortality rates in mesenteric venous thrombosis are better than arterial ones, regardless whether conservative or surgical management was performed.[3]

Brunaud et al.[1], in a retrospective comparative study of 26 patients with MVT who were either treated surgically or conservatively, have also shown that outcomes for their patients were comparable.

In our study, we had a 13% (4/31) mortality at 30 days; we studied the different variables that were present in our population as predictors for mortality and found that colon involvement was the highest predictor of mortality within this period with a 17-fold increase in risk, it is very likely that this reflects bacterial translocation of Gram-negative organisms and the ensuing multiorgan failure.[13]

In this group of patients where the colon is/or might be involved, it may be beneficial to consider an early surgical intervention with antibiotic coverage as opposed to resolution with anticoagulation alone and conservative management. Fortunately, colonic ischemia is very rare in MVT and occurs in only 5–13% of cases[1,6,8] and almost always with small bowel infarct.

Other factors that were identified within this period were failure to anticoagulate and extent of bowel resection leaving less than 100 cm of bowel. Anticoagulation is a cornerstone of treatment in bowel ischemia and has been shown to decrease the incidence of mortality as well as recurrence of thrombosis,[8] and long-term anticoagulation with warfarin needs to be considered, particularly for

patients with a hypercoaguable state. A lack of power was noted for failure to anticoagulate as a predictor for mortality in our study, as the p value was.07.

Five-year mortality was shown to be largely influenced by the extent of the resected bowel, and patients who developed short-bowel syndrome had a notably higher mortality rate, owing to their poor general nutritional status coupled with complications of long-term parenteral nutrition. Every effort to conserve bowel should be made at the time of resection, giving credibility to a second-look procedure in cases of extensive ischemia.

Other covariates in our study including age>60 years, heart failure, liver disease, portal vein thrombosis, malignancy, surgery, and second-look surgery were not found to be significantly associated with mortality; however, a power analysis revealed that our study was underpowered for these covariates particularly for malignancy, age, and heart failure.

MVT remains a rare cause of intestinal ischemia, and this is reflected in the literature particularly in regards to investigating the risk factors associated with mortality. The largest single series by Rhee and Glovyczki[8] reported on 53 cases of acute MVT. And concluded that anticoagulation was protective and that acute MVT carries a higher mortality rate than chronic MVT. Other collective studies[3] have mainly compared the mortality rates of different causes of intestinal ischemia.

As such, we believe more cases are needed to elucidate on the risk factors associated with mortality in MVT.

Conclusion

MVT remains a potentially lethal disease, owing to its vague and late presentation, making surgery a still frequent and necessary therapeutic modality. In our study, we elaborate on factors associated with mortality and have found that the predictor of early mortality is mainly colonic involvement and failure of anticoagulation and the predictor for late mortality is short-bowel syndrome. Due to the size of the study, it is difficult to conclusively rule out any factor as affecting mortality; however, our evidence shows that age>60 years, heart failure, malignancy, surgical intervention, second-look surgery, portal vein thrombosis, and liver disease do not contribute greatly to mortality in MVT.

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ORIGINAL ARTICLE

National Trends and Outcomes for the Surgical Therapy of Ileocolonic Crohn's Disease: A Population-Based Analysis of Laparoscopic vs. Open Approaches

Kelly Lesperance · Matthew J. Martin · Ryan Lehmann · Lionel Brounts · Scott R. Steele

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Abstract
Purpose The laparoscopic approach to Crohn's disease has demonstrated benefits in several small series. We sought to examine its use and outcomes on a national level.
Methods All admissions with a diagnosis of Crohn's disease requiring bowel resection were selected from the 2000–2004 Nationwide Inpatient Sample. Regression analyses were used to compare outcome measures and identify independent predictors of undergoing laparoscopy.
Results Of 396,911 patients admitted for Crohn's disease, 49,609 (12%) required surgical treatment. They were predominately Caucasian (64%), female (54%), and with ileocolic disease (72%). Most had private insurance (71%) and had surgery in urban hospitals (91%). Laparoscopic resection was performed in 2,826 cases (6%) and was associated with lower complications (8% vs. 16%), shorter length of stay (6 vs. 9 days), lower charges ($27,575 vs. $38,713), and mortality (0.2% vs. 0.9%, all $P<0.01$). Open surgery was used more often for fistulas (8% vs. 1%) and when ostomies were required (12% vs. 7%). Independent predictors of laparoscopic resection were age <35 [odds ratio (OR)=2.4], female gender (OR=1.4), admission to a teaching hospital (OR=1.2), ileocecal location (OR=1.5), and lower disease stage (OR=1.1, all $P<0.05$). Ethnic category, insurance status, and type of admission (elective vs. non-elective) were not associated with operative method ($P>0.05$).
Conclusions A variety of patient- and system-related factors influence the utilization of laparoscopy in Crohn's disease. Laparoscopic resection is associated with excellent short-term outcomes compared to open surgery.

Keywords Crohn's disease · Laparoscopic resection · Laparoscopic versus open resection

Introduction

Crohn's disease (CD) is a chronic, often debilitating, inflammatory disease without a definitive cure.[1] As Crohn's disease frequently presents during early adulthood and is associated with a lifetime risk of recurrence, the preferred treatment of CD is medical therapy with aminosalicylates, immunomodulators, and steroids.[2] When medical management fails or complications of the disease arise, surgical therapy is often required. Unfortunately, despite advancements in the medical management, Crohn's patients have a 70–90% lifetime likelihood of undergoing surgical intervention.[3,4]

Since the introduction of laparoscopic colon resection in 1991.[5] and subsequent trials leading to its acceptance for resection of malignancy,[6] its use for other intestinal pathology has increased.[7,8] Over the last decade, there have been several studies documenting the safety and feasibility of the laparoscopic approach for refractory CD.[9,10] Improvements in postoperative pain with decreased narcotic use, shorter length of hospital stay, more rapid return of bowel function, faster ability to tolerate oral intake after

"The views expressed in the article (book, speech, etc.) are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense or the US Government."

"The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46."

K. Lesperance (✉) · M. J. Martin · R. Lehmann · L. Brounts · S. R. Steele
Department of Surgery, Madigan Army Medical Center, Fort Lewis, WA, USA
e-mail: kelly025@comcast.net

surgery, and lower overall postoperative morbidity have been shown to be significantly less with a laparoscopic approach than following open resection.[5,7–9,11–22] While over 10 years of existing literature reflects benefits for laparoscopic bowel resection in CD when compared with the traditional open approach, there has been hesitancy to adopt this technique in widespread use. Deterrents include patient factors well known to CD, such as severe mesenteric thickening, widespread inflammation, and a multifocal pattern, all making the operative technical management challenging to even the most experienced surgeons in conventional settings.[7,12,14] Other factors such as the urgency of the operation and the often difficult clinical condition for which the intervention is based upon (i.e., complex phlegmons, fistulas, or high-grade obstruction) may be hindrances to the laparoscopic approach. Longer operative times for a laparoscopic resection may, for some surgeons, outweigh the benefits of a quicker recovery. Finally, concerns regarding the ability to adequately evaluate of surgical margins to provide a safe excision of inflamed tissue by this method have pushed some surgeons away from minimally invasive techniques with this disease process.

Despite these concerns, laparoscopy has been shown to be effective and safe in this patient population when both performed by surgeons possessing the necessary skills and choosing the proper patients. Although large-scale data are still lacking, the available information suggests minor benefits to laparoscopy. Highlighting this, a recent Cochrane review identified only two randomized controlled trials comparing the open and laparoscopic approaches.[5,14] The remaining studies consist of case series, mostly from single institutions, representing less than 100 patients each and often consist of specialized institutions where experience and expertise may not accurately reflect generalizable results. Thus, the objective of our study was to analyze national trends in the surgical management of ileocolic CD from a large, population-based sample by comparing demographic and outcome measures associated with undergoing a laparoscopic versus open resection, as well as the variables affecting patient selection for each approach.

Materials and Methods

Data for this study were collected from the 2000 through 2004 Nationwide Inpatient Sample (NIS), an administrative database provided by the Department of Health and Human Services and a product of the Health Care Utilization Project, Association for Healthcare Research and Quality. The NIS is the largest inpatient, all-payer database in the USA. It contains information on patient demographics and comorbidities, admission and discharge diagnoses, and multiple outcome measures for approximately eight million hospital admissions each year. This database uses a stratified sampling frame and discharge weights to create accurate national estimates from an approximate 20% sample of all nationwide discharges. This includes all hospital types (private, not-for-profit, government, state) and regions of the country (Northeast, Midwest, South, and West). During our study period, between 986 and 1,004 hospitals from 33–37 states were sampled by the NIS. States excluded from each year group were not identical from year to year. The NIS also contains multiple validated severity adjustment measures to estimate patient disease severity used for clinical comparisons.

Patients included in the study were identified within the NIS dataset for the period of 2000 through 2004 using *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. Initial inclusion criteria involved patients with a primary admission diagnosis of Crohn's disease (555.0, 555.1, 555.9). Those who did not undergo bowel resection during their admission and those with isolated anal surgeries were excluded from the cohort. In addition, those who were deemed less likely to be offered the laparoscopic approach due to disease location or extent, including patients who required a transverse colectomy (45.74), total abdominal colectomy (45.8), and all rectal cases (48) were excluded from our analysis. Patients were then classified by type of surgical procedure they received by ICD-9-CM procedure codes, including ileocectomy (45.72), small bowel resection (45.60–45.62), right hemicolectomy (45.73), left hemicolectomy (45.75), and sigmoidectomy (45.76).

Definition of Variables

The primary variable in this study was the method of repair, defined by the laparoscopic designation (ICD-9-*CM* code 54.21) versus open approach. All patients with the ICD-9-CM code documenting a laparoscopic procedure, which also accounted for those who were converted to an open procedure, were included in the laparoscopic arm of our study for intention-to-treat purposes of our analysis. This definition encompasses all variations on laparoscopic resection including laparoscopic-assisted and hand-assisted laparoscopic techniques.

Other variables included age (years), sex, race, geographic region (Northeast, Midwest, West, South), teaching status of the hospital (teaching, non-teaching), location of the hospital (urban, rural), calendar year (2000–2004), comorbidity, admission type (elective, non-elective), and insurance status (Medicare, Medicaid, private insurance, other). Disease location (ileocolic, small intestine, colon),

need for repair of a fistula or placement of an ostomy were also examined and compared between the two groups. For the purposes of comparison, we defined the remaining variables as follows.

Admission Type

Patients who were admitted under both elective and urgent or emergent settings were included in the dataset.

Race

The NIS database categorizes ethnicity as Caucasian, African-American, Hispanic, Asian, Native American, and other. Participants with Asian, Native American, and other categories (NIS variables race 4, 5, 6; $n=869$) were initially grouped together. In addition, ethnicity was also dichotomized to Caucasian and non-Caucasian for comparison in a separate analysis. Patients with missing data in the category of race were excluded from this portion of our analysis only.

Comorbidities

Comorbidity measures were identified using the Agency for Healthcare Research and Quality comorbidity software. This includes ICD-9-CM diagnoses and the diagnosis-related group in effect on the discharge date and is found within the NIS database.

Disease Severity

Patient disease severity was accounted for using two validated variables contained within the NIS provided by the Medstat Disease Staging™ software, version 5.21, *disease staging: principle stage* (DS Stage) and *disease staging: mortality scale* (DS Mtr S). Both variables use several patient specific parameters present at time of admission to provide a measure of severity for clinical comparison. Disease staging: principle stage is an assigned numerical value reflective of the level of severity of the patient's principle admitting diagnosis only. In our cohort, this would reflect the severity of Crohn's-related pathology for each admission. Disease staging: mortality scale is a calculated value used to predict in-hospital mortality and is based in part on a patient's preexisting comorbidities, as well as established mortality rates of the hospital of admission. Both variables became available within the NIS in the year 2002; therefore, admissions occurring earlier in our study time period are not included in our analysis ($n=19{,}405$). Severity scales such as the Crohn's disease activity index (CDAI) are not available in the NIS database.

Age

Age was analyzed as a continuous variable in univariate and multivariate analysis and was then subdivided into discrete age ranges (under 18, 19–35, 36–55, and 56–65 years and over 65 years) for the final multivariate model.

Insurance Status

Patients were evaluated by both primary and secondary payers (NIS variables PAY1 and PAY2, respectively). Participants were grouped into Medicare, Medicaid, and private insurance. All patients with secondary payer status private insurance were grouped and analyzed with the private insurance group. Patients with self pay, no charge, or other (NIS PAY1/PAY2=4, 5, and 6; $n=1786$) were grouped together as "Other".

Main Outcome Measures

Hospital Charges

Total hospital charges were calculated using the NIS variable TOTCHG (total charges cleaned). In general, these are charges, not costs, and do not include professional fees and non-covered charges, but do include emergency department charges prior to admission to the hospital.

Length of Hospital Stay

The length of the hospital stay was measured in days from the time of admission to the time of discharge.

In-Hospital Complications

In-hospital complications were based on ICD-9-CM codes and grouped into eight different categories as previously described by Guller et al.[23]: mechanical wound complications, infections, pulmonary, gastrointestinal tract, cardiovascular, and complications during the surgical procedure. The categories of mechanical wound and infectious complications were combined for the purpose of our analysis.

Hospital Discharge

The NIS database provides the following information about the patient's discharge status: routine discharge, short-term hospital stay, skilled nursing facility, intermediate care facility, discharge to another type of facility, home health care, left against medical advice, and died during hospitalization. Patients who died during the hospitalization ($n=446$) were excluded when evaluating this specific endpoint

only. Patients who left against medical advice were reclassified as routine discharge to home (NIS variables DISPUniform 1 and 7). Patients requiring home health care were similarly categorized and were evaluated separately (NIS variable DISPUniform 6). Patients requiring disposition to another facility were also categorized together and evaluated separately (NIS variables DISPUniform 2, 3, 4, and 5).

In-Hospital Mortality

Because the NIS database contains information regarding in-hospital stay only, deaths following discharge from the hospital are not included in this series.

Statistical Analysis

All data analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Because the NIS database is a 20% sample of the United States yearly inpatient admissions, weighted samples (NIS variable DISCWT) were used to produce national estimates for all analyses. Patients with invalid or missing data for the primary variables of interest were analyzed for any significant variance from the study population and then excluded for evaluation of that data element only. Appropriate statistical tests were used for both categorical variables (chi-square analysis or Fischer exact test) and continuous variables (Mann–Whitney *U* test or Student's *t* test) in the univariate analysis comparing laparoscopic versus open resection in surgical Crohn's disease. Variables which reached statistical significance in the univariate model were then entered into a block multiple linear or logistic regression model to identify independent factors associated with utilization of a laparoscopic approach. A separate multivariate regression analysis was conducted to identify predictors of in-hospital complications. In our model, we grouped the in-hospital complications variables into a single dependant variable.[23] We analyzed whether several demographic, diagnostic, and procedural variables of interest (including utilization of a laparoscopic approach) were predictive of in-hospital complications. Patient comorbidity profiles were accounted for in this analysis. Key variables of interest such as race, payer status, and hospital location were forced into the regression model even if they were not found to be significant on univariate analysis. Results are presented as adjusted odds ratios (OR) with 95% confidence intervals (95% CI) where appropriate. Statistical significance for this study was set an alpha of 0.05. This study was performed in accordance with the NIS Data User Agreement and approval was obtained through our local Institutional Review Board.

Results

From the 2000–2004 NIS database, we identified 396,911 patients admitted with the diagnosis of CD, of which 49,609 (12%) required resection during their admission. Patient mean age was 41.6±17.0 years, with a female (54.0%) and Caucasian (86.4%) predominance (see Table 1 for patient demographics). Patients received operations for CD mostly in urban settings (90.7%), at teaching hospitals (57.0%), and had private insurance (74.6%). The overall complication rate was 15%, with a low mortality rate of 0.9% for the entire cohort.

A laparoscopic approach was performed in 2,826 (6%) patients versus 46,783 (94%) patients undergoing open resection. For patients who received the laparoscopic approach, univariate analysis revealed a shorter length of hospital stay (6

Table 1 Patient Demographics

Variable (n=49,609)	Number	Percentage
Type of resection		
Open	46,783	94
Laparoscopic	2,826	6
Mean age (years)	41.6	N/A
Sex		
Female	27,035	54.0
Male	22,997	46.0
Race		
Caucasian	31,146	86.4
African-American	2941	8.2
Hispanic	1,075	3.0
Other	869	2.4
Calendar year		
2000	9,225	18.4
2001	10,180	20.3
2002	9,063	18.1
2003	10,796	21.6
2004	10,812	21.6
Primary payer		
Medicare	7,089	14.2
Medicaid	3,792	7.6
Private	37,291	74.6
Other	1,786	3.6
Location of hospital		
Urban	45,419	90.7
Rural	4,651	9.3
Teaching status of hospital		
Teaching	28,527	57.0
Non-teaching	21,543	43.0
In-hospital mortality	446	0.9

N/A not applicable

vs. 9 days), lower hospital charges ($27,575 vs. $38, 713), lower in-hospital complication rate (8% vs. 16%), and lower mortality (0.2% vs. 0.9%; all $P<0.01$; see Table 2). Patients undergoing laparoscopy were also more often discharged to home rather than another type of care facility or receive home health (91% vs. 85%, $P<0.01$). Laparoscopic surgery for CD was associated with fewer in-hospital pulmonary (0.4% vs. 2.6%, $P<0.01$), gastrointestinal (5.3% vs. 10.6%, $P=0.04$), and cardiovascular (0.2% vs. 0.9%, $P=0.03$) complications. Intraoperative (1.5% vs. 2.3%, $P=0.46$) and wound or infectious (0.5% vs. 1.5%, $P=0.12$) complications were not significantly different between the two groups. Of all admissions in which resection was performed laparoscopically, 51.1 % were considered elective admissions, as opposed to urgent or emergent, as reflected by NIS coding. Of admissions in which an open resection was performed, 54.2% were considered elective. Within the elective category ($n=24,995$) only 5% were approached laparoscopically. Preexisting comorbidities (Table 2) were comparable between the two groups, with the exception of anemia (12.3% vs. 5.9%, $P<0.01$) and chronic pulmonary disease (7.2% vs. 5.0%, $P=0.05$), which were more common in those receiving open resection. Renal failure, despite its overall infrequency, was more common (1.1% vs.0.4%, $P=0.03$) in those undergoing laparoscopic resection. Finally, as expected, fistula repair (8% vs. 1%) and ostomy placement (12% vs. 7%) were more common with open repair (both $P<0.01$).

Multivariate logistic regression analysis was conducted to determine factors influencing performance of a laparoscopic procedure for surgical CD. (Table 3) Predictors of undergoing laparoscopic surgery for CD were age less than 35 years (OR 2.4, 95% CI 1.9–2.8), female gender (OR 1.4, 95% CI 1.3–1.5), ileocecal disease location (OR 1.5, 95% CI 1.0–2.2), and designation of a hospital as a teaching facility (OR 1.2, 95% CI 1.1–1.4). Patients with Medicare insurance (OR 0.7, 95% CI 0.5–1.0) and increasing disease stage (OR=0.4, 95% CI 0.4–0.5) were less likely to undergo a minimally invasive approach. Race and admission type showed no significant association with operative method ($P>0.05$; Table 3). A separate multivariate logistic regression was conducted to determine predictors of wound, infectious, gastrointestinal, pulmonary, and cardiovascular postoperative complications. Fistula repair (OR 5.2, 95% CI 1.7–16.1, $P=0.05$), ostomy placement (OR 2.3, 95% CI 1.9–2.7, $P<0.01$), and open surgery (OR 3.4, 95% CI 1.4–8.1, $P<0.01$) were independently associated with in-hospital complications (Table 4).

Discussion

Proper patient selection for the laparoscopic versus open approach with CD is multifactorial, involving both patient-

Table 2 Laparoscopic Versus Open Resection: Univariate Analysis

Variable (n=49,609)	Laparoscopic	Open	P
Number	2,826 (6%)	46,783 (94%)	
Number of resections per year			<0.01
2000	531 (5.8%)	8694 (94.2%)	
2001	320(3.1%)	9860 (96.9%)	
2002	562 (6.2%)	8501 (93.8%)	
2003	670 (6.2%)	10,126 (93.8%)	
2004	748 (6.9%)	10,064 (93.1%)	
Mean age (years)	38±16.5	42±17.0	<0.01
Age range			<0.01
<18	8.8%	5.8%	
19–35	41.7%	34.5%	
36–55	32.4%	38.4%	
56–65	10.4%	10.7%	
>65	6.7%	10.5%	
Sex**			<0.01
Female	1,717 (60.9%)	25,318 (53.6%)	
Male	1,104 (39.1%)	21,893 (46.4%)	
Race			0.338
Caucasian	1,849 (88.6%)	29,947 (88.2%)	
Non-Caucasian	239 (11.6%)	3,997 (11.8%)	
Comorbidities			
Hypertension	15.1%	12.9%	0.15
Anemia	5.9%	12.3%	<0.01
Pulmonary	5.0%	7.2%	0.05
Renal	1.1%	0.4%	0.03
Diabetes	2.5%	2.7%	0.78
Cancer (without mets)	1.8%	2.3%	0.56
Obesity	0.9%	1.5%	0.28
Nutritional depletion	5.9%	6.3%	0.79
Fluid and electrolyte disorders	12.6%	14.5%	0.24
Admission type			<0.01
Elective	1,273 (51.1%)	23,772 (54.2%)	
Non-elective	1,216 (48.8%)	20,088 (45.8%)	
Primary payer			<0.01
Medicare	240 (8.5%)	6,849 (14.5%)	
Medicaid	238 (8.4%)	3,554 (7.5%)	
Private	2,120 (75.2%)	33,338 (70.7%)	
Other	223 (7.9%)	3,396 (7.2%)	
Region of hospital			<0.01
Northeast	653 (23.1%)	12,232 (25.9%)	
Midwest	825 (29.1%)	12,968 (27.4%)	
South	813 (28.7%)	15,621 (33.1%)	
West	540 (19.1%)	6,424 (13.6%)	
Location of hospital			0.24
Urban	2,556 (90.3%)	42,863 (90.7%)	
Rural	274 (9.7%)	4,377 (9.3%)	
Teaching status of hospital			<0.01

Table 2 (continued)

Variable (n=49,609)	Laparoscopic	Open	P
Teaching	1,678 (59.3%)	26,849 (56.8%)	
Non-teaching	1,152 (40.7%)	20,391 (43.2%)	
Extent resection			
Ileocecum	433 (25.0%)	9,836 (20.1%)	<0.01
Small intestine	458 (26.5%)	15,890 (32.5%)	<0.01
Right colon	749 (43.3%)	18,721 (38.3%)	0.56
Left colon	28 (1.6%)	1,811 (3.7%)	<0.01
Sigmoid	63 (3.6%)	2621 (5.4%)	0.02
Number of diagnoses per record	4.2	5.2	<0.01
Number of procedures per record	3.0	3.4	<0.01
Fistula repair	35 (1%)	3,272 (8%)	<0.01
Ostomy placement	162 (6%)	5,336 (11%)	<0.01
Length of stay (days)	6	9	<0.01
Disposition			<0.01
Home	2,267 (91.0%)	36,342 (84.7%)	
Other facility	30 (1.2%)	1,383 (3.2%)	
Home health/Hospice	194 (7.8%)	4,770 (11.1%)	
Total charges	2,267 (91.0%)	36,342 (84.7%)	<0.01
In-hospital complication	30 (1.2%)	1,383 (3.2%)	<0.01
Wound/Infection	194 (7.8%)	4,770 (11.1%)	=0.12
Pulmonary	13 (0.3%)	1,231 (2.6%)	<0.01
Gastrointestinal	149 (5.3%)	4,940 (10.6%)	0.04
Cardiovascular	5 (0.2%)	422 (0.9%)	0.03
Intraoperative complications	42 (1.5%	1,209 (2.3%)	0.46
Disease stage*	1.7	1.5	<0.01
Mortality score*	2.6	2.4	<0.01
In-hospital mortality	5 (0.2%)	441 (0.9%)	<0.01

Table 3 Independent Predictors of Undergoing Laparoscopic Resection

Variable	Odds ratio	95% CI	P
0	2.4	1.9–2.8	<0.05
Gender			
Female	1.4	1.5–1.5	<0.05
Male	1.0		
Non-white	1.0	0.9–1.2	0.64
Admission type			
Elective	0.9	0.8–1.0	0.21
Non-elective	1.0		
Teaching status of hospital			
Teaching	1.2	1.1–1.4	<0.05
Non-teaching	1.0		
Insurance status			
Medicare	0.7		
Medicaid	1.2	0.5–1.0	0.03
Private	1.1	0.9–1.7	0.27
Other	1.0	0.8–1.5	0.41
Primary disease stage (DS Stage)	0.42	0.4–0.5	<0.01
Mortality score (DS Mrt S)	0.99	0.9–1.0	0.12
Hospital region			
Northeast	0.6	0.5–0.7	<0.01
Midwest	0.9	0.7–1.0	0.15
South	0.5	0.4–0.6	<0.01
West	1.0		
Disease location			
Ileocecum	1.5	1.0–2.2	0.03
Small intestine	0.5	0.3–0.7	<0.01
Right colon	0.5	0.3–0.7	<0.01
Left colon	0.4	0.2–0.9	0.03
Sigmoid	0.3	0.2–0.7	0.01

specific and surgeon-specific factors. Variables ranging from the patient's clinical condition on presentation, prior surgical history, and even steroid use may affect this decision. Surgeon comfort level with laparoscopy also clearly plays a role, as the clinical manifestations of CD can be highly variable and technically challenging. It is with this background that we attempted to identify factors that go into choosing an operative approach.

The results of our analysis of the NIS database reflect demographic and outcomes largely similar to the existing literature. The young, predominantly Caucasian population reflected in our data mirrors the established epidemiology of CD. Approximately 10,000 patients with CD require surgery each year, and these patients receive care in urban settings, somewhat more often in teaching hospitals—all likely a reflection of the surgical complexity associated with CD. Likewise, patient selection for a laparoscopic procedure is influenced in part on surgeon level of expertise and comfort, and this choice was made more frequently at teaching institutions. Preexisting comorbidities were fairly similar between patients offered a laparoscopic versus open surgery; the mortality score, a variable within the NIS which accounts for baseline comorbidities, while different

Table 4 Independent Predictors of In-Hospital Complications

Variable	Odds ratio	95% C.I.	P
Fistula repair	5.2	1.7–16.1	0.05
Open surgery	3.4	1.4–8.1	<0.01
Ostomy placement	2.3	1.9–2.7	<0.01
Admission type			
Elective	0.8	0.6–1.1	0.22
Non-elective	1.0		
Age>35	0.9	0.2–4.6	0.98
Race	1.4	0.9–2.4	0.17
Teaching hospital	1.2	0.9–1.7	0.18

between the two groups on univariate analysis, was not predictive in the multivariate model. Not surprisingly, as evidenced by the lower primary disease stage in the laparoscopic cohort, our data showed that those who underwent an open procedure on the whole had more advanced pathology related to CD.

Disparities among race, income, gender, and insurance status have been also shown to influence treatment options in other disease processes including CD.[24–29] Although our analysis examines differences in selection between two different types of surgical therapy rather than the need for surgical management, we did not find ethnicity to be a factor in this choice. One possible explanation for our findings, acknowledging that race is often viewed as reflective of socioeconomic status, is an assumption that after decision to operate has been made, cost between the two operative approaches would not significantly differ. Technology availability in the lower socioeconomic settings could also influence method selection, but was not identified in the present series.

We did find that factors including female gender, younger age, and ileocolic resection were more likely associated to undergo a minimally invasive approach. One possible reason for this tendency is the notion that females, especially at younger ages, may be increasingly interested in a cosmetically pleasing result than males. Based on our regression analysis, this finding was independent of the disease severity, thus not simply a factor of more elective or less severe disease manifestations. Another notable difference between patients receiving laparoscopic versus open resection, possibly reflective of income, was insurance status. Our univariate analysis revealed that a higher percentage of patients undergoing laparoscopy held private insurance and that more patients who underwent open resection depended on Medicare. Multivariate analysis confirmed those with Medicare insurance more likely to undergo an approach. Though difficult to identify the exact reasons from this type of study, this may reflect advanced technology being used more often in patients with private paying insurance or, again, the technology more readily available in more affluent areas.

Although outcomes were not our primary goal, as non-randomized data such as these can lead to certain biases, we were able to identify certain trends. In addition, we attempted to evaluate whether complication rates were simply a product of our baseline differences in the two cohorts by multivariate analysis that included patient demographics and comorbidities. Similar to data from existing clinical studies which revealed a lower rate for overall postoperative morbidity for laparoscopic resection (12.8% vs. 20.2%, $P=0.01$) but no difference in individual complications,[4,5,7,11,13,16,19,21] our data showed an overall complication rate of 8% for laparoscopic and 16% for open resection ($P<0.01$). Patients undergoing laparoscopic resection had fewer cardiovascular, pulmonary, and gastrointestinal complications, again consistent with those from smaller series.[4,7,13,14] Rates of infectious or wound complications and intraoperative complications were not significantly different between those undergoing laparoscopic versus open resection in our analysis. Similarity in rates of intraoperative complications between the two groups, while likely somewhat reflective of the selection bias inherent in our comparison, may disprove the fear that a minimally invasive approach to CD could compromise patient safety. Not surprisingly, we found that patients with fistulas and cases in which a stoma was required were more apt to undergo an open exploration. With additional experience, even these cases may be more often approached via a minimally invasive technique. Increasing experience and larger randomized studies may confirm our findings and determine whether the benefits of laparoscopy extend beyond the short-term benefits.

Several studies cite the laparoscopic "learning curve" as a barrier to this technique's acceptance as a standard of care in CD.[4,19] During our study period from 2000 to 2004, the number of Crohn's resections performed laparoscopically increased at a rate that was statistically significant, though not necessarily clinically relevant. As graduating surgical residents are becoming more familiar with advanced minimally invasive surgical skills, this number is likely to increase. Due to the time period for which the NIS was available at the time of our analysis, our study may not reflect the most recent developments in this learning curve. As future data are released and experience evolves, we may see further development of these trends, including more equivalent operative times for laparoscopic surgery for CD when compared to open resection.[7,11,14]

We acknowledge several limitations to the present study. The NIS database allows examination of nationwide trends and outcomes, providing insight into how groups represented in smaller, more controlled studies compare to the general population. However, as an administrative database which relies on coding for accuracy, the NIS itself is subject to several significant limitations. Coding discrepancies are more likely to affect diagnostic and procedural variables that are not paramount to a patient's file for billing purposes. Also, as a consequence of this time period, there is a relative paucity of laparoscopic resections in the current population, with only 6% undergoing a minimally invasive operation. As increasing experience with performing laparoscopic resections in general is gained and its use is broadened, it will be interesting to see how changes may develop in the current study. Other limitations to the present study include the mere nature of an observational, retrospective study and the inherent biases associated with it. Large databases such as the NIS, while providing a large volume of information, lack specifics that could add to the study, i.e., why exactly was the method chosen, postoper-

ative stay versus total length of hospital stay, and specific severity scales such as CDAI. In addition, NIS provides no information on competency of the operation, including margins, recurrence, conversion rate to open, immunosuppressants, number of prior surgeries, readmission rates, and any data beyond the in-hospital complication or mortality data. It also does leave open the possibility of coding errors that may not only affect the type of procedure and perioperative data but also outcomes. Yet, our goal was to identify as best as possible what was taking place on a national level, and we were able to accomplish that goal. Additionally, the large sample size provided by the NIS database increases the likelihood of an even distribution of coding errors between the laparoscopic and open groups. Our analysis included patients who were admitted under both elective and urgent or emergent settings. This designation, assigned by NIS, pertains to clinical circumstance on time of admission, rather than at the time of surgery, which may differ in CD. Although considered by some to be a relative contraindication to laparoscopic resection, conditions such as complete bowel obstruction, hemorrhage, or peritonitis were also included in our analysis. A large multicenter prospective study examining outcomes for laparoscopic surgery for CD, with attention to both patient- and surgeon-related factors which contribute to the choice of operation, would add strength to the body of literature documenting the benefits of this approach.

Conclusion

Proper patient selection when choosing an operative approach is even more important in disease process such as Crohn's. In this large nationwide database evaluation, we found that laparoscopy for Crohn's disease is associated with improved outcomes such as cost, length of hospital stay, discharge disposition, postoperative gastrointestinal, pulmonary and cardiovascular complications, and mortality compared to open resection. Although factors such as younger age, female gender, and ileocecal disease location were identified as predictors of undergoing laparoscopy, we found no influence of level of urgency of admission or race on the utilization of a laparoscopic approach. Future analysis of data as laparoscopic resections for Crohn's disease gain widespread use and acceptance will further clarify factors that influence the choice of and access to this surgical approach.

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ORIGINAL ARTICLE

Quality of Life After Ileoanal Pouch: A Comparison of J and W Pouches

Alexander D. Wade · Michelle A. Mathiason · Eric F. Brekke · Shanu N. Kothari

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Abstract
Introduction Standard treatment for ulcerative colitis and prevention of malignancy is total proctocolectomy with a neoileal pouch. The ideal configuration of the pouch has been debated. We hypothesized that there was no difference in quality of life between the J pouch and the W pouch.
Material and Methods We retrospectively reviewed the medical records of all patients undergoing ileoanal anastomosis with pouch construction at a single community-based teaching hospital over an 11+-year period. We collected demographic, operative, and postoperative data and then developed and distributed a survey designed to assess patient quality of life following pouch construction. The data of patients who had J pouches were then compared with those of patients who had W pouches. Forty-nine patients were identified; 30 had J pouches and 19 had W pouches.
Results The groups did not differ significantly in age, sex, or indication for surgery. Significant differences were detected in readmission rates (J=63%, W=21%; p=0.004) and length of follow-up (J=61 months, W=117 months; p=0.001). Complication rates, length of stay, and conversion to end ileostomy rates were similar between groups. Self-reported health status, activity restrictions, urgency, seepage, protective pad use, and number of bowel movements at night were also similar. A significant difference existed in number of bowel movements per day (J=6, W=4.5, p=0.041). No difference in quality of life was found between groups. Subgroup analysis of ulcerative-colitis-only patients had no effect on results.
Conclusion Because the J pouch is less technically demanding, it should be the preferred configuration.

Keywords Ileoanal pouch · Quality of life

Introduction

Standard treatment for ulcerative colitis and prevention of malignancy is total proctocolectomy with a neoileal pouch. A variety of pouch configurations have been devised, but whether one configuration is superior to the others has been debated. Over the course of a decade, both duplicated (J) and quadruplicated (W) configurations have been employed at our institution. Our experience was largely driven by surgeon preference. Over time, various factors contributed to one configuration being preferred over the other, predominantly ongoing debate in the surgical literature regarding the merits of either approach. Some preferred the W pouch for its more physiologically normal pouch with greater capacity and fewer bowel movements per unit time, while proponents of the J pouch favored its ease of construction and adequate function. In absence of a clearly superior configuration, surgeons were left to surmise which

A. D. Wade
Department of Medical Education,
Gundersen Lutheran Medical Foundation,
1900 South Avenue, C03-006B,
La Crosse, WI 54601, USA

M. A. Mathiason
Department of Research, Gundersen Lutheran Medical Foundation,
1900 South Avenue, C03-006B,
La Crosse, WI 54601, USA

E. F. Brekke · S. N. Kothari (✉)
Department of General and Vascular Surgery,
Gundersen Lutheran Health System,
1900 South Avenue, C05-001,
La Crosse, WI 54601, USA
e-mail: snkothar@gundluth.org

factors should most heavily influence pouch choice, including the surgeon's experience, the patient's disease state and anatomy, and the expected quality-of-life outcome.

While both surgeons at our institution were experienced with both J- and W-pouch configurations, as at other institutions, the J pouch was increasingly favored. Our perception was that the more complex W pouch was not conferring any advantage to our patients. The surgical literature continued to offer no definitive answers about which was the superior configuration. Thus, as our own cohort grew, we felt we could add to the body of evidence. Our goal was to study our patient population to determine whether any differences in quality of life attributable to pouch configuration exist between patients who had the J pouch and those who had the W pouch.

Materials and Methods

Following Institutional Review Board approval, consecutive patients who had undergone open total proctocolectomy with ileoanal pouch construction at our institution over an 11-year period were identified using hospital billing records, operating room case logs, and the surgeons' schedules. All patients had undergone a planned two-stage procedure, with ileostomy takedown approximately 6 to 8 weeks after proctocolectomy with pouch construction. Pouch design was at the discretion of the operating surgeon. Pouch construction was performed in a stapled fashion, and the anastomosis was hand-sewn in all cases. All operations were performed by one of two surgeons, who had no role in data collection, recording, interpretation, or analysis.

With the assistance of the institutional survey committee, a ten-question quality-of-life survey was developed. Surveys were mailed to all patients at the same time rather than after a predetermined follow-up period. A second mailing and telephone interviews were conducted when necessary. Telephone survey was performed by an author (ADW) who was not known to the patients previously and did not have a caregiver relationship with any of the patients. Survey results were recorded by the primary author.

Electronic and paper medical records were obtained and reviewed. Demographic, operative, and postoperative data, including age at surgery, sex, indication for surgery, type of pouch, perioperative complications, length of stay (LOS), readmission between proctocolectomy/pouch construction and ileostomy takedown, and postoperative course were recorded. Readmission was defined as an unexpected admission to the hospital for any reason during the time between discharge after the ileal pouch-anal anastomosis (IPAA) and the planned readmission for ileostomy reversal approximately 6 to 8 weeks later. Deceased patients were included in the demographic review.

Student's t test and χ^2 analysis were used to evaluate for difference, with $p<0.05$ considered significant.

Results

Fifty patients were identified, one of whom underwent a total proctocolectomy with IPAA in an S configuration for ulcerative colitis. This patient was excluded from further analysis, leaving 49 patients who underwent total proctocolectomy with ileoanal pouch reconstruction and diverting ileostomy in either a J or W configuration. Thirty patients received a J pouch and 19 a W pouch. Table 1 summarizes the demographic data.

During the study period, surgeons at our institution went from creating W pouches exclusively, to creating J pouches exclusively, to creating W pouches selectively, reflecting the changing body of literature over time. As a result, we found a significant difference between groups in time from surgery to survey (J=61 months, W=117 months; $p=0.001$; Fig. 1).

Patients who underwent W-pouch construction were, on average, nearly 7 years younger than J-pouch patients, but the difference was not significant. Men and women were similarly represented in the study population (23 men and 26 women). The most common surgical indication was

Table 1 Demographic Data

Characteristic	J pouch (n=30)	W pouch (n=19)	p
Age at surgery, mean, years (range)	43.2 (17–67)	36.3 (19–63)	0.115
Age at survey, mean, years (range)	47.4 (20–73)	45.9 (27–74)	0.750
Time from surgery to survey, mean, months (range)	60.1 (12–112)	116.5 (41–151)	0.001
Women, n (%)	18 (60)	8 (42.1)	0.221
Indication, n (%)			0.452
Ulcerative colitis	25 (83.3)	16 (84.2)	
FAP	3 (10.0)	3 (15.8)	
Malignancy	2 (6.7)	–	

FAP familial adenomatous polyposis

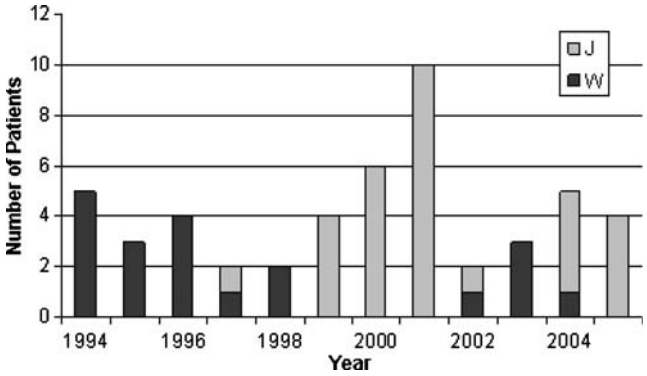

Figure 1 Distribution of the two types of pouches during the study period. Institutional preference was driven by surgeon training, literature reports, and patient factors.

ulcerative colitis, followed by familial adenomatous polyposis.

Table 2 summarizes the perioperative data. Complication rates were low and similar, and there was no difference in LOS between groups. An unexpected finding was a significant difference in readmission rates (J=63%, W=21%; p=0.004). The most common reason for readmission was dehydration and/or acute renal failure, which occurred in 12 of the 19 readmitted patients who had J pouches, but in only one of the four readmitted patients who had W pouches. Other less common causes for readmission included viral enteritis/nausea (four of 19 J readmissions), pelvic abscess (two of 19 J readmissions), small bowel obstruction (one in each group), pain (one W readmission), and wound infection (one W readmission).

Table 3 summarizes patient responses to a series of multiple-choice questions. Both self-described general health and mental health were similar between the groups, and virtually all patients described their health as excellent, very good, or good. The answers to five questions about restrictions in the areas of career, sports, hobbies, housework, and social activities were similar between groups, with most patients responding that they were either not restricted at all or were only mildly restricted in these activities.

We found no difference between groups when comparing responses to questions about a sense of urgency of defecation, seepage experienced during the day or at night, or protective pad use during the day or at night (Table 4). Most patients did occasionally experience urgency, but most had no seepage either during the day or at night. Protective pad use during the day appeared to have a bimodal distribution, with a few patients (four patients, 10%) replying that they occasionally or usually use pads, 27 (67.5%) stating that they never do, and nine (22.5%) replying that they always do. Pad use at night was similar, with six patients (15%) who occasionally or usually use them, 26 (65%) who never do, and eight (20%) who always do. Pouch function is further elucidated by the average number of bowel movements per day and the average number of bowel movements per week that occur at night (Table 5). Although the number of bowel movements per day is higher (7.6 per day vs. 5.8 per day) in the J-pouch group than in the W-pouch group, this difference was not significant. A separate question about the average number of bowel movements per week that occurred at night had similar results: a lower number for W pouches than for J pouches, but the difference was not significant.

Subgroup analysis was performed on the data for patients with an ulcerative colitis diagnosis to determine whether there was any difference between groups that could be attributable to medical treatment of the ulcerative colitis, such as preoperative steroid therapy. No such difference was identified.

Discussion

In 1978, Sir Alan Parks and Dr. R. J. Nicholls[1] described their results with an S-shaped pouch constructed from the distal 30 cm of the terminal ileum and anastomosed to the anus within a demucosalized distal rectal pouch. This treatment substantially changed the way patients, internists, and surgeons weighed the options for ulcerative colitis patients because to that point the best option had been a permanent end ileostomy. Even though five of eight patients who were analyzed had an 80% rate of self-catheterization four to eight times daily to evacuate their pouch, the operation opened the door for a better quality of life for multitudes of patients.

In 1980, Utsunomiya et al.[2] described a variant of the S pouch—a less technically demanding J-shaped pouch. Patients with the J pouch had higher rates of spontaneous evacuation (intentional defecation without pouch catheterization) but also had higher numbers of total defecations each day and, perhaps more importantly, higher numbers of nocturnal defecations. Pouch configuration then took one

Table 2 Data from the Perioperative Period

Variable	J pouch (n=30)	W pouch (n=19)	p
Complications, number (%)	4 (13.3)	1 (5.3)	0.636
Readmissions, number (%)	19 (63.3)	4 (21.1)	0.004
LOS, mean, days (range)	7.9 (3-22)	7.4 (4-21)	0.719

LOS length of stay

Table 3 Patient Responses to Survey Questions About Health Status and Activity Restriction

Survey question	Response	J pouch, *n* (%)	W pouch, *n* (%)	*p*
General health	Excellent	3 (12.0)	2 (12.5)	0.354
	Very good	11 (44.0)	7 (43.8)	
	Good	6 (24.0)	7 (43.8)	
	Fair	4 (16.0)	–	
	Poor	1 (4.0)	–	
Mental health	Excellent	8 (32.0)	5 (31.3)	0.125
	Very good	9 (36.0)	4 (25.0)	
	Good	4 (16.0)	7 (43.8)	
	Fair	4 (16.0)	–	
	Poor	–	–	
Career restricted	Not at all	12 (57.1)	11 (68.8)	0.605
	Mildly	5 (23.8)	4 (25.0)	
	Moderately	2 (9.5)	1 (6.3)	
	Severely	2 (9.5)	–	
Sports activities restricted	Not at all	8 (33.3)	8 (53.3)	0.410
	Mildly	11 (45.8)	6 (40.0)	
	Moderately	2 (8.3)	1 (6.7)	
	Severely	3 (12.5)	–	
Hobbies restricted	Not at all	9 (36.0)	10 (62.5)	0.070
	Mildly	10 (40.0)	6 (37.5)	
	Moderately	6 (24.0)	–	
	Severely	–	–	
Housework restricted	Not at all	13 (54.2)	12 (75.0)	0.384
	Mildly	7 (29.2)	3 (18.8)	
	Moderately	4 (16.7)	1 (6.3)	
	Severely	–	–	
Social activities restricted	Not at all	12 (48.0)	9 (56.3)	0.157
	Mildly	8 (32.0)	7 (43.8)	
	Moderately	5 (20.0)	–	
	Severely	–	–	

Table 4 Patient Responses to Survey Questions About Pouch Function

Survey question	Response	J pouch, *n* (%)	W pouch, *n* (%)	*p*
Urgency	Never	3 (12.5)	3 (18.8)	0.774
	Occasionally	14 (58.3)	10 (62.5)	
	Usually	6 (25.0)	2 (12.5)	
	Always	1 (4.2)	1 (6.3)	
Seepage during the day	No seepage	16 (66.7)	10 (62.5)	0.940
	Minor seepage	7 (29.2)	5 (31.3)	
	Major seepage	1 (4.2)	1 (6.3)	
Protective pad use during the day	Never	15 (62.5)	12 (75.0)	0.397
	Occasionally	2 (8.3)	1 (6.3)	
	Usually	–	1 (6.3)	
	Always	7 (29.2)	2 (12.5)	
Seepage at night	No seepage	16 (66.7)	9 (56.3)	0.791
	Minor seepage	6 (25.0)	5 (31.3)	
	Major seepage	2 (8.3)	2 (12.5)	
Protective pad use at night	Never	16 (66.7)	10 (62.5)	0.375
	Occasionally	2 (8.3)	3 (18.8)	
	Usually	–	1 (6.3)	
	Always	6 (25.0)	2 (12.5)	

One patient in the J-pouch group did not respond to the pouch function questions

Table 5 Patient Responses to Survey Questions About Number of Bowel Movements, Day and Night

Variable	J pouch	W pouch	*p*
BM per day, mean (range)[a]	6.0 (4–20)	4.5 (4–12)	0.041
Night BM per week, mean (range)[a]	7.0 (0–35)	4.5 (0–21)	0.445

BM bowel movement

[a] One outlier was excluded

more major shift with the advent of the W-shaped pouch, which appeared to have the best functional outcomes: a low number of defecations per day and a low likelihood of catheterization required for evacuation. The W pouch, however, was significantly more complicated to construct than the J pouch because it required multiple hand-sewn connections as opposed to one or two firings of a linear stapler cutter. To date, the literature is mixed regarding which pouch configuration is superior.

Quality of life may be the most important consideration for patients. The revolutionary changes in the standard of care for ulcerative colitis patients resulting from the publication of Parks and Nicholls' manuscript describing a reservoir built from the patient's terminal ileum cannot be overstated. Since that time, further innovations and refinements have been tried, some of which have endured and some of which have not. But an ileal pouch with an anal anastomosis of one configuration or another remains the preferred means of improving quality of life for these patients.[3]

As evidenced in the literature, this surgery is also useful for patients with conditions other than ulcerative colitis, particularly those properly selected patients who have colorectal cancer, familial adenomatous polyposis, or Crohn's disease. Approximately one sixth of patients undergoing IPAA at our facility did so for indications other than ulcerative colitis.

The basic principles of the procedure are well described and rarely disputed. However, over the last decade, a preponderance of the medical literature has consistently described two dominant choices: the J pouch, which is easier to create, and the W pouch, which has a lower number of bowel movements per unit time.[4] We felt that a survey comparing the experience of patients with J pouches with that of patients with W pouches would give us insight into the long-term ramifications of the choice of pouch configuration. A careful reading of the literature at the time of the development of our survey demonstrated a paucity of data directly comparing the J pouch with the W pouch in terms of quality of life. Although functional outcomes have been measured—including the number of stools, the number of nocturnal stools, the need for self-catheterization, and the use of antidiarrheal medications, to name a few—the meaning of that information from the patients' perspective is often lacking. The 1999 landmark study of long-term functional outcome and quality of life by Fazio et al.[5] introduced a validated instrument for measuring quality of life. The comparisons within that population firmly established that quality of life after pouch construction is high, does not wane with time, and varies little within subgroups such as sex, age, indication, or duration of disease prior to surgery. However, although 99.5% of the patients had either J or S pouches, the possible influence of pouch configuration on quality of life was not assessed.[5]

A recent meta-analysis by Lovegrove et al.[6] strongly supported previous reports that S pouches require intubation and that J pouches have a higher rate of antidiarrheal medication use. Those authors, albeit limited by the data reported within the studies included in their meta-analysis, did not quantify or even describe the differences identified *from the patient's perspective*. It is fair to ask whether patients believe that a higher rate of antidiarrheal medication use in return for virtual elimination of the need for anal self-catheterization is an acceptable tradeoff. A somewhat surprising finding in that study was the high number of W-pouch patients who had to self-catheterize, although the authors point out that the majority of those patients were contributed by a single study that fell outside the 95% confidence interval for study quality. One shortcoming of our study is our failure to ask patients about self-catheterization.

Recent studies that focus on specific aspects of patient quality of life, such as sexual function, have appeared, but they do not include data regarding pouch configuration.[7,8] Authors are now comparing laparoscopic versus open technique without first having settled the question of J versus W pouch. The vast majority of reports of laparoscopic-assisted IPAA utilize a J configuration, but a recent report of 65 patients documented good results with the S configuration, further clouding the picture.[9]

Another limitation of our study is the unrandomized nature of the retrospective design. As alluded to in the recent summary review by Bach and Mortensen,[10] the trend toward increasing, and now nearly exclusive, use of the J pouch has occurred incrementally based on unrandomized studies that document both the favorable aspects of the J pouch, such as ease of construction and spontaneous evacuation, as well as the tradeoffs, including more frequent stooling. No one currently disputes that patient quality of life is higher with the ileoanal pouch than without. As consensus builds that the J pouch is an acceptable configuration, one advantage is that, because it is less technically demanding than other configurations, it is available in hospitals without fellowship-trained colorectal

surgeons and specialists. A quality-of-life comparison between patients randomized to one or the other configuration would almost certainly need to be undertaken by a high-volume multicenter study with expertise in both techniques. Although our initial experience with W pouches in terms of complications was similar to that of other published series, lower volume at our institution is one factor that motivated adoption of the less technically demanding J pouch.

Another factor influencing quality of life is pouchitis. No objective data regarding pouchitis were collected in our study; this is another limitation. Our data, while exhaustive for our institution, remain a small dataset. While attempting to increase the validity of our data by including all of our patients, we necessarily diminish the strength of our conclusions by adding another confounding variable, that is, the variation in length of time between the surgery and the survey for each patient. A prospectively obtained dataset that queried patients regarding quality of life at specific time intervals from surgery would be preferable. Although, as previously mentioned, other authors have reported that pouch function does not change over time, it is hard to ignore the vastly different lengths of time between the two groups. Finally, the data we obtained could be underpowered to detect a small but perhaps clinically significant difference in quality of life between the groups. A properly powered prospective study would be needed to address this.

Conclusion

The J-pouch configuration is technically less demanding; it results in similar quality of life when compared to the W pouch. For those reasons, the J pouch should be the preferred choice.

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ORIGINAL ARTICLE

Prevalence of Adenomas and Carcinomas in the Ileal Pouch After Proctocolectomy in Patients with Familial Adenomatous Polyposis

Masahiro Tajika · Tuneya Nakamura · Osamu Nakahara · Hiroki Kawai · Kouji Komori · Takashi Hirai · Tomoyuki Kato · Vikram Bhatia · Hideo Baba · Kenji Yamao

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Abstract
Purpose Restorative proctocolectomy has become the most common surgical option for patients with familial adenomatous polyposis (FAP). However, adenomas may develop in the ileal pouch mucosa over time, and even carcinoma in the pouch has been reported. Our aim was to evaluate the prevalence, nature, and etiology of ileal pouch and nonpouch adenomas and carcinoma in patients with FAP.
Patients and methods This was a retrospective study of 31 FAP patients with Kock's continent ileostomy (Kock; $n=8$), ileorectal anastomosis (IRA; $n=7$), and ileal pouch–anal anastomosis (IPAA) (n=16). All patients were followed with a standardized protocol including chromoendoscopy and biopsies of visible polyps in the ileal pouch and nonpouch mucosa.
Results Sixteen of 24 pouch patients (Kock and IPAA) developed adenomas in the ileal pouch mucosa, and all patients with IRA developed adenomas in the rectal mucosa. The prevalence of ileal adenomas was significantly higher in pouch patients than in IRA patients ($P=0.002$). Only one patient with Kock showed adenoma in the prepouch area. Two cases of adenocarcinomas and one case of advanced adenoma were found in the ileal pouch mucosa.
Conclusion Our results show a high frequency of adenomas in the ileal pouch mucosa, with evolution into carcinoma in some patients. Regular endoscopic surveillance of the pouch is recommended at a frequency similar to that for the rectal mucosa after IRA in pouch patients with FAP.

M. Tajika (✉) · T. Nakamura · H. Kawai
Department of Endoscopy, Aichi Cancer Center Hospital,
1-1 Kanokoden, Chikusa-ku,
Nagoya 464-8681, Japan
e-mail: mtajika@aichi-cc.jp

O. Nakahara · K. Yamao
Department of Gastroenterology, Aichi Cancer Center Hospital,
Nagoya, Japan

K. Komori · T. Hirai · T. Kato
Department of Gastroenterological Surgery,
Aichi Cancer Center Hospital,
Nagoya, Japan

V. Bhatia
Department of Medical Hepatology,
All India Institute of Medical Sciences,
New Delhi, India

O. Nakahara · H. Baba
Department of Gastroenterological Surgery,
Graduate School of Medical Sciences, Kumamoto University,
Kumamoto, Japan

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Introduction

Familial adenomatous polyposis (FAP) is an inherited disease characterized by the development of hundreds of colorectal adenomas, leading to a 100% lifetime risk of colorectal cancer.[1] For this reason, a prophylactic colectomy is recommended for patients with FAP for the prevention of colorectal cancer. Four surgical strategies are available for patients with FAP: proctocolectomy with permanent ileostomy, proctocolectomy with Kock's pouch continent ileostomy (Kock), colectomy with ileorectal anastomosis (IRA), and restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA).[2] The option of a permanent ileostomy is usually reserved for cases where there is a contraindication to the other procedures. IRA

produces good functional results, and this surgery is associated with less morbidity than the other procedures.[3] However, continuing endoscopic surveillance for adenomas in the rectum is necessary, and there is a 13% to 25% cumulative risk of rectal cancer after 15–25 years despite surveillance.[4–6] On the other hand, both Kock and IPAA (pouch patients) theoretically eliminate the risk of colorectal cancer and adenomas and perhaps the need for further lower gastrointestinal surveillance. However, a recent report showed that adenomas or carcinomas appeared not only in the residual rectal mucosa or anastomosis after IRA but also in the ileal pouch mucosa after Kock or IPAA.[7–13] In addition, there were five reports of cancers arising from the ileal pouch mucosa, as opposed to from the anastomosis, in patients with FAP.[14–18]

In our center, patients with FAP underwent Kock pouch construction or an IRA until 1987. However, since the introduction of IPAA in our center in 1988, we have favored IPAA as the operation of first choice for the treatment of patients with FAP. The aim of this study was to describe the prevalence, nature, and etiology of adenomas and carcinoma developing in the ileal pouch mucosa and prepouch ileal mucosa in patients with FAP after proctocolectomy or colectomy.

Material and Methods

Endoscopic and medical records of all patients with FAP (n= 70) treated in Aichi Cancer Center Hospital, Nagoya, between January 1965 and December 2002 were reviewed. FAP was defined by the presence of more than 100 colorectal adenomas (all patients) and a family history of FAP. Thirty-one patients were enrolled in endoscopic surveillance and were included in this study. Fourteen patients had undergone Kock and IRA until May 1987. After March 1988, 16 patients had undergone IPAA and one patient had Kock as he had advanced cancer in the lower rectum. These patients were subjected to regular endoscopic examination of the ileal pouch or the rectal stump. Patient demographic data, surgical data, details of pathological specimens, and details of upper gastrointestinal endoscopy were obtained from the medical records. All patients submitted informed consent for collection and subsequent use of data for research purpose, and the study was carried out in accordance with the Helsinki Declaration.

The interval between surgery and adenoma appearance was defined as the time from surgery to the first report showing histologically confirmed adenomas in the ileal mucosa. The number, size, and histology of adenomas occurring in the ileal mucosa were determined based on the last report, or the last report before treatment. For each patient, the most advanced histologic diagnosis was taken as valid. The examination was performed with a flexible colonoscope. The monitoring procedure included systematic chromoendoscopy using 0.5% indigo carmine and biopsies of the visible polyps. A thorough examination of the pouch, the distal 15 to 20 cm of the afferent limb, and the anal canal was made. Polyps were classified into three size groups: 1–4, 5–9, and ≥10 mm in diameter. Advanced adenomas were defined as adenomas ≥10 mm in greatest diameter and/or with high-grade dysplasia.

During the follow-up of the ileal pouch or the rectal stump, endoscopic treatment of any adenoma that was found was decided according to its size and shape, as well as the number of synchronous adenomas. All adenomas <10 mm in size, regardless of their number and shape, were coagulated. Initially, Nd-YAG laser for rectal adenomas and heater probe for ileal pouch polyps were used. Since 2004, argon plasma coagulation was used for polyp fulguration. For adenomas ≥10 mm in the rectum, endoscopic mucosal resection was performed. Ileal pouch adenomas underwent coagulation, except semipedunculated adenomas, when endoscopic mucosal resection was carried out.

For statistical analysis, the Kaplan–Meier estimate was chosen to calculate cumulative incidence rates, the differences being analyzed by the log-rank test. The Mann–Whitney, Fisher's exact, and chi-square test were used to compare the different characteristics of patients with and without ileal adenomas. Pearson's correlation coefficient was used to study the relationship between the number of adenomas and time since pouch surgery. A P value <0.05 was considered statistically significant.

Results

Thirty-one patients from 23 families (16 women; median age 57.7 years; range 33 to 71 years) underwent endoscopic follow-up. Eight patients (two women; median age 65.6 years; range 53 to 70 years) with Kock pouch underwent a pouch endoscopy. The median age of the patients at the time of pouch surgery was 37.7 years (range 32 to 46 years) and the mean duration of ileal pouch endoscopic follow-up was 8.5±9.9 years (range 0.5 to 29 years). Sixteen patients with IPAA (eight women; median age 39.5 years; range 33 to 65 years) underwent a pouch endoscopy. The median age of these patients at the time of pouch surgery was 25.9 years (range 17 to 47 years), and the mean duration of ileal pouch endoscopic follow-up was 5.7±4.6 years (range 0.6 to 17 years). Seven patients with IRA (six women; median age 59.4 years; range 47 to 71 years) underwent ileoscopy. The median age at the time of pouch surgery was 34.0 years (range 20 to 48 years) and

the mean duration of ileal endoscopic follow-up was 2.0± 4.4 years (range 0.5 to 22 years).

Table 1 shows the characteristics of the pouch patients (Kock and IPAA) and IRA patients. Although the median age and median follow-up duration of IRA patients was longer than that of the pouch patients, there was no statistically significant difference. Furthermore, there were no significant differences in the median polyp count at initial treatment not only in colon but also in the rectum between the patients who underwent pouch reconstruction and the IRA patients. Only the median bowel frequency was significantly lower in IRA patients compared to the pouch patients.

The number, size, shape, and histology of polyps found in each patient and the age of the patient and pouch are shown in Table 2. In patients with ileal pouch, adenomas developed in 16 of 24 patients (67%), ranging in number from 1 to 300. The size of the adenomas ranged (ranging in size) from 2 to 20 mm (Fig. 1). Two cases of adenocarcinoma and one case of advanced adenoma developed in the ileal pouch of Kock and IPAA patients, respectively. These tumors developed in the ileal pouch mucosa itself, as opposed to the ileoanal anastomosis site. Tiny polyps of size 1 to 3 mm were observed in the prepouch ileal mucosa in five of 24 patients, one of these were adenomas with low grade atypia. In patients with IRA, from one to ten adenomas were observed in all cases in the rectum; sizes varied from 2 to 10 mm. No patient had adenomas in the ileal mucosa above the IRA site. Only one patient had a lymphoid polyp in the ileal mucosa.

There were no significant differences in the median age or the median time to adenoma development since pouch surgery in pouch patients (Kock and IPAA) and IRA patients. However, the prevalence of ileal adenomas was significantly higher in pouch patients, especially in the pouch mucosa as compared to the IRA patients (P=0.002), and there was a significant relationship between the number of ileal polyps and the duration since pouch surgery in pouch patients (P=0.016).

The risk of adenoma development in the ileal pouch was 13%, 43%, and 72% at 5, 10, and 20 years of follow-up, respectively, after proctocolectomy with Kock and IPAA (Fig. 2). The risk of rectal adenoma after colectomy with IRA was 14%, 57%, and 85%, at 5, 10, and 20 years of follow-up, respectively. There was no significant difference in the cumulative prevalence of ileal pouch adenomas and rectal adenomas.

Characteristics of patients who developed pouch adenomas were compared with those who did not develop pouch adenomas in pouch patients (Table 3). There were no significant differences between the ages of patients, duration of follow-up, severity of colon disease, presence of gastric polyps and duodenal adenomas, type of pouch construction, median bowel frequency, and presence of pouchitis.

Discussion

Kock and IPAA have been used for patients with FAP after proctocolectomy because they theoretically eliminate the risk of colorectal cancer and adenomas and the need for further lower gastrointestinal surveillance. However, development of ileal adenomas and adenocarcinomas after proctocolectomy is becoming evident.[10–13] In previous reports, the prevalence reached 13–57% at a median follow-up of 4 to 6 years after surgery.[6,7,12] Groves et al. estimated that the prevalence of adenomas in the ileal pouch increased by 6.6% per year of age and 20% per year of follow-up.[12] Parc et al. showed that the risk of adenoma development in the ileal pouch was 7%, 35%, and 75% at 5, 10, and 15 years follow-up, respectively.[11] In our study, the incidence of ileal adenomas was as high as 50% in Kock and 75% in IPAA at a median follow-up of 14.7 years

Table 1 Characteristics of Pouch Patients and IRA Patients

Factor	Pouch patients (n=24)	IRA patients (n=7)	P value
Median age, years (range)	46.0 (33–70)	59.4 (47–71)	NS
Age, years (mean ± SD)	50.7±13.9	60.4±7.3	
Median follow-up, years (range)	15.1 (4.6–30.8)	23.7 (17.3–28.4)	NS
Median polyp count at treatment			
Total	2,934 (250–20,000)	4,789 (570–9,436)	NS
Colon	2,630 (210–18,300)	4,182 (420–9,340)	NS
Rectum[a]	408 (5–2,520)	165 (1–1,071)	NS
Gastric polyp	18 (75.0%)	5 (71.4%)	NS
Papillary adenoma	15 (62.5%)	4 (57.1%)	NS
Extrapapillary adenoma	11 (45.8%)	2 (28.6%)	NS
Median bowel frequency per day	5 (2–10)	3 (2–6)	0.04

IPAA ileal pouch–anal anastomosis, *Kock* Kock's continent ileostomy

[a] Except for lower rectum in patients with IRA

Table 2 Characteristics of Polyps in Pouch Patients (Kock and IPAA) and Nonpouch Patients (IRA) with FPA

	Pouch patients (n=24)		IRA patients (n=7)	
	Ileal pouch mucosa (n=16)	Prepouch mucosa (n=5)	Rectal mucosa (n=7)	Ileal mucosa (n=1)
Median age, years (range)	41.0 (33–70)	42.1 (39–69)	59.4 (47–71)	62.4
Age, year	48.3±14.4	46.8±7.4	60.4±7.3	62.4
Greatest polyp size, *n*				
1–4 mm	5	5	6	1
5–9 mm	5	0	1	0
≧10 mm	6	0	0	0
No. of polyps				
<50	10	5	7	1
≧50	6	0	0	0
Shape of polyps				
Sessile	15	5	7	1
Semipedunculated	1	0	0	0
Histology				
Lymphoid hyperplasia	0	4	0	1
Low-grade dysplasia	13	1	7	0
High-grade dysplasia	1	0	0	0
Carcinoma	2	0	0	0
Time since operation, years	13.5±7.1	13.2±8.8	12.0±7.8	20.9

Values are mean ± SD unless otherwise noted

Kock Kock's continent ileostomy, *IRA* ileorectal anastomosis, *IPAA* ileal pouch–anal anastomosis, *FAP* familial adenomatous polyposis

after surgery, and the risk of adenoma in the pouch was 13%, 43%, and 72% at 5, 10, and 20 years of follow-up, respectively (Fig. 2). In a recent report, Moussata et al. showed the high prevalence of ileal pouch adenoma (17/23, 74%) in FAP patients with IPAA at a median interval of 8 years after surgery.[13] Our study of the high prevalence of ileal adenomas supports these recent results. To help explain the high prevalence of ileal adenomas, Moussata et al. emphasized the importance of chromoendoscopy using indigo carmine; this procedure can help in identifying flat and, in some rare cases, extensive lesions (Fig. 1).[13]

In contrast to adenomas in the ileal pouch, development of adenomas in the ileal segment immediately above the IPAA (prepouch) has rarely been reported. In previous publications, development of prepouch adenomas has been reported in ten of 26 (4%) patients by Wu et al.,[7] in two of 20 patients (10%) by Groves et al.,[12] and in one of 24 patients (4%) by Thompson-Fawcett et al.[10] In this study, we found only one ileal adenoma in the mucosa above the pouch in 24 pouch patients (4%) at a median follow-up of 15.1 years after surgery. It seems that development of prepouch adenomas is rare compared with that of pouch adenomas, although based on the present study. It is difficult to recommend reduced surveillance because of our small patient numbers.

The development of neoterminal ileal adenomas was significantly higher (P=0.002) when an ileal pouch was constructed (as in Kock and IPAA), compared with the nonpouch patients (IRA). It has been suggested that pouch patients by nature would be more likely to have ileal adenomas because of their selection for pouch surgery rather than IRA. In this study, there was no difference in polyp count at colectomy not only in colon but also in rectum. Moreover, in support of our findings, a previous study has reported that in pouch patients, adenomas were limited to the pouch and were not commonly seen in the prepouch ileum mucosa of the same patients.[7,10,12] This suggests that the pouch itself is important for enhanced adenoma risk.

The reason why ileal adenomas including prepouch adenomas are uncommon may be because of the rapid transit of the small bowel contents through this area of the gastrointestinal tract. When fecal stasis occurs such as in a reconstructed pouch, the incidence of neoplasia in ileal mucosa may increase. Several authors have implicated colonic metaplasia as the reason for the development of ileal adenomas[8,19,20] and even carcinomas in the pouch of patients with FAP.[21–23] Colonic metaplasia was frequently reported in the earlier descriptions of changes observed in the ileal pouch mucosa, and some considered it an adaptive

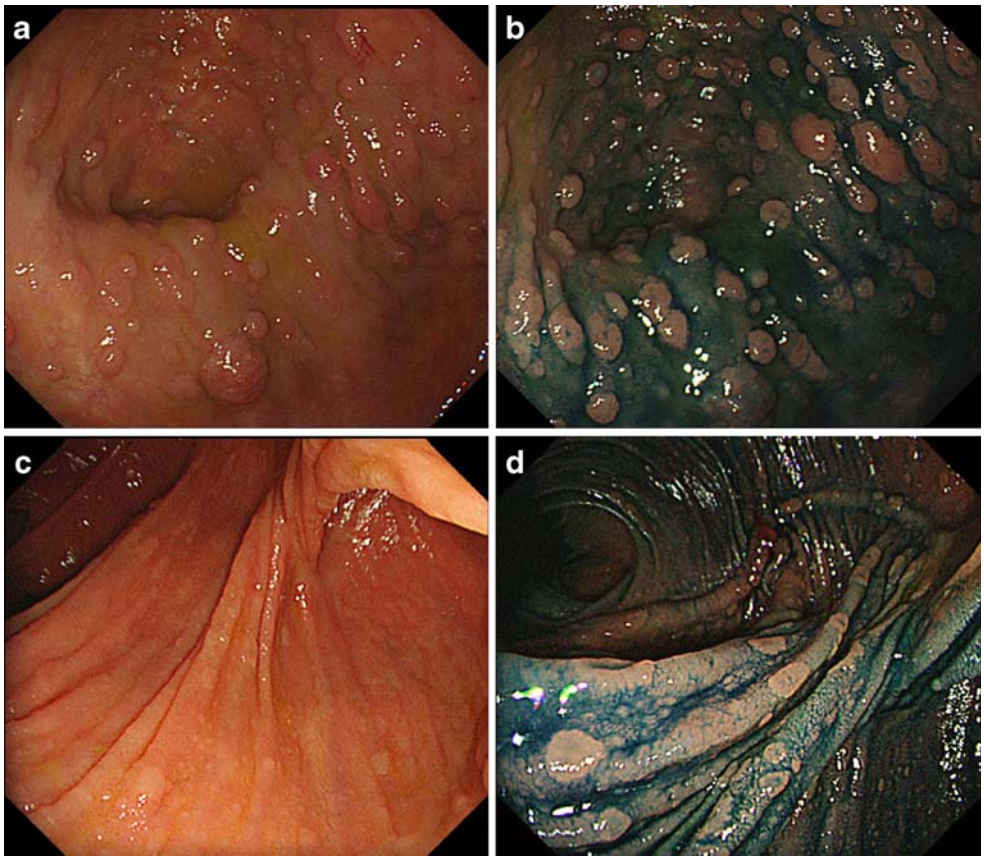

Figure 1 Endoscopic view of ileal pouch adenomas in patients with FAP. **a** Multiple grossly visible polyps are arising at the ileal pouch mucosa. **b** Chromoendoscopy view using indigo carmine. **c** Multiple white flat lesions are observed in the ileal pouch mucosa. **d** After using indigo carmine, multiple sessile polyps are revealed.

response of the pouch to its role as a neorectum. Further investigations have shown that colonic transformation is only partial. Small-bowel brush border disaccharidase activity is preserved, as is the ability to absorb vitamin B12, D-xylose, phenylalanine, and bile acids.[20,24–26] The

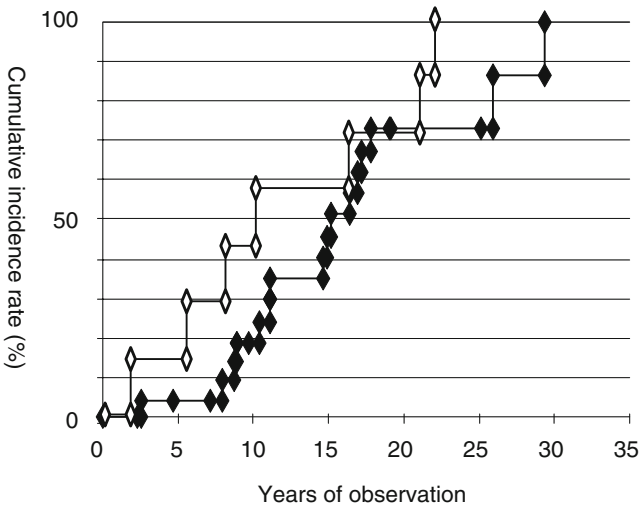

Figure 2 Cumulative incidence rate of adenomas in the ileal pouch after proctocolectomy with Kock and IPAA (*closed diamond*) and that of rectal adenomas after colectomy with IRA (*open diamond*).

mucosal change is now described as colonic metaplasia and is likely a response to chronic inflammation caused by changes in luminal contents. If colonic phenotypic changes are not the stimuli for the development of adenomas in the ileal pouch, adenomas may form as a result of changes in the luminal contents. Stasis in the pouch causes a change in luminal contents that are in contact with the ileal mucosa. In FAP, these changes may, at least in theory, favor the development of adenomas in a region of the gut where they are usually not observed. There is an increase in the concentration of short chain fatty acids to colonic levels,[27] an increase in anaerobic bacterial counts with a more colonic type flora,[28,29] and increased deconjugation and dehydroxylation of bile acid by the anaerobic bacteria.[29] In particular, deoxycholic acid and lithocholic acid, which are known carcinogens, have concentrations several times higher in an ileal pouch than in an end ileostomy.[29]

At present, it does not seem possible to predict who is at risk for developing polyps in the pouch. Our findings show that there is no apparent relationship between the presence of a particular phenotype and development of ileal polyps. Previous reports have showed the same results.[7,10] However, it seems certain that the age of the pouch is important in the development of ileal adenomas. In this study, the median follow-up period in patients without adenomas was only

Table 3 Characteristics of Pouch Patients with and Without Ileal Adenomas

Factor	With adenomas (n=16)	Without adenomas (n=8)	P value
Median age, years (range)	41.0 (33–70)	59.2 (37–67)	NS
Age, years (mean±SD)	48.3±14.4	55.3±12.5	
Median follow-up, years (range)	14.7 (2.6–29.4)	9.3 (2.3–25.1)	NS
Median polyp count at colectomy	2,707 (250–16,000)	2,934 (1,032–20,000)	NS
Gastric polyp	12 (75.0%)	6 (75.0%)	NS
Papillary adenoma	11 (68.8%)	4 (50.0%)	NS
Extrapapillary adenoma	8 (50.0%)	3 (37.5%)	NS
Type of pouch construction	IPAA/Kock=12/4	IPAA/Kock=4/4	NS
Median bowel frequency per day	5 (2–10)	5 (3–10)	NS
Pouchitis	4 (25%)	2 (25%)	NS

IPAA ileal pouch–anal anastomosis, *Kock* Kock's continent ileostomy

9.3 year. Because the incidence of pouch adenoma increases steadily with follow-up, it is possible that most if not all of these patients are destined to develop adenomas after two decades of follow-up. Many researchers have investigated adenomatosis polyposis coli gene mutations in pouch patients with FAP, although none has demonstrated obvious genotype–phenotype correlations that would predict the development of pouch adenomas.[11–13,30,31]

We observed two cases of adenocarcinoma and one case of advanced adenoma in pouch patients. Most studies of pouch adenomas have described only small polyps with a low risk of malignant change.[10–13] Several other cases of carcinoma after restorative proctocolectomy seem to have arisen from residual rectal mucosa at the ileoanal anastomosis.[32] To our knowledge, there have been five case reports of adenocarcinoma arising from the ileal pouch mucosa.[14–18] Our cases are the sixth and seventh cases of ileal pouch cancer described in the English literature (Table 4). It is not clear what malignant potential pouch adenoma may have and what is the lifetime risk of pouch cancer be for patients with FAP. If ileal adenomas progress to carcinoma following a similar pattern seen in the colon, factors that may determine the risk of malignant transformation are number of polyps, large size, severity of dysplasia, and villous architecture. In this series of 24 pouch patients, three patients (12.5%) had more advanced histological features with adenocarcinoma and high-grade dysplasia. Two cases of adenocarcinoma were large (15 and 25 mm in diameter). One case of adenocarcinoma and an advanced adenoma were observed among the multiple adenomatous polyps. Groves et al. reported that 11 of 60 pouch patients (18%) had more advanced histological features,[12] and they identified a significant minority of patients with pouch adenomas who developed multiple polyps, large sessile polyps, or adenomas with more advanced histological features. These patients may be at higher risk for malignant change and warrant closer surveillance.

On the other hand, we did not observe rectal cancer in IRA patients. The rate of rectal cancer appears very low

Table 4 Summary of Seven Cases of Ileal Pouch Cancer in Familial Adenomatous Polyposis

Author	Year	Operation	Age of pouch (years)	Gender	Shape	Size (mm)	Distance from anastomosis (cm)	Staging	No. of pouch polyps	Time to cancer years)
Bassiuni and Billings[14]	1996	IPAA	28	M	Large polypoid	ND	ND	T3,N+	ND	3
Palkar et al.[15]	1997	IPAA	39	F	Large polypoid	40×35	6 from AV	T4N0	ND	4.7
Cherki et al.[16]	2003	IPAA	35	F	ND	ND	3	T3N1M1	ND	3.5
Ulaş et al.[17]	2006	IPAA	55[a]	M	ND	ND	3 from AV	Dukes B	Flat adenoma	9
Linehan et al.[18]	2007	IPAA	30	M	ND	ND	ND	T3N0	ND	10
Present case	2008	IPAA	46	F	Type 2	15×15	10	T4N1M0	0	8.6
Present case	2008	Kock	39	M	Type 1	25×20	15	T3N0M0	>10	29

[a] This patient also underwent ileorectal anastomosis at 36 years

IPAA ileal pouch–anal anastomosis, *Kock* Kock's continent ileostomy, *ND* not described, *AV* anal verge

compared to the reported figures in the literature, with a cumulative risk of 13% to 25% after 15–25 years follow-up.[4–6] Since this is a retrospective study, with potential bias such as small number of IRA patients and the inclusion of less severe cases, it may be prudent to continue close follow-up of the rectal stump (endoscopy every 6–12 months, use of coagulation treatment of all visible adenomas) to reduces the risk of rectal cancer.

In this study, we found that 67% of patients had adenomas and 12.5% of patients showed advanced histological feature among those with a pouch. This risk is high considering the life expectancy of these patients. If patients with FAP received proctocolectomy with IPAA in their twenties, the risk of subsequent adenoma development in the ileal pouch would be 72% at 20 years follow-up. As the ideal operation for FAP should eliminate the risk of colorectal cancer while achieving good functional results with a low complication rate, proctocolectomy with IPAA is now preferred by most surgical teams. Since 1988, we have clearly favored IPAA for the patients with FAP. The main reason favoring IPAA compared to IRA is that IPAA would theoretically reduce the risk of rectal cancer development to a greater degree than IRA. However, the prevalence of two cases of ileal pouch adenocarcinoma (6.5%) as reported here, combined with previous reports,[14–18] might explode the established theory that IPAA is a definite treatment. But the potential risk cannot be compared to the risk of rectal cancer after IRA because the sample sizes are so small. Further follow-up will be necessary to assess the risk of ileal pouch adenocarcinoma.

Saurin et al. showed the methods of surveillance and therapeutic indications in patients with FAP following colectomy.[33] Although there are no validated data in the literature, on the basis of experience, follow-up is recommended from 6 months, 1 year, and then every 2 years in the case of IPAA. In terms of treatment methods, they reported that no systematic endoscopic treatment of adenomas of the ileal pouch or afferent loop can be recommended.[33] For large adenomatous formations (>1 cm) or in case of high-grade dysplasia, endoscopic treatment must be considered, but a skilled team is needed because of the thin ileal mucosa. Our current strategy in patients with IPAA is regular follow-up starting at 1 year after surgery and then every year thereafter. If adenomas are observed in the pouch, we recommend endoscopic resection or argon plasma coagulation where feasible and follow-up every 6 months thereafter. Some reports showed the efficacy of nonsteroidal anti-inflammatory drugs in suppressing ileal pouch adenomas[34,35]; its effectiveness in the ileal pouch has not been systematically studied. Further follow-up of pouch patients will be needed to elucidate the natural history and to look for risk factors for adenoma and carcinoma formation.

Conclusion

This study has shown a high prevalence of adenomas in the ileal pouches of patients with FAP and an absence of adenomas in the prepouch ileum and ileal mucosa above the IRA. These data suggest that adenomas may develop in FAP pouches with increasing time after surgery. Furthermore, we observed two cases of adenocarcinoma and one case of advanced adenoma. The natural history and the risk of pouch adenomas are not known. Because pouch adenomas in FAP patients may have a high-grade malignant potential like their colonic counterparts, we recommend careful regular endoscopic surveillance of FAP pouches and further evaluation of management and treatment strategies for pouch adenomas.

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ORIGINAL ARTICLE

Comparison of Clinical Effects Between Warm Water Spray and Sitz Bath in Post-hemorrhoidectomy Period

Kuo-Feng Hsu · Jen-Shu Chia · Shu-Wen Jao · Chang-Chieh Wu · Hsiang-Yu Yang · Chen-Ming Mai · Chun-Yu Fu · Cheng-Wen Hsiao

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Abstract
Background Warm water sitz bath is advised for a variety of anorectal disorders. However, preparation of the sitz bath is sometimes difficult for patients. As an alternative to the sitz bath, we have adapted a water spray method. A randomized, controlled study was conducted to determine if the water spray method has similar effects to the sitz bath in the post-hemorrhoidectomy period and it is easy to carry out.
Methods A total of 120 patients were randomly assigned to water spray or sitz bath groups. All patients received analgesics and a fiber-rich diet after hemorrhoidectomy. Clinical parameters including pain, irritation (burning or itching sensations), hygiene, convenience, and overall satisfaction were evaluated by a visual analog scale to assess treatment outcome in both groups.
Results There was no obvious difference in age, gender distribution, body mass index, or duration of disease between groups. There were no significant difference in scores for postoperative pain ($p=0.23$), irritation ($p=0.48$), or hygiene ($p=0.725$) between groups. However, the water spray group reported significantly greater convenience ($p<0.05$) and higher overall satisfaction ($p<0.05$) compared with the sitz bath group. At the end of the 4-week postoperative follow-up period, 90% of patients in the watery spray group and 93% of patients in the sitz bath group showed complete wound healing. There were no significant differences in postoperative complications between groups.
Conclusion Our results demonstrate that the water spray method could provide a safe and reliable alternative to the sitz bath for post-hemorrhoidectomy care. Furthermore, the water spray method could be used instead of the sitz bath as a more convenient and satisfactory form of treatment.

K.-F. Hsu · S.-W. Jao · C.-C. Wu · H.-Y. Yang · C.-M. Mai · C.-Y. Fu · C.-W. Hsiao (✉)
Division of Colon and Rectal Surgery, Department of Surgery,
Tri-Service General Hospital,
No. 325, Sec. 2, Cheng-Kung Road, Neihu 114,
Taipei, Taiwan
e-mail: chris790826@yahoo.com.tw

J.-S. Chia
Medical Service Section, Tri-Service General Hospital,
National Defense Medical Center,
Taipei, Taiwan, Republic of China

J.-S. Chia
Graduate School of Management, Yuan Ze University,
Taoyuan, Taiwan, Republic of China

C.-M. Mai
Department of Surgery, Huailien Armed Forces General Hospital,
Huailien, Taiwan, Republic of China

C.-Y. Fu
Department of Surgery,
Songshan Armed Forces General Hospital,
Taipei, Taiwan, Republic of China

Keywords Hemorrhoidectomy · Sitz bath · Water spray

Introduction

Hemorrhoidectomy is used to treat patients with hemorrhoids who fail to respond to non-operative treatments or those with extensive hemorrhoids. Hemorrhoidectomy is the most effective treatment method for hemorrhoids (especially in patients with third- or fourth-degree hemorrhoids), and approximately 5–10% of patients with hemorrhoids require hemorrhoidectomy.[1,2] Hemorrhoidectomy can be performed according to closed or open methods, which may include the Ferguson, Whitehead, or Milligan–Morgan methods.[3–5] While these various approaches involve different techniques and instruments, there is no evidence for significant differences in the results obtained between closed and open hemorrhoidectomies.[6,7]

In any surgical management of hemorrhoids, postoperative pain is the most common complaint.[8] In particular,

internal sphincter spasm is usually associated with pain. Warm water decreases pain levels by relaxing the internal sphincter, resulting in longer durations of low internal sphincter pressure.[2] The warm water sitz bath is well known as a safe method of treatment for anorectal and gynecologic conditions as a safe, low morbidity maneuver.[9–11] Most physicians, including colon and rectal surgeons, recommend the sitz bath for relieving pain in the perineal region and for promoting wound healing.[12] Thus, the sitz bath is routinely used during the post-hemorrhoidectomy period.

Despite its benefits, the sitz bath can be troublesome for some patients to perform in the hospital or at home. Therefore, taking space constraints and preparation factors into account, we have adapted a water spray method as an alternative for the sitz bath for postoperative care of patients that underwent hemorrhoidectomy at our practice over the last 5 years. Following a comprehensive review of the literature, we did not identify any treatment strategy for anorectal conditions comparable to the water spray method described here. To determine if the water spray method is an effective alternative to the sitz bath for treating patients suffering from discomfort during the post-hemorrhoidectomy recovery period, we conducted a randomized, controlled study using a visual analog scale (VAS) to assess pain, irritation, hygiene, convenience, and overall satisfaction.

Materials and Methods

We recruited patients registered at the Tri-Service General Hospital from January 2008 to September 2008. Patients who had symptomatic advanced and circumferential prolapsed hemorrhoids (grade III or IV) that failed to respond to conservative treatment and subsequently underwent elective hemorrhoidectomy were considered eligible for this study. Exclusion criteria included hemorrhoidal crisis, fistula or fissure, inflammatory bowel disease, anorectal malignancy, and dermatitis. Patients who failed to complete the 4-week follow-up study period also were excluded.

This study was performed according to a randomized, controlled design involving 120 patients. All patients (56 men and 64 women) between 28 and 75 years of age (mean age, 48 years) were randomly divided into water spray (n=60) and sitz bath (n=60) groups by computer-based sequential allocation.

Surgery

All operations were conducted by appropriately qualified and experienced surgeons. Patients underwent treatment with sodium phosphate solution on the night before surgery and were given a warm water enema immediately before surgery. The surgical procedure was performed using the prone jackknife position with the buttocks tractioned laterally by adhesive taps using local anesthesia with patients under heavy sedation. Heavy sedation was induced through intramuscular injections of meperidine (1 mg/kg) and midazolam (3–5 mg). Local anesthesia was achieved by perianal infiltration with 60-ml mixture agent (15 ml distilled water, 15 ml 2% lidocaine, 30 ml 0.5% bupivacaine, and 1:200,000 epinephrine). The surgical procedure involved a modified form of the Ferguson hemorrhoidectomy, which consisted of excision of the hemorrhoid component and primary closure of skin defects.[13] At the end of surgery, the anal canal was lightly packed with a small piece of hemostatic dressing for 4 to 6 h. Following surgery, patients were advised to limit their fluid intake before the first micturition to prevent postoperative urinary retention.

Procedure of Water Spray and Sitz Bath

Patients in the water spray group were instructed to use a shower nozzle with warm water (the water temperature was similar to what patients would favor for a whole body bath) projected to the anus for 10 min while in a bending down position. Patients in the sitz bath group were instructed to sit in a warm water tub with only the hips and buttocks immersed for 10 min. Nothing was added to the water in the tub. All patients began sitz bath therapy or warm water nozzle spray therapy after removal of the hemostatic dressing on the first postoperative day. Water spray or sitz bath sessions were performed once after defecation and four times per day in the first week, which was reduced to twice per day for the next 3 weeks to minimize patient inconvenience.

Table 1 Clinical Features in Water Spray and Sitz Bath Group

	Water spray group (n=60)	Sitz bath group (n=60)	p value
Mean age (years, SD)	46.1 (14.6)	50.5 (15.4)	0.375
Male/Female ratio	27/33	29/31	0.487
Body mass index	23.95 (4.24)	24.93 (4.53)	0.674
Mean duration of disease (months, SD)	25.7 (12.5)	24.6 (11.8)	0.769

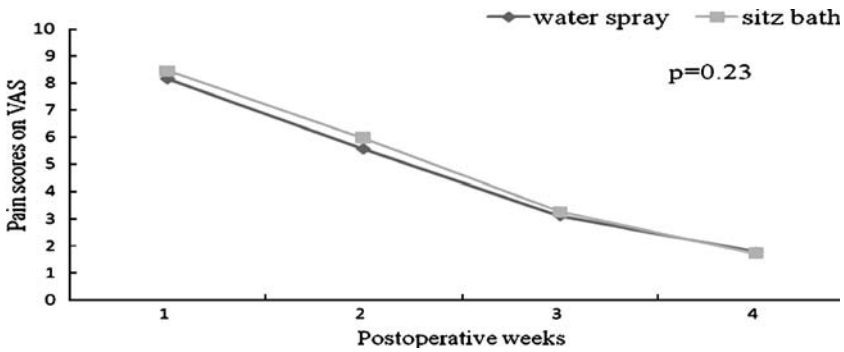

Figure 1 Postoperative pain scores in the water spray group and sitz bath group following hemorrhoidectomy during the 4-week follow-up period. *VAS* visual analogue score (0=none, 10=severe).

Diet and Medication

Patients were usually discharged on the second postoperative day, unless other clinical indications prevented this. A fiber-rich diet containing a high content of fruit and vegetables was prescribed and a high fluid intake was advised. All patients received 300 mg clindamycin via the intramuscular route immediately before the surgical procedure and 500 mg oral metronidazole (three times per day for 5 days). Senna powder (a stool softener) was prescribed for every patient with duration and dose-adjusted depending on the nature of his/her stools. Patients also were given oral flurbiprofen (100-mg tablet) twice per day (or more as needed with an upper limit of four tablets per day).

Monitoring and Assessment of Symptoms and Outcome

Patients were randomly assigned to receive water spray or sitz bath treatment for the 4-week duration of the study. Patients were interviewed weekly at the outpatient department by an independent observer to ensure that the water spray or sitz bath treatments were being performed correctly and to identify possible adverse reactions such as desquamation, perianal burns, or dizziness. Postoperative symptoms and treatment outcomes were assessed according to the following parameters: pain, irritation, hygiene, convenience, and overall satisfaction. Irritation refers to burning or itching sensations, whereas convenience refers to space constraints and the preparation involved in performing the water spray or sitz bath procedures. These parameters were evaluated according to a VAS design. A 10-VAS was applied for pain and irritation (0=none, 10=severe) and a 3-VAS was applied for hygiene, convenience, and satisfaction (0=poor, 3=excellent). Scores for pain and irritation were recorded daily, while hygiene, convenience, and satisfaction were assessed at the end of the 4-week study period. In addition, healing was examined at the end of the 4-week study period (complete healing was defined as full epithelization).

Statistical analysis

Variances in demographic and clinical values were assessed within each group using the Mann–Whitney *U* test. Weekly average VAS for clinical parameters were compared between groups by the Mann–Whitney *U* test. A p value <0.05 was considered statistically significant.

Results

No patient was excluded from this study due to adverse effects or violation of the protocol design. All patients completed the follow-up period of the study and data were collected for all participants. Characteristics of patients including age/sex distribution, body mass index, and duration of disease were compared between groups, which revealed no significant differences (Table 1).

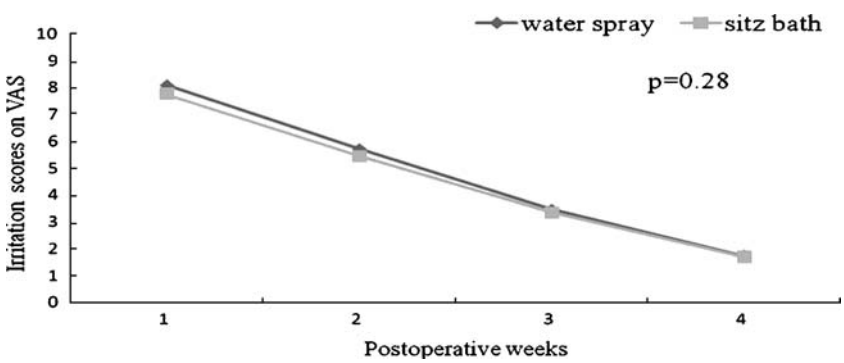

Figure 2 Postoperative irritation scores in the water spray group and sitz bath group following hemorrhoidectomy during the 4-week follow-up period. *VAS* visual analogue score (0=none, 10=severe).

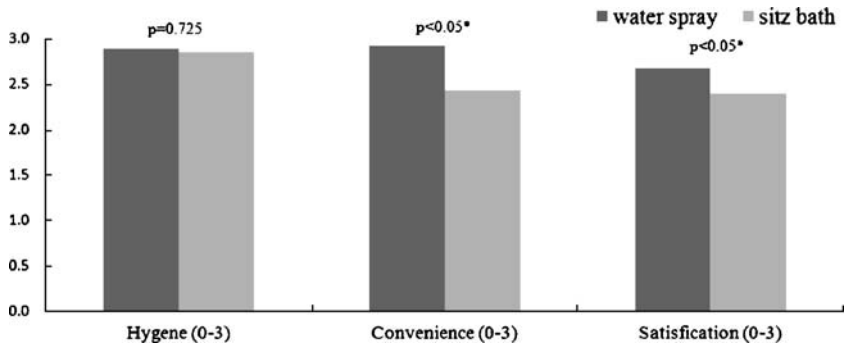

Figure 3 Scores of hygiene, convenience, and satisfaction in the water spray group and the sitz bath group following hemorrhoidectomy at the end of the 4-week follow-up period (0=poor, 3=excellent).

Analysis of Clinical Effects

No significant differences were found between groups in postoperative mean pain or irritation VAS scores for the 4-week study period (p=0.23 and p=0.48, respectively; Figs. 1 and 2). Likewise, there was no significant difference in hygiene maintenance between groups (p=0.725; Fig. 3). Higher convenience and satisfaction scores were observed for patients in the water spray group relative to patients in the sitz bath group (p<0.05; Fig. 3). Complications that affected patients in the water spray group and the sitz bath group during the 4-week follow-up period are listed in Table 2. Postoperative acute urine retention (resolved by urinary catheterization) affected seven patients in the water spray group and nine patients in the sitz bath group. With regard to wound healing, 54 of 60 patients (90%) in the water spray group and 56 of 60 patients (93%) in the sitz bath group showed complete wound healing at the end of 4-week study period. No erythematous perianal burn rash or dizziness was observed for any patient in either group.

Discussion

Hemorrhoid disease is the most prevalent anorectal condition and has a peak period of onset between 45 and 65 years old.[14] It is defined as abnormal cushions of tissue containing vessels, elastic tissue, connective tissue, and smooth muscle in the submucosal space of the anal canal. Clinical symptoms associated with hemorrhoids include pain, bleeding, mucosal protrusions, and discharge.[15] Hemorrhoidectomy is frequently used to treat advanced hemorrhoids, and patients who have undergone this procedure are routinely advised to take warm sitz baths, along with analgesics and stool softeners as part of their postoperative care.[16]

The warm sitz bath is widely accepted as a therapy for anorectal or gynecologic conditions (with or without surgery) due to its low risks and the possible benefits it may confer.[11] The warm sitz bath may relieve pain by decreasing spasms and reducing internal sphincter pressure through a mechanism involving the thermosphincteric reflex.[17] The same mechanism also was proposed for relaxation of the internal urethral sphincter to induce urination.[18] The perceived advantages of the sitz bath include improvements in hygiene, relief of discomfort such as burning sensations or itching, and wound healing.[19] In addition, the sitz bath has been reported as beneficial for limiting infectious disease and preventing sepsis following surgery.[20–22]

In our clinical experience, the feasibility of the sitz bath is a subject that is frequently raised by patients. However, the complications are rarely reported in the scientific literature. Space limitations and effort involved in preparing the sitz bath are problems often cited by patients. Therefore, we introduced a water spray method in our clinic as a simple and convenient alternative to the sitz bath. No significant differences in outcome measures were detected for the two approaches. For the water spray concept, we adapted the basic mechanism of warm water treatment in anorectal disease and used this method for postoperative treatment. No experimental data are available from previous studies that suggest the water spray method confers similar benefits to the sitz bath. In this randomized, controlled study, we used a single, standard method whereby patients assigned to water spray or sitz bath groups were monitored during weekly follow-up sessions. While there were no notable differences in pain, irritation, hygiene, or wound

Table 2 Complications in Water Spray and Sitz Bath Group During 5-week Follow-up

	Water spray group (n=60)	Sitz bath group (n=60)
Urine retention	7	9
Wound unhealed	6	4
Perianal burn rash	0	0
Dizziness	0	0

healing between water spray and sitz bath groups, patients were more satisfied with the water spray method and found it more convenient. Our results show that the beneficial effects of warm water in hemorrhoidectomy patients can be achieved by the water spray method. Thus, the water spray method may represent a viable alternative to the sitz bath in relieving postoperative symptoms in hemorrhoidectomy patients.

Patients using the water spray method or sitz bath should be instructed on the correct way to perform these therapies. Precise instructions for appropriate use of the sitz bath for patients with anorectal disease have been provided by Hatagawa et al.[23] The water spray method uses a comparable water temperature to the sitz bath and involves a similar duration and localization of immersion, which minimizes the risk of burns and systemic vasodilatation.[24–25] In our study, no burn injury or dizziness/syncope related to hypotension was noted in either group.

In conclusion, patients with hemorrhoids after hemorrhoidectomy receiving water spray treatment experienced similar levels of pain and irritation to those receiving the sitz bath treatment. Hygiene standards were also similar between these two groups. However, patients that underwent water spray treatment reported greater convenience and higher overall satisfaction compared to those treated in the sitz bath. No patient in either group was affected by any adverse event, and no significant difference in wound healing was observed between groups. We suggest that the water spray may be viable as an alternative to the sitz bath as part of the postoperative care recommended to hemorrhoidectomy patients.

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ORIGINAL ARTICLE

A Comparison Between the Results of Fissurectomy and Lateral Internal Sphincterotomy in the Surgical Management of Chronic Anal Fissure

S. R. Mousavi · M. Sharifi · Zohreh Mehdikhah

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Abstract
Background We compare lateral internal sphincterotomy as an effective treatment of chronic fissure in ano to fissurectomy, which is as an alternative surgical treatment.
Methods Sixty two consecutive patients were divided into two groups through sequential sampling. Thirty patients underwent fissurectomy and 32 underwent lateral internal sphincterotomy. After a median follow-up of 22 months, we compared the results of the two procedures. In addition to frequent visits on a predetermined basis, a telephone inquiry into fissure recurrence and continence status was made.
Results All patients in both groups were pain-free and without bleeding within 1 week. In both groups, urinary retention was noted in one patient. Incontinence to flatus was noted in the fissurectomy (F) group in two (6.2%) patients, but no incontinence was noted in the lateral internal sphincterotomy (LIS) group. There was one patient (3.1%) with fissure recurrence in the F group but none in the LIS group. No patient in either group was afflicted with anal stenosis or perianal infections. All wounds healed within 8 weeks. Twenty nine patients (96.6%) in the LIS group and 28 (87.5%) in the F group reported satisfactory results with their procedure.
Conclusion In the surgical treatment of chronic anal fissure not responding to conservative management, LIS may be the better treatment and, perhaps, the preferable surgical technique with fewer total complications ($P<0.005$).

Keywords Fissurectomy (F) · Lateral internal sphincterotomy (LIS) · Chronic fissure in ano

S. R. Mousavi (✉)
Shohada Hospital, Shahid Beheshti University of Medical Sciences and Health Services,
Tajrish square,
Tehran, Iran
e-mail: seyed29@yahoo.com

M. Sharifi
Shahid Beheshti University of Medical Sciences and Health Services,
Tehran, Iran

Z. Mehdikhah
Mofid Hospital, Shahid Beheshti University of Medical Sciences,
Tehran, Iran

Introduction

Despite the advent of new modalities in the conservative treatment of chronic fissures, such as nitric oxide donors, they frequently need surgical treatment. Lateral internal sphincterotomy heals chronic fissure in ano in over 90% of cases, but it is associated with potential long-term complications. Incontinence to flatus and fecal soiling are distressing complications of sphincterotomy that may occur in up to 35% of patients.[8,9,12,16] Surgical techniques that preserve the anal sphincters should reduce the possibility of postoperative fecal incontinence. This study was designed to study the hypothesis that chronic anal fissures unresponsive to conservative treatment may be regarded as unstable scar tissue. Fissurectomy or fissure excision to create a fresh surgical wound might then allow stable wound healing.

Table 1 Postop Complications in F and LIS Patients

Complication	Operation	
	F	LIS
Persistence of pain	–	–
Persistence of bleeding	–	–
Urinary retention	1 (3.3%)	1 (3.1%)
Incontinence to flatus or fecal soiling	2 (6.2%)	–
Infection (abscess or fistula)	–	–
Fissure recurrence	1 (3.1%)	–
Anal stenosis	–	–
Total complications	4 (12.5%)	1 (3.1%)

Patients and Methods

We performed a randomized clinical trial on 62 consecutive patients with chronic anal fissures not responding to conservative treatment to compare the results of lateral internal sphincterotomy (LIS) vs fissurectomy (F). All patients were informed that they would be entered in a clinical trial study. Via systematic random sampling, the patients were divided into two groups. In view of the distribution of age, sex, and intervening variables, including the location of fissure and other associated disorders such as hemorrhoids, we considered a desirable matching between the two groups. Out of 62 patients, 30 underwent F and 32 underwent LIS. In total, 37 patients (59.6%) were male and 25 (40.3%) were female. The mean age was 34, ranging from 24 to 52 years old. Location of fissure was posterior in 56 (90.3%) and anterior in six (9.7%) patients. Considering associated anorectal disease, grade I hemorrhoid was noted in two (3.2%) patients. All patients had classical symptoms of chronic anal fissure, unresponsive to medical treatment for at least 3 months. All patients had skin tags or sentinel piles. Patients with multiple fissures were not included in the study.

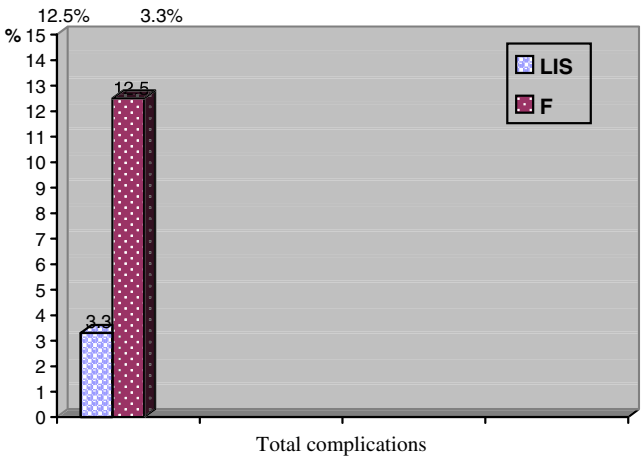

Figure 1 Total complications in patients undergoing F and LIS.

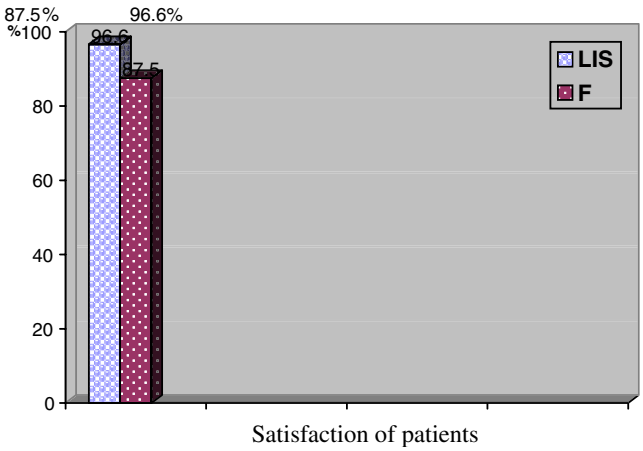

Figure 2 Rate of satisfaction of patients undergoing F and LIS.

Irrespective of the method of surgery, prior to and after the operation, we drew up a questionnaire for patients, including specifications of the patient, pre- and postoperative symptoms, and postoperative complications. First, those items related to preoperative time were recorded in the questionnaire, and then we proceeded with the operation (F or LIS).

Two days before the operation, patients started to take an oral stool-bulking agent twice daily. Additionally, patients went on a liquid diet 24 h before the operation. F was performed by a single surgeon under spinal or general anesthesia in the prone–flexed (jacknife) position. The excision of fissure complex with a margin of healthy mucosa and scar tissue down the level of internal sphincter was carried out. Sphincterotomy was not conducted. As such, a fresh ulcer without any fibrous and scar tissue was established to precipitate its healing process. All wounds were left open. No anal tampons were used. The day after surgery, the patients were discharged with warm sitz bath and bulking agents for at least 2–3 weeks. The second group of patients underwent the traditional approach of LIS, and they were discharged the day after with the above-mentioned recommendations. The first visit was scheduled within 1 week and the others within 1 and 2 months, and at last at the end of the follow-up period. Furthermore, patients were told that they would be followed subsequently by telephone regarding symptoms and postoperative continence. The median follow-up was 22 months (ranging from 18 to 26 months). At the end of the follow-up, the rest of the questionnaire concerning postoperative complications and symptoms was filled out.

Results

During follow up, all patients got rid of pain and bleeding within 1 week of the operation. In both groups, urinary

retention was noted in one patient, which was transient. Incontinence to flatus was seen in the F group in two (6.2%) patients, but no incontinence was noted in the LIS group. There was one patient (3.1%) with fissure recurrence in the F group after 20 months, but none with the F group.

No patient in either group suffered from anal stenosis or perianal infections. Given the total complications, in patients who underwent LIS, only one case was affected with complications (3.3%), but in the F group, four patients (12.5%) sustained injury due to complications. In the LIS group, 29 patients (96.6%) and, in the F group, 28 patients (87.5%) described their operation as satisfactory. All wounds were healed within 8 weeks. No keyhole defects were present in the anal canal.

We used chi square test to compare any of the mentioned complications between the two groups, and finally, we compared total complications (Table 1 and Fig. 1). Except for urinary retention, the difference between the two groups was meaningful for any of the mentioned variables ($P<0.005$).

Discussion

This study has shown that LIS is a safe, sphincter-sparing, and better alternative in the treatment of chronic fissure in ano not responding to conservative treatment. Recent studies have shown that LIS is detrimental to the continence mechanism.[5,6,10] The length of the sphincterotomy and whether an open or closed technique is used are related to the incidence of incontinence. This is due to the fact that surgical estimates of the length of the sphincterotomy are not always correct, and F is not as standardized a procedure as might otherwise be thought.

To examine the more sparing surgical technique, it is important to look at the etiology of chronic fissure in ano. Both hypovascularization and hypoperfusion occur in the posterior anal commissure in approximately 85% of normal people. Combination of these factors with internal anal sphincter hypertonia, causing ischemia, explains the poor wound healing and pain associated with chronic anal fissure.[13,4] It does not explain why anterior chronic fissure in ano occurs in at least 10% of female patients and why pain, if ischemic in nature, occurs only for a certain period after defecation. Also, the actual causative or initiating mechanism is unknown and the mechanism of the transition from acute to chronic fissure remains obscure. Repetitive trauma, for example, large-diameter fecal bolus, may cause defects in the anal lining that heal poorly, leading to unstable scar tissue and a defect termed chronic anal fissure. The central hypothesis in this study was that chronic fissure in ano is unstable scar tissue with a central defect in a hemodynamically unfavorable location.

Another aspect of our study is that it deals with a single procedure without any combination with other modalities, such as topical isosorbide dinitrate or injection with botulinum toxin. Both techniques have been used in recent studies in combination with F to cause temporary chemical sphincterotomy and to improve tissue perfusion.[1,2] However, in other studies, such as that by Meier et al. in Germany in 2001, F has been used as a separate procedure in the treatment of chronic anal fissure with favorable results.[3] Again, in other studies, F has been combined with posterior midline sphincterotomy.[7,11,14,15,17] The main disadvantage of this latter procedure is keyhole deformity, which may lead to fecal soiling. When F is not combined with a midline sphincterotomy, wound dehiscence and keyhole deformities, such as those that occur after anal fistulotomy, do not occur.

The gradual improvement in pain in the F group as compared to immediate pain relief in the LIS group should not be regarded as a main difference between the two procedures, since all patients were eventually pain-free within 1 week of the operation. To emphasize the results, no patient in the LIS group suffered from incontinence to flatus. There was no fissure recurrence in this group during the follow-up period. In total, 29 patients (96.6%) reported satisfactory results with their operation.

Finally, we conclude that, given the lower rate of distressing complications, especially incontinence, and greater satisfaction of the patients (Fig. 2), LIS could be considered as a better alternative, sphincter-saving, and perhaps preferable approach in the surgical management of chronic anal fissures. However, much remains to be done regarding its long-term results through more extensive and larger clinical trials.

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ORIGINAL ARTICLE

Glyceryl Trinitrate Ointment (0.25%) and Anal Cryothermal Dilators in the Treatment of Chronic Anal Fissures

Michele Schiano di Visconte · Gabriele Munegato

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Abstract
Introduction Chronic anal fissure is a common benign disorder; for this condition, lateral internal sphincterotomy is the "gold standard" of treatment. Alternative medical treatments have not proven to be as effective as left lateral internal sphincterotomy.
Aim This randomized trial was designed to compare the use of 0.25% glyceryl trinitrate ointment and anal cryothermal dilators with the use of 0.4% glyceryl trinitrate ointment alone in the treatment of chronic anal fissures.
Methods Between 1 June 2006 and 31 December 2007, 60 consecutive patients who were suffering from chronic anal fissures were randomized into two groups. The patients in group A (n=30) were treated with 0.25% glyceryl trinitrate ointment and anal cryothermal dilators twice daily, and those in group B (n=30) were treated with 0.4% glyceryl trinitrate ointment alone twice daily. The treatment was administered to the patients in each group for 6 weeks, and all patients were examined 7 weeks after the start of the trial.
Results Prior to treatment, the symptoms and the measurements of anal pressure were similar in both groups. At 7 weeks, the maximum resting pressure was significantly lower in group A (P<0.05), in which 86.6% of the patients were asymptomatic in comparison with 73.3% of the patients in group B. After 1 year of follow-up, 25 patients (83.3%) in group A and 18 patients (60%) in group B presented no recurrence of symptoms (P<0.05)
Conclusions Treatment of chronic anal fissures with 0.25% glyceryl trinitrate ointment and anal cryothermal dilators was more effective than the administration of 0.4% glyceryl trinitrate ointment alone.

Keywords Chronic anal fissure · Glyceryl trinitrate ointment · Anal cryothermal dilators

Introduction

Chronic anal fissure is one of the main causes of anal pain and bleeding in young adults. The condition is often diagnosed in young adults, and there are no significant differences in incidence between the two genders.[1] The true incidence of anal fissures is not well defined.[2] Reports estimate that approximately 10% of the patients who attend coloproctology outpatient clinics present with chronic anal fissures.[3]

The etiopathogenesis of idiopathic anal fissures has also not been explained fully. Most patients present with hypertonia of the internal anal sphincter,[4–7] and therefore, the passage of hard feces lacerates the anal skin. Although such lacerations would heal spontaneously in subjects with normal anal pressures, in those with high resting anal pressures, the lacerations become chronic due to the abnormal activity of the internal sphincter.[8]

Klosterhalfen et al.[9] advanced the theory that the process described above alters the vascular supply of the posterior region of the anal canal, as shown by angiographic studies

M. Schiano di Visconte · G. Munegato
General Surgery Department, "S. Maria dei Battuti" Hospital,
Via Brigata Bisagno, 4
31015 Conegliano (Treviso), Italy

M. Schiano di Visconte (✉)
Via Jesolo, 46
30027 San Donà di Piave (Venice), Italy
e-mail: dr.schianodivisconte@tiscali.it

that were conducted on corpses and that the reduced blood flow is the cause of the abnormal resting anal pressure.[10] Gibbons and Read[11] proposed that muscular spasm reduces blood flow near the posterior commissure and thus encourages the development of chronic anal fissures. Hence, hypertonicity in the sphincter plays a key role in the process, and it is therefore the main target of both surgical and medical treatments for the condition.

A significant drop in anal pressure, similar to that observed in patients who undergo left lateral internal sphincterotomy (LIS),[12] is associated with a considerable increase in blood flow to the posterior commissure. This may explain the healing process[13,14] that occurs in >90% of patients.[15]

A reduction in pressure can be induced effectively by manual dilation of the anus,[16] but in a large number of patients, this process causes iatrogenic lesions in the external anal sphincter.[17,18] Temporary chemical sphincterotomy, which involves the administration of drugs that induce a transitory reduction in sphincter tone, can encourage the process of re-epithelialization in these patients.

Many protocols for the conservative treatment of anal fissures have been proposed, and these are based on the use of glyceryl trinitrate (GTN), botulinum toxin, and topical calcium channel blockers. However, all the therapeutic regimens that have been proposed so far result in a high incidence of relapse[19] and are only slightly more effective than the administration of a placebo.[20]

The use of anal dilators alone is more controversial. Satisfactory results have been reported[21]; Sileri et al.[22] reported a rate of healing of 46%, which is slightly higher than that obtained with GTN. However, the use of anal dilators does not seem to reduce the number of patients who require LIS surgery to treat anal fissures.[19,23,24]

The standard management of chronic anal fissure involves the use of medical treatment followed by LIS surgery. In recent years, it has also been shown that combined therapy can favor the healing of fissures.[25]

In our first trial was compared the efficacy of 0.25% glyceryl trinitrate ointment in association with cryothermal anal dilators by only applying 0.25% gliceryl ointment and only using cryothermal anal dilators, during 2 years of follow-up. We reported a healing rate of 87.5%, at the 2-year follow-up visit, in patients who used anal dilators and 0.25% glyceryl trinitrate. In contrast, treatment with the anal dilator alone gave a healing rate that was comparable to that for treatment with GTN alone. We believe that the use of cryothermal anal dilators alone cannot increase the success rate above that seen with medical therapy. However, we hypothesize that anal dilators can be of great use in the treatment of chronic anal fissures when administered in association with 0.25% glyceryl trinitrate ointment.[26]

This prospective randomized study was designed to evaluate and compare the efficacies of regimes that involved a combination of anal dilators and 0.25% glyceryl trinitrate ointment with that of the application of 0.4% glyceryl trinitrate alone for the treatment of chronic anal fissures. The results were assessed during a follow-up period of 1 year.

Materials and Methods

Between 1 June 2006 and 31 December 2007, 60 patients who had been diagnosed consecutively with chronic anal fissures were enrolled in this prospective randomized trial. The diagnosis of chronic anal fissures was based on a duration of symptoms of at least 8 weeks, irrespective of the presence of hypertrophic anal papillae or of a sentinel nodule. The patients were allocated randomly to two groups by the use of GraphPad Software® (GraphPad Software, Inc., San Diego, CA, USA). Patients in group A were treated with 0.25% glyceryl trinitrate ointment and anal cryothermal dilators (DilatanPlus®; Sapi Med, Alessandria, Italy), whereas the patients in group B were given 0.4% glyceryl trinitrate ointment alone. The exclusion criteria were as follows: patients with systemic diseases whose clinical expression included anal fissures; those who had fecal incontinence, 3rd–4th degree hemorrhoids, migraines, a history of heart failure, or a history of myocardial infarction; individuals who had received prior anorectal surgery or radiotherapy for diseases in the pelvic and perineal region; and patients who were currently receiving anti-arrhythmic therapy.

Patients were enrolled prior to the commencement of medical treatment, and they received a clinical evaluation and were assessed by anorectal manometry. The clinical evaluation recorded the nature, duration, and location of the symptoms, and the degree of severity of the anal fissure was classified on the basis of the extent of exposure of the internal sphincter fibers, as proposed by Kennedy et al.[27] The intensity of pain was evaluated with a visual analog scale (VAS; 0 = no pain; 10 = maximum pain). The clinical evaluation was completed by calculating the constipation score, using criteria that were established by the Cleveland Clinic Florida's Constipation Scoring System.[28] Quality of life was assessed by administering the questionnaire of the Short-Form Health Status Survey (SF-36).

The enrolled patients were required to record their defecation habits in a special diary during administration of the proposed therapeutic protocol. The patients were requested to note the onset of headaches, hypotension, and tachycardia, and if these symptoms required the intake of drugs, they were requested to specify the drug and the dose used.

The patients who were assigned to group A were also asked to report any discomfort that arose from the use of the dilators on a VAS (0 = no discomfort; 10 = maximum discomfort). The Wexner Incontinence Score Questionnaire was adopted to evaluate the presence of fecal incontinence at the completion of treatment.[29]

Anorectal manometry was performed using a computerized system that was based on eight channels, with flexible probes 4.5 mm in diameter that were perfused with water and placed on the circumference (the Polygraf™ID Multi-Parametric Recorder with POLYGRAM NET® analysis software; Medtronic, Minneapolis, MN, USA). A continuous and stable pull-through procedure was used. The following parameters were considered: the length of the sphincter in millimeters, the maximum resting pressure (MRP) and maximum squeezing pressure (MSP) in millimeters of mercury, and the presence or absence of the rectal–anal inhibiting reflex.

Patients in group A used a small anal cryothermal dilator (23 mm) for the 1st week of treatment (Fig. 1). The device was heated for 15 min by soaking it in warm water (40°C); a standard mercury thermometer was used to check its temperature. It was then introduced completely into the anal canal, with the patient in the left lateral decubitus position, and was left in place for 10 min. Insertion was facilitated by lubricating the dilator with a gel preparation that contained the active principles calendula, klamath weed, horse chestnut, wild chamomile, allantoin, and propolis (Dilatan Crema®; Sapi Med, Alessandria, Italy). Subsequently, 0.5–1 g (approximately 2 cm) of 0.25% glyceryl trinitrate ointment was applied after local hygiene of the anal edge and just inside the anus. This procedure was repeated twice daily (morning and evening). During the 2nd week of the treatment protocol, a medium-sized anal cryothermal dilator (27 mm) was used, and from the 3rd to the 6th weeks, the patient was required to use a large dilator (30 mm). The total duration of treatment was 6 weeks.

The anal dilator that was used in this study, Dilatan Plus®, was developed specifically for this type of condition. It has a cylindrical shape, which becomes conical toward one end. The surface of the dilator is perfectly smooth. The internal compartment is hermetically sealed and contains a jelly that is capable of retaining heat.

Patients in group B applied a dose of 0.4% glyceryl trinitrate ointment on the anal edge and just inside the anus twice daily for 6 weeks. The 4 mg/g dose of ointment contained approximately 1.5 mg of glycerine trinitrate (in a length of approximately 2.5 cm).

The 30 patients that were enrolled in group B were treated with a 0.4% glyceryl trinitrate ointment because recent large dose-finding studies showed that a concentration of 0.4% was most effective in relieving pain from chronic anal fissure without affecting the process of healing. In addition, this concentration is licensed for the treatment of chronic anal fissure in Europe.[30]

Patients belonging to each group were prescribed a diet rich in fiber and took a supplement of bulking agent (*Psyllium plantago*) 30 min before main meals, together with a large volume of fluids. One week after completion of the trial, all the patients were evaluated once again by clinical examination, anorectal manometry, assessment of pain and discomfort issuing from the use of dilators, and the SF-36 questionnaire. The clinical diaries were studied closely. Patients were deemed to be healed if the symptoms had resolved and the anal skin had re-epithelialized. Healing was considered to be incomplete when the lesion had failed to re-epithelialize completely, despite the resolution of symptoms. Such patients were evaluated to investigate whether the failed re-epithelialization was associated with the presence of chronic anal fissure (i.e., present for over 8 weeks) with factors such as cornified edges of the lesion, exposure of sphincter fibers that were undergoing fibrotic evolution, and/or relative anal stenosis secondary to spasm or fibrosis of the internal sphincter. The secondary endpoints were improvement in the intensity of pain and the development of side effects.

Recurrence was defined as a fissure that had been healed previously by treatments but relapsed subsequently and was detectable on clinical examination. The follow-up evaluation included a clinical examination that was performed 12 months after completion of the treatment. Anorectal manometry was repeated only in patients in whom the

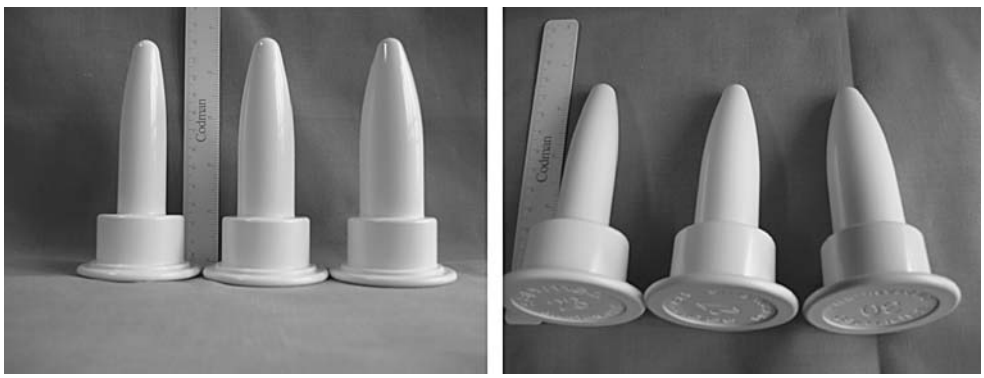

Figure 1 Anal cryothermal dilators.

symptoms did not resolve and those who suffered a recurrence of the condition.

Statistical Analysis

The data were analyzed using GraphPad Software®, and the results were recorded as the mean value ± standard deviation (SD). The paired sample *t* test was performed to compare the variations in MRP and MSP within the groups before and after clinical treatment. The values were deemed to be statistically significant at $P<0.05$.

Data on the intensity of pain and discomfort that were obtained prior to treatment and during the follow-up and those obtained from the SF-36 questionnaire were compared. Continuous variables were analyzed using the Student *t* test for those variables with Gaussian distributions and with the nonparametric Mann–Whitney test for non-normal distributions. *P* values<0.05 were deemed significant. Differences between percentages were analyzed using the Fisher exact test.

Results

The demographics of the patients and characteristics of the fissure are shown in Table 1. The study enrolled 27 males (45%) and 33 females (55%). In 35 patients (58.3%), the fissure was located in the posterior commissure of the anus, and 35 patients (58.3%) complained of the concurrent presence of pain and bleeding during defecation. Forty-five patients (75%) complained of constipation, which was assessed with the criteria that were established by the Constipation Scoring System of the Cleveland Clinic in Florida, USA.[28] The mean intensity of anal pain was 7.1 in group A and 7.2 in group B. No statistically significant differences were detected between the two groups with respect to patient characteristics and the duration of symptoms.

Anal Manometry

The mean (SD) MRP was 106.1 (18.92) and 109.8 (17.50) mmHg in groups A and B, respectively. The mean (SD) MSP was 189.3 (29.88) and 195.2 (31.79) mmHg in groups A and B, respectively. All patients had an intact recto-anal inhibitory reflex. The average length of the anal canal was 4 cm (range, 2–4 cm). Before the treatment, there were no statistically significant differences in the results of the anal manometry between the two groups ($P>0.05$; Table 2).

Follow-up Examinations

In group A, 26 patients (86.6%) reported complete resolution of their symptoms during the follow-up visit 7 weeks after the initiation of treatment. The anal fissure persisted in three patients (10%). One patient in group A did not follow the advised protocol and was therefore excluded from the trial. The discomfort and the pain, which were evaluated with a VAS, were 3.9 and 4.0, respectively. Patients whose lesions had healed demonstrated a consid-

Table 1 Patients Demographics and Fissure Characteristics

Characteristics	Group A[b] (*n*=30)	Group B[c] (*n*=30)	*P*
Gender (men/women)	13/17	14/16	
Mean age (years)	23.67 (range 18–40)	22.93 (range 18–42)	ns[d]
Mean symptoms duration (weeks)	15.87 (range 8–31)	15.73 (range 8–34)	ns[d]
Fissure position			
Posterior midline	18 (60%)	17 (56.66%)	
Anterior midline	12 (40%)	13 (43.33%)	
Pain	5 (16.66%)	6 (20%)	ns[d]
Bleeding	7 (23.33%)	7 (23.33%)	ns[d]
Pain and bleeding	18 (60%)	17 (56.66%)	ns[d]
Pain score	7.133 (range 2–9)	7.233 (range 3–9)	ns[d]
Sentinel pile	8 (26.66%)	9 (30%)	ns[d]
Anal papilla	15 (50%)	12 (40%)	ns[d]
Sentinel pile and anal papilla	3 (10%)	6 (20%)	ns[d]
Constipation	22 (73.33%)	23 (76.66%)	ns[d]
CCF-CS	15.63 (range 8–20)	15.37 (range 8–19)	ns[d]
Fissure score[a]			
Grade 1	10 (33.33%)	10 (33.33%)	ns[d]
Grade 2	16 (53.33%)	15 (50%)	ns[d]
Grade 3	4 (13.335)	5 (16.66%)	ns[d]

CCF-CS Cleveland Clinic Florida's Constipation Scoring System

[a] Fissure grade: grade 1—fissure with exposed internal anal sphincter; grade 2—deeper fissure with widely exposed internal anal sphincter; grade 3—deep undermined fissure

[b] Group A—0.25% glycerine trinitrate ointment and anal dilators

[c] Group B—0.4% glycerine trinitrate ointment

[d] One-way analysis of variance with Bonferroni's multiple comparison test (ns=$P>0.05$)

Table 2 Anorectal Physiology Results Before the Treatment

Anorectal physiology results	Group A[a] (n=30)	Group B[b] (n=30)	P
MRP (mmHg)	106.1±18.92 (range 83.0 -148.0)	109.8±17.50 (range 85.0–142.0)	ns[c]
MSP (mmHg)	189.3±29.88 (range 144.0–259.0)	195.2±31.79 (range 146.0–264.0)	ns[c]
Sphincter length (cm)	4 (2–4)	4 (2–4)	
Inhibitory recto-anal reflex	present	present	

Data are presented in mmHg with mean values ± SD

MRP maximum resting pressure, *MSP* maximum squeezing pressure

[a] Group A—0.25% glycerine trinitrate ointment and anal dilators

[b] Group B—0.45% glycerine trinitrate ointment

[c] One-way analysis of variance with Bonferroni's multiple comparison test (ns=P>0.05)

erable reduction in values of anal pressure as measured by manometry. The mean (SD), in group A, MRP was 83.70 (14.79) mmHg (P<0.05 [t test]). The mean (SD) MRP was 135.8 (20.57) mmHg (P<0.05 [t test]). No patients, in group A, developed side effects such as fecal incontinence or leakage of stool. The median score on the Wexner Incontinence Questionnaire was 0 (range, 0–2).[29]

Twenty-five patients in group A (83.3%) were healed completely, and they reported no further symptoms during the follow-up period of 1 year. One patient (3.3%) reported a recurrence at the follow-up assessment 1 year after the initiation of treatment. At the end of the follow-up period, no other recurrence had been observed in group A.

In group B, complete healing of the fissure occurred in 22 patients (73.3%) after 7 weeks. Seven patients (23.3%) complained of persistent symptoms. Four patients (13.3%) complained of intense headaches that required analgesics (nonsteroidal anti-inflammatory drugs, NSAIDs), while one patient (3.3%) reported suffering from severe orthostatic hypotension that required admission to an Emergency Department and resulted in subsequent exclusion from the study. This patient complained of persistent symptoms at the following clinical examination. Four patients (13.3%) complained of transitory mild headaches that required no treatment, and four patients reported anal pruritus. The pain, which was evaluated with a VAS, was scored as 3.6. For the patients whose anal fissures had healed, the results of the anorectal manometry showed a significant decrease in anal pressure. The mean (SD), in group B, MRP was 93.67 (17.57) mmHg (P<0.05 [t test]) and the mean (SD) MSP was 145.5 (22.01) mmHg (P<0.05 [t test]). No patient in group B reported on the Wexner Incontinence Score Questionnaire[29] that they had experienced fecal incontinence. The mean score for assessment of continence by means of the Wexner Incontinence Questionnaire in this group was 0 (range 0–3).

Complete healing occurred in 18 patients in group B (60%) after 1 year. A recurrence of anal fissure in four patients (13.3%) was detected at the follow-up assessment 1 year after the completion of treatment (see Table 3).

The evaluation of the outcome also considered the quality of life, which was gauged by use of the SF-36 form. This questionnaire gives a general nonspecific score, which showed a statistically significant improvement in the domains that measure vitality, physical function, social function, and body pain as compared with the baseline

Table 3 Clinical Results of Treatment

Symptoms	Group A[a] (n=30) No. (%)	Group B[b] (n=30) No. (%)
Gas incontinence	0	0
Fecal soiling	0	0
Fecal Incontinence	0	0
Orthostatic hypotension	0	1[c] (3.3%)
Headaches	0	8 (26.6%)
Pruritus ani	0	4 (13.3%)
Failure to comply with the protocol	1 (3.33%)	0
Persistence of fissure	3 (10%)	7 (23.3%)
Healing of fissure at 7 weeks	26 (86.6%)	22 (73.3%)
Healing at 1-year follow-up	25 (83.3%)	18 (60%)
Recurrence at 1-year follow-up	1 (3.3%)	4 (13.3%)

[a] Group A—0.25% glycerine trinitrate ointment and anal dilators

[b] Group B—0.4% glycerine trinitrate ointment

[c] The patient was excluded from the trial

measurements and follow-up records ($P<0.05$). All patients who failed to respond to the conservative treatment underwent left lateral internal sphincterotomy, except for the patient in group B who had suffered an episode of severe orthostatic hypotension and declined all further treatment.

Discussion

Chronic anal fissure manifests as a linear ulcer in the lower region of the anal canal. This painful condition is characterized by pain and bleeding that is associated with defecation. The therapeutic approach to patients with anal fissures is controversial. Numerous medical and surgical treatments have been proposed over the past three decades in an attempt to reduce the hypertonicity of the internal anal sphincter and to facilitate the process of re-epithelialization.[28]

Left lateral internal sphincterotomy is the "gold standard" treatment for chronic anal fissures and has resulted in a rate of healing of approximately 90%.[15,20] The reported postoperative incidence of fecal incontinence ranges from 1.3% to 66%. In general, the transitory episodes of gas and liquid fecal incontinence that can occur after surgery resolve spontaneously within a few weeks.[31–35]

On the basis of theoretical considerations, fecal incontinence following sphincterotomy can be attributed either to a surgical error or to mistaken recording of the case history. Young women with a history of obstetrical lesions present a higher risk of incontinence; therefore, patients must be selected carefully for surgery. An intra-anal ultrasound scan should be performed on all patients whose case history reports sphincter injuries, in order to detect those patients who are at risk of suffering from incontinence after sphincterotomy. However, the need to minimize the risk of incontinence may require the use of surgical procedures that involve insufficient sectioning of the internal sphincter and thus expose the patient to a risk of relapse.

Manual anal dilation has long been considered a valid therapeutic approach to chronic anal fissures. However, many studies have questioned the efficacy of manual anal dilation in the prevention of damage to the external sphincter[17] and have reported a high incidence of incontinence following the procedure.[1,18] Only a few studies have demonstrated the effectiveness of the method.[16] McNamara et al.[36] reported that the anal sphincter pressure had returned to normal levels by 5 months after the procedure. The poor efficacy and risks of side effects that are associated with manual anal dilation were stressed recently by the results of a randomized prospective study that recommended against its use.[37]

Other techniques have been developed to minimize lesions of the external sphincter. Renzi et al.[38] reported an incidence of healing of 83.3% when using the pneumatic balloon dilatation system. This technique was associated with a significant reduction in postoperative pain and the avoidance of lesions of the sphincter.

The use of cryothermal anal dilators is controversial. There is very little evidence for the efficacy of cryothermal anal dilators in the literature.[15,20,21,23] However, Sileri et al.[22] reported recently that approximately 46% of patients were healed with the use of anal dilators. Gaj and Trecca[39] claimed that anal dilators are effective and usually well tolerated by patients as a treatment for anal fissures. In general, however, case histories show that the therapeutic approaches that have been attempted are associated either with the risk of various complications[1,38] or with poor compliance in the use of anal dilators. Therefore, experts have focused on the so-called "temporary chemical sphincterotomy", which involves the use of drugs that induce a transitory reduction in sphincter tone, and subsequently facilitate cicatrization of the fissure.

Glyceryl trinitrate releases nitric oxide, which is one of the most important nonadrenergic noncholinergic neurotransmitters, and causes relaxation of the internal anal sphincter.[40] It can induce a significant reduction in both anal resting and strain pressures, which facilitates vasodilation and increases blood flow, especially in the posterior commissure.[41] Moreover, the treatment can be repeated shortly after completion of the first cycle.

However, the role of glycerine trinitrate in the treatment of anal fissure still remains uncertain. The failure of medical treatment with trinitrate appears to be associated with those fissures that have a history of more than 6 months and cases in which a sentinel pile is present.[27] In addition, many patients complain of the onset of headache following administration of trinitrate, the intensity, and duration of which is related to the dose administered and can result in discontinuation of the treatment.[42–43] Glycerine trinitrate at a concentration of 0.25% possesses the same therapeutic effects as a higher dose (0.5%), and the lower dose has been used to reduce the incidence of side effects.[40,41]

Dose-finding studies have found a glycerine trinitrate concentration of 0.4% to be the most effective. However, the efficacy of the ointment depends on the amount of nitrate that is delivered to the internal anal sphincter. The major adverse effect of topical nitrate treatment is headache. This can sometimes be severe but it rarely causes a patient to stop treatment.[44–45] Our study has demonstrated the efficacy of the combined use of anal dilators and 0.25% glycerine trinitrate as a treatment for chronic anal fissures.

All enrolled patients presented high values of MRP and MSP. Statistical assessments revealed a significant reduction in anal pressure in each group ($P<0.05$) after treatment. Statistical analysis of this reduction in pressure

also showed a significant difference between groups A and B ($P<0.05$). The reduction in mean resting pressure was greater in patients in group A than in those in group B (Table 4). The greater reduction in mean sphincter pressure in group A could explain the larger number of patients who were healed as compared to group B. This demonstrates the essential role that is played by hypertonicity of the anal sphincter in the pathogenesis of this disease.

There was persistence of the fissure in three patients (10%) in group A and in seven patients in group B (23.3%; $P<0.05$ [t test]) at the 7-week follow-up visit. In both groups, those patients who presented with a 3rd degree fissure that was associated with abnormal pressure values failed to respond to treatment. Thornton et al. claim that the healing of fissures is correlated positively with a lower baseline fissure score and with lower pressure values that show a greater percentage reduction after the treatment.[42] However, in our trial, fissures were significantly less likely to heal in patients in whom the condition had been present for long time and who had a sentinel pile and hypertrophy of the anal papillae. Persistence of these structures can reduce the overall rate of cure because they hinder the introduction of the anal dilator and they can also reduce the effectiveness of treatment with glyceryl trinitrate.

Five patients reported recurrence of the anal fissure after complete healing during the study period. One of the five incidents of recurrence occurred in group A (rate of recurrence 3.3%) and the other four in group B (rate of recurrence 13.3%). All the patients who suffered from a recurrent fissure underwent left lateral internal sphincterotomy.

The surgical procedures were performed with the patient under general anesthesia and in the lithotomy position. Lateral subcutaneous internal sphincterotomy was performed on the left side of the patient. Excision of a skin tag or hypertrophied papillae (if present) was performed just before the sphincterotomy.

For the patients in whom the medical treatment failed, we preferred to perform lateral sphincterotomy according to the Association of Coloproctology of Great Britain and Ireland Position.[46] Botulinum toxin, which is very popular in the USA before sphincterotomy, is more expensive than glycerine trinitrate and is associated with a similar rate of healing. In addition, there is no consensus on the dosage, the precise site of administration, or the number of injections that are required.[12]

The follow-up examination that was conducted 1 year after the completion of treatment established that 25 patients (83.3%) in group A and 18 patients (60%) in group B neither developed a relapse of symptoms nor complained of anal continence disorders. Treatment with 0.25% glycerine trinitrate (group A) was not associated with any severe episodes of headache, tachycardia, or orthostatic hypotension that required treatment. Twelve patients in group B (40%) complained of disorders that were associated with the use of a higher concentration of glycerine trinitrate. Most headaches that are associated with the use of glycerine trinitrate are mild to moderate, improve with time, and can be treated effectively with simple analgesia. No patients stopped treatment because of headaches. We have also observed that, in comparison to our trial,[26] the increased dose of glycerine trinitrate does not result in a higher rate of cure, but only in a higher incidence of side effects. The occurrence of relapses appears to result from the rise in pressure of the anal sphincter when drug treatment is discontinued.

One patient in group A (4.16%) did not follow the proposed therapeutic protocol. His treatment was interrupted from the 3rd week, when he was required to use the largest dilator (30 mm), because of the associated discomfort. This discomfort, which was evaluated with a VAS after 3 weeks, was rated 7.5.

The use of anal dilators can indeed be a cause of discomfort to the patient. With these patients, we stress the importance of heating the dilator and the use of the lubricant to facilitate its insertion. In addition, use of a bidet that contains warm water before the insertion of the device can be recommended to patients in whom pain causes problems with insertion. However, the correct education and motivation of patients is fundamental to the success of the technique. The use of analgesic drugs (NSAIDs) can be recommended during the first few days of treatment when the insertion of the device is associated with pain.

Table 4 Mean Pre-treatment and Post-treatment Resting and Squeeze Manometric Pressures

	Group A		Group B	
	MRP	MSP	MRP	MSP
Pretreatment	106.1±18.92	189.3±29.88	109.8±17.50	195.2±31.79
7 weeks	83.70±14.79	135.8±20.57	93.67 ±17.57	145.5±22.01

Data are presented in millimeters of mercury. Values are means ± SD. Group A—0.25% glycerine trinitrate ointment and anal dilators. Group B—0.4% glycerine trinitrate ointment

MRP maximum resting pressure, *MSP* maximum squeezing pressure

Finally, we considered the improvement in quality of life following treatment and made use of a general SF-36 questionnaire, which is the only such tool to have been validated in Italian. There are other more specific questionnaires on intestinal function, especially for constipation, that demonstrate the correlation between the intensity of symptoms and a poor quality of life,[47–49] but our study showed that certain domains, such as social and physical functions, vitality, and pain, show a parallel improvement.

With regard to the results represented by the resolution of symptoms and reduced pressure in the anal sphincter, we have demonstrated a synergistic action between glycerine trinitrate and anal dilators in inducing a statistically significant reduction in pressure compared to the pressure reduction seen in patients given trinitrate alone. The process of warming the dilators before introduction is essential for encouraging muscle relaxation. Heating induces vasodilation and thus facilitates blood flow to the anal skin. The use of preventively heated anal dilators that increase gradually in size does not seem to cause sphincter lesions, probably because of the capacity of the muscles to adjust. The relapse of symptoms in several patients in group A 1 year after the trial was undoubtedly associated with a rise in pressure of the anal sphincter. The reason for the recurrence of sphincter hypertonicity in certain patients is not known, because we do not yet understand the exact pathophysiological processes that are involved in the development of anal fissures.

Conclusions

The use of anal dilators can cause such discomfort to a patient that they discontinue treatment. Precise information and motivation are essential in enhancing compliance with the treatment protocol. Overall, patients that were treated with dilators formed a good opinion of the treatment, as compared with those who reported the onset of side effects that resulted from the administration of glycerine trinitrate.

However, a critical analysis of the results of this study established that patients with abnormal resting and strain pressure values in the anal canal and 3rd to 4th degree persistent chronic anal fissures, as assessed by Kennedy's score, failed to obtain any benefit from the treatment protocol that was used in this study. Many studies have reported that patients with such lesions can only be healed by surgical treatment.[12]

We have found that the combination therapy used here (anal dilators with glycerine trinitrate) may be more effective than the use of single agents in the treatment of chronic anal fissure. By acting through different mechanisms simultaneously, the two agents may elicit a greater reduction in sphincter hypertonicity, which may in turn allow more effective healing of the fissure.

Our study enables us to propose a conservative treatment regime for chronic anal fissures that seems to be more effective than conventional conservative treatment. It is characterized by a lower incidence of side effects than has been recorded for other conservative and surgical treatments. However, the data must be confirmed by additional trials that involve the enrolment of a larger cohort of patients.

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ORIGINAL ARTICLE

Staging Anal Cancer: Prospective Comparison of Transanal Endoscopic Ultrasound and Magnetic Resonance Imaging

S. D. Otto · L. Lee · H. J. Buhr · B. Frericks · S. Höcht · A. J. Kroesen

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Abstract
Purpose The staging of anal cancer is extremely important for therapy and prognosis. Transanal endoscopic ultrasound and magnetic resonance imaging are routinely applied. The aim of this prospective comparative study is to evaluate whether tumor staging is concordant between these techniques.
Methods Forty-five anal cancer patients underwent endoscopic ultrasound and magnetic resonance imaging. Histological confirmation was obtained in all patients. The two test methods were compared with the kappa concordance index and sensitivity for the initial method of tumor detection was calculated. For six patients who were operated upon because of tumor progression, the results were evaluated against the histological tumor stage.
Results High concordance was found in the assessment of tumor size and nodal status (kappa index 0.63 and 0.77). Cancer patients were correctly identified with 100% sensitivity (45/45) by endoscopic ultrasound and with 88.9% (40/45) sensitivity by magnetic resonance imaging. In the six operated patients, T stage was correctly assessed in four of six patients by endoscopic ultrasound and in three of six patients by magnetic resonance imaging.
Conclusion The results of endoscopic ultrasound strongly coincide with those of magnetic resonance imaging. Endoscopic ultrasound may be superior to magnetic resonance imaging for detection of small superficial tumors. However, magnetic resonance imaging is needed for N staging.

Keywords Anal cancer · Staging · MRI · Endoscopic ultrasound

Introduction

Anal cancer comprises only about 0.3% of all cancers. With an incidence of approximately 1:100,000 persons per year,[1] it is one of the less common types of cancer. Staging and therapy is, therefore, usually performed in specialized clinics.

Until the mid-1980s, surgery was the primary treatment for anal cancer. Radiation treatments were first successfully performed in the 1970s and 1980s.[2–4] Today, the therapy of anal cancer depends on the tumor stage.[5–9] Staging by TNM classification prior to therapy is, thus, extremely important. The standard therapy consists of radiotherapy of the anal canal, the perianal region, the distal rectum, and the perirectal, internal iliac, and inguinal and presacral lymph nodes. It is combined with simultaneous chemotherapy using 5-FU and Mitomycin C or 5-FU and Cisplatin. Radiotherapy varies depending on the tumor stage: for T1 and T2 tumors, the total dose is about 50 Gy ranging up to 60 Gy in T4 tumors. The extent radiotherapy of the lymph node regions depends on the tumor stage as well. If no lymph nodes were staged positive, the total dose is about 45–50 Gy, whereas with positive lymph nodes, in general, higher doses will be applied. Furthermore, in patients with small tumors without lymph node metastasis (T1N0), surgery alone or radiation of only the anal canal and perirectal lymphnodes could be performed.[5–9] The choice of therapy based on the tumor spread and nodal status will determine the 5-year survival rate (55–80%).[10–17]

S. D. Otto (✉) · L. Lee · H. J. Buhr · B. Frericks · S. Höcht · A. J. Kroesen
Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Hindenburgdamm 30,
12200 Berlin, Germany
e-mail: s.otto@charite.de

Transanal endoscopic ultrasound (TAUS) and magnetic resonance imaging (MRI) are routinely applied for rectal and anal cancer.[18–23] In TAUS, a 7–10-MHz rotating ultrasound transducer is rectally inserted. The examiner obtains a real-time axial image that is two- or three-dimensional, depending on the device.[18] MRI of the pelvis enables good assessment particularly of large tumors with marked craniocaudal and lateral expansion.[24]. MRI is more expensive and its interpretation may be more difficult for non-radiologists than TAUS.

The staging of anal cancer is extremely important for therapy and prognosis. TAUS and MRI are predominantly utilized but have not been compared up to now, to our knowledge. Thus, the aim of this prospective comparative study is to evaluate whether tumor staging is concordant between these two independently performed examination techniques and whether one of them yields additional information regarding tumor spread in the anal canal. Most of the patients did not undergo surgery and, thus, had no histological tumor stage as the gold standard. Assessment of the sensitivity and specificity was replaced by a comparison of the results obtained by endoscopic ultrasound and MRI with regard to tumor spread (T stage) and nodal status (N stage). Where possible, a comparison was also made with the histological tumor stage of the surgical specimen as the gold standard. Since cancer was histologically confirmed by biopsy in all cases, the two techniques were also assessed for sensitivity in the correct detection of cancer per se.

Material and Methods

Patients

The study chronologically recruited all patients with primary staging of anal cancer by both TAUS and MRI of the pelvis prior to the initiation of therapy. The performance of both examinations is routine practice in our clinic for this diagnosis for more than 10 years. The diagnosis of anal cancer was histologically confirmed by biopsy in all patients. The two examinations and the biopsy were done within a 1-week time period. A total of 45 patients were included in the study.

After initial diagnosis, patients underwent combined stage-oriented radiochemotherapy (radiation combined with the administration of 5-FU and Mitomycin C). During follow-up, abdominoperineal rectum extirpation was performed in six of the 45 patients because of tumor progression. The preoperative staging results were compared with the histological findings in the surgical specimen as gold standard. The two examinations were done in the week prior to the operation.

Examination Methods

TAUS was performed by a surgeon with a rigid Bruel/Kjaer probe. During the examination of patients in the dorsosacral position, a 7-MHz rotating ultrasound transducer with a plastic anal cap was rectally inserted up to the level above the levator ani muscle and then slowly withdrawn. This yielded a two-dimensional real-time image. Lymph nodes were presumed to be metastases with a size of 1 cm or larger.

MRI was performed by a radiologist in a 1.5-T MR scanner (Magnetom Vision, Siemens Medical Solutions, Germany) using a phased-array surface coil. Axial T2-weighted (T2) and T1-weighted (T1) turbo-spin-echo (TSE) sequences of the entire pelvis with a slice thickness of 8 mm were acquired. Subsequently, thin-sliced (3 mm) axial T2-TSE and axial, coronal and sagittal post i.v. contrast T1-TSE with fat-suppression of the anal canal were acquired. Lymph nodes were presumed to be metastases with a size of 1 cm or larger.

All images were evaluated prospectively as part of the clinical routine work-up of the patients. However, care was taken that both the radiologists evaluating the MR images and the surgeons, evaluating the endosonography were blinded to the results of the other imaging modality. Results were assessed according to the international UICC TNM classification (Table 1).

Statistics

The kappa concordance index[25] was used as a measure of agreement between the two examination methods. It relates to a contingency table with the diagonal corresponding to the concordant examination results (Tables 4 and 5). The kappa index describes the ratio between the concordances actually found and those theoretically possible. The index is 1 for maximum and 0 for minimum concordance (Table 2). All calculation was done with SPSS software program.

Results

The 45 patients included (Table 3) had a median age of 61 years (43–90 years). Women were preponderant (30 women, 15 men). Histology revealed a squamous cell carcinoma in most cases (35 patients), a cloacogenic carcinoma in five, and a basaloid carcinoma in five others. Twenty-nine tumors were located in the proximal anal canal and 16 in the distal anal canal. In dorsosacral position, the tumor was located at 12 o'clock to 3 o'clock in 13 patients, at 3 o'clock to 6 o'clock in 12 patients, in 6 o'clock to 9 o'clock in 14 patients, and in 9 o'clock to 12 o'clock in 14

Table 1 Staging of Anal Cancer by UICC TNM Classification 2002

TNM classification	Definition
Primary tumor (T)	
T x	Tumor cannot be assessed
T 0	No evidence of tumor
T is	Carcinoma in situ
T 1	Tumor≤2 cm
T 2	Tumor>2 cm and ≤ 5 cm
T 3	Tumor>5 cm
T 4	Invasion of adjacent organ, any size
Lymph nodes (N)	
N x	Lymph nodes cannot be assessed
N 0	No regional lymph node metastases
N 1	Perirectal lymph node metastases
N 2	Unilateral internal iliac or inguinal lymph node metastases
N 3	Perirectal and inguinal or bilateral N2 lymph node metastases
Distant metastases (M)	
M x	Metastases cannot be assessed
M 1	No distant metastases
M 2	Distant metastases

patients (Fig. 1). Main symptoms were anal discomfort (19 patients), weight loss (12 patients), bleeding (11 patients), and change of bowel habits (eight patients).

Comparing the results of T staging by TAUS and MRI yielded a kappa index of 0.63 and, thus, high concordance. Among the divergent examination findings were five cancers (histologically confirmed) correctly identified as such by TAUS but not detected by MRI (Table 4).

The concordance assessment without these five cases yielded a kappa index 0.75 for the remaining 40 patients and, thus, an even higher concordance of the results. There are two patients in whom stage T4 was assessed by endoscopic ultrasound and stage T2 by MRI (Table 4). Infiltration of adjacent organs was not confirmed during the clinical course in either of the patients. However, the endoscopic ultrasound results were already rated as difficult to interpret at the time they were obtained: in one case, the vagina was not sharply delimited in a patient with a history of cervical cancer and irradiation of the pelvis (finding interpreted as T4); in the other patient, an extensive complex perianal fistula with multiple abscesses rendered assessment difficult, and the inflammatory signs were misinterpreted as a T4 tumor.

Irrespective of the tumor extension and T stage, correct identification of cancers as such was achieved in all cases by TAUS (100% sensitivity) but in only 40 of 45 cases by MRI (88.9% sensitivity).

Assessment of the nodal status N0 and N1 yielded a concordance index of 0.77 and, thus, high concordance of the two examination methods here as well. Two patients were diagnosed with N1 lymph node metastases by MRI but not by TAUS (Table 5). The concordance assessment referring to every nodal status (N0, N1, N2, N3) is not

Table 2 Interpretation of the Kappa Index

Kappa	Strength of agreement
<0.21	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	High
0.81–1.00	Nearly complete

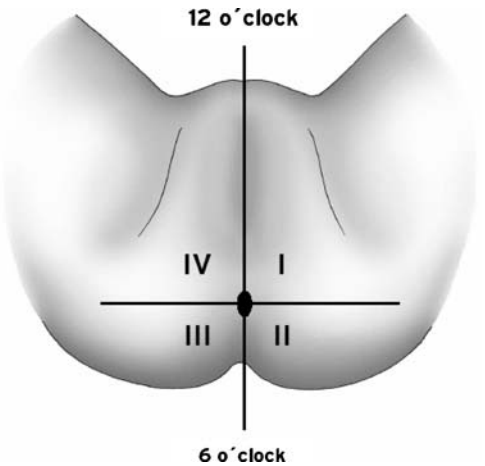

Figure 1 The tumor position is given as illustrated above. With the patient in dorsosacral position, the tumors were classified according to the clock face: *I* (12 o'clock to 3 o'clock), *II* (3 o'clock to 6 o'clock), *III* (6 o'clock to 9 o'clock), and *IV* (9 o'clock to 12 o'clock).

Table 3 Histology and Localization of Tumors (Fig. 1)

	Variable	Number of patients (n=45)
Histology	Squamous cell carcinoma	35
	Cloacogenic carcinoma	5
	Basaloid carcinoma	5
Tumor localization	Proximal anal canal	29
	Distal anal canal	16
	12 o'clock to 3 o'clock dorsosacral position	13
	3 o'clock to 6 o'clock dorsosacral position	12
	6 o'clock to 9 o'clock dorsosacral position	14
	9 o'clock to 12 o'clock dorsosacral position	14
Symptoms	Anal discomfort	19
	Weight loss	12
	Bleeding	11
	Change of bowel habits	8

Main symptoms (n=45)

evaluable, as the endoscopic ultrasound cannot detect N2 and N3 lymph nodes; therefore, there cannot be any concordance concerning these lymph nodes. For completeness, the kappa index is given in Table 5 (0.48).

During follow-up, six patients showed tumor progression despite radiochemotherapy and surgery was performed. In these six patients with histological tumor staging as the gold standard, the examination results of the two methods showed agreement in four of the six patients. Both deviations were errors in MRI: an undetected T1 tumor and a lymph node falsely diagnosed as invaded. The T stage was correctly assessed in four of six patients by TAUS and in three of six patients by MRI. Cancers were detected in all cases (six of six) by TAUS but in only five of six cases by MRI. The nodal status was correctly assessed in only two of six patients by TAUS and in only one of six patients by MRI (Table 6).

The follow-up results of the patients without tumor recurrence (n=39) were concordantly negative for both examination methods in all of these cases.

Discussion

In our opinion, this study demonstrates that TAUS and MRI appear to be highly concordant. TAUS may be superior for detection of small superficial tumors, though supplementary MRI is needed for N staging. Since the standard therapy is usually nonoperative,[5–7] there is no surgical specimen in most of our cases; therefore, no histological assessment is possible. Thus, sensitivity and specificity could not be calculated for the T and N stages. Alternatively, TAUS and MRI were compared with regard to the T and N stages using the kappa concordance index. As anal cancer was histologically confirmed by biopsy in all patients, sensitivity could be determined for cancer detection irrespective of the stage. As anal cancer is a rare tumor and is usually not treated surgically, we could only include 45 patients and only six of them were operated because of tumor progression.

Noteworthy when considering the divergent findings is the fact that in the T stage examination, histologically

Table 4 Comparison of *T Stages*

TAUS	MRI				
	T0	T1	T2	T3	T4
T0	0	0	0	0	0
T1	4	8	1	0	0
T2	1	2	19	0	0
T3	0	0	1	1	0
T4	0	0	2	0	6

The diagonal shows the concordant examination results (n=45): kappa=0.63 (all patients); kappa=0.75 (without the five cancers not detected by MRI)

TAUS transrectal endoscopic ultrasound, *MRI* magnetic resonance imaging

Table 5 Comparison of *N Stages*

TAUS	MRI			
	N0	N1	N2	N3
N0	34	2	5	0
N1	0	4	0	0
–	0	0	0	0
–	0	0	0	0

The diagonal shows the concordant examination results (n=45); kappa=0.77 (stage N0/N1 only); kappa=0.48 (all patients)

TAUS transrectal endoscopic ultrasound, *MRI* magnetic resonance imaging

Table 6 Comparison of Preoperative Tumor Stages in Transrectal Endoscopic Ultrasound (**TAUS**) and Magnetic Resonance Imaging (MRI) in Relation to the Histological Findings in the Surgical Specimen (n=6)

	Histological findings	TAUS	MRI
Patient 1	T2N1	T2N0	T2N0
Patient 2	T1N0	T1N0	T0N0
Patient 3	T3N2	T2N0	T2N0
Patient 4	T1N1	T1N0	T1N0
Patient 5	T3N0	T2N0	T2N1
Patient 6	T2N1	T2N0	T2N0

confirmed anal cancer could only be identified by TAUS in all cases and not by MRI. Four of the five tumors, which were missed by MRI were stage T1 cancers. These small cancers (maximum size 2 cm) are difficult to detect with this technique. In contrast, endoscopic ultrasound has the advantage of having the transducer located directly at the wall of the anal channel and, therefore, may be superior in detecting small superficial tumors. These results coincide with those of the six patients with a complete surgical specimen as the gold standard (recognition rate—6/6 for TAUS 5/6 for MRI).

Pathological lymph nodes were seen more often by MRI. This may be partially method-related since TAUS obviously cannot visualize inguinal or iliac lymph nodes (N2 and N3). However, it must be noted that nodal invasion was not histologically confirmed here.

It has to be noted though that the two methods only assessed the T-stage in four (TAUS) and three (MRI) and the lymph nodes only in two (TAUS) and one (MRI) of six operated patients correctly. A possible reason might be the earlier chemoradiation in these patients. Radiotherapy causes inflammatory changes and fibrosis, which might lead to misinterpretation and overstaging in rectal carcinoma. The overstaging of lymph node status is primary caused by the presence of reactive swollen lymph nodes that could be considered as malignant.[26] In the investigated six operated patients, all but one mistake were done by understaging the tumor. Since the therapy of anal cancer is rarely operative, there is a lack of control of the diagnostic results through a surgical specimen. This might be a reason for the understaging in the difficult situation of post-radiotherapy tumors.

Our results are in agreement with those of other studies that recommend TAUS for staging and follow-up: Tarantino et al. investigated the suitability of endoscopic ultrasound for T staging in 12 patients. A surgical specimen was available as the gold standard in five patients, in whom the tumor was also correctly identified by endoscopic ultrasound. However, no comparison was made with MRI or other examination methods.[27] Giovanni et al. compared the staging accuracy of endoscopic ultrasound and rectal examination with respect to the recurrence rate and survival in 115 patients. The better results were achieved by endoscopic ultrasound.[28] Drudi et al. also compared endoscopic ultrasound and rectal examination in 66 patients and obtained the same results.[29] In the latter two studies, there were no histological findings and no other examination method as a reference standard; the results were only measured against the long-term clinical course (recurrence, survival). All three studies recommend endoscopic ultrasound for T staging, which is also in accordance with the recommendations of other survey studies.[30]

Treatment options for anal cancer is highly depend on the stage at presentation,[5–9] which makes staging extremely important. TAUS and MRI are the modalities predominantly utilized. A meta-analysis of Bipat et al. about staging of rectal cancer found that TAUS was the best technique for assessing local invasion but showed its limitations too: operator dependency, inability to detect lymph nodes outside the range of the transducer, and no assessment of stenotic tumors.[31]

Recently, three-dimensional TAUS and endorectal coil MRI have been introduced for staging of rectal cancer. Three dimensional ultrasound images are based on multiple serial sections over the region of interest; therefore, the quality of images is equivalent to those of conventional TAUS. Additional scan planes can be used to determine size, location, and local extent of a lesion precisely.[32] Endorectal coil MRI might have an advantage because of higher imaging resolution near the coil;[33] however, the exact role is still unclear. In studies that compared the accuracy of three-dimensional endoscopic ultrasound, endorectal coil MRI, and conventional ultrasound in the staging of the infiltration depth of rectal cancer, the results of all three methods were comparable.[32,34] Ultrasmall superparamagnetic iron oxide particles (USPIO), a promising group of new MR contrast agents, are taken up by cells of the reticuloendothelial system, for example in lymph nodes.[35,36] The benefit of USPIOs for the differentiation of benign (contrast uptake) and malignant (no contrast uptake) lymph nodes has been demonstrated in several studies.[37,38] Therefore, the use of USPIOs might have further decreased the number of false positive lymph nodes in this study. However, this imaging modality is still experimental and not approved for clinical use.

Conclusion

TAUS and MRI yield comparable results in the assessment of local tumor spread. Endoscopic ultrasound may be superior to magnetic resonance imaging for detection of small superficial tumors. But as regional lymph nodes are

outside the field of view for endosonography, supplementary MRI is needed for N staging.

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ORIGINAL ARTICLE

A Simple Scoring System Based on Clinical Features to Predict Locally Advanced Rectal Cancers

Guoxiang Cai · Ye Xu · Xiaoli Zhu · Junjie Peng · Zuofeng Li · Changchun Xiao · Xiang Du · Ji Zhu · Peng Lian · Weiqi Sheng · Zuqing Guan · Sanjun Cai

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Abstract
Purpose The purpose of this study was to identify clinical risk factors and establish a prediction scoring system for locally advanced rectal cancer.
Materials and methods Retrospective univariate and multivariate logistic analyses were conducted for 413 curable rectal cancer patients. Clinical factors found to be significantly related with tumor stages were incorporated into a scoring system to predict locally advanced stages, which was validated in an independent cohort of 279 rectal cancer patients.
Results In the training set, tumor size, differentiation, and serum carcinoembryonic antigen (CEA) level ($P<0.01$) were significant predictors of locally advanced rectal cancer in both univariate and multivariate analyses, which were incorporated into a proposed scoring system to predict locally advanced stages. The area under the receiver operating characteristic curve (AUROC) of this scoring system was 0.751 and the prediction accuracy was 78.2%. Patients were categorized into three subsets according to the total score. The low-risk group (score 0) had a smaller chance (18.2%) to have locally advanced rectal cancer, compared to mean 49.2% for the intermediate-risk group (score 1) and mean 83.0% for the high-risk group (score of 2–4; $P<0.05$). In the validation set, the AUROC of the scoring system was 0.756 and the prediction accuracy was 75.3%.
Conclusions Tumor size more than 2 cm, poor differentiation, and elevated serum CEA level are high-risk factors of locally advanced rectal cancer. A simple scoring system based on these three factors may be valuable to predict locally advanced rectal cancer.

G. Cai · Y. Xu · J. Peng · C. Xiao · P. Lian · Z. Guan · S. Cai (✉)
Department of Colorectal Surgery, Cancer Hospital,
Fudan University,
270 Dong An Road,
Shanghai 200032, People's Republic of China
e-mail: caisanjun@tom.com

X. Zhu · X. Du · W. Sheng
Department of Pathology, Cancer Hospital, Fudan University,
270 Dong An Road,
Shanghai 200032, China

J. Zhu
Department of Radiation Oncology,
Cancer Hospital, Fudan University,
270 Dong An Road,
Shanghai 200032, China

Z. Li
Shanghai Center for Bioinformation Technology,
100 Qinzhou Road,
Shanghai, China

Keywords Rectal cancer · Stage · Size · Differentiation · Carcinoembryonic antigen

Introduction

Preoperative staging is crucial in determining the initial therapeutic regimen of rectal cancers.[1–4] The optimal treatment for different stages of rectal cancers is different: surgical resection is reasonable and enough for early-stage rectal cancers (0/I stage) while neoadjuvant radiochemotherapy in addition to surgery may be the first choice for locally advanced rectal cancers (II/III stage).[5,6] Several methods have been applied to preoperative staging, among which magnetic resonance imaging (MRI) and transrectal ultrasonography (TRUS) are most valuable.[1,7,8] The precision of measuring the penetrating depth of rectal cancer (T staging) by MRI or TRUS is up to 80% to 90%.[1,2,9–13] However,

these methods have several limitations. They are less useful in the identifying lymph node metastasis (N staging) with an accuracy of 70% to 80%.[1,3,12,14–18] In addition, both transrectal coil MRI and TRUS are unable to examine stenotic rectal cancer.[1,2,19] Furthermore, these methods are far from being routine procedures for the evaluation of rectal cancer in China and considerably increase medical expenditure. Is there any simple and inexpensive method that helps determine the preoperative stage of rectal cancers? This issue motivated us to investigate the relationship between the stage and clinical parameters of rectal cancers which can be easily and objectively obtained preoperatively. Our study identified several important factors highly correlated with TNM stage and established a simple scoring system based on these factors, which could be used to predict for locally advanced rectal cancers effectively. To our knowledge, this is the first report of a risk scoring system developed to predict for stages of rectal cancer.

Materials and Methods

Data used to develop a scoring system were obtained from consecutive patients with primary rectal cancer (less than 12 cm from anal verge) who underwent surgical treatment in the Cancer Hospital of Fudan University from November 1999 to January 2004. Included were those patients who had tumors confirmed to be adenocarcinoma or mucinous adenocarcinoma or signet-ring cell carcinoma by surgical histological examination and had complete medical records including patient's gender and age, tumor distance from anal verge, tumor size, tumor histology, tumor differentiation, pathological TNM stage and preoperative serum carcinoembryonic antigen (CEA) level. Rectal adenocarcinomas in situ (Tis stage) having received radical resection were also included. The study did not include rectal cancers with either recurrence or distant metastasis. Patients having received local excision were excluded. Patients who had familial adenomatous polyposis or simultaneous multiple colorectal cancers or had received neoadjuvant therapy were also excluded from the analysis. The study design was approved by the institutional ethics review board of the Cancer Hospital of Fudan University. A final cohort of 413 rectal cancer patients was eligible for analysis as the training set. Table 1 summarizes clinical features of patients of the training set.

The same selection criteria were used to collect 279 consecutive rectal cancer patients surgically treated in the Cancer Hospital of Fudan University from March 2007 to February 2008, which was used as the validation set to evaluate the performance of the above scoring system. The sample size of the validation set was about two thirds of that of the training set. Table 1 also summarizes clinical data on this validation cohort, which was comparable with the training set.

Patients were divided into two subsets: early stages (ES) and locally advanced stages (LAS). ES meant stages 0 and I while LAS included stages II and III. Factors compared between the above two groups were gender (female, male), age (<60, ≥60 years), distance from anal verge (≤8, 9–12 cm), size (≤2.0, 2.1–3.0, >3.0 cm), histology (adenocarcinoma, mucinous adenocarcinoma/signet-ring cell carcinoma), differentiation (well/moderate, poor), and serum CEA level (normal, abnormal). The reference range of normal CEA level is 0–10 μg/L in the laboratory of our hospital, so serum CEA level more than 10 μg/L was defined as abnormal. Two-tailed Pearson chi-squared tests were used univariately to explore the relationship between these variables and tumor stages. Factors found to be significant in the univariate analysis were then evaluated multivariately using binary logistic regression (backward conditional stepwise). In tumor size analysis, patients with tumors ≤2.0 cm were chosen as the reference group. The statistical significance level was set at 0.05 (two-sided). The statistical analyses were conducted with software of SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Factors identified to be significant in the multivariate analysis were used to establish a scoring system to predict rectal cancer with LAS. The performance of the established scoring system was evaluated by the receiver operating characteristic (ROC) curve analysis and calculation of the prediction accuracy and further validated in a second independent cohort.

Results

Training Set

Univariate Predictors

Of the 413 eligible patients, 308 (74.6%) were classified as LAS rectal cancers. The univariate analysis (Table 2) demonstrated that factors significantly associated with LAS were tumor size ($P<0.001$), histology ($P=0.001$), differentiation ($P<0.001$), and serum CEA level ($P<0.001$). Having tumors with a diameter greater than 2.0 cm or with poor differentiation or with elevated serum CEA level were indicators of later stages of rectal cancer. The tumor size was categorized into three subsets (≤2.0, 2.1–3.0, >3.0 cm) and the univariate binary logistic regression analysis demonstrated that the proportion of LAS differed significantly between any two subsets (26.9% vs. 60.0% vs. 82.4%, all P values less than 0.01). There were no significant differences in gender, age, or tumor distance from anal verge ($P>0.05$).

Table 1 Clinical Characteristics of the Training Set and Validation Set

Variable	Training set (n=413) [no. (%)]	Validation set (n=279) [no. (%)]
Gender		
Male	233 (56.4)	160 (57.3)
Female	180 (43.6)	119 (42.7)
Age (years)[a]	56.8±12.9	57.3±12.6
Distance from anal verge (cm)[a]	6.5±2.5	6.4±2.8
Size (maximum diameter, cm)[a]	4.4±1.5	3.9±1.6
Histology		
Adenocarcinoma	359 (86.9)	248 (88.9)
Mucinous or signet-ring cancer	54 (13.1)	31 (11.1)
Differentiation		
Well/moderate	327 (79.2)	215 (77.1)
Poor	86 (20.8)	64 (22.9)
CEA level		
Normal	333 (80.6)	233 (83.5)
Abnormal	80 (19.4)	46 (16.5)
Extent of invasion		
Tis	11 (2.7)	3 (1.1)
T1/2	134 (32.4)	98 (35.1)
T3/4	268 (64.9)	178 (63.8)
Regional lymph node involvement		
N0	215 (52.1)	141 (50.5)
N1/2	198 (47.9)	138 (49.5)
Stage (TNM)		
0	11 (2.7)	3 (1.1)
I	94 (22.8)	71 (25.4)
II	110 (26.6)	67 (24.0)
III	198 (47.9)	138 (49.5)

CEA indicates carcinoembryonic antigen

[a] Arithmetic mean ± standard deviation

Multivariate Predictors

Further multivariate analysis (Table 3) showed that three variables (tumor size, differentiation, and serum CEA level were significantly correlated with LAS while tumor histology (P<0.01) was not independently associated with the stages of rectal cancer (P>0.05).

Risk Scoring System

In addition to being significantly associated with rectal cancer stages, these three factors (tumor size, differentiation, and serum CEA level) have the advantage of being easily determined preoperatively and can therefore be used in a preoperative prediction model of rectal cancer stages. These three variables were incorporated into a risk scoring system by assigning points to various features according to their odds ratios (OR) values in the multivariate analysis (Table 3), as listed in Table 4. A score of 0 was assigned to features with OR value equal to1, score 1 for those with OR value close to 5, and score 2 for those with OR value near to 9. Points of these three variables were then totaled to yield an overall risk score. The mean total score was 1.4± 0.9 points for ES tumors and 2.3±0.8 points for LAS cancers. LAS had a significantly higher total score than ES (P<0.001 based on t test). The probability of having LAS rectal cancers increased stepwise with the total score (Table 5). The ROC curve analysis of the total score is shown in Fig. 1.The area under ROC (AUROC) curve of the scoring system in the training set was 0.751 (95% confidence interval (CI) 0.697–0.805, P<0.001). When the cutoff value was set between score1 and score 2, the Youden's index (sensitivity+specificity−1) reached the largest value (0.357). The sensitivity was 89.0%; the specificity was 46.7%; the prediction accuracy was 78.2% and the positive predictive value (PPV) was 83.0% at this cutoff value (score 0–1 vs. score 2–4). However, the negative predictive value (NPV) was relatively as low as 59.0%. When the cutoff value was chosen between score 0 and score 1, the NPV increased to 81.8% by more than 20% while the prediction accuracy and PPV only decreased slightly to 78.0% and 77.7% (score 0 vs. score 1–4). Therefore, two cutoff values were set finally

Table 2 Univariate Analysis of Clinical Factors in the Training Set

Variable	Total (n=413)	Stage 0/I (n=105) [no. (%)]	Stage II/III (n=308) [no. (%)]	P value
Gender				
Male	233	54 (51.4)	179 (58.1)	0.233
Female	180	51 (48.6)	129 (41.9)	
Age				
<60 years	239	59 (56.2)	180 (58.4)	0.687
≥60 years	174	46 (43.8)	128 (41.6)	
Distance from anal verge				
≤8 cm	323	88 (83.8)	235 (76.3)	0.107
9–12 cm	90	17 (16.2)	73 (23.7)	
Size				
≤2.0 cm	26	19 (18.1)	7 (2.3)	<0.001
2.1–3.0 cm	80	32 (30.5)	48 (15.6)	
>3.0 cm	307	54 (51.4)	253 (82.1)	
Histology				
Adenocarcinoma	359	101 (96.2)	258 (83.8)	0.001
Mucinous or signet-ring cancer	54	4 (3.8)	50 (16.2)	
Differentiation				
Well/moderate	327	100 (95.2)	227 (73.7)	<0.001
Poor	86	5 (4.8)	81 (26.3)	
CEA level				
Normal	333	99 (94.3)	234 (76.0)	<0.001
Abnormal	80	6 (5.7)	74 (24.0)	

CEA indicates carcinoembryonic antigen

and patients were accordingly categorized into three risk categories as shown in Table 6. Patients having a total score of 0 were defined as low-risk category with a chance less than 20% of being LAS. Patients having a total score of 2–4 were defined as high-risk category because the mean probability of being LAS was more than 80% in this group (83.0%). Patients with a total score of 1 were defined as intermediate-risk category because about 50% of them were LAS. Univariate binary logistic regression analysis indicated that these three risk categories differed significantly on the probability of being LAS. All P values were less than 0.05.

Table 3 Multivariate Analysis of Clinical Factors in the Training Set

Variable	OR (95% CI)	P value
Histology	0.463 (0.048–4.494)	0.507
Size[a]		<0.001
2.1–3.0 cm	3.722 (1.330–10.416)	0.012
>3.0 cm	10.944 (4.175–28.689)	<0.001
Differentiation	6.243 (2.384–16.350)	<0.001
CEA level	5.066 (2.026–12.669)	0.001

OR odds ratio, *CI* confidence interval, *CEA*, carcinoembryonic antigen

[a] In tumor size analysis, ≤2.0 cm was chosen as contrast indicator

Validation Set

According to the scoring system established in the training set, 22 cases of the validation set had a total score of 0 (low-risk category) and only 18.2% of them was LAS. There were 61 cases with a total score of 1 (intermediate-risk category) and the proportion of LAS was 57.4%. There were 196 patients with a total score of 2–4 (high-risk category), among whom 84.7% was LAS. The performance of the scoring system in the validation set was similar to that of the training set. AUROC of the scoring system in the validation

Table 4 Points Assignment of Various Clinical Features

Point	Size (cm)	Differentiation	CEA level
0	≤2.0	Well/moderate	Normal
1	2.1–3.0	Poor	Abnormal
2	>3.0		

CEA carcinoembryonic antigen

Table 5 Distribution of Stages in Various Total Scores

Total points	0 [no. (%)]	1 [no. (%)]	2 [no. (%)]	3 [no. (%)]	4 [no. (%)]
ES	18 (81.8)	31 (50.8)	49 (23.0)	8 (6.3)	1 (4.5)
LAS	4 (18.2)	30 (49.2)	164 (77.0)	84 (93.7)	21 (95.5)

ES early stage, *LAS* locally advanced stage

set was 0.756 (95% CI 0.691–0.821, $P<0.001$) and the prediction accuracy was 75.3% (score 0–1 vs. score 2–4).

Discussion

Emergence of modern imaging technique such as high-resolution MRI and TRUS facilitates the preoperative staging of rectal cancer. The accuracy of T staging is about 80–90%.[1,2,9–13] However, the precision of N staging is less satisfying, less than 80% in most studies.[1,3,12,14–18] Imaging methods identify lymph node metastasis mainly relying on the size of lymph node. However, enlarged lymph nodes can be inflammatory and even small lymph nodes can be metastatic. Besides, no consensus has been well reached on the morphological criterion of metastatic lymph nodes. In clinical practice, doctors of diagnostic radiology or endoscopic ultrasonography sometimes provide an ambiguous staging result by MRI or TRUS without firsthand detailed clinical information of patients. And about 20% of staging results by MRI or TRUS are found to be incorrect. Besides, MRI or TRUS is not always affordable and applicable. In China, many patients with colorectal cancer are still treated in primary hospitals without MRI or TRUS equipment. And the fine technique of staging of rectal cancer by MRI is not prevalent even in many superior hospitals. In China, contraceptive rings are widely used in reproductive women, which are contraindications of MRI examination. Therefore, the scoring system developed in this study could play an important role as an additional reference for staging. It can even act as a substitute staging method when MRI and TRUS are unavailable. In addition, the scoring system has its own superiority to modern imaging staging methods and other mathematical models. It is simple and inexpensive. Clinical parameters used in the system can be easily obtained preoperatively through digital rectal examination, colonoscopy, biopsy, conventional imaging method, and serum biochemical test. Logistic equations developed in previous studies are impossible to be remembered and must be applied in the aid of computer program, but the scoring system established in this study is easy to remember and much more practical in clinical settings.

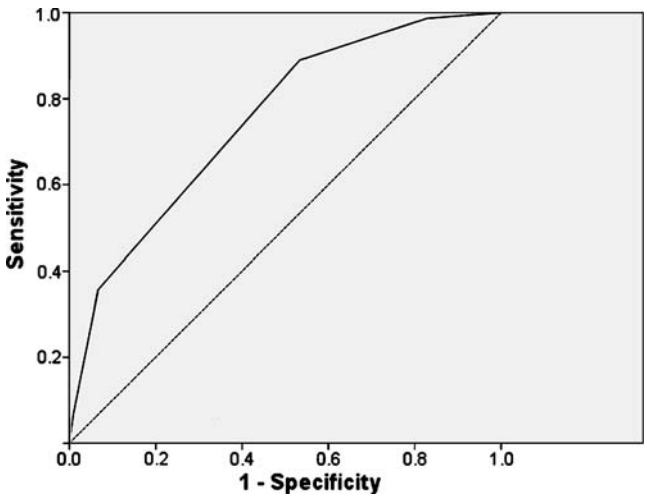

Figure 1 ROC curve of total scores of clinical parameters to predict locally advanced rectal cancer in the training set.

In the present study, rectal cancers were categorized into two subgroups, ES (0/I stage) and LAS (II/III stage). This classification is simpler and more practical than isolated stages because both stage II and stage III rectal cancers need neoadjuvant radiochemotherapy and discrimination of them may be unnecessary preoperatively. We focused on those clinicopathologic parameters that can be determined easily and objectively prior to surgery. According to the univariate and multivariate statistical analysis, we identified three variables which were valuable to predict LAS rectal cancers: tumor size, tumor differentiation, and serum CEA level.

Several studies supported that tumor size is correlated with penetration depth and nodal metastasis of colorectal cancer. An analysis of 924 colorectal cancer patients by the National Surgical Adjuvant Project for Breast and Bowel Cancer showed that the mean longest tumor diameter of Dukes C1 (according to Astler–Coller staging system, equal to T1/2 N+ M0) colorectal cancer (mean 4.2 cm) was significantly less than that of both Dukes B (T3/4 N− M0, mean 5.6 cm) and C2 (T3/4 N+ M0, mean 5.5 cm) tumors ($P<0.001$),[20] supporting the significant correlation between tumor size and penetrating depth of colorectal cancer. The study of Zhang et al.[21] revealed that rectal cancers with the diameter of 2 to 3 cm were significantly more likely to have lymph node metastasis than tumors less than 2 cm, indicating a strong correlation between tumor size and nodal metastasis. This study also demonstrated that the possibility of LAS rectal cancer stepwise increased with tumor size (Table 2). In the training set, when tumor size was less than 2 cm, the probability of LAS was only 26.9%. But the possibility of LAS increased to 82.4% in patients with tumor size more than 3 cm.

Table 6 Risk Stratification for LAS Rectal Cancers and Recommendation of Management

Total points	Risk category	Probability of LAS	Recommendation
0	Low	<20%	Surgery
1	Intermediate	About 50%	Staging by TRUS or MRI to determine the therapy plan
2–4	High	>80%	Neoadjuvant radiochemotherapy + surgery

LAS locally advanced stage

Poor differentiation of tumor is considered to be associated with later stages and worse prognosis of rectal cancers. This study indicated that only 3.8% of ES rectal cancers in the training set were poorly differentiated while 16.2% of LAS rectal cancers had poor differentiation. The results are corroborated by other studies.[22,23] The study by Brodsky et al.[22] evidenced that no well-differentiated pT1 or pT2 rectal cancers had lymph node metastasis while 22% moderately differentiated and 50% poorly differentiated had nodal involvement. Similar results were seen in another study: 16% well-differentiated, 47% moderately differentiated, and 82% poorly differentiated rectal cancers were lymph node positive ($P<0.0001$), respectively, and a strong correlation between poor differentiation and deeper penetration was also witnessed ($P<0.001$).[23]

Preoperative serum CEA is also well accepted to be related with the stage and prognosis of rectal cancer.[24,25] The study of Marchena et al.[25] demonstrated that preoperative level of serum CEA was positively associated with tumoral intramural spread, lymph node involvement, and TNM stage significantly. In the present study, elevated CEA level was more frequent in LAS rectal cancers than in ES, which indicated that elevated CEA level was a high-risk feature of later tumor stages, consistent with previous reports.[24,25]

A scoring system was established to evaluate the risk of being LAS rectal cancers in the present study, taking into account the comprehensive influence of the above three individual variables. Various features had different extent of impact on the stage of rectal cancers, which formed the basis of point assignment in the scoring system. Tumor size more than 3 cm had the highest OR value in multivariate analysis and was assigned to the highest score. If patients have more risk factors, their total score will be higher and they will have more chance to be LAS rectal cancer. Patients were divided into three subsets according to their total score. Patients without high-risk features, less than 2.0 cm, well/moderately differentiated, normal serum CEA level, had a relatively low risk, less than 20%, to be LAS. By contrast, patients with a total score of 2–4 were predominantly LAS (more than 80%) in this study. Specially, patients with a total score of 4 were at an extreme high risk (more than 95%) of being LAS. The performance of this scoring system was further validated in an independent cohort and showed a similar accuracy of predicting rectal cancer with LAS.

Although 18.2% patients with a total score of 0 and 17.0% patients with a total score of 2–4 were still misclassified in staging, such a rate of misjudgment is acceptable because even the most accurate imaging method (MRI or TRUS) available at present has an accuracy not more than 90% in staging of rectal cancer. When rectal cancer patients had a total score of 0 or 2–4, less than 20% of them were misclassified in staging. Specially, patients with a total score of 3 or 4 had a very small chance less than 10% to be misclassified. In such conditions, the clinical scoring system has a significant value as an additional reference method to determine the stage of tumors and doctors should be cautious of the staging result of MRI or TRUS when it is not consistent with that of the clinical scoring system because the result of MRI or TRUS is not always correct. However, when patients had a total score of 1, the value of the scoring system is limited. It is hard to estimate the true stage of rectal cancer for the scoring system and MRI or TRUS is essential absolutely. Fortunately, such embarrassment was not frequent because only about 15% of patients had a total score of 1. The recommendation of the management of rectal cancer patients according to the clinical scoring system was summarized in Table 6. The recommendation in Table 6 does not exclude the application of TRUS and MRI in patients with a total score of 0 or 2–4 because these two examinations are important to provide a more detailed profile of the tumor and help determine the extent of the operation or neoadjuvant radiotherapy.

Conclusion

In summary, clinical features including tumor size, tumor differentiation, and serum CEA level indicate different probability to be LAS rectal cancers. Tumor size more than 2.0 cm, poor differentiation, and elevated serum CEA level all predict a higher risk to be LAS. A simple scoring system on the basis of these three factors can be used to evaluate the risk of being LAS rectal cancers. Such a scoring system has several merits: simple, easily rememberable, preoperative, and practical. It provides an additional reference to doctors besides TRUS and MRI in the preoperative stage

evaluation. It can be complementary to modern imaging staging methods such as TRUS and MRI when the staging results are ambiguous or when imaging staging methods are not affordable or applicable.

Conflict of interest None.

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ORIGINAL ARTICLE

CT Scans and Acute Appendicitis: A Five-Year Analysis from a Rural Teaching Hospital

Toms Augustin · Siddharth Bhende · Keyur Chavda · Thomas VanderMeer · Burt Cagir

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Abstract
Introduction Studies examining the relationship between computed tomography (CT) scans and appendiceal perforation have largely been conducted in urban centers. The present study sought to evaluate this relationship in a rural hospital.
Methods and Procedures This is a retrospective analysis of 445 patients who underwent appendectomies from January 2000 to June 2005 at a rural teaching hospital.
Results Four hundred forty-five patients were analyzed in two groups; those who underwent CT scans (N=245) and those who did not (N=200). Patients undergoing CT scans were significantly older (median age 38 vs. 22 years, P<0.0001), were more likely to have perforated appendicitis (P 0.001), were less likely to undergo a negative appendectomy (P=0.003), and had a significantly longer length of stay than those who did not (P 0.009). Analysis by gender showed that perforation rates continued to be significantly higher in males undergoing CT scans (P 0.004). To examine the possibility that sicker patients were more likely to receive CT scans and also be found to have perforated appendicitis, a sensitivity analysis was performed. Patients showing perforated appendicitis on initial CT scans were excluded and the analysis was repeated. The difference in perforation rates continued to remain significant (P 0.037).
Conclusion Males undergoing CT scans are significantly more likely to have perforated appendicitis. A protocol-driven rational approach to CT evaluation of suspected appendicitis may lower perforation rates, especially in males.

Keywords Perforated appendicitis · CT scan · Delay in treatment · Gender difference · Rural population

Introduction

The diagnosis of acute appendicitis continues to be a challenge. Up to a third of patients may present with atypical clinical findings.[1,2] Computerized tomography (CT) scan has thus emerged as one of the most widely used imaging modalities to supplement clinical examination.

CT scan has a high sensitivity and specificity for the diagnosis of acute appendicitis.[3–5] However, clinical studies specifically addressing the role of this imaging modality have come up with varied and often contradictory results. Some studies have advocated routine use of CT scans in all patients in whom acute appendicitis is suspected,[6,7] while others have supported selective use based on clinical examination.[8–10] Still other studies have not found a benefit to the routine use of CT scans[11–16] including two studies which found that obtaining CT scans significantly increases the emergency department (ED) length of stay.[14,15] Also, another group found an increased percentage of perforated appendicitis in patients undergoing CT scans.[16] The discrepancy between the various study results may in part be explained by the heterogeneity of clinical practice and the study designs employed.

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T. Augustin (✉) · S. Bhende · K. Chavda · T. VanderMeer · B. Cagir
Department of General Surgery Residency,
Robert Packer Hospital,
One Guthrie Square,
Sayre, PA 18840, USA
e-mail: augustin_toms@guthrie.org

Most of these studies have been done at urban centers and may not be entirely applicable to rural patients because of differences in overall age, socioeconomic status, insurance coverage, and access to health care. [17] Some authors have suggested these factors may predispose rural patients to present later in the course of their illness.[17–19] Additionally, hospitals in rural settings may more likely be challenged with workforce shortages that result in further delays in obtaining care once these patients present to the ED.

With these issues in mind, this study tested the hypothesis that patients undergoing CT scans at a rural tertiary medical center were more likely to have advanced disease on final pathology than patients in whom CT scans were not performed. We also tested the above hypothesis based on gender.

Material and Methods

This study is a retrospective analysis of all patients who underwent appendectomy at the Guthrie-Robert Packer Hospital, Sayre, PA, USA from January 2000 to June 2005. Robert Packer is a tertiary community teaching hospital with 240 beds that serves rural areas stretching over a 100-mile radius. The vast majority of patients undergoing appendectomies at this hospital are admitted through the ED where they are first seen by the ED physicians. Surgical consults are then obtained as deemed appropriate by the ED physician.

Initially, we identified all patients who underwent appendectomy at this institution during the above period. On a case-by-case basis, we then excluded patients who had an incidental or interval appendectomy. Of the total 492 patients who underwent appendectomies during this time period, 45 patients were thus excluded. Since this hospital is not a pediatric center, we had only two patients under 5 years who had undergone an appendectomy. These patients were also excluded.

Data were then collected on the remaining 445 patients. Chart review was done to collect information on patient demographics including age, race, sex, relevant clinical history, radiological tests including CT scans, and pathology results. CT scan results were interpreted based on the final radiologist report. CT scans in this institution are interpreted by an attending radiologist from 8 a.m. to 9 p.m. and by consultant radiology service at night. All the consultant radiology reports are reinterpreted by an attending radiologist the next day for accuracy and quality assurance. In cases of ambiguity about reports, results were coded in consultation with an in-house attending radiologist**.** We categorized the findings on CT scan into normal appendix, acute appendicitis, acute appendicitis with perforation, and acute appendicitis with abscess formation. This was based on an internal consensus about the definitions to be used due to lack of a standard scale as well as the low sensitivity and specificity of CT scans for the diagnosis of perforated appendicitis.[20] Presence of periappendiceal fluid with or without extraluminal gas was used to differentiate between perforated and non-perforated appendicitis. Presence of a loculated fluid collection with or without fluid level along with findings of acute appendicitis was used to classify acute appendicitis with abscess formation. Information was also collected on the insurance status of the patient and the distance from the hospital based on the zip code of residence. The diagnosis of perforated appendicitis was based on the final pathology report. All specimens were examined by an attending pathologist. Perforated appendectomy rate was calculated based on all the appendectomies performed at this institution including the negative appendectomies.

Statistical analysis was performed using STATA (version 8, College Station, TX, USA). Bivariate associations were evaluated using chi-squared tests for pairs of ordinal variables. Wilcoxon rank-sum test was used to examine differences in central tendency. This study was approved by the Institutional Review Board at the Robert Packer Hospital.

Results

Demographics

Four hundred forty-five patients underwent appendectomy at this institution from January 2000 to June 2005. Of these, 255 were males (57% of the total population) and 190 were females. The median age for the population was 29 years with 27% older than 45 years and 9% of the total population older than 60 years. Twenty-four percent of the patients either did not have insurance or were Medicaid-insured. The mean distance from the hospital was 35 miles. The majority of the patients (62%) underwent laparoscopic appendectomy during this time period. More than 97% of the patients were White Americans, with African Americans and Asians constituting the rest (result not shown).

CT Utilization

The percentage of patients undergoing CT scan on admission increased through the study period with a peak in the year 2004 when 74% of the patients received a CT scan prior to appendectomy. The overall negative appendectomy rate was 14%. Seventeen percent of the patients were noted to have perforated appendicitis on final pathology. However, there was no trend noted in either

the negative appendectomy or the perforated appendectomy rates during this time period (Fig. 1).

Overall Population and CT Scans

Table 1 compares patient characteristics based on whether patients underwent CT scan on admission or not. CT scans were obtained in 55% of the total population and 75% of the patients older than 45 years of age. There was no significant gender difference in the CT scan rate. Patients who underwent CT scans were significantly older (38 vs. 22 years) and had a significantly longer hospital length of stay (3 days) compared to patients who did not (2 days). There was no significant difference in distance from the hospital or insurance status between the two groups. However, the negative appendectomy rate was significantly lower and the rate of perforated appendicitis was significantly higher in patients who underwent CT scans. In order to check if the difference in perforation rate between the two groups was due to patients presenting with perforated appendicitis on admission receiving CT scans, we excluded patients with perforated appendicitis on initial CT scans and repeated the analyses. The difference in perforation rates continued to remain significant (*P* value 0.037) between patients undergoing CT scans and those in whom CT scans were not performed (result not shown in table). We next repeated the analysis in patients younger than 45 years of age. Patient who underwent CT scan continued to have significantly increased rate of perforation on final pathology (*P* value 0.01). This relationship continued to remain significant in analyses of only males younger than 45 years (*P* value 0.012).

CT Scan and Genders

Next, we repeated the above analyses by gender (Table 2). In both males and females, the median age again was significantly higher in the group that underwent CT scans. In males who underwent CT scans, the rate of perforated appendicitis as well as the length of stay was significantly higher than the group that did not. The difference in negative and positive appendectomy rates was however not significant. In a sensitivity analysis, we analyzed the difference in perforated appendicitis rate after excluding all males who were found to have perforated appendicitis on preoperative CT scans (result not shown in table). The difference in perforation rates persisted and continued to be significant (66% in CT scan versus 34% in no CT scan group, *P* value 0.02). On the other hand, in females who underwent CT scans, the positive appendectomy rate was significantly higher and negative appendectomy rate was significantly lower compared to patients who did not undergo CT scan. The perforated appendicitis rates as well as the length of stay were not significantly different in the two groups among females. The difference in insurance status and the distance from the hospital continued to be nonsignificant for both genders. As noted in Fig. 1, our center had a higher perforated appendectomy rate in 2003 compared to the other years. To exclude the possibility that our results were explained by this year, we excluded all patients who underwent an appendectomy in 2003 and repeated the analyses. Our results were unchanged in the overall as well as the gender subanalyses.

Findings on CT Scan

Next, we analyzed the results of the admission CT scan on patients who were found to have perforated appendicitis on

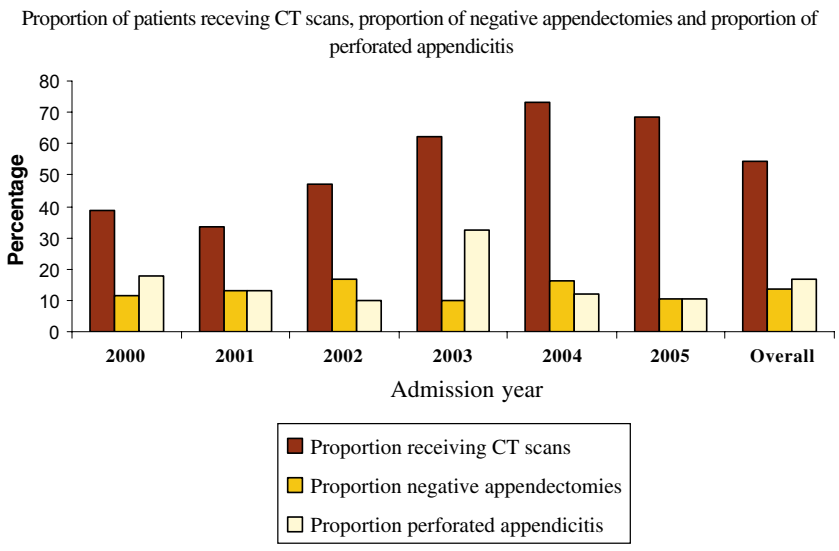

Figure 1 Figure showing the proportion of patients receiving CT scans on admission along with negative appendectomy rate and perforated appendicitis rate for all patients undergoing appendectomy by admission year.

Table 1 Summary of Selected Variables Based on Whether CT Scan Was Performed or Not

	Overall population	CT scan obtained	CT scan not obtained	*P* value
Total population (%)[a]	*N*=445	245 (55%)	200 (45%)	
Age				
≤15 years	96 (22)	36 (15)	60 (30)	
15–45 years	225 (51)	116 (47)	109 (54.5)	
>45 years	124 (27)	93 (38)	31 (15.5)	<0.001[b]
Median age (years)	29	38	22	<0.001[c]
Gender				
Male	255 (57)	135 (55)	120 (60)	
Female	190 (43)	110 (45)	80 (40)	0.299
Insurance				
Self-pay or Medicaid	98 (24)	58 (24)	40 (20)	
Other insurance	347 (76)	187 (76)	160 (80)	0.354
Mean distance from hospital in miles	35	40	30.4	0.45
Mean length of stay (days)	2.8	3	2	0.009
Type of procedure				
Open	167 (38)	90 (37)	77 (40)	0.577
Laparoscopic	271 (62)	154 (63)	117 (60)	0.23
Final pathology				
Negative appendectomy	62 (14)	24 (8)	38 (18)	0.003
Positive appendectomy including perforated	378 (69)	220 (74)	158 (73)	0.004
Perforated appendicitis	74 (17)	54 (18)	20 (9)	0.001

[a] All percentages are column percentages

[b] *P* value for a two-tailed test of difference of row between the CT scan obtained and the CT scan not obtained groups in the proportion reporting each event

[c] *P* value for difference in means between the CT scan obtained and the CT scan not obtained group using the Wilcoxon rank-sum test

final pathology (Table 3). Preoperative CT scans were obtained in 54 of the total 73 patients finally found to have perforated appendicitis. Of these patients, 94% had evidence of acute appendicitis; 35% showed findings suggestive of perforation and 24% revealed abscess formation on the initial CT scan. The initial CT scan revealed a normal appendix in 6% of patients.

Discussion

The utilization of CT scans in the evaluation of patients with suspected appendicitis has more than tripled over the past decade.[21,22] A similar trend was observed at this hospital in that almost 75% of all patients undergoing an appendectomy in 2004 had a preoperative CT scan (Fig. 1). This trend is likely due to improvements in the sensitivity and specificity of CT imaging in the diagnosis of appendicitis.[23–25] In a recent paper, the routine use of CT scans in the evaluation of all patients with suspected appendicitis was shown to reduce the overall use of hospital resources.[6] However, other papers have supported the conventional view that acute appendicitis is primarily a clinical diagnosis and have found that the routine use of CT scans might increase the utilization of hospital resources.[14,21,26,27] In large population-based studies and smaller analyses of hospitalized patients, no change in negative appendectomy rate has been shown after CT scans became widely used.[11,28] Other papers have shown that obtaining CT scans increases the in-hospital delay in the treatment of acute appendicitis.[14,15] The reason for these contrasting results is not clear but may reflect different clinical practices and diversity of patient population. Thus, the data regarding the usefulness of CT scans in the evaluation of patients with acute right lower-quadrant pain remain unclear, especially in patients with a high pretest probability of having appendicitis, such as young males.

The results of the present study show that the patients were more likely to have perforated appendicitis if their preoperative evaluation included a CT scan. To explain this finding, we considered that patients with perforated appendicitis were more likely to present with atypical symptoms and, therefore, be more likely to have a CT scan as part of their initial evaluation. However, when patients

Table 2 Summary of Selected Variables Based on Gender and Whether Preoperative CT Scan Was Obtained or Not

	Males			Females		
	CT scan obtained	CT scan not obtained	*P* value	CT scan obtained	CT scan not obtained	*P* value
Total population (%)[a]	135 (53)	120 (47)		110 (58)	80 (42)	
Age						
≤15 years	22 (17)	37 (31)		14 (13)	23 (29)	
15–45 years	58 (47)	67 (55)		58 (53)	42 (53)	
>45 years	53 (36)	18 (14)	<0.0001	38 (34)	15 (18)	0.003[b]
Median age	41	20	0.00	25	35	0.002[c]
Insurance						
Medicaid/self-pay	27 (44)	34 (56)		13 (12)	24 (30)	
Other	108 (56)	86 (44)	0.609	97 (88)	56 (70)	0.355
Mean distance from the hospital (miles)	32	37	0.4083	52	22	0.157
Mean length of stay (days)	3.7	2.2	0.0004	2.6	2.2	0.278
Type of procedure						
Open	55 (41)	53 (44)	0.6154	35 (32)	24 (32)	0.979
Laparoscopic	79 (59)	67 (56)	0.6154	75 (68)	50 (68)	0.829
Final pathology						
Negative	9 (5)	15 (12)	0.1106	15 (12)	23 (28)	0.007
Positive	125 (74)	104 (78)	0.17	95 (74)	54 (65)	0.007
Perforated	36 (21)	14 (10)	0.004	18 (14)	6 (7)	0.08

[a] All percentages are column percentages

[b] *P* value for a two-tailed test of difference between two groups in the proportion reporting each event

[c] *P* value for difference in means between the CT scan obtained and the CT scan not obtained using Wilcoxon rank-sum test

with perforated appendicitis on preoperative CT were excluded from the analysis, we continued to find that patients were more likely to have perforated appendicitis if their preoperative evaluation included a CT scan. We also considered that age may have contributed to this finding since the group that underwent CT scans was also significantly older than the other group and it is known that older patients have higher perforation rates.[29,30] However, we also noted that perforation was more likely in young males (less than 45 years old) who had CT scans. It is interesting to note that preoperative CT diagnosed perforated appendicitis in only 35% of patients ultimately found to have perforated appendicitis on final pathology (Table 3). This is consistent with other studies which have found that CT scans may have a low sensitivity and specificity for the diagnosis of acute appendicitis.[20] In various studies, the presence of extraluminal gas, severe periappendiceal stranding, periappendiceal fluid collection, or abscess has been suggested to be a marker for perforated appendicitis.[20,31,32] Whether our finding is also attributable to the low sensitivity of CT scans in the study period analyzed or to the inherent delay in treatment associated with CT scans remains an open question. Multiple factors may thus have contributed to the higher rate of perforation in the group of patients that underwent preoperative CT scans in this study.

Table 3 Summary of the Findings on the Preoperative CT Scan for Patients Found to Have Perforated Appendicitis on Final Pathology

Total population with perforated appendicitis (percentage of total population)	73 (17%)
Preoperative CT scan obtained (percentage of total with perforation)	54 (73%)
Findings on CT Scan (percentage of total with CT scan)	
Acute appendicitis without perforation or abscess formation	32 (59%)
Perforation without abscess formation	6 (11%)
Perforation with abscess formation	13 (24%)
Normal appendix	3 (6%)

This study also found differences in outcomes based on gender. The diagnosis of acute appendicitis is usually straightforward in young males.[33] However, in females and older adults, the diagnosis can be more challenging. In this study, females undergoing preoperative CT scans had a lower rate of negative appendectomy and perforation as compared to those not having CT scans done. The higher negative appendectomy rate in females not undergoing CT scans may be due to a higher likelihood of other causes of right lower-quadrant pain in females and the inability to differentiate these solely based on clinical exam. Males who undergo CT scans have a higher rate of perforated appendicitis with no significant difference in negative or positive appendectomy rate. This finding is true even when only males younger than 45 years of age were analyzed separately. The reason for this finding is unclear. It is possible that males who present early are diagnosed solely on clinical grounds and undergo appendectomy without preoperative CT scan. Alternatively, males with perforated appendicitis may present with atypical symptoms that are more likely to be evaluated with CT scan. This practice would tend to increase the proportion of patients with perforated appendicitis in the CT group. Females on the other hand may undergo CT scans more uniformly irrespective of symptom complex on presentation. Regardless, based on our results, it appears that the benefit of CT scans in males may be limited even with regard to negative appendectomy rate. Currently, there is no evidence to suggest that the progression of acute appendicitis is different in males compared to females.

This study also brings out interesting differences and similarities between urban and rural population presenting with acute appendicitis. Robert Packer Hospital is located in Sayre, PA, USA with a population of about 5,500 and outside urbanized areas as defined by the US Census Bureau in 2000.[34] Although Robert Packer Hospital is a tertiary referral hospital serving a large geographic region that includes urbanized areas, patients with acute appendicitis are generally cared for in local hospitals within those urbanized areas. In an effort to define our rural population, we analyzed a number of demographic and clinical factors. In this study, we found that median age, insurance status, and rates of negative appendectomy and perforated appendicitis were similar to other studies of appendicitis in urban populations.[35–37] Our study population was mostly White Americans as compared to urban centers where the population includes a higher percentage of minority groups. We also found that the ratio of males to females in our population was higher than urban population.[10] In our study, patients lived an average of 35 miles from the hospital. We did not find any recent paper providing distance from the hospital. With regard to CT utilization, there was no difference in insurance status in those patients that had preoperative CT scans and those that did not. Although papers from urban populations have shown a difference in perforation rates based on insurance status,[38,39] we could not find a recent paper comparing CT scan utilization based on insurance status.

One of the main weaknesses of this paper is the retrospective nature of the analyses and the limited definition of the study population to include only those patients undergoing appendectomy. Therefore, the value of CT in avoiding operation cannot be accurately assessed. Additionally, the study may not accurately reflect the sensitivity and specificity of current and future CT technology. Future studies might concentrate on whether protocol-based management of patients presenting to rural centers with right lower-quadrant pain may decrease perforation rates in patients undergoing CT scans. Such a protocol might involve a surgical consultation prior to CT scan in male patients under the age of 45 with suspected appendicitis. If the surgical consultant has a high degree of suspicion for acute appendicitis, surgery would be performed without a CT scan. All females with suspected appendicitis will be evaluated with a CT scan.

Conclusion

In this retrospective study of patients undergoing appendectomies at Robert Packer Hospital from January 2000 to June 2005, the clinical and demographic factors analyzed in this study suggest that the outcomes of acute appendicitis is similar in rural and urban populations. Males undergoing CT scans on admission were found to have a significantly higher rate of perforated appendicitis. In contrast, females undergoing CT scans had a favorable negative appendectomy rate without increased perforation rate. Overall, the difference in perforation rate on final pathology continued to remain significant even after exclusion of patients with perforated appendicitis seen on the admission CT scan. A protocol-driven approach to CT evaluation of suspected appendicitis may lower perforation rates, especially in males.

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2008 SSAT QUICKSHOT PRESENTATION

Is Liver Resection Justified in Advanced Hepatocellular Carcinoma? Results of an Observational Study in 464 Patients

Andrea Ruzzenente · Franco Capra · Silvia Pachera · Calogero Iacono · Gianluca Piccirillo · Marta Lunardi · Stefano Pistoso · Alessandro Valdegamberi · Mirko D'Onofrio · Alfredo Guglielmi

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Abstract
Background and Objective The role of liver resection in advanced hepatocellular carcinoma (multinodular or with macroscopic vascular involvement) is still controversial. The aim of this study is to evaluate the role of surgical resection compared to other therapeutic modalities in patients with advanced hepatocellular carcinoma (HCC).
Methods Four hundred sixty four patients with HCC observed from 1991 to 2007 were included in the study. All the patients were evaluated for the treatment of HCC in relation to the severity of liver impairment and tumor stage. All the patients included in the study had no evidence of distant metastases.
Results Median follow up time for surviving patients was 25 months (range 1–155). Two-hundred and eighty-three patients were in Child–Pugh class A, 161 in class B, and 20 in class C. Two-hundred and seventy-one patients had single HCC, 121 patients had two or three HCCs, and 72 more than three HCCs. One-hundred and thirty-six patients (29.3%) were submitted to liver resection (LR), 232 (50.0%) to local ablative therapies (LAT) (ethanol injection, radiofrequency ablation, chemoembolization), eight (1.7%) to liver transplantation (LT), and 88 (19%) to supportive therapy (ST). Median survival time for all patients was 36 months (95% CI 24–36). Median survival time was 57 months for LR, 30 months for LAT, and 8 months for ST, with a 5-year survival of 47%, 20%, and 2.5%, respectively (p=0.001). Actuarial 5-year survival for patients submitted to LT was 75%. Overall survival was significantly shorter in patients with multiple HCCs compared to single HCC, with median survival times of 39, 16, and 11 months for patients with a single HCC, with two to three HCCs, and with more than three HCCs, respectively (p=0.01). Survival for patients with single HCC was significantly longer in patients submitted to LR compared to LAT and ST with median survival times of 57, 37, and 14 months, respectively

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A. Ruzzenente (✉) · S. Pachera · C. Iacono · G. Piccirillo · A. Valdegamberi · A. Guglielmi
Department of Surgery and Gastroenterology,
Division of General Surgery "A", GB Rossi University Hospital,
University of Verona Medical School,
Piazzale LA Scuro 10,
37134 Verona, Italy
e-mail: andrea.ruzzenente@fastwebnet.it

F. Capra · M. Lunardi
Department of Biomedical and Surgical Science,
University of Verona Medical School,
Verona, Italy

S. Pistoso
Department of Internal Medicine,
Desenzano Hospital,
Desenzano, Italy

M. D'Onofrio
Department of Radiology,
University of Verona Medical School,
Verona, Italy

(p=0.02). Also, in patients with multinodular HCCs (2–3 HCCs) LR showed the best results with a median survival time of 58 months compared to 22 and 8 months for LAT and ST (p=0.01). In patients with more than three HCCs, LR did not show different results compared to LAT and ST. Seventy-three patients had evidence of macroscopic vascular involvement; median survival in this subgroup of patients was significantly shorter compared to patients without vascular involvement, 10 and 36 months, respectively. Survival for patients with macroscopic vascular involvement submitted to LR or LAT was significant longer compared to ST, with mean survivals of 27, 30, and 12 months, respectively (p=0.01).
Conclusions The present study shows that the surgery can achieve good results in patients with single HCC and good liver function. Also, patients with multinodular HCCs (two to three nodules) *could* benefit from LR where survival is longer than after LAT or ST. In patients with more than three HCCs, LR have similar results of LAT. Macroscopic vascular invasion is a major prognostic factor, and the LR is justified in selected patients, where it can allow good long-term results compared to ST.

Keywords Hepatocellular carcinoma · Liver surgery · Local ablative therapy

Introduction

Hepatocellular carcinoma (HCC) is a common cancer worldwide and is the third most common cause of cancer-related deaths.[1] The choice upon different types of treatment depends on tumor stage and the functional status of the liver.[2] Liver resection (LR) and liver transplantation (LT) are considered the mainstay of curative therapy, although application of LT is limited by the shortage of organs.

Several local ablative therapies (percutaneous ethanol injection, radiofrequency ablation, microwave ablation, chemoembolization) have been proposed for patients with advanced HCC or severe liver impairment and showed benefits for long-term survival. In patients with multiple HCC or with macroscopic vascular involvement, the choice of treatment is still controversial, and LR is frequently contraindicated.[3,4]

Several authors have proposed hepatic resection in selected groups of patients for multiple HCC and with macroscopic vascular involvement demonstrating encouraging results.[5] The objective of this study is to evaluate the results of LR compared to local ablative therapies (LAT) and to best supportive therapy (ST) in different groups of cirrhotic patients with advanced HCCs (multinodular or with macroscopic vascular involvement).

Patients and Methods

In this study, we review data of a multi-institutional database that included four different departments (one surgical department, two departments of internal medicine, and one department of gastroenterology). This database comprises 464 patients with liver cirrhosis and HCC observed during the period from January 1991 to March 2007.

All patients had liver cirrhosis. The diagnosis of liver cirrhosis was made with biopsy or with clinical and laboratory criteria of chronic hepatic disease associated with portal hypertension. The diagnosis of HCC was made with cytological or histological criteria or with radiological criteria. From 2001 the diagnosis of HCC was based on concordance between two imaging techniques [ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI)] showing arterial hypervascularity in a focal lesion ≥2 cm or with the combined criteria of an imaging technique and a serum alpha-fetoprotein (AFP) level greater than 400 ng/ml, according to the criteria of the consensus conference of the European Association for Study of the Liver.[6] A fine-needle cytology was performed only in patients with an otherwise uncertain diagnosis.

Before treatment, all patients had serum liver function tests (bilirubin, alkaline phosphatase, transaminase, albumin, prothrombin time), blood count, and serum creatinine level. All patients were staged according to the Child–Pugh classification. The assessment of tumor stage was made with different imaging techniques: ultrasonography, contrast-enhanced CT, and contrast-enhanced MRI.

We reviewed patients' records for demographic variables (age, gender, etiology of liver cirrhosis), severity of liver cirrhosis (Child–Pugh class), and tumor stage (size, number, macroscopic vascular invasion and AFP). The patients were evaluated for different therapies (LT, LR, LAT, or ST) according to the degree of liver dysfunction and the stage of tumor. All the patients included into the study did not have extrahepatic metastasis.

LT was considered for patients within Milan criteria and for patients with absence of macroscopic vascular invasion or extrahepatic metastasis by imaging techniques.

LR was the treatment of choice for patients with single HCC and well preserved liver function (Child–Pugh A) without portal vein hypertension. Surgical resection was also applied in a selected group of patients with multiple HCCs or with Child–Pugh class B liver dysfunction.

During surgery, intraoperative ultrasonography was routinely used in order to confirm preoperative diagnosis, to evaluate relationship between tumor and blood vessel and to evaluate the presence of additional tumors.

LAT (radiofrequency ablation, ethanol injection, chemoembolization) were indicated for patients excluded from surgery with single or multiple HCCs with Child–Pugh A

and B liver cirrhosis. From 1991, percutaneous ethanol injection (PEI) was applied to lesions up to 3 cm, and from 1998, radiofrequency ablation (RFA) was introduced to treat lesions up to 6 cm. PEI and RFA were applied in patients with fewer than four nodules of HCCs. Chemoembolization (TACE) was indicated for patients excluded from surgical therapy and for patients with single or multiple HCCs and preserved liver function (Child–Pugh class A and B) without main portal vein thrombosis. TACE was also applied in selected patients in conjunction with other LAT (PEI, RFA). Patients excluded from other treatment due to severe liver dysfunction (Child–Pugh C class) or advanced tumor stage (multinodular, main portal vein thrombosis) were submitted to ST.

After treatment, all patients underwent regular follow up with serum AFP and ultrasonography every 6 months. Suspect recurrences were confirmed with CT or MRI. Chest CT or bone scan were performed in case of recurrence or of clinical suspect of distant metastases. All recurrences were evaluated for new treatment; the choice of the type of treatment was related to the number and size of tumors, the presence of extrahepatic disease, the liver function, and the general status of the patient.

Statistical Analysis

Data were collected and analyzed with SPSS statistical software (SPSS version 16.0, Chicago, IL, USA). The differences between categorical variables were analyzed with a chi-square test. The differences between continuous variables were analyzed with *t* test.

Survival analysis was carried out with Kaplan–Meier method; we considered the treatment day as time zero, and patients that were alive at the end of follow-up were considered censored.

Univariate analysis for survival was performed with the Kaplan–Meier method with the log rank test to verify significance of differences. Cox's regression model was utilized for multivariate analysis.

Table 1 Characteristics of Patients Included into the Study

Variable	*N*	Percent
Age		
≤70 years	269	58.0
>70 years	195	42.0
Gender		
Male	381	82.1
Female	83	17.9
Chronic liver disease etiology		
Alcohol	157	33.9
HCV	222	47.9
HBV	45	9.6
Others	40	8.7
Child–Pugh class		
A	283	61.0
B	161	34.7
C	20	4.2
Number of tumors		
Single	271	58.4
2–3 HCC	121	26.1
>3 HCC	72	15.5
Tumor size		
≤3 cm	184	39.7
3–5 cm	175	37.6
>5 cm	105	22.6
Serum AFP level		
≤100 ng/ml	357	77.0
>100 ng/ml	107	23.0
Macroscopic vascular involvement		
No	391	84.3
Yes	73	15.7
Therapy		
Liver transplantation	8	1.7
LR	136	29.3
RFA	128	27.6
PEI	29	6.2
TACE + RFA	36	7.8
TACE	39	8.4
Supportive therapy	88	19.0

Results

The clinical features of the 464 patients included in the study are reported in Table 1. There were 381 males and 83 females, for a male-to-female ratio of 4.6:1. The median patients' age was 68 years (range 28–90). The preoperative liver function according to Child–Pugh classification classified 283 patients in class A, 161 patients in class B, and 20 patients in class C. The liver cirrhosis was related to alcohol intake in 157 patients, to HCV infection in 222, to HBV infection in 45, and to other causes in 40. Tumors were single in 271 patients and multiple in 193. The mean number of tumors was 1.9 (range 1–5), with 121 patients with two to three tumors and 72 with more than three tumors. The mean tumor diameter was 4.3 cm (range 1.5–20 cm). The mean AFP level was 385 ng/ml (range 1–21,000), with 357 patients (77%) with AFP level lower than 100 ng/ml.

Among 464 patients, eight underwent LT (1.7%), 136 underwent LR (29.3%), 232 underwent LAT (50%), and 88 (19%) underwent ST. Among patients submitted to LAT, 29

Table 2 Univariate Analysis of Factors Related with Survival of Patients Included into the Study

	N	Median survival (range)	5-Year survival	Log rak test (*p*)
Number of tumors				0.01 (pooled)
Single	271	39 (34–43)	32	
2–3 nodules	121	29 (17–41)	16	
>3 nodules	72	11 (6–16)	15	
Etiology of chronic liver disease				0.7 (pooled)
Alcohol	157	35 (27–43)	22	
HCV	222	28 (19–36)	28	
HBV	45	30 (10–50)	0	
Other causes	40	24 (7–41)	30	
Child–Pugh class				0.01 (pooled)
A	283	40 (35–46)	32	
B	161	22 (15–28)	15	
C	20	8 (1–21)	0	
Tumor size				0.01 (pooled)
<=3 cm	184	43 (32–53)	38	
3–5 cm	175	28 (20–36)	19	
>5 cm	105	14 (7–21)	16	
Serum AFP level				0.01 (pooled)
<=100 ng/ml	357	41 (37–45)	30	
>100 ng/ml	107	20 (12–28)	8	
Macroscopic vascular involvement				0.01 (pooled)
No	391	36 (30–42)	28	
Yes	73	10 (5–15)	5	

patients underwent PEI, 128 underwent RFA, 39 underwent TACE, and 36 underwent TACE associated with RFA.

The survival analysis of the entire group of study identified a median survival time of 30 months, with actuarial 3-, 5-, and 10-year survivals of 46%, 25%, and 10%, respectively. The univariate analysis for factors related with survival identified that the number and the size of HCC, Child–Pugh class, serum AFP level, and presence of macroscopic vascular involvement were significantly related with shorter survival time (Table 2). Cox's multivariate regression model identified that survival-related factors were AFP level, type of therapy, and size and number of HCC, with hazard ratios of 1.73, 0.71, 1.40, and 1.29, respectively (Table 3).

The survival according to the type of treatment showed median survival times for patients submitted to LR, LAT, and ST of 57, 30, and 8 months and with 5-year actuarial survival rates of 47%, 20%, and 2.5%, respectively. Actuarial 5-year survival for patients submitted to LT was 75%. Patients submitted to LT were not included in further statistical analysis due to small sample size in this group.

The univariate analysis for prognostic factor for survival in patients submitted to LR identified that the number and the size of HCC, Child–Pugh class, and presence of macroscopic vascular involvement were significantly related with shorter survival time (Table 4). Cox's multivariate regression model identified that the presence of macroscopic vascular involvement was the most significant factor related with survival with a hazard ratio of 7.1.

During the follow up, 223 patients that submitted to LR or LAT showed recurrence of the HCC; the median disease-free survival was 16 months, with actuarial 3- and 5-year disease-free survival rates of 30% and 15%. The recurrence rate was significantly different among patients submitted to LR and LAT, with 5-year disease-free survivals of 22% and 12%, respectively ($p<0.001$).

Subgroup Analysis

Further survival analyses among different categories are reported in Table 5. In patients with well preserved liver function (Child–Pugh A) and single HCC, LR showed the best results compared to LAT or ST, with median survival times of 63, 41, and 4 months, respectively ($p=0.01$). In patients with single HCC and Child Pugh B cirrhosis, LR and LAT did not show significant differences, with median survival times of 24 and 30 months, respectively.

Patients with multiple HCCs (two to three HCCs) submitted to LR showed a longer survival compared to LAT and ST, with median survival times of 58, 22, and 8 months, respectively ($p=0.01$). In patients with more than three HCCs, the results of LR and LAT did not show significant differences.

In the study group, 73 patients showed macroscopic vascular involvement at preoperative imaging. Among these patients, 17 were submitted to LR, 17 to LAT, and 39 to ST. Macroscopic vascular involvement was a negative

Table 3 Multivariate Cox's Model for Factors Related with Survival of Patients Included into the Study

Variable	HR	*p* Value	95% CI for HR
AFP (>100 ng/ml vs <100 ng/ml)	1.737	0.005	1.182–2.553
Size (>5 cm vs 3–5 cm vs <3 cm)	1.402	0.002	1.134–1.734
Number (>3 vs 2–3 HCC vs single)	1.296	0.020	1.043–1.611
Therapy (LR vs LAT vs ST)	0.719	0.001	0.626–0.826

Table 4 Univariate Analysis of Factors Related with Survival of Patients Submitted to LR

	N	Median survival (range)	5-Year survival	Log rak test (*p*)
Number of tumors				0.01 (pooled)
Single	100	57 (39–75)	49	
2–3 nodules	30	58 (–)	46	
>3 nodules	6	10 (3–3.5)	0	
Etiology of chronic liver disease				0.7 (pooled)
Alcohol	37	56 (17–95)	34	
HCV	67	64 (57–71)	55	
HBV	16	55 (4–98)	0	
Other causes	16	64 (14–113)	55	
Child–Pugh class				0.01 (pooled)
A	107	60 (52–68)	53	
B	29	24 (12–36)	25	
Tumor size				0.01 (pooled)
<=3 cm	44	65 (30–100)	64	
3–5 cm	46	60 (34–86)	52	
>5 cm	46	32 (1–63)	29	
Serum AFP level				0.19 (pooled)
<=100 ng/ml	113	64 (53–75)	52	
>100 ng/ml	13	35 (1–68)	44	
Macroscopic vascular involvement				0.01 (pooled)
No	119	63 (31–94)	54	
Yes	17	10 (4–16)	20	

prognostic factor with a 5-year survival of 5% compare to 28% for patients without macroscopic vascular involvement. Survival analysis showed no differences in survival between LR and LAT, whereas we identified a significantly longer survival for patients submitted to LR compared to ST, with median survival times of 10 and 7, respectively (p=0.05).

Discussion

HCC is the most common primary liver cancer and is the most severe complication of chronic liver diseases.[7] The prognosis is poor even after potentially curative treatments, with a 5-year survival rate of 47% and a 5-year recurrence rate of 80%, respectively.[8]

A peculiar feature of HCC is that several therapeutic approaches (liver transplantation, surgical resection, LAT, chemoembolization) can be chosen in relation to the stage of disease and severity of liver impairment. Liver transplantation is indicated for early HCC in order to treat both the neoplastic disease and the liver impairment.[9] The Milan criteria are widely accepted for liver transplantation in patients with HCC, and when these criteria are fulfilled, 5-year survival reaches 60–80%, with a recurrence rate lower than 20%.[10]

The local ablative treatments (PEI and RFA) are widespread and allow good results, with 3-year survivals of 83% in Child–Pugh A cirrhotic patients and 31% in Child–Pugh B patients.[11]

The TACE is indicated for patients with multifocal, asymptomatic liver tumor, with a Child A–B liver function, without extrahepatic spread.[7] After TACE, a significant tumor response is achieved in 17–61.9%, but a complete tumor response is rare (0%–4.8%); however, significant improvement in long-term survival had been demonstrated in meta-analysis studies.[12,13]

Resective surgery with curative intent is applied for early HCC in patients with well preserved liver function. However, only less than 30% of patients can be submitted to surgery for the advanced stage of tumor or severe liver function impairment. According to literature, surgery can achieve the best results in patients with a single nodule, smaller than 5 cm, without vascular invasion in patients with compensated liver cirrhosis (class A according to the Child–Pugh classification) and without portal hypertension. In these patients, the 5-year survival can reach 70%, but the major issue of surgical treatment of HCC is sill the high recurrence rate (80–100% after 5 years).[14]

The role of resective surgery in patients with advanced HCC (large, multifocal, or with macroscopic vascular invasion) is still under debate, and few studies in literature analyze the long-term results of surgery in these patients.[4,15–17]

In the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan, 27,062 patients submitted to hepatic resection for HCC in the period from 1992 to 2003 were followed up. The 5-year survival rate was 59.2% for patients with a single HCC, 46.4% for patients with two nodules, and 30.0% for patients with three nodules.[8]

In a multi-institutional study, 308 patients with large (more than 3 cm) or multiple HCC (more than three nodules) were compared to 404 patients with small HCC. This study reported a 5-year survival of 26% for advanced HCC compared to 39% for early HCC.[5] A recent study of by Ishizawa et al. in 434 patients who underwent to LR for single or multiple HCC (more than two nodules) reported a 5-year survival of 58% for Child A patients with multiple nodules, compared to 68% for Child A patients with a single nodule (p=0.035).[18] In Child B patients, 5-year survival decreased to 19% for patients with multiple nodules compared to 45% for patients with a single nodule (p=0.13).[18] Patients with HCC with multiple tumors in both hepatic lobes (TNM stage IVa) are generally considered unsuitable for surgery. However, recent data of the literature showed a significant improvement in survival after resective surgery

Table 5 Univariate Analysis for Factors Related with Survival According to the Stage of HCC, Severity of Liver Cirrhosis and Type of Treatment

	N	Median survival in months	5-Year survival %	Log rank test (*p* value)
Overall				0.01 (pooled)
LR	136	57 (43–71)	47	
LAT	232	30 (24–37)	20	LR vs LAT 0.01
ST	88	8 (7–9)	2.5	LR vs ST 0.01
Child–Pugh A				0.01 (pooled)
LR	107	60 (52–68)	53	
LAT	151	37 (31–44)	22	LR vs LAT 0.01
ST	33	7 (4–10)	7	LR vs ST 0.01
Child–Pugh B				0.01 (pooled)
LR	29	24 (12–36)	25	
LAT	81	28 (21–35)	22	LR vs LAT 0.8
ST	55	8 (6–10)	0	LR vs ST 0.01
Single HCC				0.02 (pooled)
LR	100	57 (39–75)	49	
LAT	135	37 (31–44)	22	LR vs LAT 0.05
ST	32	14 (6–22)	4	LR vs ST 0.01
Single HCC and Child–Pugh A				0.01 (pooled)
LR	78	63 (34–64)	54	
LAT	85	41 (34–48)	23	LR vs LAT 0.05
ST	11	4 (0–12)	18	LR vs ST 0.01
Single HCC and Child–Pugh B				0.05 (pooled)
LR	22	24 (−)	29	
LAT	50	30 (−)	27	LR vs LAT 0.82
ST	21	14 (−)	0	LR vs ST 0.05
2–3 HCC				0.01 (pooled)
LR	30	58 (−)	46	
LAT	71	22 (16–28)	10	LR vs LAT 0.01
ST	16	8 (1–18)	0	LR vs ST 0.01
2–3 HCC and Child–Pugh A				0.01 (pooled)
LR	23	58 (−)	48	
LAT	49	22 (−)	6	LR vs LAT 0.01
ST	9	13 (−)	0	LR vs ST 0.01
2–3 HCC and Child–Pugh B				0.36 (pooled)
LR	7	15 (0–36)	20	
LAT	22	24 (3–46)	16	LR vs LAT 0.84
ST	7	15 (4–26)	–	LR vs ST 0.62
>3 HCC				0.01 (pooled)
LR	6	10 (3–16)	–	
LAT	26	29 (14–45)	32	LR vs LAT 0.01
ST	40	8 (3–15)	–	LR vs ST 0.94
>3 HCC and Child–Pugh A				0.01 (pooled)
LR	6	10 (3–16)	–	
LAT	17	40 (−)	38	LR vs LAT 0.01
ST	13	7 (−)	–	LR vs ST 0.64
>3 HCC and Child–Pugh B				0.17 (pooled)
LR	0	–	–	
LAT	9	15 (0–36)	22	LR vs LAT-
ST	27	7 (3–12)	0	LR vs ST-

Table 5 (continued)

	N	Median survival in months	5-Year survival %	Log rank test (*p* value)
No macroscopic vascular involvement				0.01 (pooled)
LR	119	63 (31–94)	54	
LAT	215	32 (26–39)	20	LR vs LAT 0.01
ST	49	8 (2–14)	5	LR vs ST 0.01
Macroscopic vascular involvement				0.01 (pooled)
LR	17	10 (4–10)	20	
LAT	17	29 (13–46)	–	LR vs LAT 0.46
ST	39	7 (4–10)	0	LR vs ST 0.05

LR liver resection, *LAT* local ablative therapies, *ST* best supportive therapy

compared to nonsurgical treatments, with median survivals of 19.5 and 7.1 months, respectively (p=0.08).[19]

In our study, we analyzed a large group (464 patients) of cirrhotic patients with HCC, who underwent different therapeutic approaches in relation to the tumor stage and degree of liver impairment. The major limitation of our study is its retrospective design that implies biases of selection of patients, although the large number of patients included in the study and the subgroup analyses of patients with different tumor and liver function stages should lower the impact of these limitations. Our data confirm the good results of LR in patients with single HCC and class Child–Pugh A cirrhosis with 5-year survival of 54%. Even in patients with two or three nodules, the LR shows good performance compared to LAT or ST with actuarial 5-year survival of 46%, 10%, and 0%, respectively. In patients with more than three nodules, the LR decreases their efficacy and it is probably not justified. According to our study, surgical resection in patients with well preserved liver function and single or oligonodular HCC (two to three nodules) seem to have superior results compared to other therapies, and the presence of multiple HCC (up to three nodules) should not be considered an absolute contraindication to surgical resection.

The presence of macroscopic vascular invasion is an important prognostic factor in patients affected by HCC. The median of survival in patients with macroscopic vascular involvement without treatment is very poor: about 10 weeks.[20,21] The choice of the best treatment for these patients is still under debate. Nonsurgical treatments such as TACE or RFA give a 1-year overall survival of 14%.[22] Transplantation is contraindicated because of a high frequency of recurrences and short survival. Also, surgical resection in patients with macroscopic vascular invasion is contraindicated in the majority of patients, and few data in literature report long-term results in these patients. Poon et al., in a retrospective analysis, showed a 5-year prognosis of 13% in patients with macroscopic vascular invasion.[23] Chen et al. reported a median survival of patients with portal vein tumor thrombosis located in the hepatic resection area or in the first division branch of the portal vein of 18.8 months.[4] The author showed a reduction in survival, 10.1 months, in patients who underwent to thrombectomy of main portal vein tumor thrombus (p=0.0275). Minigawa et al. proposed a combined therapeutic approach with preoperative TACE, obtaining a 5-year survival of 42% in 18 patients with no more than two nodules HCC and macroscopic portal invasion with a good liver function.[24] Also, Fan et al. reported that surgical resection associated with thrombectomy followed by adjuvant TACE has better results than TACE alone, with median survivals of 12 and 5 months, respectively, with an actuarial 5-year survival of 16.6% in patients undergoing surgical resection followed by TACE vs 0% in patients undergoing only TACE.[25]

In our study, we confirmed the prognostic significance of macroscopic vascular involvement. Less than 25% of patients with macroscopic vascular involvement were submitted to LR. In this group, survival was not significantly different from patients submitted to LAT with actuarial 3-year survival of 40% and 47%, respectively (p=0.46). However, survival after LR and LAT was significantly longer than in patients submitted to ST who showed actuarial 3-year survival of 10%. Our results suggest that, even if the prognosis of patients with macroscopic vascular involvement is very poor, the presence of macroscopic vascular invasion should not considered an absolute contraindication to surgery because LR in selected cases can improve survival compared to ST.

Conclusions

The present study shows that the surgery can achieve good results in patients with single HCC and good liver function. Also, patients with multinodular HCCs (two to three nodules) could benefit from LR where survival is longer

than after LAT or ST, whereas, in patients with more than three HCCs, LR have results similar to those of LAT. Macroscopic vascular invasion is a major prognostic factor, and LR can be applied in highly selected patients, where it can allow good long-term results compared to ST.

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ORIGINAL ARTICLE

Predictive Factors for Exocrine Pancreatic Insufficiency After Pancreatoduodenectomy with Pancreaticogastrostomy

Hiroyuki Nakamura · Yoshiaki Murakami · Kenichiro Uemura · Yasuo Hayashidani · Takeshi Sudo · Hiroki Ohge · Taijiro Sueda

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Abstract
Introduction The aim of this study was to determine risk factors for exocrine pancreatic insufficiency after pancreatoduodenectomy (PD) with pancreaticogastrostomy (PG).
Material and Methods A ^{13}C-labeled mixed triglyceride breath test was performed in 61 patients after PD to assess exocrine pancreatic function. Percent $^{13}CO_2$ cumulative dose at 7 h <5% was considered diagnostic of exocrine pancreatic insufficiency. Abdominal computed tomography scans were utilized to assess the dilatation of the main pancreatic duct (MPD dilatation) in the remnant.
Results Thirty-eight of 61 patients (62.3%) were diagnosed with exocrine pancreatic insufficiency. Univariate analysis identified significant associations between two preoperative factors (preoperative impaired endocrine function and a hard pancreatic texture induced by preexisting obstructive pancreatitis), plus one postoperative factor (MPD dilatation caused by PG stricture) and exocrine pancreatic insufficiency ($P<0.05$). Multivariate analysis determined that all three of these factors were independent factors ($P<0.05$).
Conclusions Although exocrine pancreatic insufficiency after PD may be partly explainable by preexisting obstructive pancreatitis prior to surgery, surgeons desiring to obtain better postoperative exocrine pancreatic function after PD would be well-advised to devote considerable attention to preventing PG stricture.

Keywords Pancreatoduodenectomy · ^{13}C-labeled mixed triglyceride breath test · Postoperative exocrine pancreatic insufficiency · Risk factors · Multivariate analysis

Introduction

Pancreatoduodenectomy (PD), including both pylorus-preserving pancreatoduodenectomy (PPPD) and the classic Whipple procedure, has been established as a safe surgical technique and a standard operation for malignant and benign diseases in pancreatic and periampullary regions. The extensive resection of organs and reconstruction of the alimentary tract associated with PD lead to *inhibition* of pancreatic function in most patients.[1] Since impaired exocrine pancreatic function can often lead to malnutrition, maldigestion, and steatorrhea, evaluation of postoperative exocrine pancreatic function is important to ensure proper nutritional management of patients after PD and to quantify the effects of pancreatic enzyme supplementation.

Evaluation of exocrine pancreatic function typically requires duodenal intubation and aspiration of contents after stimulation of pancreatic secretory activity, or collection of feces to measure the amount of fat and/or enzymes.[2] Although direct measurements of pancreatic function are the gold standard for evaluating exocrine function, they are invasive, time consuming, and expensive.[3] Fecal fat determination has not been well accepted by either doctors or patients because these measurements are complicated procedures that have poor sensitivity and are unpleasant to repeat.[4] Although measurements of fecal enzymes, such as the fecal chymotrypsin[5] or fecal elastase-1 tests,[6] are noninvasive and have been reported to have a high sensitivity and specificity,

H. Nakamura (✉) · Y. Murakami · K. Uemura · Y. Hayashidani · T. Sudo · H. Ohge · T. Sueda
Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: hsurgeon1017@aioros.ocn.ne.jp

several external factors can affect the accuracy of these measurement. For instance, the fecal water content influences the fecal enzyme concentration, and nonpancreatogenic diarrhea can result in falsely decreased fecal enzyme levels.[7]

We recently reported finding a significant correlation between fecal elastese-1 concentration and 7-h cumulative $^{13}CO_2$ excretion in breath (percent $^{13}CO_2$ cumulative dose at 7 h) after oral administration of a nonradioactive ^{13}C-labeled mixed triglyceride.[8] Although identification of the associated risk factors is critical to predicting postoperative exocrine pancreatic insufficiency, to our knowledge, few published studies have performed such a risk factor analysis of exocrine pancreatic insufficiency after PD. The aim of this study was to assess exocrine pancreatic function after PD with the ^{13}C-labeled mixed triglyceride breath test and to determine the risk factors for exocrine pancreatic insufficiency after PD with duct-to-mucosa pancreaticogastrostomy.

Material and Methods

Study Design

We evaluated 61 patients (37 men and 24 women; mean age 67.5 years, range 43–84 years) who had previously undergone PD and reconstruction by duct-to-mucosa PG at Hiroshima University Hospital between April 1998 and June 2008. During this study period, 177 similar procedures were performed for various indications by a single team of experienced hepatobiliary–pancreatic surgeons. Patients were excluded from this study for the following reasons: clinical evidence of tumor recurrence, evidence of biliary stricture, loss to follow-up, death, or refusal to participate. Appropriate informed consent was obtained from patients, and study approval was granted by the ethical committee of Hiroshima University. The median interval between surgery and evaluation was 17 months (range 3–108 months).

The following factors with the potential to affect the incidence of postoperative exocrine pancreatic insufficiency were analyzed: general factors (age and gender distribution), preoperative factors (preoperative endocrine pancreatic function, preoperative diameter of the main pancreatic duct, pathological diagnosis, and pancreatic texture), intraoperative factors (operative procedure, type of reconstruction, and stenting tube through the pancreatic anastomosis), and postoperative factors (follow-up period, pancreatic fistula, bile leakage, postoperative dilatation of the main pancreatic duct, and postoperative endocrine pancreatic function).

Surgical Procedures

For most patients, pylorus-preserving pancreatoduodenectomy[9–11] was performed. If the tumor was close to the duodenal bulb in the superior pancreatic head, PD with anterectomy was performed. Regional lymphadenectomy was performed depending on the grade of malignancy. To prevent severe postoperative diarrhea, dissection of the nerve plexus around the superior mesenteric artery was not performed in any patient. After pancreatoduodenal resection with or without preservation of the pylorus, the pancreatic stump was dissected from the superior mesenteric vein and splenic vein for a distance of 2 cm. PG was performed using the duct-to-mucosa method. The pancreatic juice was either drained externally or rerouted internally into the stomach via a pancreaticogastric stent. This stent typically migrated spontaneously within 1 to 2 months after surgery. After pancreatic reconstruction, an end-to-side hepaticojejunostomy was performed in conjunction with either an end-to-side or end-to-end duodenojejunostomy in PPPD or a gastrojejunostomy in PD with anterectomy to restore biliary enteric continuity through a retrocolic Billroth I or an antecolic Roux-en Y type reconstruction.

Evaluation of Exocrine Pancreatic Function After Pancreatoduodenectomy

A description of the ^{13}C-labeled mixed triglyceride breath test has been previously published.[8] The breath test was analyzed in all 61 patients, and all patients could tolerate a normal solid diet. In brief, oral pancreatic enzyme substitution was stopped 4 days before the day of the breath test. The test meal consisted of 90 g of toast with 15 g of margarine, 200 ml of milk, and 200 mg of ^{13}C-labeled mixed triglyceride consisted of naturally occurring long-chain fatty acids (Chlorella Industry Co., LTD, Tokyo, Japan). This ^{13}C substrate, an algal product with uniformly ^{13}C-labeled mixed triglyceride derived from $^{13}CO_2$ as the sole atmospheric carbon source for the assimilation process, is 97.3% uniformly labeled, thereby facilitating the use of small tracer doses to generate detectable amounts of $^{13}CO_2$ in the subject' breath. All subjects were studied under resting conditions after an overnight fast of at least 12 h. Basal breath samples (retention volume 1,300 ml) were obtained before the meals from the subjects, who breathed into a specially designed collection bag, supplied by Otsuka Pharmaceutical. Postprandial breath samples were collected by subjects breathing into another collection bag every hour after the meal for 7 h (retention volume 250 ml per hourly sample). Enrichment of $^{13}CO_2/^{12}CO_2$ in collected breath samples was measured by infrared spectrophotometry using POCone (Otuka Electronics), and results were expressed in accordance with the Pee Dee Belemnite international standard, as described previously.[12,13] Measurements were also made of the parts per thousand excess of $\delta^{13}CO_2$ ($\Delta^{13}CO_2$). The $\Delta^{13}CO_2$ values were converted to percent-

age ^{13}C recovery of the initial amount administrated per hour per body surface area, following the calculation method described in detail by Ghoos et al.[14] Cumulative excretions were calculated from the time course of $^{13}CO_2$ excretion and expressed as the percent $^{13}CO_2$ cumulative dose at 7 h (%CD-7 h).

Definitions

The %CD-7 h values less than 5% were considered diagnostic of exocrine pancreatic insufficiency.[8] The pancreatic parenchyma was classified as having either a soft texture *or* a hard texture based upon intraoperative impressions of the texture of the remnant pancreas and upon postoperative pathological examination of the pancreatic cut margins.[9]

Serum levels of hemoglobin A_{1c} (HbA_{1c}) were determined preoperatively and very close to the time of the breath test to assess endocrine pancreatic function. Impaired endocrine pancreatic function was diagnosed in patients whose serum levels of HbA_{1c} exceeded 6.5% or in patients who required initiation of diabetic treatment (oral hypoglycemic agent or insulin).[15]

A pancreatic fistula was defined either as a radiographically documented communication between the placed drain and the gastric lumen or was inferred by the collection of more than 1,000 U/l of amylase-rich fluid through the placed drain on the fifth postoperative day.[16–18] A bile leakage was defined as persistence of biliary drainage for more than 5 days, confirmed by fistulography.[17]

We compared abdominal computed tomography (CT) scans obtained preoperatively with later CT scans obtained very close to the time of the breath test to assess whether the patient had the dilatation of the main pancreatic duct (MPD dilatation). Before surgery, the diameter of MPD was measured along the presumed transection line of the pancreas, which usually ran through the body of the pancreas anterior to the aorta or portal vein.[19] After PD, patients were considered to have MPD dilatation if the maximum MPD diameter in the pancreatic remnant was greater than 3 mm. Patients with preoperative MPD dilatation (i.e., diameter >3 mm) were considered to have postoperative MPD dilatation only if their MPDs failed to decrease in size.[20]

Statistical Analysis

All results were expressed as mean ± standard deviation. Categorical data were compared using the χ^2 test with Yates correction when necessary. The paired *t* test or Student's *t* test was used to compare the means of the two groups. Multivariate analysis was performed using a multiple logistic regression model. Significance was defined at P values<0.05. Statistical analysis was performed using the Windows version of StatView (Version 5.0; SAS Institute, Cary, NC, USA).

Results

Patients were divided into two study groups. The 38 of the 61 study patients (62.3%) with detectable postoperative exocrine pancreatic insufficiency, defined as %CD-7 h less than 5%, were assigned to the exocrine pancreatic insufficiency group (EPI group). The remaining 23 patients whose %CD-7 h was equal to or higher than 5% were assigned to the normal group.

Among the set of general, preoperative, intraoperative, and postoperative factors previously listed as possible determinations of exocrine pancreatic insufficiency, only three factors differed significantly between the two study groups (Table 1). Specifically, a significantly higher percentage of patients in the EPI group, compared with patients in the normal group, had preoperative impaired endocrine pancreatic function (P=0.028), a hard pancreatic texture (P=0.021), and postoperative MPD dilatation (P=0.010). In addition, the postoperative to preoperative body weight ratio was significantly lower in the EPI group than in the normal group (P=0.016). None of the other factors (mean age, gender distribution, pathological diagnosis, mean preoperative diameter of MPD, operative procedure, type of reconstruction, stenting tube through the pancreatic anastomosis, mean follow-up time, postoperative complications including pancreatic fistula and bile leakage, and postoperative endocrine pancreatic function) demonstrated statistical significance.

These three factors were then subjected to a multivariate analysis using a multiple logistic regression model (Table 2). The analysis identified all three of these factors—preoperative impaired endocrine pancreatic function (P=0.049), hard pancreatic texture (P=0.014), and postoperative MPD dilatation (P=0.005)—as independent factors associated with postoperative exocrine pancreatic insufficiency.

Discussion

Exocrine pancreatic insufficiency can be assessed by direct function tests, such as duodenal intubation and aspiration after pancreatic secretory stimulation, or by indirect function tests, such as measurements of fat and enzymes in feces. However, because of the reasons discussed in the "Introduction" section above, we did not perform these specific tests for all patients in our study. Rather, we employed ^{13}C-breath tests as an indirect and noninvasive means to measure exocrine pancreatic function. ^{13}C is a

Table 1 Perioperative Characteristics of Patients with Normal Exocrine Pancreatic Function or Exocrine Pancreatic Insufficiency After Pancreatoduodenectomy

	Postoperative exocrine pancreatic function		*P* value
	Normal group (n=23)	EPI group (n=38)	
Age, years	70.9±10.2	65.4±10.3	0.066
Gender, *n*			
Male	13	24	0.755
Female	10	14	
Pathological diagnosis, *n*			
IPMN	8	13	0.433
Ampullary carcinoma	7	6	
Pancreatic carcinoma	1	7	
Distal cholangiocarcinoma	3	4	
Carcinoma of gallbladder	1	2	
SCN/MCN	2	1	
Miscellaneous	1	5	
Preoperative endocrine pancreatic function, *n*			
Normal	22	26	0.028
Impaired	1	12	
Pancreatic texture, *n*			
Soft	21	23	0.021
Hard	2	15	
Preoperative diameter of MPD, mm	3.8±2.2	4.4±2.7	0.404
Operative procedure, *n*			
PD with anterectomy	5	4	0.410
PPPD	18	34	
Reconstruction, *n*			
Billroth I type	3	6	0.937
Roux-en Y type	20	32	
Stenting tube through the pancreatic anastomosis, *n*			
External	14	18	0.301
Internal	9	20	
Follow-up time, months	25.7±23.5	25.1±26.0	0.931
Pancreatic fistula, *n*			
Yes	4	5	0.937
No	19	33	
Bile leakage, *n*			
Yes	1	2	0.652
No	22	36	
Postoperative MPD, *n*			
Nondilated	19	17	0.010
Dilated	4	21	
Postoperative endocrine pancreatic function, *n*			
Normal	16	28	0.728
Impaired	7	10	
BW change, %	95.8±9.6	90.3±7.5	0.016

EPI exocrine pancreatic insufficiency, *IPMN* intraductal papillary-mucinous neoplasm, *SCN* serous cystic neoplasm, *MCN* mucinous cystic neoplasm, *MPD* main pancreatic duct, *PD* pancreatoduodenectomy, *PPPD* pylorus-preserving pancreatoduodenectomy, *BW change* the body weight at the breath test to preoperative body weight ratio

stable isotope, which comprises 1.1% of naturally occurring carbon atoms.[21]

In our study, the breath test was performed using a ^{13}C-labeled mixed triglyceride as the substrate. Vantrappen et al.[22] reported that their ^{13}C-labeled mixed triglyceride breath test had a sensitivity of 0.89 and a specificity of 0.81 for diagnosing exocrine pancreatic insufficiency; they also reported a strong correlation between lipase activity in the duodenum and $^{13}CO_2$ excretion in normal subjects and in patients with pancreatic disease. In contrast with ^{13}C-labeled medium-chain triglycerides, such as ^{13}C-trioctanoin[23] and ^{13}C-octanoate,[24] which require no micelle formation for their solubilization, ^{13}C-labeled mixed triglyceride is a mixture of different uniformly ^{13}C-labeled triglycerides with naturally

Table 2 Multivariate Analysis of Perioperative Factors Influencing Exocrine Pancreatic Insufficiency in Patients Undergoing Pancreatoduodenectomy

	Odds ratio	95% CI	*P* value
Preoperative impaired endocrine pancreatic function			
Yes	9.685	1.011–92.740	0.049
No	1.000		
Hard pancreatic texture			
Yes	9.033	1.562–52.257	0.014
No	1.000		
Postoperative dilatation of the main pancreatic duct			
Yes	6.865	1.772–26.595	0.005
No	1.000		

CI confidence interval

occurring long-chain fatty acids, similar to the normal constituents of food.[25] Although absorption of mixed triglycerides depends on the adequacy of lipolysis, bile salt solubilization, and the mucosal surface, the rate-limiting step in the absorption of the mixed triglyceride is hydrolysis by pancreatic lipases. Therefore, cumulative $^{13}CO_2$ excretion in breath is proportional to duodenal activity.[26]

In our study, serum levels of HbA_{1c} were measured as a proxy for endocrine pancreatic function. Although an oral 75-g glucose tolerance test is the standard method for evaluating endocrine pancreatic function, we judged that this method was not suitable for assessing endocrine pancreatic function after PD because of the frequent occurrence of hyperglycemia following the intake of 75-g glucose in post-PD patients.[27] On the other hand, the serum level of HbA_{1c} is known to be a useful indicator of glycemic control in the recent past and dose not subject the patient to the risks of a glucose challenge.[28]

Previous studies have identified a definite relationship between the patency of the pancreatic anastomosis and the severity of exocrine changes and have conducted that patency of the pancreatic anastomosis is the most important factor influencing the function of the pancreatic remnant after PD.[29–32] Therefore, preserving the patency of the pancreatic anastomosis may be essential for good remnant pancreatic function.[33] Because the degree of postoperative dilatation of the remnant pancreatic duct appears to correspond to the likelihood of anastomotic stenosis of the PG,[34] in our study, we considered a dilated MPD to represent "PG stricture". For assessment of the patency of the pancreatic anastomosis, endoscopic retrograde pancreatography and magnetic resonance cholangiopancreatography after a stimulation of secretin[35] often provide important morphologic and functional information. However, the former one is invasive and carries substantial risk for complications such as acute pancreatitis, and the orifice of the pancreatic duct after PG is difficult to detect in some patients by swelling of the gastric mucosa.[36] The latter one is a noninvasive technique allowing direct visualization of the biliopancreatic system, but this modality has been difficult to perform because secretin has not been available recently. For these reasons, we did not perform these examinations, but considered the postoperative MPD dilatation to be the PG stricture.[20]

In our study, PG stricture was one of the three independent factors significantly influencing exocrine pancreatic function after PD according to our multivariate analysis. Although 25 (41%) of our 61 patients had PG strictures, a total of 38 (62%) patients had exocrine pancreatic insufficiency. This discrepancy in numbers indicates that PG patency itself is not a sufficient explanation of exocrine pancreatic insufficiency. Tanaka et al.[37] suggested that postoperative exocrine pancreatic function might be influenced by several complex factors, including preexisting obstructive pancreatitis, quantitative diminution of the pancreatic parenchyma as a result of the resection, impairment of pancreatic juice outflow due to possible stenosis of the pancreatic anastomosis, and malnutrition resulting from resection of the upper digestive tract.

Several published studies have reported that exocrine pancreatic function after PD depends on the degree of fibrosis in the pancreatic remnant[38–42] and/or loss of functional tissue in the distal remnant of the gland resulting from preexisting obstructive pancreatitis secondary to tumor occluding the pancreatic duct.[40–42] Furthermore, a strong correlation exists between endocrine tissue loss and extent of fibrosis.[40] In our study, a hard pancreatic texture, which is indicative of fibrosis, was another independent factor for exocrine pancreatic insufficiency after PD. We also documented that preoperative impaired endocrine pancreatic function, which likely reflected endocrine tissue loss due to preexisting obstructive pancreatitis, was closely associated with postoperative exocrine pancreatic insufficiency. Based on these results, we believe that patients with preexisting obstructive pancreatitis are at high risk of developing exocrine pancreatic insufficiency after PD.

Our study involved several limitations. First, because the study population consisted of a nonconsecutive series of patients who were enrolled over a relatively long study period, an unintended patient selection bias might skew our results. However, previous studies of pancreatic cancer have also encountered many patients who died before enrollment, developed recurrent disease, or were lost to follow-up.[40] Second, because this was a retrospective study, we did not have preoperative exocrine pancreatic function measurements available. Therefore, further studies involving larger number of patients that include evaluation of preoperative exocrine pancreatic function are needed.

In conclusion, 62% of study patients were diagnosed with exocrine pancreatic insufficiency at a median of

17 months after PD with duct-to-mucosa PG. Exocrine pancreatic insufficiency after PD occurred more frequently in patients with preoperative impaired endocrine pancreatic function and a hard pancreatic texture induced by preexisting obstructive pancreatitis, as well as in patients with postoperative MPD dilatation caused by PG stricture. Therefore, pancreatic enzyme supplementation should be considered in patients with at least on of these three risk factors. Although exocrine pancreatic insufficiency after PD may be partly explainable by preexisting obstructive pancreatitis prior to surgery, surgeons desiring to obtain better exocrine pancreatic function after PD would be well advised to devote considerable attention to preventing PG stricture.

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ORIGINAL ARTICLE

Severe Acute Pancreatitis: The Life After

Rajesh Gupta · Jai Dev Wig · Deepak Kumar Bhasin · Paramjit Singh · Sudha Suri · Mandeep Kang · Surinder Singh Rana · Satyawati Rana

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Abstract
Background The present study reports functional and morphological changes noted over long-term follow-up in patients with severe acute pancreatitis.
Methods Thirty patients who had completed at least 6 months after recovery were included. Fecal fat, urinary D-xylose, blood sugar, C-peptide, pancreatic changes, and recurrences were studied.
Results Etiology was gallstones (12), alcohol (10), both gallstone and alcohol (3), and idiopathic (5). Five patients were managed conservatively while 25 underwent surgery. Mean follow-up was 31.3 months. Exocrine and endocrine insufficiencies were noted in 12 (40%) and were more common in no-necrosis group compared to necrosis group (p=0.04 and 0.28, respectively) and infected compared to sterile pancreatitis (45% vs. 25%, p=0.55 and 50% vs. 12%, p=0.15, respectively). Higher frequency was noted in nonvisualized, partly visualized, and dilated segment of duct. Significant proportion (8/12) had both exocrine and endocrine abnormalities and their incidence decreased as duration of follow-up increased. Urinary D-xylose excretion was abnormal in 16% and noted >1 year postrecovery. Thirty percent required >1 readmission and pain was the commonest cause.
Conclusions Forty percent had functional abnormality; 16% had mucosal absorption abnormality while 30% required >1 readmission. Exocrine and endocrine insufficiencies were more prevalent in first year, and a significant proportion had both. A trend for higher functional insufficiency was observed in infected necrosis, complete or incomplete visualization of main pancreatic duct (MPD), dilated segment of MPD, and pseudocyst.

Keywords Severe acute pancreatitis · Exocrine insufficiency · Endocrine insufficiency · Urinary D-xylose excretion · Pancreatic morphology

R. Gupta (✉) · J. D. Wig
Surgical Gastroenterology Division,
Department of General Surgery,
Postgraduate Institute of Medical Education and Research,
Sector 12,
Chandigarh, India 160012
e-mail: rajsarakshi@yahoo.co.in

D. K. Bhasin · S. S. Rana · S. Rana
Department of Gastroenterology,
Postgraduate Institute of Medical Education and Research,
Chandigarh, India

P. Singh · S. Suri · M. Kang
Department of Radiodiagnosis and Imaging,
Postgraduate Institute of Medical Education and Research,
Chandigarh, India

Introduction

It is generally assumed that pancreatic function recovers completely after mild but not after severe acute pancreatitis (SAP). However, it has been reported earlier that morphologic and functional recovery of the pancreas was complete after resolution of even severe acute pancreatitis.[1] More recent evaluations of endocrine and exocrine function in patients with necrotizing pancreatitis have established some new important aspects. The degree of long-term functional and morphologic abnormalities parallels the severity of the attack and the extent of necrosis.[2] Based on the long-term follow-up of 40 months after onset of the attack, Beger et al.[3] made two important observations: (1) exocrine function and morphologic changes tend to ameliorate within 12 to 14 months even after severe pancreatitis and (2) etiologic factors play an additional role in long-term outcome.

The data available on long-term morphological and functional outcome after treatment of severe acute pancreatitis reveal a wide range of incidence of functional

abnormalities.[4–10] There are studies which report that long-term functional and morphological changes do not occur.[7,11] Also, based on etiology, variable long-term functional and morphological changes have been described in alcoholic and biliary pancreatitis[2,11–14] and details of morbidity associated with long-term outcome have been reported only in few series.[15,16] Large group of patients after necrotizing pancreatitis have been reported to suffer long-lasting exocrine and endocrine insufficiencies.[3] The studies reporting a high percentage of exocrine functional impairment after acute pancreatitis primarily included patients after severe necrotizing pancreatitis with up to 85% of patients showing functional impairment[12] compared to only 13% after mild acute pancreatitis.[5] Patients with pancreatic necrosis or pseudocyst have been reported to develop significantly higher exocrine insufficiency than those who did not.[12,17] Symersky et al.[4] observed that exocrine and endocrine functional impairment was not confined only to patients after severe acute pancreatitis and recommended routine evaluation of pancreatic function after all patients with acute pancreatitis.

After subsidence of acute pancreatitis, healing fibrotic tissue may result in pancreatic duct obstruction. Clinically, it often presents as episodes of recurring acute pancreatitis, although a direct relation to development into chronic pancreatitis has not been established. Thus, the question remains whether pancreas can recover following severe acute pancreatitis. The residual pancreas has been shown to demonstrate regenerating capacity that can overcome to some extent the functional impairment.[9,18] It is again not clear regarding the time taken for functional changes to resolve and the degree of resolution.

Therefore, no definite conclusion can be drawn based on these reported studies on the long-term consequences of acute pancreatitis. It is also not clear why some patients remain well after recovery from incident attack while others have recurrence of symptoms or develop delayed complications. Differences in the proportion of patients studied depending on the etiology, differences among the tests used to assess pancreatic function, and different time intervals at which such tests were performed following the episode of pancreatitis have led to nonhomogeneous and thus noncomparable survey populations of patients, which may account for these contradictory results and make conclusions difficult. In the present study, long-term follow-up (more than 6 months postrecovery) of these patients has been studied in terms of pancreatic exocrine and endocrine function, recurrent pancreatitis, and other related complications.

Patients and Methods

This study was conducted between July 2005 and December 2006. All patients of SAP as per Atlanta classification[19] managed during this period in the Surgical Gastroenterology Division of the Department of General Surgery and Gastroenterology and were more than 6 months postrecovery were enrolled. Besides, we also included those patients who had been treated before July 2005 in our division and had completed 6 months of follow-up after recovery from attack of SAP. Recovery was defined as an asymptomatic patient with resumption of normal activities after discharge from the hospital. The research protocol was approved by the institutional ethics/thesis committee and all participants gave written informed consent.

Exclusion criteria were:

1. Patients with documented or suspected chronic alcoholic pancreatitis, based on history of chronic alcohol intake and history of recurrent upper abdominal pain or other symptoms suggestive of chronic pancreatitis
2. Patients not undergoing complete evaluation of endocrine, exocrine, and morphological evaluation as stipulated for this study

Data of patients managed during this period were maintained prospectively on the proforma. The data of patients who underwent treatment earlier were also retrieved on the same proforma by scanning their admission records and also referring to previous proformas if they were part of the other studies on pancreatitis. During the acute phase, severity of the disease was assessed by using Balthazar computed tomography severity index (CTSI)[20] and APACHE II score[21] at admission. The type of management—medical, percutaneous drainage, or necrosectomy—was recorded.

Follow-up Investigations All patients who were at least 6 months postrecovery from attack of SAP underwent evaluation of the recurrent symptoms and pancreatic function, i.e., exocrine and endocrine functions. These patients were also evaluated by magnetic resonance imaging (MRI) and/or computerized tomography (CT) for the morphological changes in the glandular architecture. Patients who were treated earlier and were more than 6 months postrecovery underwent these investigations at the time of follow-up after inclusion in the study. The time interval of each patient after recovery from SAP was noted and patients were categorized into three groups according to duration from recovery, i.e., 6–12, 13–36, and >36 months.

Exocrine Function Tests Fecal fat content was analyzed using the Van de Kamer et al.[22] method. Pancreatic enzyme supplementation was stopped at least 3 days prior to the test. A fecal fat excretion of >7g/24 h was considered abnormal.

Urinary D-xylose excretion was performed after overnight fasting. The levels of D-xylose were measured by analysis of 5-h urine collection by colorimetric method of Haeney et al.[23] Urinary D-xylose excretion <20% was abnormal.

Endocrine Function Tests Fasting and postprandial blood sugar levels were used to screen patients for endocrine insufficiency. Patients with normal fasting and postprandial sugar levels underwent oral glucose tolerance test. Fasting serum C-peptide levels were measured by radioimmunoassay in diabetic patients to differentiate between diabetes because of endocrine failure and diabetes of insulin resistance.

Morphological Changes The glandular and ductal changes of the pancreas were recorded using MRI and CT.

Magnetic Resonance Imaging All the MRI pictures in the study were acquired using 1.5-T machine (Siemens Vision, Erlangen, Germany). Pancreatic morphology was assessed by using T_1 gradient echo (with and without contrast and fat suppression) and T_2 half-Fourier acquisition single-shot turbo spin-echo (HASTE; breath hold) sequences in axial and coronal planes. Magnetic resonance cholangiopancreatography (MRCP) was performed to evaluate fluid-containing structure using HASTE/rapid acquisition with relaxation enhancement sequences.

CT Scan The CT pictures in the study were acquired by dynamic contrast-enhanced CT scan performed on 16-slice multidetector row CT scanner (Siemens Sensation) after oral and intravenous contrast. Limited noncontrast CT sections were also taken in the region of the pancreas.

Statistical Analysis Data were analyzed using SPSS for Windows version 13. The categorical variables were described as proportion and percentages. Frequency of values has been calculated using mean and standard error of mean as well as median with range. Univariate analysis was performed to examine the effect of variables on outcome measures using Chi-squared test. The mean values of variables of two groups were compared by independent-sample *t* test procedure. *p* values less than 0.05 were considered significant in the study.

Results

Thirty-nine patients were enrolled. Nine patients were excluded as they refused fecal fat estimation. Twelve patients were enrolled prospectively during study period while 18 patients treated previously and were more than 6 months after recovery from attack of severe acute pancreatitis were also included. Male to female ratio was 4:1. Mean age was 37.5±2.0 SEM (range 14–65). Etiology was alcohol in ten and gallstone in 12 patients while three patients had both. No cause could be identified in five.

Severity of Disease At the time of initial admission, there were 28 patients with Balthazar grade E and two with grade D. CTSI was 4 in nine patients, 6 in two patients, 7 in one, 8 in five, 9 in one, and 10 in 12 patients. Admission CT scan revealed necrotizing pancreatitis in 21 while nine patients did not have necrosis. One patient whose initial CT scan showed only peripancreatic fluid collection subsequently developed necrosis.

Eight patients had sterile pancreatitis (necrosis in six and peripancreatic fluid in two) while 22 patients developed infection (necrosis in 15 and peripancreatic fluid in seven).

Management Twenty-five patients underwent operative management (necrosectomy and closed lesser sac lavage in 21 and drainage of pancreatic abscess with closed lesser sac lavage in four). Preoperative pigtail catheter drainage was performed in 11 of these 25 patients. The indications of surgery were infected pancreatic necrosis or pancreatic abscess not responding to antibiotics ± percutaneous catheter drainage, sterile necrosis with continuing deterioration or locoregional complications. Five patients (four peripancreatic fluid collection, one sterile necrosis) recovered without surgical intervention. Of these five patients, three with pancreatic abscess were managed with pigtail catheter drainage.

Hospital Stay Mean hospital stay was 49.5 days±6.0 SEM and postoperative stay was 37.4 days±5.1 SEM. Mean hospital stay was significantly longer in patients with gall stone disease (66 vs. 32 days, $p=0.002$) and in patients who subsequently developed endocrine insufficiency (64 vs. 39 days, $p=0.04$).

Follow-up The mean follow-up was 31.3 months±5.1 SEM (range of 7–118 months). Eleven patients were between 7 and 12 months postrecovery; nine were between 13 and 36 months; six were between 37 and 59 months and four patients were more than 5 years after recovery. Follow-up MRI revealed that main pancreatic duct (MPD) was completely delineated in ten patients, incompletely visualized in 16 (Fig. 1), and was not seen at all in four. Seven patients had dilated segment (Fig. 2b, d); six had stenosis (Fig. 2c), while 13 had irregularity of MPD (Figs. 2a and 3a–d).

Exocrine Insufficiency Exocrine insufficiency (abnormal fecal fat excretion) was present in 12 (40%) patients. Of the three patients with symptoms suggestive of exocrine insufficiency, abnormal fecal fat excretion was present in one of them. There were four patients on pancreatic enzyme supplementation and three of these had abnormal fecal fat excretion. The data showed higher frequency in the first year after recovery compared to 13–36-month interval and >36-month interval (63.6%, 22.2%, and 30%, respectively, $p=0.12$).

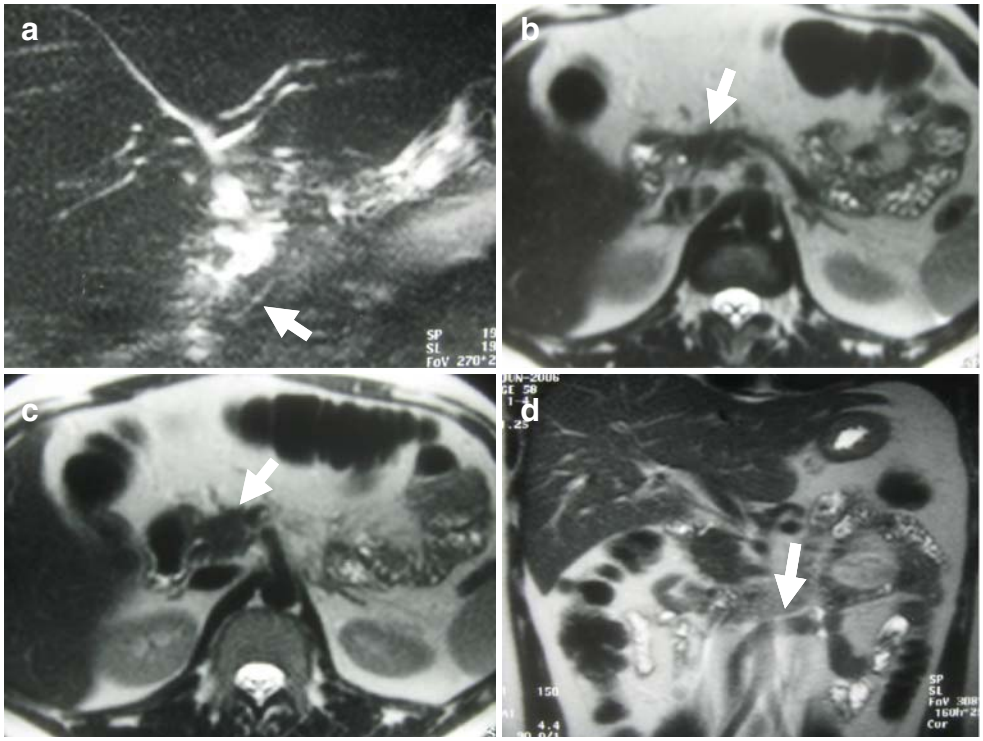

Figure 1 MRI of a patient 4 years postrecovery with CTSI 10 after necrosectomy. MRCP coronal (**a**), T2 axial (**b** and **c**), and coronal T2 (**d**) images show nonvisualized pancreatic body and tail. Head remnant is seen (*arrows* in **b** and **c**) with an intact pancreatic duct (**a**, **d**).

There was no significant correlation of exocrine insufficiency with etiology ($p=1$). Patients with no demonstrable necrosis at admission had significantly higher incidence. In necrosis group, exocrine insufficiency was noted in only those patients having >50% necrosis. A trend towards higher incidence was observed in patients with infected necrosis (Table 1).

When association of exocrine insufficiency was investigated with morphological changes in pancreas, we observed that insufficiency was insignificantly higher in patients when MPD was not visible at all and in those with presence of dilated segment (Table 2). We noticed that patients with endocrine insufficiency had significantly higher incidence of exocrine insufficiency compared to those without endocrine insufficiency (8/12 vs. 4/18, $p=0.04$).

Endocrine Insufficiency Endocrine insufficiency was present in 12 (40%) patients. Seven patients developed

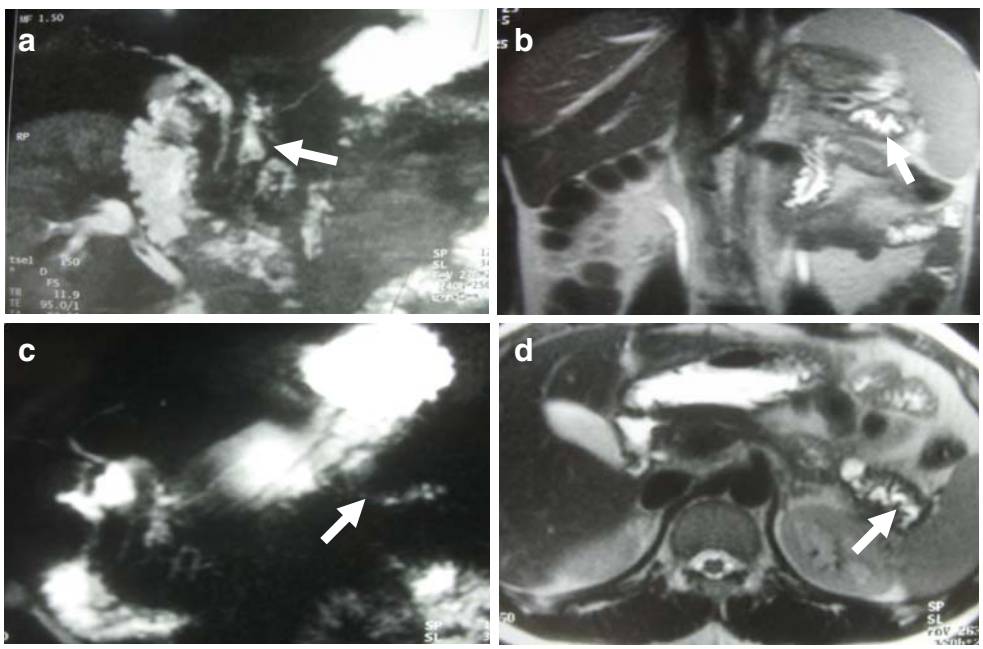

Figure 2 MRI of a patient 10 months postrecovery with CTSI-8, after necrosectomy. MRCP coronal (**a**–**c**) and axial (**d**) show irregularity of pancreatic duct in the head area (*arrow* in **a**). Duct is dilated in tail area (*arrows* **b** and **d**) and not visualized in the body region (likely due to stricture, *arrow* in **c**).

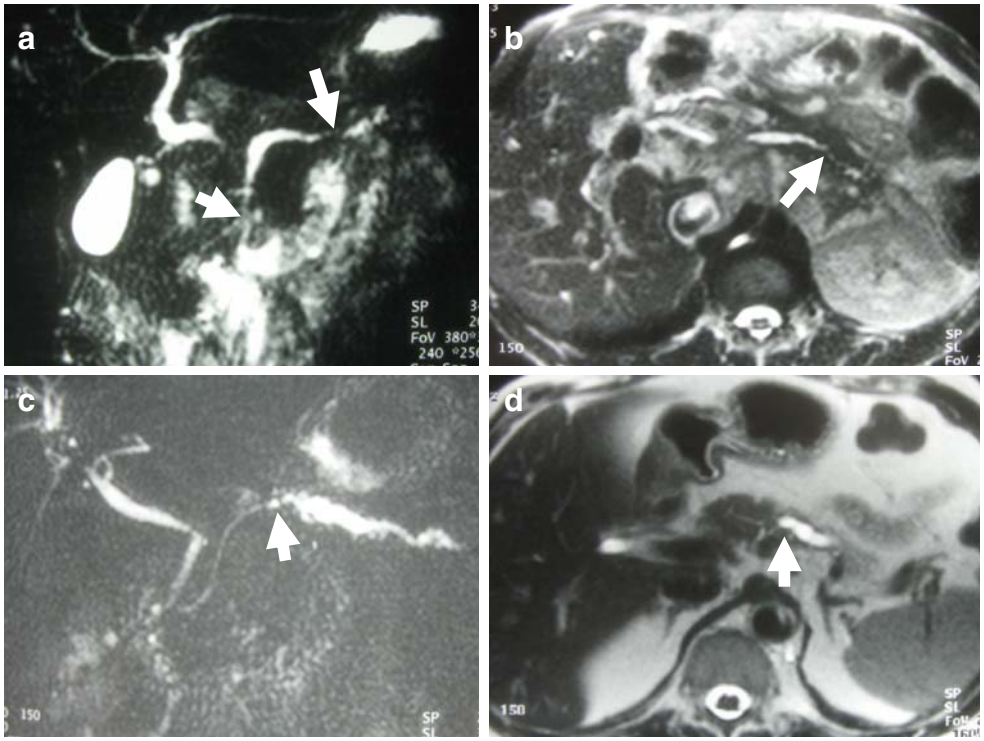

Figure 3 MRI of a patient (**a** and **b**) 10 years postrecovery with CTSI 6 after splenectomy for a splenic pseudocyst. MRCP coronal (**a**) and T2 axial (**b**) show multifocal strictures involving junction of head and body and body and tail area (*arrows*) with pancreatic duct irregularity and dilation of the intervening segment of the duct. Duct in head appears normal (*small arrow* in **a**). MRI of another patient (**c** and **d**) 5 years postrecovery with CTSI 8 after necrosectomy. MRCP (**c**) and axial T2 images (**d**) show stricture segment in body region (*arrow* in **c**) with dilation and irregularity of pancreatic duct in distal body and tail area (*arrow* in **d**).

postoperative diabetes mellitus. In one patient, diabetes resolved 1 month postrecovery. The remaining six patients had insulin-dependent diabetes. Impaired glucose tolerance was detected in another six patients. The incidence was higher in the first year after recovery compared to 13–36-month interval and >36-month interval (54.5%, 33.3%, and 30%, respectively, $p=0.46$).

There was no significant correlation of endocrine insufficiency with alcohol intake or gall stone disease ($p=0.6$). The trend for higher incidence was noted in subgroup with infected pancreatitis and necrosectomy (Table 1).

Endocrine insufficiency was also higher though insignificantly in the presence of irregular outline of MPD, incomplete visualization or absent MPD, dilated segment, and pseudocyst (Table 2).

Abnormal D-Xylose Urinary Excretion Abnormality of the urinary D-xylose excretion was observed in five patients.

Table 1 Association of Functional Abnormalities with Severity of Disease

	Exocrine insufficiency, $n=12$ (percent)	p value	Endocrine insufficiency, $n=12$ (percent)	p value	Abnormal D-xylose, $n=5$ (percent)	p value
Percent of necrosis						
No necrosis (9)	6 (66.6)	0.04	4 (44.4)	0.28	1 (11.1)	0.805
<30% (2)	0		0		0	
30–50% (6)	0		1 (16.6)		1 (16.6)	
>50% (13)	6 (46.1)		7 (53.8)		3 (23)	
Admission APACHE II						
<6 (14)	7 (50)	0.38	3 (21.4)	0.14	2 (14.2)	0.45
6–8 (6)	1 (16.6)		3 (50)		2 (33.3)	
>8 (10)	4 (40)		6 (60)		1 (10)	
Pancreatitis						
Sterile (8)	2 (25)	0.55	1 (12.5)	0.15	0	0.35
Infected (22)	10 (45.4)		11 (50)		5 (22.7)	
Management						
Operative (25)	9 (36)	0.62	11 (44)	0.62	5 (20)	0.66
Conservative (5)	3 (60)		1 (20)		0	

Table 2 Association of Functional Abnormalities with Pancreatic Morphology

	Exocrine insufficiency, n=12 (percent)	p value	Endocrine insufficiency, n=12 (percent)	p value	Abnormal D-xylose, n=5 (percent)	p value
MPD visualization						
Not visualized (4)	2 (50)	0.71	3 (75)	0.15	1 (25)	0.78
Incomplete (16)	7 (43.7)		7 (43.7)		2 (12.5)	
Complete (10)	3 (30)		2 (20)		2 (20)	
MPD outline						
Irregular (13)	6 (46.1)	0.82	6 (46.1)	0.82	1 (7.6)	0.51
Regular (17)	6 (35.2)		6 (35.2)		4 (23.5)	
Stenotic segment						
Present (6)	1 (16.6)	0.40	1 (16.6)	0.19	1 (16.6)	1.00
Nil (24)	11 (45.8)		11 (45.8)		4 (16.6)	
Dilated segment						
Present (7)	4 (57.4)	0.54	3 (42.8)	1.00	0	0.44
Nil (23)	8 (34.7)		9 (39.1)		5 (21.7)	
Pseudocyst						
Present (8)	4 (50)	0.80	4 (50)	0.80	1 (12.5)	1.00
Nil (22)	8 (36.3)		8 (36.3)		4 (18.1)	

MPD main pancreatic duct

All patients with this abnormality had undergone surgery and most had necrosis (Table 1).

Readmission Twenty-two patients required readmission after discharge. Various indication included pain (17), fever (7), vomiting (1), cholangitis (1), cholecystectomy (3), restoration of bowel (2), incisional hernia repair (1), and cystogastrostomy (3).

Nine patients required >1 admission due to recurrent symptoms and were analyzed further. Recurrent symptoms were noted more frequently in 7–12- and 13–36-month interval compared to >3 years postrecovery (36%, 44%, and 10%, respectively, p=0.16). Etiology was alcohol in four, gallstones in three, and idiopathic in two patients. All the alcohol abusers had turned abstinent. No significant relationship was observed with necrosis vs. no necrosis (p=1) and sterile vs. infected necrosis (p=1). Patients managed conservatively had insignificantly higher incidence of recurrent symptoms (3/5 vs. 6/25, p=0.28). Patients with nonvisualized duct, dilated segment, and pseudocyst had a trend for higher recurrences (p=0.53, p=0.7, and p=0.32, respectively).

Pseudocyst Pseudocyst was noted in 8/30 patients and occurred significantly less commonly in patients with alcohol abuse (1/13 vs. 7/17, p=0.04). Frequency of pseudocyst occurrence was not significantly different in three time intervals postrecovery (3/11 in 7–12-month, 3/9 in 13–36-month, and 2/10 in >36-month interval, p=0.35). The occurrence of pseudocyst was higher in patients managed conservatively compared to those undergoing necrosectomy (3/5 vs. 5/25, p=0.19). No relationship was observed with functional abnormality.

We further analyzed subset of patients with multiple insufficiencies, i.e., both exocrine and endocrine insufficiencies (eight patients), and tried to find out significant predictors of multiple insufficiencies compared with those who recovered without impaired function (14 patients). No significant predictors were observed (Table 3).

Discussion

Although abnormalities in pancreatic endocrine and exocrine function during AP are known to occur especially with pancreatic necrosis, long-term pancreatic function after SAP has not been studied, probably because the main focus of clinical research in this disease has centered on high mortality and immediate postoperative morbidity rates. Some believe that the pancreas tends to recover its normal functioning state over an indeterminate period of time[1,2,17] whereas others opine that pancreatic dysfunction does not return to normal in certain patients.[24] In an attempt to minimize the effects of acute attack on pancreatic function, our study included patients who were asymptomatic for at least 6 months after the resolution of the attack while some authors believed that even 4 months postrecovery was good enough.[25]

Exocrine Insufficiency Exocrine insufficiency (abnormal fecal fat excretion) was present in 12 (40%) patients. Previous studies have reported variable figures ranging up

Table 3 Odds Ratio (with 95% Confidence Intervals) of Individual Risk Factors Influencing Onset of Both Exocrine and Endocrine Insufficiency

Probable factors	Odds ratio (with confidence interval)
Sex	
Male[a]	1.000
Female	2.000 (0.224–17.89)
CT severity index	
<6[a]	1.000
7–8	0.000
>8	2.083
Percentage necrosis	
No necrosis[a]	1.000
<30%	0.000
30–50%	0.000
>50%	2.083 (0.298–14.549)
Admission APACHE score	
<8[a]	1.000
>8	2.500 (0.410–15.230)
Infective necrosis	
No[a]	1.000
Yes	3.889 (0.366–41.325)
Necrosectomy	
No[a]	1.000
Yes	0.538
Readmission	
No[a]	1.000
Yes	0.164
Duration of follow-up	
6–12 months[a]	1.000
13–36 months	0.150 (.011–2.055)
>36 months	0.171 (0.020–1.436)
MPD regularity	
Regular outline[a]	1.000
Irregular	1.800 (0.308–10.517)
MPD visualization	
Complete[a]	1.000
Incomplete	5.000 (0.459–54.513)
Absent	1E+010
MPD stenosis	
No[a]	1.000
Yes	0.000
MPD dilatation	
Absent[a]	1.000
Present	2.000 (0.224–17.894)
Presence of pseudocyst	
No[a]	1.000
Yes	3.600 (0.454–28.562)

MPD main pancreatic duct

[a] Reference category

to 85% following severe acute pancreatitis.[5–8,12–14,17,25–29] In the present series, insufficiency was 63.6% in the first year and 30% after 3 years of recovery. Improvement in exocrine insufficiency has been noted with passage of time earlier also.[8,30] Bavare et al.[30] reported exocrine insufficiency in 11% patients of necrotizing pancreatitis at mean follow-up of 19 months from the immediate postoperative frequency of 72%.

It is known that the degree of long-term functional abnormalities parallels the severity of the attack and the extent of necrosis.[2] However, Ibars et al.[8] and Symersky et al.[4] did not find statistically significant differences when the pancreatic function and severity of the pancreatitis were assessed. In the present study, we observed a trend for higher incidence of both exocrine as well as endocrine insufficiency in patients without necrosis compared to those with necrosis (66.6% versus 28.5%). The authors believe that one reason could be contrast-enhanced CT abdomen done early in the course when the disease was still evolving and pancreatitis was sterile. Subsequent progression of necrosis and onset of infection may have shifted some of the initial low-severity patients to higher severity as evidenced by later development of necrosis in one patient and infected pancreatitis in 22 patients. Patients with infected necrosis also showed higher exocrine and endocrine insufficiencies compared to sterile necrosis (Table 1). Onset of infection may lead to further extension of necrosis and probably impaired regeneration of parenchyma.

The exocrine and endocrine insufficiencies were insignificantly more in patients with completely absent or incompletely visualized as well as with presence of dilated segment of MPD (Table 2). These morphological changes can result in impediment to the flow of the exocrine secretions, as described previously also in disconnected duct.[31,32] Backpressure changes and increased intraparenchymal pressure in the obstructed system can adversely affect the production of exocrine and endocrine glands as noted earlier.[31,32]

Endocrine Insufficiency It has been observed that once endocrine insufficiency was established, it tended to deteriorate with time or, at best, remained stable. No patient had improvement in endocrine function in the study by Tsiotos et al.[14] Our findings are at variance as endocrine status had remained stable or improved with passage of time. In one patient, diabetes resolved after 1 month of discharge. The dose of insulin was stable in five while it had decreased in one patient. As in exocrine insufficiency, prevalence of endocrine insufficiency was highest during the first year of follow-up which improved later (54.5% at 7–12 months to 30% at >36 months).

There are differences of opinion regarding functional changes after biliary or alcoholic pancreatitis.[10,24,25,29] No

difference in functional insufficiency was observed by Bavare et al.[30] based on etiology as noticed in present series also. One reason in patients with alcoholic etiology could be that those who stopped drinking after attack of acute pancreatitis get improvement in pancreatic function. In our study, all such patients turned abstinent after the attack. In the present series, significant number of patients with exocrine insufficiency developed endocrine insufficiency (8/12). These results suggest that any patient who develops either of the two functional abnormalities would be a likely candidate to develop other functional abnormality and thus warrant screening for other abnormality. Though there was a subset of patients (eight patients) who developed multiple insufficiencies, i.e., both exocrine and endocrine insufficiencies, and another subset of patients who recovered without impaired function, we did not find any significant factors to predict onset of multiple insufficiencies in the present study (Table 3).

Abnormal D-Xylose Urinary Excretion Pancreatic juice and bile are thought to have trophic effect on the intestinal mucosa and there is probable existence of adaptation mechanism when exocrine pancreatic secretion is suppressed as in chronic pancreatitis.[33] Such changes have not been studied in follow-up of patients of severe acute pancreatitis earlier. Abnormal D-xylose urinary excretion was observed in five (16.6%) patients and occurred >1 year postrecovery. However, no significant association with ductal abnormality or exocrine insufficiency was observed and this merits further investigations in a larger setting.

Readmission Thirteen percent to 30% recurrent episodes of pancreatitis have been reported earlier in necrotizing pancreatitis.[17,34] In the present series, 30% patients required >1 admission with incidence falling to 10% after 3 years of recovery. Various reasons cited in the literature for these recurrences include presence of pseudocysts, localized pancreatic duct stricture, upstream ductal dilatation and focal upstream inflammation,[31] continued alcohol abuse,[34,35] and progression to chronic pancreatitis.[17] In the present series also, patients with completely non-visualized duct, dilated segment of MPD, and presence of pseudocyst had a trend for higher incidence. Type of management, i.e., operative versus conservative, or the type of surgery has not been found to affect the overall development of relapses.[35] We observed that patients managed conservatively had a trend towards higher frequency of recurrent symptoms than those subjected to surgery (60% vs. 24%) which could be due to higher incidence of pseudocysts noted in these patients.

In conclusion, results of our study showed 40% incidence of exocrine and endocrine insufficiencies in patients of severe acute pancreatitis. Exocrine and endocrine insufficiencies were more prevalent in the first year after recovery which improved later. Significant proportion of patients (8/12) had both functional abnormalities. Recurrent symptoms were present in 30%. There was no significant correlation of functional abnormality with etiology or severity of disease. A trend for higher functional insufficiency was observed in the presence of infected necrosis, complete or incomplete visualization of MPD, dilated segment of MPD, and pseudocyst.

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ORIGINAL ARTICLE

The Lymph Node Ratio is the Strongest Prognostic Factor after Resection of Pancreatic Cancer

Hartwig Riediger · Tobias Keck · Ulrich Wellner · Axel zur Hausen · Ulrich Adam · Ulrich T. Hopt · Frank Makowiec

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Abstract
Introduction Survival after surgery of pancreatic cancer is still poor, even after curative resection. Some prognostic factors like the status of the resection margin, lymph node (LN) status, or tumor grading have been identified. However, only few data have been published regarding the prognostic influence of the LN ratio (number of LN involved to number of examined LN). We, therefore, evaluated potential prognostic factors in 182 patients after resection of pancreatic cancer including assessment of LN ratio.
Methods Since 1994, 204 patients underwent pancreatic resection for ductal pancreatic adenocarcinoma. Survival was evaluated in 182 patients with complete follow-up evaluations. Of those 182 patients, 88% had cancer of the pancreatic head, 5% of the body, and 7% of the pancreatic tail. Patients underwent pancreatoduodenectomy (85%), distal resection (12%), or total pancreatectomy (3%). Survival was analyzed by the Kaplan–Meier and Cox methods.
Results In all 204 resected patients, operative mortality was 3.9% (n=8). In the 182 patients with follow-up, 70% had free resection margins, 62% had G1- or G2-classified tumors, and 70% positive LN. Median tumor size was 30 (7–80) mm. The median number of examined LN was 16 and median number of involved LN 1 (range 0–22). Median LN ratio was 0.1 (0–0.79). Cumulative 5-year survival (5-year SV) in all patients was 15%. In univariate analysis, a LN ratio≥0.2 (5-year SV 6% vs. 19% with LN ratio<0.2; p=0.003), LN ratio≥0.3 (5-year SV 0% vs. 18% with LN ratio<0.3; p<0.001), a positive resection margin (p<0.01) and poor differentiation (G3/G4; p<0.03) were associated with poorer survival. In multivariate analysis, a LN ratio≥0.2 (p<0.02; relative risk RR 1.6), LN ratio≥0.3 (p<0.001; RR 2.2), positive margins (p<0.02; RR 1.7), and poor differentiation (p<0.03; RR 1.5) were independent factors predicting a poorer outcome. The conventional nodal status or the number of examined nodes (in all patients and in the subgroups of node positive or negative patients) had no significant influence on survival. Patients with one metastatic LN had the same outcome as patients with negative nodes, but prognosis decreased significantly in patients with two or more LN involved.
Conclusions Not the lymph node involvement per se but especially the LN ratio is an independent prognostic factor after resection of pancreatic cancers. In our series, the LN ratio was even the strongest predictor of survival. The routine estimation of the LN ratio may be helpful not only for the individual prediction of prognosis but also for the indication of adjuvant therapy and herein related outcome and therapy studies.

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H. Riediger · T. Keck · U. Wellner · U. Adam · U. T. Hopt · F. Makowiec (✉)
Department of Surgery, University of Freiburg,
Hugstetter Str. 55,
79106 Freiburg, Germany
e-mail: frank.makowiec@uniklinik-freiburg.de

A. zur Hausen
Institute of Pathology, University of Freiburg,
Freiburg, Germany

Keywords Pancreatic cancer · Resection · Survival · Prognostic factors · Lymph node ratio

Introduction

Prognosis in patients diagnosed to have pancreatic cancer is very poor. Only a relative small proportion of patients are candidates for resection. However, even after potentially curative resection, actuarial 5-year survival after resection is reported in the range between only 15% and

25% in most series.[1–4] The extent of surgery in potentially resectable pancreatic cancer is well defined especially regarding the extent of lymphadenectomy.[5–7] In addition to surgery, recent randomized multicenter studies could identify a favorable role of adjuvant chemotherapy[8,9] adding a further standard in the treatment of resectable pancreatic cancer.

Lymph node involvement in pancreatic cancer has been described to be a poor prognostic factor.[2,3,10–12] However, the status on presence or absence of nodal disease has not always been an independent prognostic factor as shown in one of the earlier results of the Johns Hopkins group[13] and in a prior report of our group.[14]

To better define the prognostic role of nodal disease in resected pancreatic cancer, a few groups recently assessed the influence of the lymph node ratio (number of metastatic LN divided by number of examined nodes; LNR) instead of nodal disease alone.[1,15–17] They all found comparable results regarding the influence of LNR on prognosis. LNR as categorical variable (cutoff point around 0.15–0.20) or the LNR as a continuous variable were found to represent strong prognostic parameters.

In this study, we report the outcome of 182 patients resected for pancreatic cancer. In addition to well known and described prognostic parameters, we evaluated the independent prognostic influence of LNR using two different cutoff values.

Patients and Methods

From 1994 to 2006, 204 patients underwent pancreatic resection for ductal pancreatic adenocarcinoma at our institution. One hundred eighty-two of those patients (who survived surgery and had sufficient postoperative follow-up information) were included in our survival analysis. A detailed description of patient and tumor-related data of those 182 patients is given in Table 1.

The surgical techniques applied by our group during pancreaticoduodenectomy (either pylorus-preserving or

Table 1 Clinical and Morphologic Features of 182 Patients with Resected Pancreatic Adenocarcinoma

Age in years (median, range)		65 (31–84)
Gender	Female (*n*, %)	98 (54%)
	Male (*n*, %)	84 (46%)
Body mass index (median, range)		24 (15–35)
Tumor location (*n*, %)	Head	161 (88%)
	Neck	9 (5%)
	Tail	12 (7%)
Tumor size in mm (median, range)		30 (7–80)
Type of resection	Pancreatoduodenectomy	155 (85%)
	(PPPD)	(126)
	(Whipple)	(29)
	Distal resection	21 (12%)
	Total pancreatectomy	6 (3%)
Superior mesenteric-portal vein resection		64 (35%)
Tumor differentiation (*n*, %)	G1	9 (5%)
	G2	102 (56%)
	G3	62 (34%)
	G4	5 (3%)
	Unknown	4 (2%)
Resection margin negative (*n*, %)		128 (70.3%)
Nodal status (*n*, %)	Positive	119 (65%)
	Negative	61 (34%)
No. of examined nodes (median, range)[a]		16 (2–47)
No of involved nodes (median, range)		1 (0–22)
Lymph node ratio (median, range)[a]		0.095 (0–0.79)
Lymph node ratio (*n*, %)[a]	0	55 (30%)
	>0–0.199	66 (36%)
	0.2–0.299	19 (10%)
	≥0.3	32 (18%)
	Unknown	10 (5%)

[a] Exact results were unavailable in a few patients (see Table 2 for numbers)

classical Whipple procedure) have, in detail, been described before.[14,18] With the exception of extended lymphadenectomy performed in a few patients, standard lymphadenectomy was carried out along the hepatoduodenal ligament, the common hepatic artery, the vena cava, and the right side of the superior mesenteric artery. Until 2003, a pancreatojejunostomy was the routine reconstruction procedure after pancreaticoduodenectomy and was performed by anastomosing the pancreatic parenchyma to the jejunal mucosa in an end-to-side single-layer full thickness anastomosis. Since 2004, pancreatogastrostomy is increasingly performed in our department, currently in the context of a randomized trial comparing it to duct-to-mucosa pancreaticojejunostomy.

Superior mesenteric portal vein resection (SM-PVR) was performed in the case of pre- or intraoperatively suspected infiltration of the portal vein.[14] Thrombosis of the superior mesenteric/portal vein was always a contraindication for pancreatic head resection at our institution. In this series SM-PVR was performed in every third patient (Table 1).

Histopathological Evaluation

The operative specimen underwent standard histopathological evaluation including the documentation of tumor size. Parameters like perineural invasion and invasion of veins or lymphatics were not routinely documented in the first years of our study and were, therefore, not included in our analysis. The specimens of the 12 patients surviving more than 5 years until now were reviewed by two experienced pathologists. Ductal pancreatic adenocarcinoma was reconfirmed in all those 12 cases.

Data Collection and Statistics

The results of our study were gained by retrospective analysis of our prospective pancreatic database. Perioperative data and long-term outcome are recorded and entered into a SPSS database (SPSS for Windows, Version 15.0 finally used; SPSS Inc., Chicago, IL, USA). Until 2001, the survival status of each patient was obtained by contacting the patients and/or the home physicians. Since 2001, survival data are systematically obtained by the cancer registry of the Comprehensive Cancer Center of our university hospital.

Some single histopathological data were unavailable in a few patients from the first years of our study (see Table 2 for numbers). Only patients with complete data for all relevant parameters were included in the final multivariate survival analysis (n=166).

Survival was univariately analyzed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed by the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic) including the report of relative risks and their 95% confidential interval. For uni- and multivariate subgroup survival analysis, most demographic and disease-related parameters were classified as shown in Table 2.

Results

Of 204 patients who underwent resection for pancreatic cancer, perioperative mortality was 3.9%. Follow-up data were not available in further 14 patients leaving 182 patients for final evaluation of survival. Median postoperative follow-up in the 182 patients was 1.3 (range 0.3–11.1) years.

Resection Margin and Nodal Disease

A free resection margin was obtained in 70% of the patients. The median number of examined lymph nodes was 16 (range 2–47). Sixty-five percent of all 182 patients had nodal disease. Out of the 173 patients with available exact numbers of involved nodes, 61 (35%) were node negative, 26 (15%) had one LN involved by tumor cells, and 86 (50%) had more than one LN involved. Median number of involved nodes was 1 (0–22). LNR could be calculated in 172 patients with known numbers of involved and examined LNs. The median LNR in those patients was 0.095 (range 0–0.79, Table 1). The proportion of patients after stratification of LNR into groups <0.2, 0.2 to 0.29, or ≥0.3 is shown in Table 1.

Survival

Until now, 135 of the 182 patients died (median time to death 14.4 months); 47 patients were censored. The actuarial 3- and 5-year survival rates were 20% and 15%, respectively. The median overall survival was 18 months. Up to now, 12 patients with ductal adenocarcinoma of the pancreas survived for more than 5 years after resection. Three of those 12 5-year survivors died between 5.8 and 6.6 years after surgery; the remaining nine patients were alive (i.e. censored during actuarial survival analysis) at the last follow-up 5 to 11 years after resection.

Univariate Survival Analysis

As shown by univariate analysis, the resection margin (p=0.003; Fig. 1), tumor grading (p=0.03; Fig. 2), LNR

Table 2 Univariate Survival Analysis after Resection of Pancreatic Cancer

Parameter		Parameter (*N*)	3-year-survival (%)	5-year-survival (%)	*p* Value
Resection margin	Negative	128	25	19	0.003
	Positive	54	10	7	
Grading	G1/2	110	23	19	<0.03
	G3/4	69	16	10	
LN ratio A	LNR<0.2	121	24	19	0.003
	LNR≥0.2	51	12	6	
LN ratio B	LNR<0.3	140	24	18	<0.001
	LNR≥0.3	32	4	0[a]	
Nodal disease	No (N0)	61	24	19	0.22
	Yes (N+)	119	18	13	
No. of involved LNs	0 or 1	87	24	21	<0.04
	>1	86	16	9	
No. of examined LNs	≤15	85	22	17	0.78
	>15	86	19	14	
Tumor size	≤30 mm	82	21	14	0.19
	>30 mm	94	19	16	
Gender	Female	98	16	13	0.32
	Male	84	24	17	
Age	≤65	90	25	18	0.18
	>65	92	15	13	
Perioperative blood transfusion	No	61	24	19	0.22
	Yes	119	18	13	
Vein resection	No	118	21	18	0.69
	Yes	64	18	10	
BMI	<25	104	24	20	0.30
	≥25	73	15	9	
Subgroup analysis					
Preoperative CA 19–9 (U/ml)[b]	<200	67	24	17	0.28
	≥200	58	15	15	
Number of examined LN in *node positive* patients	≤15	55	21	16	0.77
	>15	62	14	10	
Number of examined LN in *node negative* patients	≤15	30	24	18	0.82
	>15	24	28	23	
LN ratio in node positive patients	LN ratio<0.2	66	22	17	<0.02
	LN ratio≥0.2	51	12	6	
LN ratio in node positive patients	LN ratio<0.3	85	22	17	<0.001
	LN ratio≥0.3	32	4	0[a]	

[a] No patient at risk after 5 years

[b] CA 19–9 available in 125 patients

(cutoff 0.2 $p=0.003$; cutoff 0.3 $p<0.001$; Figs. 3 and 4), and number of involved nodes (zero or one LN vs. more than one involved LN; $p<0.04$; Fig. 5) were parameters significantly influencing survival. It is of note that the nodal status per se (i.e. node negative or positive) did not correlate with survival ($p=0.22$; Table 2). The reason for this phenomenon is the fact that patients with one single metastatic node had the same survival as node negative patients. By univariate analysis, the subgroup of patients with a LNR≥0.3 had clearly the worst outcome with an actuarial survival reaching zero at 3 years (Table 2 and Fig. 4). All further examined parameters like number of examined nodes (cutoff 15), age, gender, BMI, tumor size, perioperative transfusions, preoperative CA 19–9 level, or superior mesenteric-portal vein resection did not influence survival (Table 2).

As already shown for the entire patient group, the LNR did significantly influence survival in the subgroup of patients with positive LNs (Table 2, subgroup analysis). As also demonstrated for the entire patient group, the number of examined LNs (≤15 versus >15) had no influence on survival in the subgroups of node positive ($p=0.77$; Table 2, subgroup analysis) or node negative patients ($p=0.82$; Table 2).

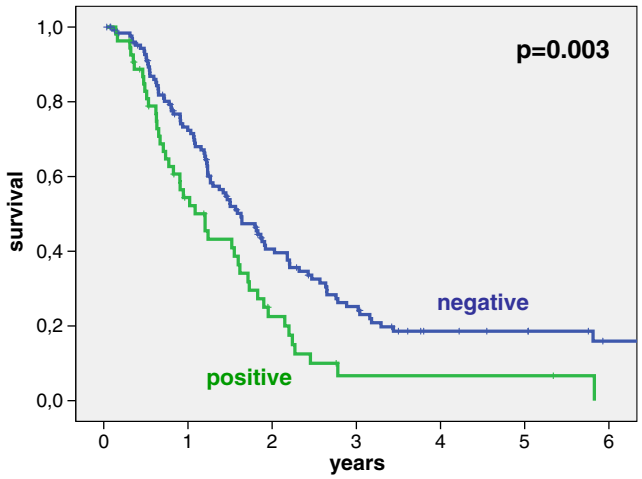

Figure 1 Actuarial survival (Kaplan–Meier analysis) after resection of pancreatic cancer: influence of resection margin.

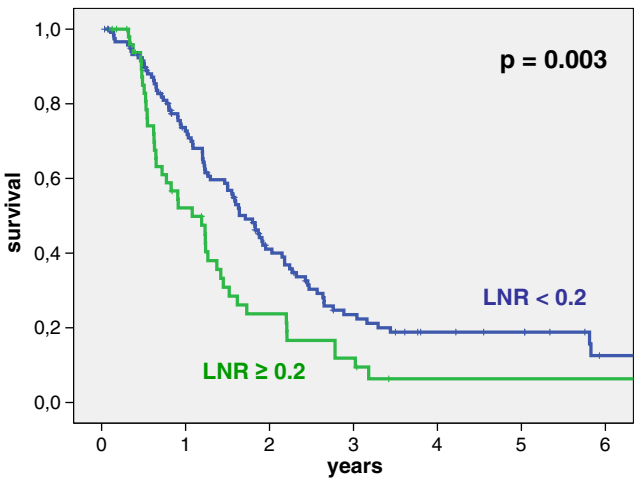

Figure 3 Actuarial survival (Kaplan–Meier analysis) after resection of pancreatic cancer: influence of lymph node ratio (cutoff 0.2).

Multivariate Survival Analysis

Multivariate survival analysis was performed using two different models (one with LNR cutoff 0.2, the other with LNR cutoff 0.3; Table 3) without inclusion of nodal disease per se (p=0.22 in univariate analysis). Already significant by univariate analysis, the resection margin, grading, and LNR (both cutoff classifications) now also were shown to independently influence survival. A LNR≥0.3 again was the strongest factor determining the outcome (p<0.001; relative risk 2.2; Table 3).

Discussion

Although long-term survival is achieved in only a minority of patients, the complete surgical resection of pancreatic adenocarcinoma represents the only potential curative option. The presence of nodal disease has been established as a factor predicting poor survival in numerous studies.[2,3,10,12,19] It is of note, however, that nodal disease per se was not always a significant prognostic factor, even in larger series. In a prior study from the Johns Hopkins group reporting the outcome in 606 resected pancreatic adenocarcinoma, for example, nodal disease was not significantly influencing survival in multivariate analysis.[13] In our series, nodal disease alone also did not correlate with the outcome due to a similar prognosis of patients without nodal disease or with only one involved lymph node. Regarding the absolute LN count, prognosis significantly decreased in our study in patients with at least two involved nodes.

The use of nodal disease alone (i.e. node positive or negative) or of the absolute number of involved LNs in evaluating prognosis may carry the bias of inadequate lymphadenectomy or inadequate histopathological evaluation potentially missing or leaving metastatic nodes.[1,15,16]

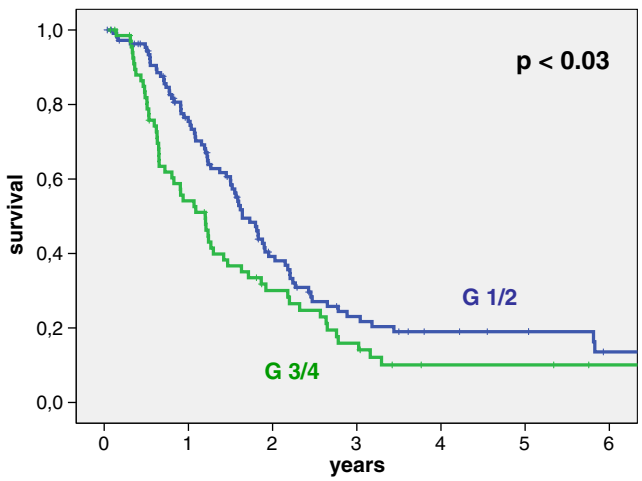

Figure 2 Actuarial survival (Kaplan–Meier analysis) after resection of pancreatic cancer: influence of tumor grading.

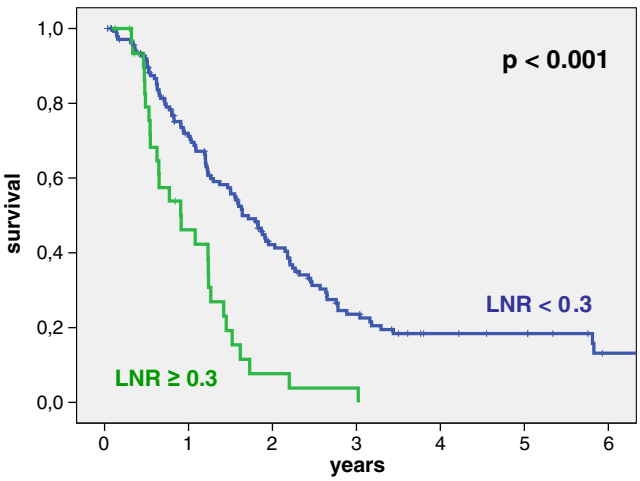

Figure 4 Actuarial survival (Kaplan–Meier analysis) after resection of pancreatic cancer: influence of lymph node ratio (cutoff 0.3).

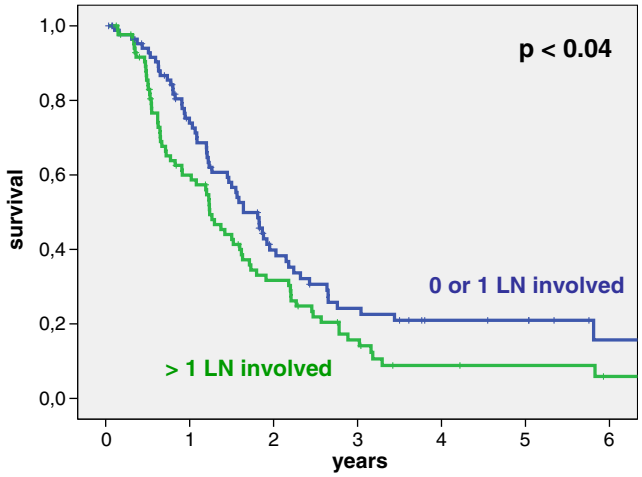

Figure 5 Actuarial survival (Kaplan–Meier analysis) after resection of pancreatic cancer: comparison of patients without or with one involved node versus patients with more than one involved lymph node.

Based on potentially improved lymphatic clearance and prognosis, some older retrospective reports from the 1980s had suggested that extended lymphadenectomy may be associated with a better outcome.[20,21] Two subsequent large randomized studies, however, could not demonstrate any survival benefit of extended lymphadenectomy in pancreatic cancer.[5–7]

To overcome the above-mentioned problems of reporting nodal staging and to better define the prognostic role of nodal disease, several reports have not only examined nodal disease per se but also focused on the prognostic value of the lymph node ratio in various gastrointestinal cancers. Strong prognostic influences of LNR were recently described in esophageal,[22,23] gastric,[24,25] and colorectal cancer.[26] In pancreatic cancer, four studies were published during the recent years evaluating the prognostic role of LNR after resection. In the first study including 128 patients, Berger et al. from the Fox Chase Cancer Center found a significant prognostic influence of LNR not only by univariate but also by multivariate analysis.[16] In their study, prognosis worsened especially in patients with a LNR>0.15. These initial results regarding the value of LNR were later confirmed in a small study from Poland in 64 node positive patients.[17] The authors found that prognosis worsened significantly in patients with a LNR of 0.2 or higher.

After these two initial studies, two papers with very large patient numbers were recently published by two high-volume centers from the USA. With the analysis of histopathological and survival data from 696 patients, a LNR of 0.18 was the best cutoff value in predicting outcome in the paper by House et al. from the Memorial Sloan Kettering Cancer Center.[1] In addition to that, median survival declined in a linear relationship to the absolute number of metastatic lymph nodes in the range of one to eight nodes.[1]

In a series of 905 patients, Pawlik et al. from the Johns Hopkins University[15] described the LNR as the most potent predictor of survival after pancreaticoduodenectomy for pancreatic cancer. This prognostic effect of LNR was shown in the entire patient group as well as in the subgroup of node positive patients. In the conclusion of both large studies, the authors suggested the future use of LNR in the stratification of prognosis.

As in the previous reports, we also identified the LNR to be a potent prognostic determinant for the outcome after resection of pancreatic cancer in 182 patients. Interestingly, in all four mentioned studies as well as in our evaluations the cutoff values of LNR determining a relevant poorer outcome were in a comparable range (0.15–0.2). In our series, LNR significantly predicted prognosis not only in the entire patient group but also in the subgroup of patients with positive nodes. As described by House et al. in their large study, we also found some correlation between the absolute number of metastatic nodes and prognosis. It is of note, however, that in our evaluations, patients with one involved node had the same prognosis as node negative patients, and prognosis worsened only when at least two metastatic nodes were present.

There is an ongoing discussion whether a low number of assessed lymph nodes may understage disease by possibly

Table 3 Results of Multivariate Survival (Cox regression) Analysis after Resection of Pancreatic Cancer

Parameter	*p* Value	Relative risk	95% confidential interval
Model 1			
Poor grading (G 3/4)	0.029	1.5	1.1–2.1
Positive margins	0.011	1.7	1.1–2.4
LN ratio≥0.2	0.017	1.6	1.1–2.3
Model 2			
Poor grading (G3/4)	0.04	1.5	1.0–2.1
Positive margins	0.034	1.5	1.0–2.3
LN ratio≥0.3	<0.001	2.2	1.4–3.6

Model 1 was calculated with a cutoff of LN ratio of 0.2, model 2 with a cutoff of LN ratio of 0.3

missing metastatic nodes. In our study, we could not demonstrate any correlation between the number of examined nodes and survival, neither for node negative nor node positive patients. House et al.[1] found a poorer survival in N0 patients (which was similar to survival in N1 patients) in the case of less than 12 assessed nodes. In patients with one metastatic LN, they described a tendency for poorer outcome in the subgroup with less than 12 examined nodes. They concluded from these results that prognosis may be better estimated in N0 patients by pathological assessment of more than 12 LNs. In the other large series by Pawlik et al.,[15] in the study by Berger et al.,[16] and in our series, however, the number of assessed nodes did not correlate with survival (in our results, neither in node positive nor in node negative patients). It is possible, therefore, that some metastatic lymph nodes may be missed in the case of a low number of harvested lymph nodes, but the overall prognostic influence of this effect is certainly weak compared with more stronger parameters like LNR or resection margins and potentially relevant only in node negative patients. In this context, it should also be remarked that not only missing lymph node metastases by inadequate lymphadenectomy or by inadequate pathological examination of the specimen may understage disease. Recent data have shown that a more refined pathological analysis of conventionally negative lymph nodes by immunohistochemistry may detect nodal micrometastases independently influencing prognosis.[27]

During the recent years, two large randomized studies from Europe[8,9] have found improved survival in patients receiving adjuvant chemotherapy. It is of note that the influence of adjuvant therapy after resection of pancreatic cancer has only been reported in one of the four cited studies evaluating LNR (adjuvant chemoradiation in the paper by Berger et al.).[16] In our series, systematic adjuvant chemotherapy is only given since 2004 and in the period before only a few selected patients received adjuvant chemotherapy or chemoradiation. Due to the rather low numbers of patients with adjuvant therapy, we, therefore, did not calculate the potential effect on survival. However, we do not believe that this might influence the reported results of our study.

Conclusion

The results of our study confirm data from other centers that LNR represents an important prognostic factor in patients after resection of pancreatic cancer. These results suggest the use of LNR in further therapy and outcome studies in addition to or even instead of conventional nodal staging. Due to similar outcomes, the patient groups with less than 16 lymph nodes examined were probably not understaged in our experience.

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ORIGINAL ARTICLE

The Ancient Technique of "Gastrorrhaphy"

Niki Papavramidou · Helen Christopoulou-Aletra

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Abstract
Objective The paper describes "gastrorrhaphy," deriving from the Greek words "gastir" meaning "abdomen" and "rhaphy" meaning "suturing," which was a technique used for the treatment of abdominal wounds.
Methods The technique is described in detail in the texts of Celsus (first century A.D.) and in those of Galen (second century A.D.). Furthermore, references were found in Oribasius' texts (fourth century A.D.) and in the writings of two veterinarian doctors of the same period. We provide our drawings in order to elucidate the different techniques of suturing.
Results Celsus described one method of "gastrorrhaphy" while Galen presented two different methods for this procedure. All three methods agree on the processes required: replacement of the prolapsed viscera, cleaning of the wound, and suturing. The difference in methods is in the way of suturing the wound; Celsus suggests stitches in layers. While Galen's first method refers to stitching of the peritoneum with the abdominal wall, his second method refers to stitching of similar structures, meaning peritoneum to peritoneum and abdominal wall to abdominal wall.
Conclusions Celsus' method strongly resembles stitching in layers with cross-sutures, while both of the Galenic techniques of gastrorrhaphy are versions of the full-thickness sutures used nowadays. It should be stressed out that Galen's methods of "gastrorrhaphy" were used by Andreas Vesalius and Ambroise Paré many centuries later.

Keywords Gastrorrhaphy · Abdominal trauma · History of medicine · History of surgery

Surgery was invented in order to cure illnesses and to help heal wounds inflicted due to accidents occurring from every day practices, such as hunting or exercising, or wounds inflicted due to war. More or less, everyone might have had some kind of experience of how to treat fractures or bone dislocations, how to stop hemorrhage, or how to extract an arrow from the body. It was the fear of death that was teaching the members of the tribes how to treat efficiently a patient.[1] Nevertheless, it is the Hippocratic surgery that sets the foundations of modern surgery. The *Hippocratic Corpus* contains several treatises that describe surgical procedures, such as *On fractures*, *On injuries of the head*, etc. The Hippocratic physicians were familiar with many types of operations, such as trephination, resetting of fractures, etc.

Trauma was also well known to ancient physicians. In the Homeric epic poems and, in particular, in the *Iliad*, numerous references are found with respect to wounds inflicted by foreign objects during the Trojan War. This empiric knowledge was transmitted to the next generations of physicians. From the Alexandrian period, surgery took a new, more scientific meaning given that dissections were allowed and universal knowledge was available for every-

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N. Papavramidou
History of Medicine, School of Medicine,
Democritus University of Thrace,
Alexandroupolis, Greece

H. Christopoulou-Aletra (✉)
History of Medicine, School of Medicine,
Aristotle University of Thessaloniki,
73 Nikis Ave,
54622 Thessaloniki, Greece
e-mail: ealetra@hotmail.com

one in the library of Alexandria. It was Herophilus and Erasistratus who separated medicine in three distinct branches (even though these do not actually correspond to the modern meaning of the words): "surgery," "dietetics," and "pharmaceutics." After this separation, it was only the surgeon who practiced surgery.[1]

As a method for closing wounds, suturing is thousands of years old. Although suture materials have changed, the goals remain the same: closing the wound, supporting, and strengthening wounds until healing increases their tensile strength approximating skin edges and minimizing the risks of bleeding and infection.

Celsus' Method of "Gastrorrhaphy"

Celsus, a physician of the first century A.D., adopted most of the Hippocratic theories and advanced them by presenting a complete description of etiology, clinical manifestations, and treatment of all diseases and illnesses in his book entitled *De medicina*. There are doubts whether Celsus was a true medical practitioner or just an encyclopedist, gathering up the existing medical knowledge. Among many other important topics that appear in his book, the description of a surgical procedure called "gastrorrhaphy" draws attention. It is the first time that this word arises in the medical terminology and its actual etymology denotes suturing of the abdomen ("gastir" = abdomen and "rhaphy" = suturing).

Celsus first provides the reader with a very detailed description of the actual positioning of the patient: he should lie on his back with his hips slightly raised. Then, the use of young assistants in surgery is noted. These are used in order to separate the margins of the wound with the hands or by using two hooks inserted deeper in the margins of the wound. Following this, intestinal prolapse should be dealt with first, by making a larger incision: "if the wound is too narrow for the intestines to be easily replaced, it is to be cut until sufficiently wide." In case the intestines have been out of the abdominal cavity for a long period of time and they have dried up, they should be washed with water to which a small quantity of oil has been added. In order to preserve the order of the coils in the abdomen, the surgeon should first replace the intestines that prolapsed last, and the patient should then be shaken gently so that all coils return to their original position. The surgeon should also examine exhaustively and excise the omenta that appear to be black, since they are necrotic.

After these procedures have been completed, the surgeon should stand on the patient's left side: the surgeon should have his back towards the face of the patient. Celsus believes that stitching only the superficial layer of the skin or the parietal layer of the peritoneum and the muscular wall is not enough; instead, they must be all stitched with two close rows of stitches. Therefore, he proposes the use of two threaded needles, one held in each hand. The stitches should be inserted, first through the parietal layer of the peritoneum, "so that the surgeon's left hand pushes the needle from within outwards through the right margin of the wound, and his right hand through the left margin, beginning from one end of the wound....When each margin has been once traversed, the hands interchange needles, so that into the right hand comes the needle which was in the left, and into the left the needle which was in the right; and again, after the same method, they are to be passed through the margins; and when for the third and fourth time, the needles have changed hands, the wound is to be closed. Afterwards, the same threads and the same needles are now transferred to the skin, and stitches are to be inserted by a like method into this as well, always directing the needles from within outwards, and with the same change, between the hands" (Fig. 1). After the stitching has been accomplished, Celsus prescribes the use of agglutinants on the wound and light bandaging of the area.[2]

Galen's Method of "Gastrorrhaphy"

Galen (second century A.D.) also mentions in his writings the subject of gastrorrhaphy. He respects the Hippocratic theories on diseases, but he is more eclectic in his medicine. He wrote on numerous subjects covering almost all aspects of medicine. His opinion on how to perform gastrorrhaphy does not coincide with Celsus' and besides, he believes that the physicians of his time have no idea on how to perform gastrorrhaphy, since they only sew the peritoneum, leaving unattached the rest of the structures.[3] Thus, he suggests two other methods which he describes in detail. In the first one, the needle penetrates the peritoneum to the muscles of the lower abdomen while in the second the physician reunites the homonymous structures. Surgery, according to Galen, is a systematic removal of what is called "foreign" in the human body, through incisions and "restorations" for the treatment of wounds and ulcers. He believes that there are two types of surgical procedures, synthesis and dieresis, and that gastrorrhaphy is a type of synthesis.[4]

According to Galen, there are four stages of treating all the wounds of the abdomen: first, replacing the herniated parts, then reuniting the wound, then applying the convenient medicaments, and finally, preventing the creation of "sympathetic affections" (affections appearing to an organ due to a malfunction of another structure or system) to the vital organs. As for the replacement of the herniated parts, Galen believes that the wounds that heal without problems are those of medium size because in the large ones, a big mass of viscera comes out while in small wounds, viscera

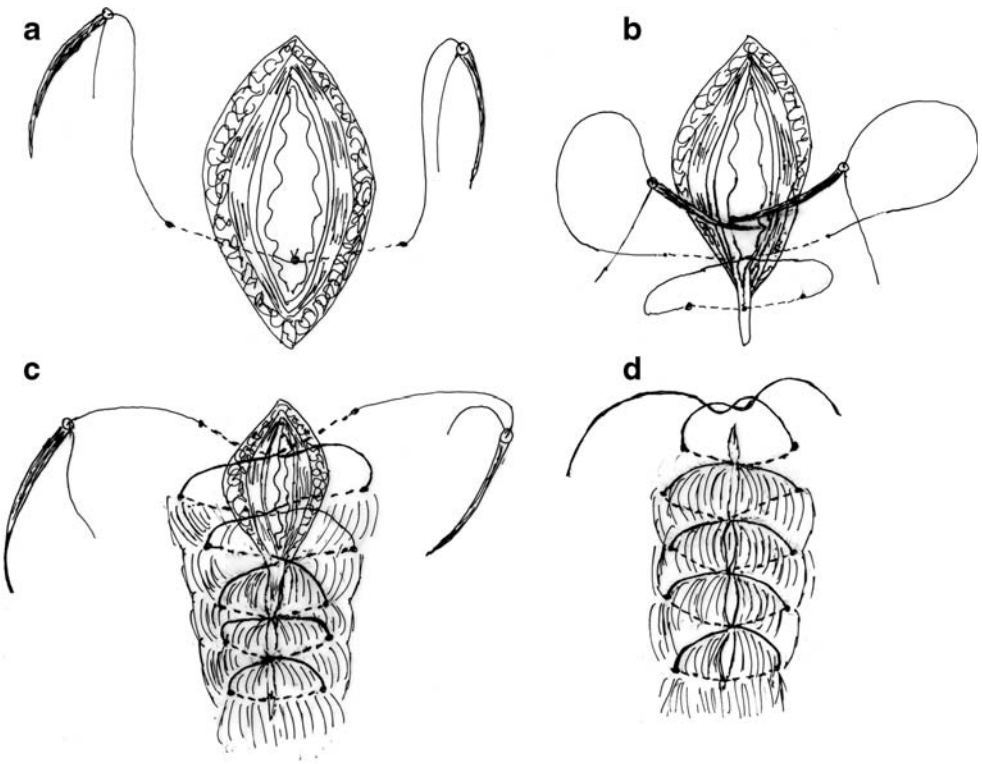

Figure 1 Celsus' technique of gastrorrhaphy with suturing of the superficial layer of the skin or the parietal layer of the peritoneum and the muscular wall with two rows of stitches.

may be easily strangulated. If the wound is small but the herniated parts are large, the doctor should either diminish their size by applying hot towels or extend the incision by cutting the peritoneum with the aid of a "syringotomon." At this time, the herniated parts should be pushed back to the abdominal cavity, after being washed with black tepid wine and then the reunion of the lips of the wound should take place. If the physician chooses to use the first type of suture described by Galen, he should pass a needle with a thread through one of the lips of the wound, from outwards to inwards, through the skin and the muscles, without touching the peritoneum; then, after the needle reappears ahead of this membrane, to the depth of the wound, the physician should pass the needle through the opposite lip, from inwards to outwards, piercing the peritoneum, the muscles, and the skin; then, he should push the needle near to the point it came out, again from outwards to inwards, being careful with the peritoneum, and bring the needle forward, from inwards to outwards, to the lip that was first pierced, where he should reunite this spot with the peritoneum, the muscles, and the skin; he continues in this way to suture one end of the peritoneum with the muscles of the other end, all along the wound, while a skillful assistant holds the lips of the wound and pushes in the herniated parts. The sutures should not be too close to one another because there is a risk of tearing off the skin (Fig. 2). If, on the other hand, the physician wants to have a more solid procedure by sewing together the similar structures, he has to use the second Galenic method of gastrorrhaphy. According to it, he should pierce one lip of the wound, from outward to inward, excluding the peritoneum; he should then move back the needle, pierce the two lips of the peritoneum, move back the needle again, and pierce through the muscles and the skin of the opposite lip of the wound (Fig. 3). Galen considers this method better than the first one because it reunites the parts of the peritoneum with great accuracy.[5]

"Gastrorrhaphy" after Oribasius

Oribasius, a physician of the fourth century A.D., does not describe in his book gastrorrhaphy in detail but rather provides the readers with comments on what the common mistakes during this operation are and the time when it should be performed.

In order to explain the most common mistakes, Oribasius describes the anatomy of the area. According to him, the word "peritoneum" derives from the verb "periteino" (meaning to stretch, to spread around, or to lie on something),[6] and it obtains this name because it expands around all the entrails, intestines, and vessels existing between the diaphragm and the structures beneath it, such as the uterus, the bladder, etc. The peritoneum is described as a very thin membrane, easy to shred, especially at the level of the diaphragm, and of the muscles cross-sectioning the abdomen. At the point where these muscles have a large and thin tendon produced by their "transformation to nerves", the peritoneum adheres to them in such a way

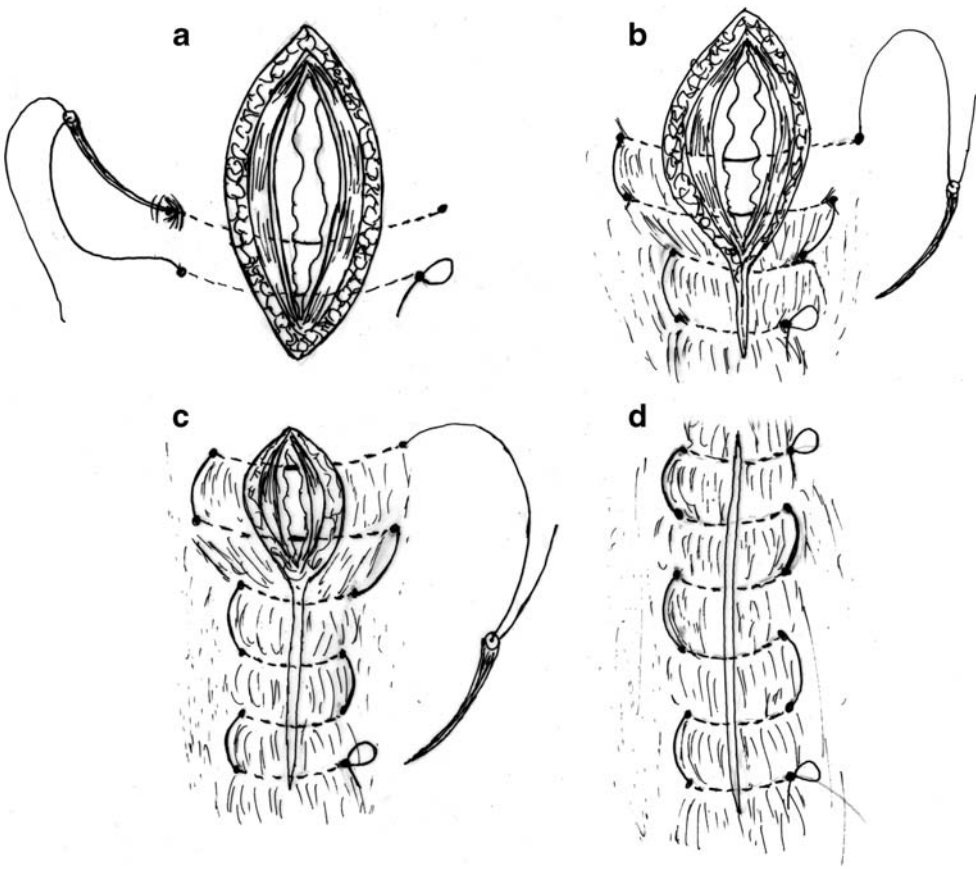

Figure 2 Galen's first technique of gastrorrhaphy where the needle penetrates the peritoneum to the muscles of the lower abdomen.

that it is difficult to be detached. This is the reason, according to Oribasius, why gastrorrhaphy should also include the stitching of the muscle's tendons endings and not only the peritoneum, as some physicians erroneously believe.[7]

Another common mistake made by some physicians while performing gastrorrhaphy is caused due to ignorance of anatomy. Oribasius presents eight muscles that exist at the epigastrium, four on each side: At the outer region lie the biggest muscles, those that descend obliquely from the thorax to the bone of the pubic area. Then, the muscles that mount from the loins are described; after that, the "straight muscles," and lastly, the muscles that adhere to the peritoneum and are "cross-sectional." According to Oribasius, "the nature of the layer that is composed by those four muscles and by the peritoneum is unknown to the greatest number of doctors who believe that it is just the peritoneum." Consequently, during gastrorrhaphy, they stitch together the disrupted parts of this layer as if they were just one membrane.[7]

Finally, Oribasius suggests one more condition for which gastrorrhaphy should be performed (aside from the aforementioned existence of trauma). This is the case of where a fistula ends up to the peritoneum alone. In this case, the physician should use mirth for cleaning the area and then perform gastrorrhaphy.[7]

During the same period, it seems that gastrorrhaphy was performed also in animals, using the exact identical method that was used for humans. Two authors of veterinary medical treatises, Apsyrtos and Hierocles, mention the use of such gastrorrhaphy. Apsyrtos was born in Bithynia and most likely lived during the fourth century A.D. He was a very well-known veterinary surgeon. We do not have enough information about Hierocles' life, except that he might have been a lawyer and not a veterinary doctor. Only fragments of his writings exist. Both authors provide us with the same description of gastrorrhaphy performed in horses. According to them, gastrorrhaphy is used for the treatment of abdominal wounds in the same way physicians perform it in humans. A larger woolen thread is used than the one used for humans. The lips of the wound should be held outside, and the physician should bind with a clip the fat and use a waxed hempen cord for the skin. After a week, the thread should be removed.[8]

Discussion

The modern meaning of gastrorrhaphy is "suture of perforated duodenal or gastric ulcer, wound, or injury";[9] this definition demonstrates the similarity of the meaning of the term between ancient and modern medicine, even

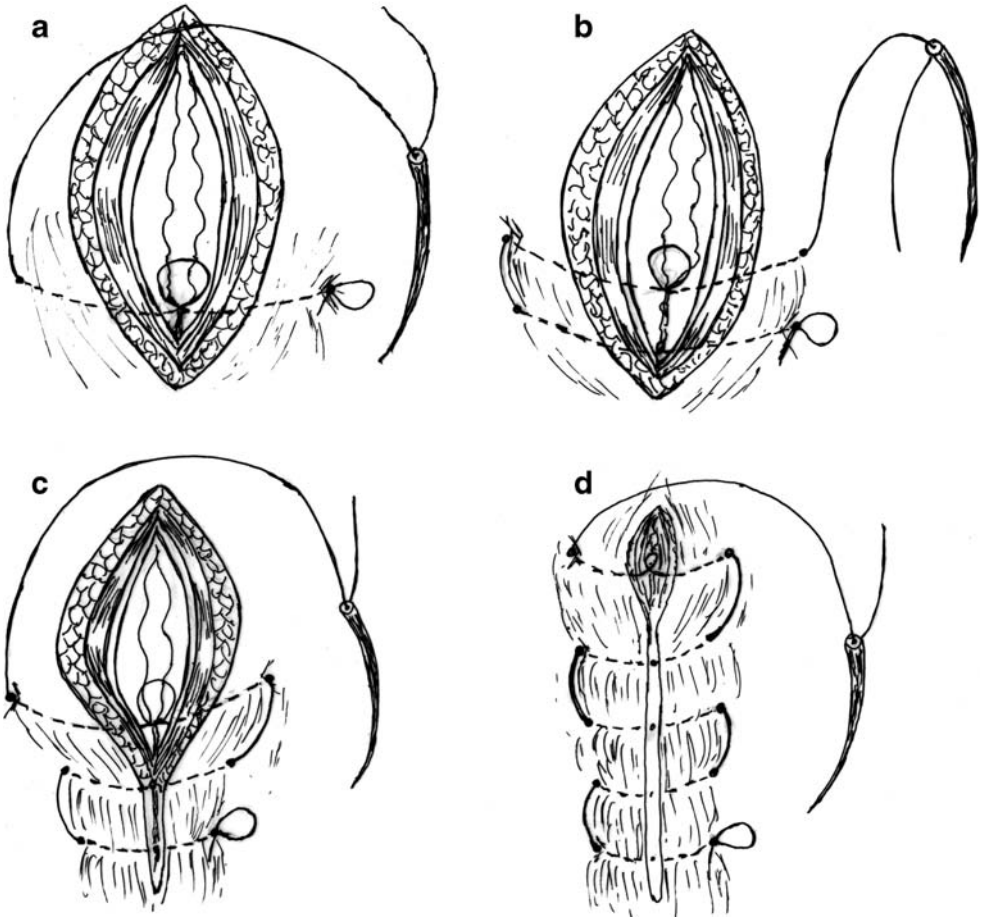

Figure 3 Galen's second technique of gastrorrhaphy where the homonymous structures are reunited.

though the etymology per se leads the reader to an entirely erroneous assumption that gastrorrhaphy concerns suturing of the abdomen.

The obvious questions that may arise concern, among others, the substances used for anesthesia, the dealing with possible inflammation, the way the intestines were anastomozed, the instruments used, etc. With respect to anesthesia, during the Roman period, unconsciousness was provoked with the aid of plants such as cannabis, opium, mandragoras, hyoscyamos, hellebore, and nightshade.[10] Celsus refers to these plants as anodynes which were frequently used, while Galen classifies them as "warm remedies" provoking sleep and anesthesia.[11] The prevention of an inflammatory response was another important matter. In these specific references to gastrorrhaphy, both Celsus and Galen mention the cleaning of the prolapsed viscera with wine or oil before replacing them inside the abdominal cavity. Wine was the main substance used almost in all aspects of medical practice during the antiquity as antiseptic.[12]

Though from a practical point of view the instruments used are also of great importance, Celsus mentions only the use of scissors for cutting possibly necrotic parts of the prolapsed intestines and the use of two needles used at the same time by

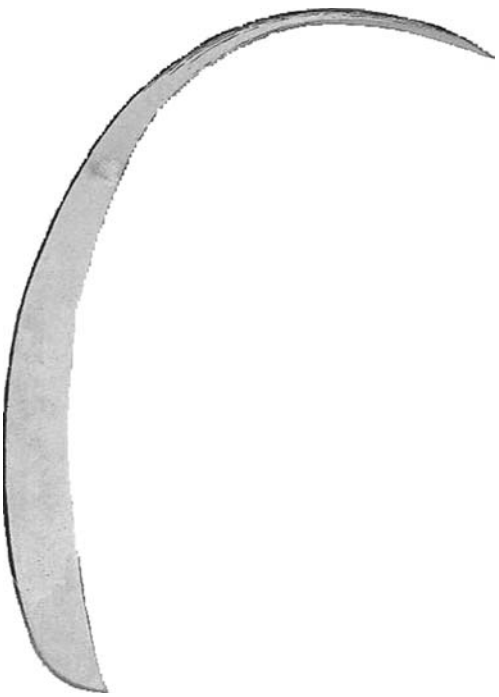

Figure 4 Syringotomos. Figure taken from Milne JS. Surgical instruments in Greek and Roman times. Oxford: Clarendon press; 1907.

the surgeon without, however, providing any detailed description. Galen, on the other hand, mentions the use of an instrument called "syringotomos." According to Milne, this instrument, which remained in use until the nineteenth century, was "a falciform blade the end or which was blunt, but the handle end was prolonged into a slender, rounded sound-like portion with a sharp point. The narrow point was passed into a fistula…and the whole instrument pulled outwards by means of it, thus, dividing the overlying tissues with the falciform blade"[13] (Fig. 4).

Another important issue discussed by the authors is the excision of any part of the intestine or of the omentum that was "black." Both Celsus and Galen suggest the same procedure, knowing that the blackened part has undergone necrosis and that it is of great importance to excise it to avoid sepsis. Unfortunately, no reference whatsoever may be found in all ancient texts concerning the anastomosis of the intestine, after having cut off the necrotic part.

Nowadays, the choice of suture technique depends on several key factors such as the type and the location of the wound, the thickness of the skin, the degree of tension, and the desirable aesthetic result. In the antiquity, the choice of suture technique depended on the surgeon who performed it: Celsus used a specific technique for suturing abdominal wounds while Galen used two other different techniques for the same purpose. From a modern point of view, it is likely that the technique of gastrorrhaphy described by Celsus is stitching in layers with cross-sutures, while both of the Galenic techniques of gastrorrhaphy are versions of the full-thickness sutures used nowadays.[14] The second Galenic type of gastrorrhaphy may be identified with the vertical mattress sutures, which promotes wound edge eversion and less prominent scarring. Vertical mattress sutures allow for skin edges to be closed under tension when wound edges have to be brought together over a distance. It is noteworthy that according to Sprengel, Andreas Vesalius, and Ambroise Paré, at least ten centuries later, surgeons still used Galen's first type of gastrorrhaphy suggesting that it was a more efficient abdominal stitching procedure.[15]

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ORIGINAL ARTICLE

Acute Abdominal Pain in Patients with Systemic Lupus Erythematosus

Omar Vergara-Fernandez · Jorge Zeron-Medina · Carlos Mendez-Probst · Noel Salgado-Nesme · Daniel Borja-Cacho · Jorge Sanchez-Guerrero · Heriberto Medina-Franco

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Abstract
Background Patients with Systemic Lupus Erythematosus (SLE) that present with acute abdominal pain (AAP) represent a challenge for the general surgeon. The purpose of this study was to identify the major causes of AAP among these patients and to define the role of disease activity scores and the APACHE II score in identifying patients with an increased perioperative risk.
Methods We conducted a prospective study of patients admitted to the ER with AAP and SLE in an 11-year period. Demographic, diagnostic, and treatment data were recorded. Systemic lupus erythematosus disease activity index (SLEDAI), systemic lupus international collaboration clinics damage index (SLICC/DI), and APACHE II Score were analyzed. The main outcome variables were morbidity and mortality within 30 days of admission.
Results Seventy-three patients were included. Ninety-three percent were female. Most common causes of AAP were: pancreatitis (29%), intestinal ischemia (16%), gallbladder disease (15%), and appendicitis (14%). Most causes of AAP in patients with LES were not related to the disease. APACHE II score>12 was statistically associated with the diagnosis of intestinal ischemia compared to other causes. No relationship was observed between SLEDAI and outcome. Furthermore, this index did not have impact on diagnosis or decision making. Overall morbidity was 57% and overall mortality 11%. On multivariate analysis, only APACHE II>12 was associated with mortality (P=0.0001).
Conclusion This is one of the largest series of AAP and SLE. Most common causes of AAP were pancreatitis and intestinal ischemia. APACHE II score in patients with intestinal ischemia was higher than those with serositis; further studies are needed to examine whether this score may help to differentiate these ethiologies when CT findings are inconclusive. APACHE II score was the most important factor associated with mortality. Furthermore, a prompt diagnosis and an appropriate surgical management are essential in order to improve patient outcome.

Keywords Acute abdominal pain · Systemic lupus erythematosus · APACHE II · SLEDAI · Pancreas

O. Vergara-Fernandez (✉) · J. Zeron-Medina · C. Mendez-Probst · N. Salgado-Nesme · D. Borja-Cacho · H. Medina-Franco
Departments of Surgery, Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran",
Vasco de Quiroga No. 15, Col. Seccion XVI Tlalpan,
Mexico City, CP 14000, Mexico
e-mail: omarvergara74@hotmail.com

J. Sanchez-Guerrero
Departments of Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion "Salvador Zubiran",
Mexico City, Mexico

Introduction

Despite the fact that acute abdominal pain (AAP) is one of the most common causes of admission to the Emergency Department, it can represent a challenge to surgeons. This is especially true in patients with a concomitant systemic disease like systemic lupus erythematosus (SLE). The incidence of AAP in patients with SLE has been reported to vary from 8% to 40%.[1,2] A delayed diagnosis in these patients is not uncommon; the use of antirheumatic drugs like steroids and azathioprine, which cause gastrointestinal symptoms, and the gastrointestinal manifestations of the disease itself yield a broad spectrum of differential diagnoses.[3,4]

The most frequent etiologies of AAP in patients with SLE remain controversial. A number of studies have found SLE-associated diseases, like lupus enteritis and vasculitis, to be the most common causes.[5,6] However, other studies have shown that the majority of cases of AAP are caused by conventional illnesses.[7] Also, there is conflicting data about how factors like lupus activity or delayed surgical intervention influence the final outcome.[8,9]

The purpose of this study was to identify the major causes of AAP in patients with SLE. Conjointly, we aimed to define the role of acute and chronic disease activity scores and APACHE II score in identifying patients with an increase perioperative risk.

Methods

A prospective study of patients admitted to the Emergency Department of a tertiary care referral center with diagnosis of SLE and AAP in an 11-year period from 1996 to 2007 was performed. Patients who fulfilled more than four of the American Rheumatology Association criteria for the classification of SLE were included.[10] Patients with peritoneal dialysis, abdominal trauma, nonspecific abdominal pain, urinary tract infection, uremia, acute gastroenteritis, obstruction of the ureter, pelvic inflammatory disease, pain from neurologic, toxic, and extraabdominal sources were excluded.

The following information was recorded: demographic data, medical history, medication used, clinical, laboratory and radiological findings, surgical record, systemic lupus erythematous disease activity index (SLEDAI),[11] systemic lupus international collaboration clinics damage index (SLICC/DI),[12] and APACHE II score.[13]

Radiologic studies and laboratory data were obtained at the Emergency Department at the discretion of the attending physician. If an abdominal CT scan was performed, it was obtained with 8–10-mm thick sections and 8–10-mm intervals with contrast material, as long as patients did not have renal failure (creatinine>1.5 mg/dl) or a documented allergic reaction. All patients were evaluated by a general surgeon as well as an internist.

We defined lupus activity when SLEDAI score was greater than three points. SLEDAI consists of 24 variables covering nine organ systems; disease activity is measured by weighing the importance of each organ system involved using multiple regression techniques.[14] Eight points are given for each of the following: seizures, psychosis, organic brain syndrome, visual disturbances, cranial nerve disorder, lupus headache, CVA, and vasculitis; four points for arthritis, myositis, urinary casts, hematuria, and proteinuria; two points for pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, and fever; and one point for thrombocytopenia and leucopenia.[11] The SLICC/DI is valid and reliable for assessing accumulated damage—during the past 6 months—in patients with SLE 20. The index has 41 items covering 12 systems. It includes specific comorbidities associated with SLE and features that are often due to toxicity attributable to treatment.[12] We analyzed this index as positive or negative.

The diagnosis of pancreatitis was based on the presence of typical clinical symptoms, more than threefold increase in serum amylase or lipase and/or anatomical confirmation by CT scan, ultrasonography, or laparotomy. Diagnosis of LES-associated pancreatitis was made in patients with biochemical evidence of pancreatitis and active LES, without radiological evidence of mechanical obstruction and no other explainable cause (including toxic-metabolic etiologies).[15]

When surgery was indicated, the type of operation was based on clinical judgment and personal preference of the attending surgeon. The main outcomes were morbidity and mortality within 30 days of admission. Operative mortality was defined as death occurring within 30 days of the surgical procedure or at any time during the same hospital admission. Means and standard deviations were used as data summaries for continuous measures and counts, and percentages were used for discrete variables. Fisher's exact test was used to evaluate each risk factor with operative mortality and associations were performed with Spearman correlation test. A logistic regression model using stepwise selection was used, including each of the univariately significant factors as potential covariates. The analyses were performed using SPSS (16.0) statistical software. All statistical test were two-sided, and $P<0.05$ were considered as statistically significant.

Results

Seventy-three patients met the study criteria. Sixty-seven (93%) were female; mean age was 32 (range 14–68) years. Mean time from the diagnosis of SLE to the episode of AAP was 8 years (range 1 month to 40 years). Mean duration time of abdominal pain before admission was 3.3 days (range <24 h to 13 days). The principal causes of AAP were: pancreatitis (29%), intestinal ischemia (16%), cholecystitis (15%), and appendicitis (14%). Other etiologies are shown in Table 1.

In 21 patients (29%), a diagnosis of pancreatitis was made. The mean serum amylase and lipase levels were 1,076 and 1,314 U/L, respectively. Mean APACHE II score was 16. Thirteen patients (62%) had severe pancreatitis (APACHE II score>8). Pancreatitis was associated to gallstones in 28.5% and to drugs in 23.8% of the cases. Of the patients with drug-associated pancreatitis, five were

Table 1 Causes of Acute Abdominal Pain

	Parameter (n)	Percentage (%)
Pancreatitis	21	29
Gallstones	6	
Medications	5	
Associated to lupus activity	4	
Unknown	4	
Alcohol	2	
Intestinal ischemia	12	16
Arterial thrombosis	7	
Vasculitis	3	
Mesenteric venous thrombosis	2	
Gallbladder diseases	11	15
Acute cholecystitis	8	
Pyocholecystitis	3	
Acute appendicitis	10	14
Non-complicated	6	
Complicated	4	
Gynecological causes	6	8
Ruptured ovarian cyst	5	
Endometriosis	1	
Miscellaneous	5	7
Negative laparotomies	2	
Perforated colonic cancer	1	
Perforated pseudomembranous colitis	1	
Fungal peritonitis due to *Actinomyces*	1	
Serositis	4	5
Intestinal obstruction	4	5
Adhesions	1	
Internal hernia	1	
Intussusception	1	
Incarcerated inguinal hernia	1	
TOTAL	73	

on prednisolone, of these two, were on low-dose prednisolone (<0.2 mg/kg/day), one on moderate-dose (0.2–0.5 mg/kg/day), and two on high-dose (>0.5 mg/kg/day). Three patients were taking azathioprine; one was on methotrexate and another patient was taking phenytoin. Four patients had lupus-associated pancreatitis. Mean SLEDAI score in this subgroup was 17 (range 14–20). Patients with this etiology improved with medical treatment and steroid pulse therapy. Of the entire pancreatitis group, 18 patients improved with nonsurgical management. Four patients with severe pancreatitis required CT-guided drainage; three of them presented infected necrosis and underwent pancreatic necrosectomies. Three patients with pancreatitis died, all due to sepsis, while two had drug-associated pancreatitis and one pancreatitis secondary to gallstones.

Intestinal ischemia was diagnosed in 12 patients. All of them had an APACHE II score>9, with a mean of 14 (range 10–29) and a mean SLEDAI index of 4 (range 0–15). Initially, because of SLE-associated mesenteric vasculitis, these patients received steroid pulse therapy. The intestinal ischemia mortality rate was 42%; four deaths occurred due to sepsis and one due to pulmonary hemorrhage. Excluding patients with pancreatitis who received nonsurgical management, only APACHE II score >12 was statistically associated with the diagnosis of intestinal ischemia (5/12) compared to other causes of acute abdominal pain (3/43; 41.6% vs. 6.9%, respectively; P=0.0001). Neither symptoms lasting more than three days (25% vs. 13%, P=0.23), antiphospholipid antibodies (25% vs. 15%, P=0.388), SLEDAI>4 (11.3% vs. 24%, P=0.154), SLICC/DI>1 (23% vs. 9%, P=0.104), nor LDH>200 UI/l (17% vs. 16%, P=0.943), correlated with intestinal ischemia. However, lactate>2.2 mmol/L (36% vs. 13%) and leukocytosis (29% vs. 12%) showed a borderline significance with P values of 0.05 and 0.07, respectively. Regarding radiologic evaluation, ten out of 12 CT scans showed positive findings for intestinal ischemia

including bowel wall thickening (one patient), typhlitis (one patient), pneumatosis (two patients), bowel dilatation (three patients), and free-air (three patients).

Other observed causes of AAP are described on Table 1. Six patients underwent a negative a laparotomy or laparoscopy. In four of these patients, the operative findings were diagnostic of serositis; nonbacterial peritonitis without bowel perforation. These four patients presented with severe abdominal pain, absent peristalsis, systemic inflammatory response, and negative CT scans that did not provide enough evidence to rule out ischemia or serositis. In order to exclude medical causes of AAP, laparotomy was delayed in these patients after a 6-h observation period with a short course of steroids. Mean age in this subset was 28 years (ranges, 18 to 42), mean SLEDAI index was 5 (ranges, 3–11), and mean APACHE II score was 6.5 (ranges, 6 to 8). Laparoscopy was only used in one patient, a 19-year-old woman, without postoperative complications. Taking into account only patients who underwent surgical procedures, the rate of negative laparotomies was 11%.

In total, fifty-five (75%) patients underwent a surgical procedure. The types of surgical procedures are shown in Table 2. Overall morbidity was 57%. The most common complications were intra-abdominal abscesses (23%) and pneumonia (11%); other morbidities are shown in Table 3. There were eight perioperative deaths, five patients had intestinal ischemia and three had pancreatitis. All of these patients had APACHE II score greater than 9 (mean 19; range 10–26). The overall mortality rate was 11%. Causes of death were sepsis (87.5%) and pulmonary hemorrhage (12.5%).

On the univariate analysis, factors associated with mortality were intestinal ischemia, pancreatitis, APACHE II score>12, SLICC/DI>1, leukocytosis, lactate>2.2 mmol/L, hypoxemia, and antiphospholipid syndrome. On multivariate analysis only APACHE II score>12 maintained statistical significance (P=0.0001). Seven out of 25 patients with APACHE II>12 deceased (28%), compared to one out of 48 patients with APACHE II≤12 (2%; Table 4).

Table 2 Surgical Procedures

Type of procedures	Parameter (n)
Cholecystectomies	11
Small bowel resections with primary anastomosis	8
Appendectomies	7
Ovarian cyst resections	6
Right hemicolectomies	6
Laparotomies	5
Pancreatic necrosectomies	3
Left hemicolectomies	3
Total colectomies	2
Diagnostic laparoscopy	1
Adhesiolysis	1
Sigmoid colonic resection	1
Hernioplasty with small bowel resection	1
TOTAL	55

Table 3 Postoperative Complications

Type of complications in 73 patients[a]	Parameter (n)
Abdominal abscess	14
Pneumonia	7
Septic shock	5
Wound infection	4
Lobar atelectasia	4
Urinary tract infection	3
Wound dehiscence	3
Wound seroma	3
Disseminated intravascular coagulation	3
Respiratory distress syndrome	3
Seizures	2
Anastomotic leak	2
Others	6
TOTAL	59

[a] There were patients with more than one complication

Discussion

Diagnosing and offering optimum treatment to patients with SLE who present with AAP can be a challenging task. The attending physician or surgeon is faced with a wide range of differential diagnoses including infrequent conditions such as vasculitis, segmental intestinal ischemia, spontaneous rupture of liver and spleen, and total colonic necrosis.[16–20] If the leading causes of AAP among patients with SLE are lupus-associated pathologies or common illness remains controversial. A number of studies have reported intestinal vasculitis as the leading cause of AAP. Medina et al.[5] found this etiology in 43% of patients. Conversely, Al-Hakeem et al.[7] reported a series of 13 patients in whom common causes of AAP were diagnosed. Our results show that most causes of AAP in patients with LES are not related to the disease. Nevertheless, when compared with the general population the expected frequency for each etiology differs with increase rates of pancreatitis and intestinal ischemia.

In accordance to other reports,[21] we found that pancreatitis was the leading cause of AAP; seen in 29% of the patients. Even though some studies show that lupus activity is the primary etiologic factor of SLE pancreatitis,[22–24] we found that biliary and drug-related pancreatitis were the

Table 4 Univariate Analysis of Factors Associated with Mortality

		Mortality (%)	*P* value
Length of abdominal pain	≥5 days	33	0.03
	<5 days	9	
Intestinal ischemia		38	0.003
Other causes		8	
SLEDAI	≥4	18	0.61
	<4	12	
SLIC	(+)	20	0.07
	(−)	3	
WBC	≥12,000/mm^3	29	0.006
	<12,000/mm^3	6	
Creatinine	≥1.2 mg/dL	26	0.02
	<1.2 mg/dL	6	
Oxygen	≤55 mmHg	39	0.01
	>55 mmHg	12	
Lactate	≥2.2 mmol/l[a]	50	0.001
	<2.2 mmol/l	37	
aPL	(+)	37	0.01
	(–)	9	
APACHE II	>12[b]	28	0.007
	≤12	2	

[a] Only in 15 patients

[b] On multivariate analysis only APACHE II score>12 retained statistical significance (P=0.0001)

main etiologies. Additionally, mortality rate was 14% lower than other series of lupus-associated pancreatitis.[25] This study supports findings reported by other groups in our institution that the most frequent cause of acute pancreatitis in SLE patients is mechanical obstruction due to biliary disease.[26] The incidence of drug induced pancreatitis in the general population is 0.1–2%.[27] This is much lower of what we observed in our study. However, one the reasons that could explain this is that most of the individuals included in our study are taking at least one of the drugs associated with this condition.

Al-Hakeem and Medina et al. found overall morbidity rates of 44% and 31%, respectively.[5,7] The latter author concludes that systematic measurement of lupus activity and early laparotomy may improve prognosis in these patients. In our series, a systematic measurement of lupus activity was performed with morbidity and mortality rates of 57% and 11%, respectively. However, SLEDAI did not have impact on diagnosis or decision making when medical causes of acute abdominal pain have been excluded.

Lee et al.[6] found that SLEDAI calculated at the time of AAP was lower than at the time of lupus diagnosis, emphasizing that AAP may occur in patients whose disease activity had been under control. In our study, neither SLEDAI nor aPL correlated with intestinal ischemia; this is similar to the results reported by Lee et al. when analyzing lupus enteritis.[6] Other studies have demonstrated that SLICC/DI has a high predictive value for survival in SLE patients.[28] In our series, SLICC/DI had statistical significance in the univariate analysis. Hence, our data does not support the hypothesis that acute lupus activity influences the mortality; it rather implies that chronic damage may be associated with it.

The hypothesis for the development of the APACHE score was that severity of the acutely ill patient can be measured by the abnormality degree of multiple physiological variables.[13] The APACHE II score is available in most of hospitals worldwide and has been validated as predictor of morbidity and mortality in surgical patients.[29–32] We recognize that this score is complex to calculate and not often used for clinical care. However, since it has shown to be a strong predictive factor and can be easily calculated with the aid of most handheld devices we encourage clinicians to take it into account when managing these patients. Additionally, since fever is the only superimposed value between APACHE II score and SLEDAI index, these scores can be considered independently in patients with SLE.[11,13]

In some patients, it is difficult to determine whether abdominal pain is due to enteritis or serositis because some CT signs are subjectively interpreted.[33] CT findings such as bowel-wall thickening, increased or decreased bowel wall enhancement, bowel dilatation, and ascites are superimposed in patients with intestinal ischemia and vasculitis involving the gastrointestinal tract.[33,34] Due to the fact that APACHE II score in patients with intestinal ischemia was higher than those with serositis, we propose to evaluate whether this score may help to differentiate these etiologies when CT findings are inconclusive.

Lee et al. emphasized on his report that laparotomy could be delayed unless there is definite evidence that GI perforation has occurred. However, it is important to highlight that most of the patients included in their series had medical causes of AAP; such as lupus enteritis, urinary tract infections, acute gastroenteritis, pancreatitis, and serositis.[6] Our findings support evidence that the evaluation of patients with AAP and SLE must be individualized because some of them will benefit from an early surgical intervention.

In summary, this is one of the largest reported series of acute abdominal pain and systemic lupus erythematosus. Most causes of AAP in patients with LES are not related to the disease. Pancreatitis was the main cause of AAP and intestinal ischemia was the main cause of death. Intestinal ischemia can present without lupus activity or antiphospolipid syndrome. APACHE II score in patients with intestinal ischemia was higher than those with serositis; we feel that further studies are needed to examine whether this score may help to differentiate these ethiologies when CT findings are inconclusive. Furthermore, since SLE disease activity index does not impact on patient's outcome, this has no bearing on the diagnosis and the management when medical causes have been excluded. APACHE II score was the most important factor associated with mortality in this group of patients. A prompt diagnosis and an appropriate surgical management are essential in order to improve patient outcome.

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ORIGINAL ARTICLE

Identification of Patients at Risk for Development of Tertiary Peritonitis on a Surgical Intensive Care Unit

Ansgar M. Chromik · Andreas Meiser · Janine Hölling · Dominique Sülberg · Adrien Daigeler · Kirsten Meurer · Heike Vogelsang · Matthias H. Seelig · Waldemar Uhl

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Abstract
Background Tertiary peritonitis (TP) is defined as a severe recurrent or persistent intra-abdominal infection after adequate surgical source control of secondary peritonitis (SP). The aim of this study was to analyze the characteristics of patients with SP who will further develop TP in order to define early diagnostic markers for TP.
Study Design Over a 1-year period, all patients on the surgical intensive care unit (ICU) with SP were prospectively assessed for the development of TP applying the definition of the ICU consensus conference. The Mannheim Peritonitis Index (MPI), C-reactive protein (CRP) and Simplified Acute Physiology Score II (SAPS II) were assessed at the initial operation (IO) that was diagnostic for SP and in the postoperative period.
Results Among 69 patients with SP, 15 patients further developed TP, whereas 54 patients did not develop TP. Compared to SP, patients with transition to TP had significantly higher MPI at IO (28.6 vs. 19.8; $p<0.001$), relaparotomy rate (2.00 vs. 0.11; $p<0.001$), mortality (60% vs. 9%; $p<0.001$), duration of ICU stay (14 vs. 4 days; $p<0.005$), as well as SAPS II (45.1 vs. 28.4; $p<0.005$) and CRP (265 mg/dL vs. 217 mg/dL; $p<0.05$) on the second postoperative day after IO.
Conclusions The MPI at IO as well as CRP and SAPS II at the second postoperative day helps to identify patients at risk for tertiary peritonitis.

Keywords C-reactive protein · SAPS II · Mannheim Peritonitis Index · Sepsis · Secondary peritonitis

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Ansgar M. Chromik and Andreas Meiser contributed equally to this publication.

A. M. Chromik · J. Hölling · D. Sülberg · K. Meurer · M. H. Seelig · W. Uhl (✉)
Department of General and Visceral Surgery, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany
e-mail: w.uhl@klinikum-bochum.de

A. Meiser · H. Vogelsang
Department of Anesthesiology, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

A. Daigeler
Department of Plastic Surgery, Burn Center, Hand Center, Sarcoma Reference Center, BG-University Hospital Bergmannsheil, Ruhr-University Bochum, Bochum, Germany

Abbreviations

CRP	C-reactive protein
ICU	Intensive care unit
IO	Initial operation
MPI	Mannheim Peritonitis Index
SAPS II	Simplified Acute Physiology Score II
SP	Secondary peritonitis
TP	Tertiary peritonitis
SP patient	Patient with SP who did not further develop TP
TP patient	Patient with SP who further developed TP

Introduction

Definition of Tertiary Peritonitis

Peritonitis is one of the most frequent diagnoses on a surgical intensive care unit leading to severe sepsis.[1] It is defined as an intra-abdominal peritoneal infection and can be classified into three major groups—primary, secondary,

and tertiary peritonitis. Primary peritonitis—also referred to as spontaneous bacterial peritonitis—arises in the absence of an identifiable anatomical derangement and has a low incidence on surgical intensive care units. The most frequent entity is secondary peritonitis (SP) which is defined as an infection of the peritoneal cavity resulting from perforation, anastomotic disruption, ischemic necrosis, or other injuries of the gastrointestinal tract.[2] Operative therapy is the treatment of choice and comprises surgical source control of the infectious focus and reduction of the bacterial load. Tertiary peritonitis (TP) is less common and is defined as a severe recurrent or persistent intra-abdominal infection after apparently successful and adequate surgical source control of SP.[2] It is characterized by a prolonged systemic inflammation and organ dysfunction leading to a high rate of SIRS, sepsis, severe sepsis, or septic shock.[1,3] As a result, mortality of TP ranges between 30% and 64%.[2,4,5] The microbial flora encountered in TP is different from SP and displays mostly opportunistic and nosocomial facultative pathogenic bacteria and fungi (e.g., *Enterococci*, *Enterobacter*, *Candida*). Due to broad-spectrum antibiotic therapy, a significant proportion of microbes develop multi-resistance to antibiotics.

Diagnosis of TP

It is often difficult to differentiate between SP and TP since there is a continuum between both clinical situations and the exact time point when SP turns into TP is often missed. Figure 1 illustrates different clinical scenarios for patients with SP. If SP is diagnosed during an operation—which is referred to as "the initial operation" (IO) in this context—the patient will receive surgical source control (e.g., Hartmann's procedure for colonic perforation). If surgical source control is successful, the majority of patients will recover. However, a subset of patients will develop clinical signs of recurrent or persistent intra-abdominal infection in spite of apparently successful source control, which often results in a reoperation. During subsequent relaparotomies, recurrent or persistent peritonitis is encountered in spite of adequate and successful surgical source control during the IO. This form of peritonitis is referred to as TP. Importantly, the diagnosis of TP can only be made in the absence of an obvious anatomical defect or disruption of the gastrointestinal hollow viscera; otherwise, the peritonitis has to be classified as ongoing SP—characterized by a primary failure of surgical source control (e.g., breakdown of the closure of the Hartmann's pouch or breakdown of the suture repair following gastric perforation; Fig. 1). In fact, the most frequent way to diagnose TP, is a "planned" or "on demand" relaparotomy, which is performed in the interval after the IO (Fig. 1).[6,7] However, a relaparotomy—either "planned" or "on demand"—may represent a late event in the management of peritonitis, and it is not necessarily the first relaparotomy after the IO when TP is encountered. Therefore, timely—non-operative—diagnosis of TP after the IO and subsequent initiation of an appropriate therapy may help to reduce the complication rate and to improve the prognosis. It is desirable to identify patients at risk for developing TP as early as possible or at least during the first days after the IO for SP.

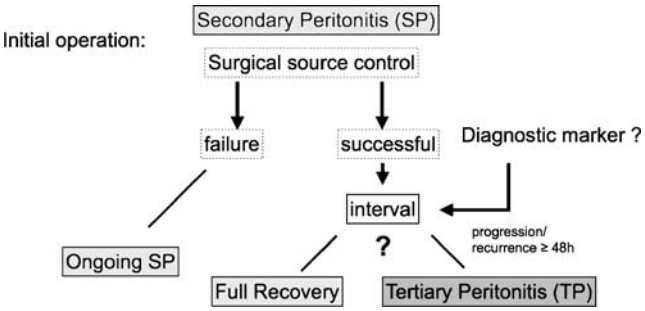

Figure 1 The diagnostic criteria for tertiary peritonitis (*TP*) and the diagnostic challenge.

Diagnostic Challenge

The value of clinical and laboratory parameters and scoring systems for sufficient diagnosis and monitoring of TP is still discussed controversially.[5] However, the intensive care unit (ICU) consensus conference provided three categories for the diagnostic certainty of TP: "microbiologically confirmed", "probable", and "possible".[2] The Mannheim Peritonitis Index (MPI) represents a scoring system that estimates the severity and prognosis of secondary peritonitis at the onset of SP. It is applied easily under routine conditions during initial surgery for SP in the operating room. It was developed and first described in 1987 by Linder et al.[8] and validated in several studies for SP.[9,10] Recent studies reported encouraging results for the Mannheim Peritonitis Index regarding detection patients at risk for TP.[11,12] Another score that has shown a potential to be successfully applied in TP is the Simplified Acute Physiology Score II (SAPS II) score.[12] It was initially designed to predict mortality and disease severity of critically ill patients on surgical intensive care units.[13,14] Laboratory parameters like C-reactive protein or procalcitonin have rarely been evaluated in the diagnosis of TP.[5,15]

However, there is still a lack of studies addressing the identification of risk factors for patients prone to develop TP. It would be desirable to have diagnostic markers that could predict at the onset of peritonitis—during the initial operation or the first postoperative days after—whether the individual patient will develop TP or not (Fig. 1).

The aims of this study were therefore (1) to compare patients' characteristics, clinical outcome and microbial flora of patients with SP and TP and (2) to investigate the efficacy of clinical and laboratory parameters like C-reactive protein,

Mannheim Peritonitis Index and SAPS II to early identify patients with SP at risk for the development of TP.

Material and Methods

Study Population and Definition of Secondary/Tertiary Peritonitis

During a 1-year period (01.01.2006–31.12.2006), all patients admitted to the surgical intensive care unit with a SP were recorded in a prospective database. Due to hospital policy, all patients with a secondary peritonitis are mandatorily admitted to the surgical intensive care unit—for at least 24 h. SP had to be diagnosed during a laparotomy, which was referred to as the IO (Fig. 1). During follow-up, patients with SP were continuously analyzed for the diagnosis of TP—in accordance with the "International Sepsis Forum Consensus Conference".[2] TP was therefore defined as intra-abdominal infection that persists or recurs ≥48 h following successful and adequate surgical source control during the IO.[2] As indicated in Fig. 1, patients with an obvious failure of surgical source control after the IO or following procedures (e.g., insufficiency of the rectal stump, anastomotic insufficiency, etc.) were considered as ongoing SP and not as TP.

Demographic data, origin of peritonitis and intra-operative findings during IO, type of surgical procedure performed during IO, antibiotic treatment, and follow-up procedures like relaparotomies were collected. In order to assess the severity of peritonitis as early as at the IO, the Mannheim Peritonitis Index was calculated routinely during the IO as previously described.[8,9] Furthermore, C-reactive protein was monitored daily during the first three postoperative days and on postoperative day 7 after IO. SAPS II scores were recorded during the first three postoperative days after IO as previously described.[14] Mortality was defined as any death during postoperative hospitalization. Furthermore, intra-operative specimens of abdominal fluid were analyzed by standard microbiological techniques.

Statistical Analysis

Results for the Mannheim Peritonitis Index were expressed as median and displayed in box plots. Box plots are representing the lower, median, and upper quartile whereas whiskers indicate the 10th–90th percentile. Outliers are illustrated by dots. Age, body mass index, Mannheim Peritonitis Index, intensive care unit stay, and the number of relaparotomies per patient were compared by Mann–Whitney test. Frequencies for co-morbidities, underlying malignancy as well as mortality data, frequency of relaparotomies and frequency of specific bacteria were compared by Fisher's exact test. C-reactive protein values and SAPS II scores are expressed as means ± SEM and compared by T test. p values ≤ 0.05 were considered statistically significant. To determine the diagnostic accuracy of the Mannheim Peritonitis Index measurement during initial operation as well as C-reactive protein and SAPS II measurements 2 days after initial operation, for the distinction between TP and SP, corresponding receiver operating characteristic curves were calculated. Furthermore, the area under the receiver operator characteristic curve was defined. Cut-off values for the Mannheim Peritonitis Index, C-reactive protein, and SAPS II with the corresponding sensitivity, specificity, and confidence intervals were given. Data were processed with SPSS 16.0/GraphPadPrism 5.

Results

Demographic Data of the Study Population

Over a 1-year period (2006), 1,091 patients were admitted to the surgical intensive care unit. Among the 1,091 intensive care unit patients, 69 were diagnosed having SP. The diagnosis of SP was made intra-operatively in all 69 patients during the IO. Among those, 15 patients (21.7%) further developed TP—according to the ICU consensus conference definition.[2] These patients were referred to as TP patients throughout this study. The remaining 54 patients with SP (78.3%) did not develop TP and were therefore referred to as SP patients. Demographic data of the study population are summarized in Table 1. There was no significant difference in gender distribution, age, body mass index, cardiovascular and pulmonary co-morbidities as well as malignant diseases between SP and TP patients (Table 1).

Etiology and Source of Peritonitis

Etiologies and infection source of secondary peritonitis for all patients ($n=69$) found at the IO are depicted in Fig. 2, separately for TP patients ($n=15$) and SP patients ($n=54$). The majority of patients had perforated diverticulitis or other colonic perforations at the IO. Less frequent were other causes like gastric/duodenal perforations, anastomotic insufficiencies, or appendicitis. However, there was no significant difference in terms of anatomical site and source of infection between TP and SP patients.

Detailed Characteristics of TP patients

Detailed patient characteristics of TP patients are summarized in Table 2. In only one out of the 15 patients (6.7%), TP was diagnosed non-operatively. In this patient (patient #14), the diagnosis of TP was made 5 days after the IO by clinical signs of infection and laboratory and CT radiographic

Table 1 Demographic Data of Patients with Secondary Peritonitis Who Further Developed Tertiary Peritonitis (TP Patients) and Who Did not Develop Tertiary Peritonitis (SP Patients)

	SP patients	TP patients	
Patients	78.3% (n=54)	21.7% (n=15)	
Female	53.7% (n=29)	60.0% (n=9)	n.s.
Male	46.3% (n=25)	40.0% (n=6)	n.s.
Median age (range), years	72 (14–93)	76 (37–96)	n.s.
Mean age (±SD), years	67.1 (±18.3)	70.0 (±18.6)	n.s.
Mean BMI (±SD)	25.0 (±5.7)	25.0 (±3.4)	n.s.
Cardiovascular co-morbidity (%)	74.1	73.3	n.s.
Pulmonary co-morbidity (%)	38.9	53.3	n.s.
Malignancy (%)	22.2	13.3	n.s.

BMI body mass index, *SD* standard deviation, *n.s.* not significant

measurements. In the remaining 14/15 patients (93.3%), TP was diagnosed intra-operatively by relaparotomies after the IO (either first or second relaparotomy; Table 2). As required by the ICU consensus conference definition of TP, these patients showed persistent or recurrent peritonitis ≥48 h following successful and adequate surgical source control which was achieved during IO.[2] There was no failure of surgical source control of the IO (e.g., insufficiency of the rectal stump, anastomotic insufficiency, etc.). The median time period between initial operation and diagnosis of TP was 87 h (range 48–338 h).

Severity, Clinical Course, and Outcome of Secondary and Tertiary Peritonitis

The mean Mannheim Peritonitis Index, which was recorded at the IO in all patients (n=69), revealed significant higher values for TP patients (28.6±SD 7.0; median 20, range 17–39) compared to SP patients (19.8±SD 8.2; median 20, range 4–37; $p \leq 0.001$, Mann–Whitney test) as illustrated in Fig. 3. Elevated severity of peritonitis at the IO of TP patients was paralleled by a higher frequency of relaparotomies following the IO (14/15 patients; 93.3%) compared to SP patients (5/54 patients; 9.3%; $p \leq 0.001$; Fisher's exact test; Table 3). The mean number of relaparotomies following IO per patient was 2.00 (±0.93 SD) for TP patients compared to 0.11 (±0.37 SD) for SP patients ($p \leq 0.001$; Mann–Whitney test; Table 3). All relaparotomies in the five SP patients were "programmed relaparotomies". In the TP group, there were nine patients with "programmed relaparotomies" and five patients with "on demand relaparotomies" that were initiated by clinical detection. As a consequence, the concept of "programmed relaparotomies" was applied with a significantly higher frequency in TP patients (60.0%) compared to SP (9.3%; $p \leq 0.001$; Fisher's exact test; Table 3). The timing and chronology of relaparotomies in relation to the IO is illustrated

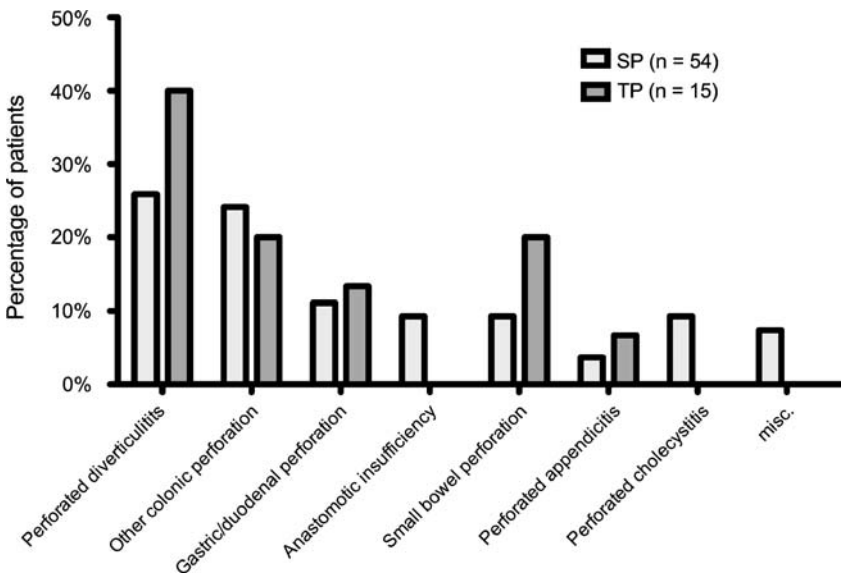

Figure 2 Etiology and infection source of secondary peritonitis found at the initial operation for patients who further developed tertiary peritonitis (*TP*; n=15) and for patients who did not (*SP*; n=54). Definitions of TP and SP are according to the ICU consensus conference.

Table 2 Detailed Clinical Data for Patients with Tertiary Peritonitis (n=15)

Patient no.	Age (years)	Sex	Diagnosis at initial operation (IO)	Initial operation (IO)	MPI at IO	Num. relap.	1st relap (h)	2nd relap (h)	Diag. TP (h)	ICU stay (days)	f/u (days)
1	85	f	Perforated diverticulitis with ileocecal abscess	Hartmann's procedure + ileocecal resection	33	2	56	96	56	30	Died (30)
2	76	f	Rectum perforation and ischemic ileocecal region	Subtotal colectomy with terminal ileostomy	35	1	48	n.a.	48	3	Died (5)
3	80	f	Perforation of the ascending colon	Right hemicolectomy with terminal ileostomy and colostomy (mucous fistula)	23	4	41	87	87	77	Surv.
4	89	f	Gastric ulcer perforation	Gastric resection (Billroth II)	33	2	41	233	233	10	Died (10)
5	80	f	Perforated diverticulitis with multiple interenteric abscesses and small bowel perforations	Hartmann's procedure + 2 small bowel resections with primary anastomoses	37	2	338	386	338	17	Died (17)
6	50	m	Perforated diverticulitis with interenteric abscesses	Hartmann's procedure	23	2	42	144	144	16	Surv.
7	37	m	Perforated appendicitis	Open appendectomy	20	2	36	90	90	10	Surv.
8	83	f	Perforated diverticulitis	Hartmann's procedure	35	2	52	120	52	6	Died (6)
9	72	m	Colostomy perforation following parastomal hernia repair	Segmental resection of descending colon, colostomy redo	23	2	42	89	89	27	Surv.
10	67	f	Ileal perforation following subtotal colectomy and ileo-rectal anastomosis (anastomosis intact)	Loop ileostomy	39	2	49	99	49	36	Died (36)
h11	48	f	Ileal perforation following anterior rectum resection (anastomosis intact)	Closure of perforation, lavage	17	3	58	131	58	10	Surv.
12	37	m	Small bowel perforation due to briden ileus, Crohn's disease	Ileocecal resection, loop ileostomy	20	3	36	96	96	13	Surv.
13	70	f	Perforated diverticulitis	Hartmann's procedure	29	2	86	264	86	34	Died (38)
14	80	m	Gastric perforation due to advanced gastric cancer	Closure of perforation	32	0	n.a.	n.a.	120[a]	9	Died (9)
15	96	m	Perforated diverticulitis	Hartmann's procedure	30	1	60	n.a.	60	2	Died (3)

f female, *m* male, *IO* initial operation, *MPI* Mannheim Peritonitis Index, *Num. Relap*. number of relaparotomies, *1st/2nd relap* Time period between initial operation and first/second relaparotomy in hours, *Diag. TP* time period between initial operation and diagnose of tertiary peritonitis (*TP*), *f/u* follow-up, *Surv.* patient still alive, *Died (x)* patient died *x* days after the initial operation in the hospital

[a] Diagnosis of TP was made based in clinical and laboratory findings only (patient # 14)

in Fig. 4. Impaired outcome of TP patients compared to SP patients was paralleled by significantly longer hospitalization on the intensive care unit, since median intensive care unit stay for TP patients was 13 days (range 3–77 days) compared to 4 days (range 1–50 days) for SP patients (p=0.002, Mann–Whitney test; Table 3). Compared to SP patients, TP patients were characterized by higher frequency of multi-organ failure (73.3% vs. 18.5%; $p\leq0.001$, Fisher's exact test) and higher mortality (60.0% vs. 9.3%; $p\leq0.001$, Fisher's exact test; Table 3). All deaths in the TP group (9/15) were due to septic multi-organ failure as a result of tertiary peritonitis. There were no autopsies performed.

Microbiological Data

Figures 5 and 6 illustrate the microbiological spectrum of microbial isolates obtained from the IO and the antibiotic therapy initiated during the IO—separately for TP patients (n=15 specimens) compared to SP patients (n=54 specimens). The distribution of microbiological species at the time of the IO did not differ significantly between TP and SP patients with the exception of *Escherichia coli*. There was a significantly higher proportion of *E. coli* in isolates from TP patients compared to SP patients (73.3% vs. 37.0%; $p\leq0.05$; Fisher's exact test; Fig. 5). As depicted in Fig. 6, antibiotic

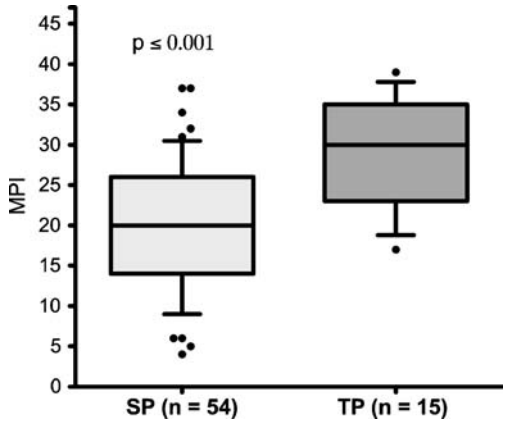

Figure 3 Mannheim Peritonitis Index (*MPI*) at the initial operation. Significantly higher MPI values for patients who further developed tertiary peritonitis (*TP*; $n=15$) compared to patients who did not (*SP*; $n=54$; $p\leq0.001$; Mann–Whitney test). *Boxes* represent the lower, median, and upper quartiles; *whiskers* indicate the 10th–90th percentile and outliers are illustrated by *dots*.

therapy initiated during IO after detection of secondary peritonitis did not differ significantly between TP and SP patients. The majority of patients were treated with imipenem/cilastatin (SP 27.8%; TP 46.7%; $p=0.21$; Fisher's exact test) or piperacillin/tazobactam (SP 51.9%; TP 53.3%; $p=1.00$; Fisher's exact test). Figure 7 delineates the changes in the microbiological spectrum in TP patients compared to SP patients. This analysis compares isolates of TP patients from the relaparotomy that was diagnostic for TP and isolates from the IO of SP patients ($n=54$ specimens). In the TP group ($n=15$ patients), only 11 specimens were obtained during relaparotomy and could be included into the analysis. There was a significant microbiological shift towards *Enterococcus* and *Candida* species in TP with significantly higher proportions of *Enterococcus* (*$p\leq0.05$; Fisher's exact test) and *Candida* (**$p\leq0.01$; Fisher's exact test) in TP patients compared to SP patients (Fig. 7).

Laboratory Parameters

The mean C-reactive protein (±SEM) during the first postoperative days after the IO (postoperative day 1–postoperative day 7) was significantly higher in TP patients (204±13 mg/L) compared to SP patients (166±8 mg/L; $p\leq0.05$, *T* test). The time course of C-reactive protein values during the first postoperative days after the IO is displayed in Fig. 8 for SP and TP patients. Both curves decline from preoperative values to postoperative day 1. On the second postoperative day, C-reactive protein is at its maximum and again declining over the next days. Although both curves run parallel to each other, mean C-reactive protein values for TP patients are significantly higher compared to SP patients on the second postoperative day (265±17 vs. 217±12 mg/L; $p=0.05$, *T* test) and on postoperative day 7 (174±23 vs. 119±11 mg/L; $p=0.03$, *T* test; Fig. 8).

The mean SAPS II score (±SEM) during the first three postoperative days after the IO operation was significantly higher in TP patients (46.1±3.7) compared to SP patients (29.7±2.0) ($p\leq0.001$, *T* test). The time course of SAPS II values during the first three postoperative days after the initial operation is depicted in Fig. 9. SAPS II scores for TP patients on the first (47.1±4.2), second (45.1±4.0), and third postoperative days (44.9±4.0) were significantly higher compared to SP patients on the respective days (30.7±2.1, 28.4±2.0, and 30.3±2.5, respectively; $p\leq0.001$, $p\leq0.001$, and $p=0.004$, respectively; *T* test; Fig. 9).

Early Detection of Tertiary Peritonitis

In order to asses to what extent intra-operative Mannheim Peritonitis Index measurement during the IO and C-reactive protein and SAPS II measurements on postoperative day 2 could differentiate between TP patients and SP patients, the corresponding receiver operating characteristic curve was constructed and the area under the receiver operator characteristic curve was calculated. The area under the receiver operator characteristic curve for the Mannheim Peritonitis Index at the initial operation was 0.794 (95% confidence interval=0.672–0.915; $p\leq0.001$). A sensitivity of 80.0% and specificity of 68.5% were achieved with a Mannheim Peritonitis Index cut-off value of 22 (Table 3). The area under the receiver operator characteristic curve for C-reactive protein and SAPS II on the second postoperative

Table 3 Clinical Course and Outcome of Patients with Secondary and Tertiary Peritonitis

	Secondary Peritonitis	Tertiary Peritonitis	
Patients	78.3% ($n=54$)	21.7% ($n=15$)	
Frequency of relaparotomy	9.3% ($n=5$)	93.3% ($n=14$)	$p\leq0.001$
Relaparotomy/patient (±SD)	0.11 (±0.37)	2.00 (±0.93)	$p\leq0.001$
Frequency of "programmed" relaparotomy	9.3% ($n=5$)	60.0% ($n=9$)	$p\leq0.001$
Frequency of "on demand" relaparotomy	0% ($n=0$)	33.3% ($n=5$)	$p\leq0.001$
Median ICU stay (range)	4 days (1–50)	13 days (3–77 years)	$p=0.002$
Frequency of MOF	18.5%	73.3%	$p\leq0.001$
Mortality	9.3%	60.0%	$p\leq0.001$

SD standard deviation, *ICU* intensive care unit, *MOF* multiple organ failure

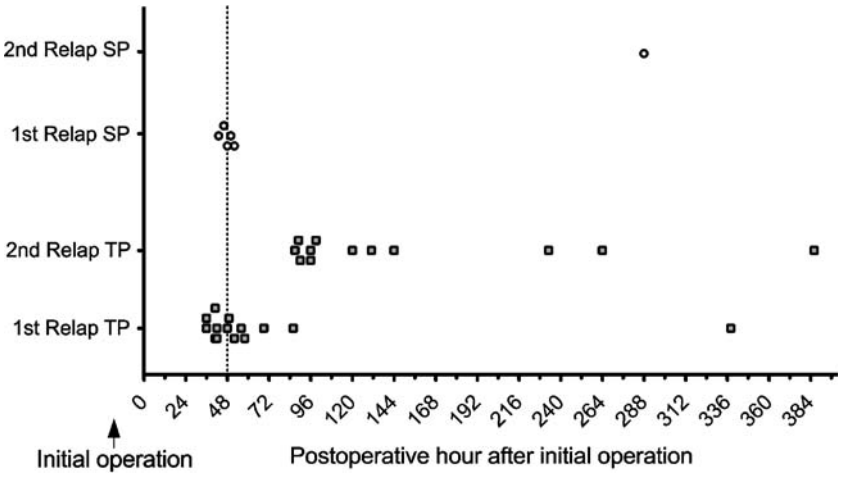

Figure 4 Timing and chronology of the first relaparotomy (*1st Relap*) and second relaparotomy (*2nd Relap*) for patients who further developed tertiary peritonitis (*TP*; $n=15$) compared to patients who did not (*SP*; $n=54$) in relation to the initial operation. *Each dot* represents an individual patient.

day after initial operation was 0.696 (95% confidence interval=0.562–0.830; $p=0.02$) and 0.797 (95% confidence interval=0.634–0.960; $p\leq0.001$), respectively. A cut-off value for C-reactive protein of 215 mg/L led to a sensitivity of 80.0% and a specificity of 57.4%. A cut-off value of 39 for the SAPS II score revealed a sensitivity of 80.0% with a specificity of 74.5% (Table 4).

Discussion

Definition of Tertiary Peritonitis

The standard treatment for SP is an immediate laparotomy with surgical source control and antibiotic therapy. However, a few patients will develop a clinical syndrome—also referred to as TP, which is characterized by a persistent intra-abdominal infection, an altered microbial flora, failure of the immune response, and progressive organ dysfunction leading to high mortality. There is still an ongoing debate about the definition of TP. In fact, some opinions deny the existence of TP as a distinct entity. In the past, TP has simply been defined as failed surgical source control or inadequate antibiotic therapy of SP. Other definitions emphasized the impaired host response to peritoneal infection.[16] This heterogeneity of definitions resulted in varying inclusion criteria and incommensurable results in clinical studies focusing on TP.[5] In the current study, we applied the latest ICU consensus conference guideline that provides a precise definition. TP was defined as intra-abdominal infection that persists or recurs ≥48 h following successful and adequate surgical source control.[2] This definition contains two essential conditions, which have to be met: the time period (≥48 h) and successful surgical source control. Although the ICU guideline does not provide further explanation for "successful surgical source control",[2] our interpretation of this term was a complete and sustainable eradication of the surgical focus. If a patient

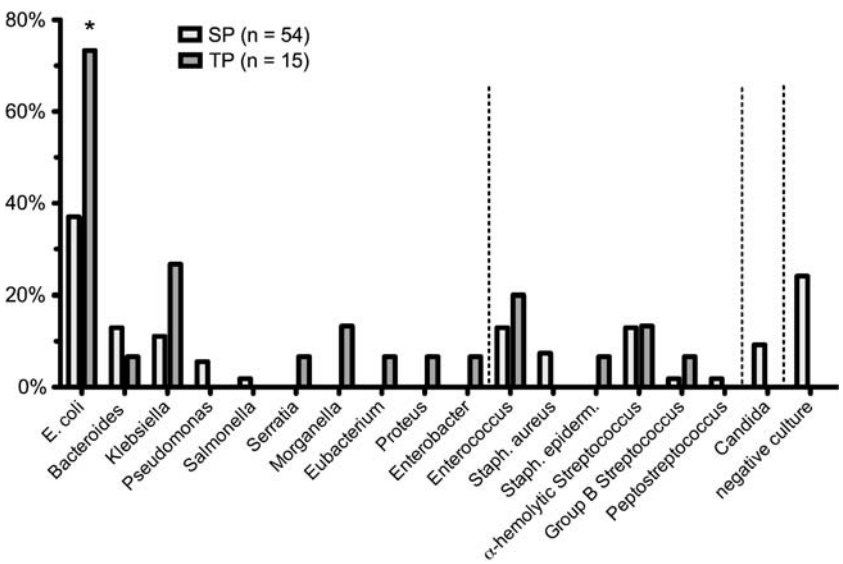

Figure 5 Microbiological spectrum of microbial isolates obtained from the initial operation. Comparison between patients who further developed tertiary peritonitis (*TP*; $n=15$ specimens) compared to patients who did not (*SP*; $n=54$ specimens). Significantly higher proportion of *E. coli* in TP compared to SP (*$p\leq0.05$; Fisher's exact test). *Dotted lines* separate gram-negative bacteria, gram-positive bacteria, and fungi.

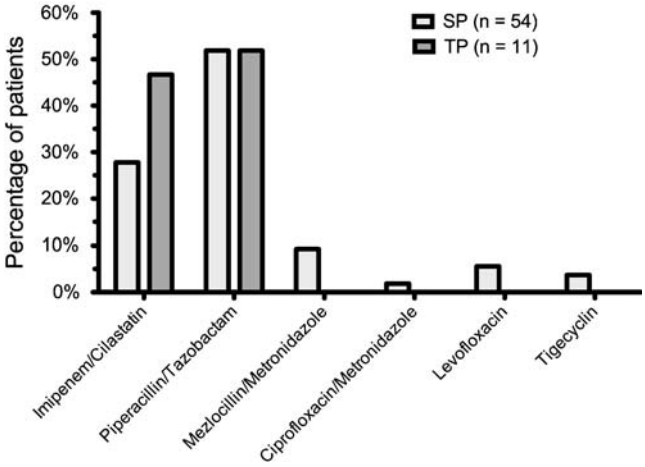

Figure 6 Antibiotic treatment initiated during the initial operation at the onset of secondary peritonitis. There was no difference in the antibiotic spectrum between patients who further developed tertiary peritonitis (*TP*; $n=15$) compared to patients who did not (*SP*; $n=54$ specimens; Fisher's exact test).

presented—during relaparotomy or clinically—with an obvious failure of previous surgical source control in terms of a "technical problem", this patient was not classified as TP but as SP patient. Other examples of "failure of surgical source" control comprise insufficiency of the rectal stump after Hartmann's procedure, anastomotic insufficiency, or other technical problems that lead to disruption of the physical integrity of the gastrointestinal hollow organs.

Nevertheless, there is consensus that SP and TP exist in a continuum and the transition between both may be quite subtle. Although TP may be diagnosed during relaparotomy as a simple discrete point in the illness, in reality, it evolves gradually over several hours or days. In the current study, TP was diagnosed during relaparotomy in 14/15 patients. Only one patient was diagnosed having TP by clinical and laboratory measures 120 h after initial operation. For all patients with TP, the time interval between the initial operation and the diagnosis of TP was 87 h (median) and thus considerably long. In addition, it is important to emphasize that in six patients the diagnosis was made not until the second relaparotomy, while during the first relaparotomy the intra-abdominal situation was estimated innocuously. It was therefore the aim of this study to compare clinical and laboratory parameters between patients with SP who will further develop TP (TP patients) and who will not (SP patients). The necessity to define early predictors for TP becomes evident looking upon the devastating mortality rate for TP of 60% encountered in this study, which was relatively high compared to other studies—reporting mortality rates ranging between 27% and 64%.[11,12,17] We also observed a clear relationship between peritonitis type (TP vs. SP) and mortality, which was in contrast to other publications.[16]

Risk Factors and Microbial Flora of TP

Several epidemiologic and clinical risk factors have already been identified that might predispose to TP, which include age, etiology of peritonitis, malnutrition, and multi-resistant microorganisms.[15] With regard to the patient's age or etiology and infection source of peritonitis, we were unable to detect significant differences between TP and SP. Concerning the microbial flora encountered in the initial operation, we did only find a higher proportion of *E. coli* in TP patients compared to SP patients. All other bacteria were equally distributed. It has recently been shown that there is a microbial shift in TP towards *Enterococcus*, *Enterobacter*, *Pseudomonas*, *Candida albicans* and other opportunistic bacteria and fungi.[11,12,17] However, in this study, we could only demonstrate a significant shift towards *Enterococcus* and *C. albicans* between patients who suffered from TP compared to SP. In our opinion,

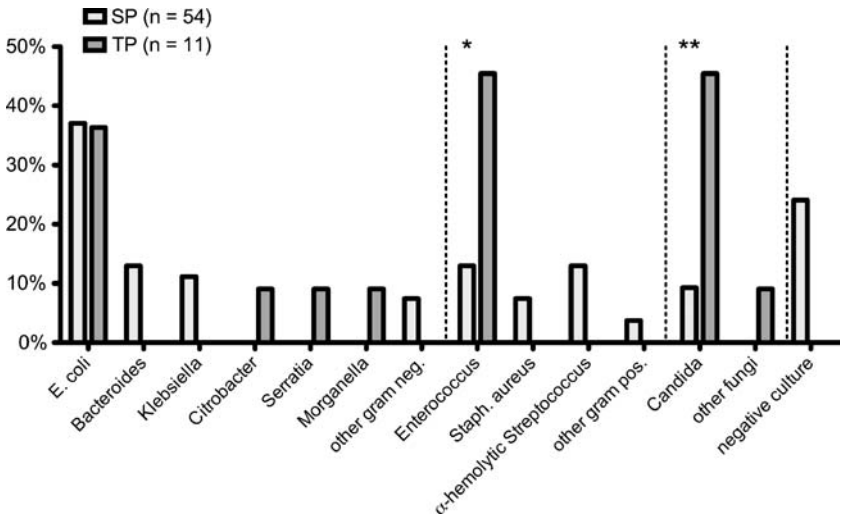

Figure 7 Comparison of the microbiological spectrum between secondary peritonitis (*SP*) and tertiary peritonitis (*TP*). The microbial isolates of patients with TP were obtained from the relaparotomy that was diagnostic for TP ($n=11$ specimens). Isolates of patients with SP were obtained from the initial operation ($n=54$ specimens). Significantly higher proportion of *Enterococcus* ($*p\leq0.05$; Fisher's exact test) and *Candida* ($**p\leq 0.01$; Fisher's exact test) in TP compared to SP. *Dotted lines* separate gram-negative bacteria, gram-positive bacteria, and fungi.

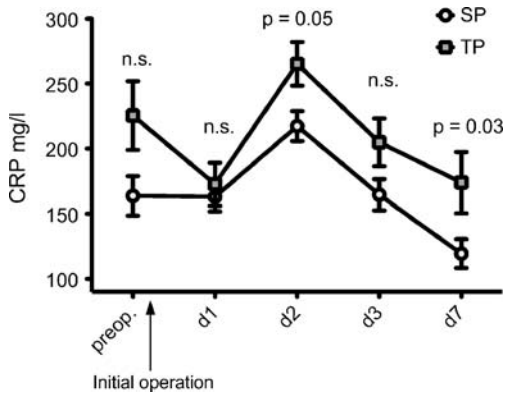

Figure 8 Time course of C-reactive protein (*CRP*) in the perioperative period of the initial operation in patients who further developed tertiary peritonitis (*TP*) and patients who did not (*SP*). Mean CRP ± SEM values are indicated preoperatively (*preop.*) and on postoperative days 1, 2, 3, and 7 (*d1*, *d2*, *d3*, and *d7*). Significantly higher CRP values for TP compared to SP on the second postoperative day (p=0.05) and postoperative day 7 (p=0.03; *T* test).

microbiology is not suited as an early diagnostic marker for the identification of patients at risk for TP, since microbiological studies—including resistance analysis—take up to 1 week. Nevertheless, future studies will be necessary to investigate the microbial shift as well as the antibiotic resistance data in our patients.

Predictive Parameters for TP

In the current study, we analyzed three early and easily accessible parameters for identification of patients who might further develop TP: Mannheim Peritonitis Index, SAPS II, and C-reactive protein. Some might argue that due to persisting systemic inflammation repeated surgical procedures or intermittent nosocomial infections, the value of clinical (Mannheim

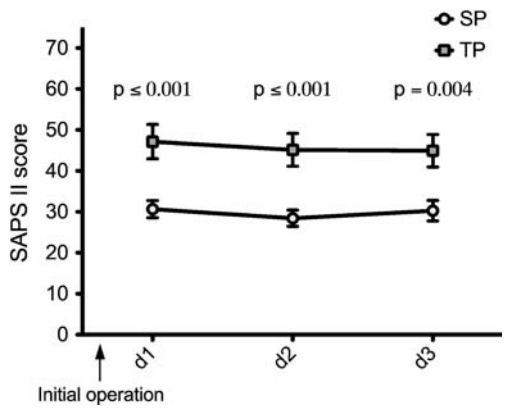

Figure 9 Time course of SAPS II scores in the postoperative period after the initial operation in patients who further developed tertiary peritonitis (*TP*) and patients who did not (*SP*). Mean SAPS II scores ± SEM values are indicated on the first three postoperative days (*d1–d3*). Significantly higher SAPS II scores for TP compared to SP during the whole period ($p \leq 0.001$, $p \leq 0.001$, and p=0.004, respectively; *T* test).

Table 4 Diagnostic Accuracy of MPI at Initial Operation and CRP/SAPS II on the Second Postoperative Day for the Discrimination Between Tertiary Peritonitis and Secondary Peritonitis

	Cut-off value	Sensitivity (%)	Specificity (%)	LR+
MPI	22	80.0 [51.9–95.7]	68.5 [54.5–80.5]	2.54
CRP	215 (mg/L)	80.0 [51.9–95.7]	57.4 [43.2–70.8]	1.88
SAPS II	39	80.0 [51.9–95.7]	74.5 [59.7–86.1]	3.13

Values in square brackets are 95% confidence interval

MPI Mannheim Peritonitis Index, *CRP* C-reactive protein (milligram per liter), *MPI* Mannheim Peritonitis Index, *SAPS II* Simplified Acute Physiology Score II, *LR+* positive likelihood ratio

Peritonitis Index, SPAS II) and laboratory parameters (C-reactive protein) for sufficient diagnosis of TP is limited.[5] In fact, there are conflicting data concerning the value applying such parameters for the detection of TP.[15,17] Unlike other studies, our approach was to analyze these parameters as early as possible—at the IO that was diagnostic for SP and on the first postoperative days.

The Mannheim Peritonitis Index was initially designed to estimate the prognosis and predict mortality of patients with SP.[8–10] In our study population, the Mannheim Peritonitis Index was significantly higher in patients that later on developed TP compared to SP (28.6 vs. 19.8). Similar results have been shown in two recent publications analyzing the Mannheim Peritonitis Index in TP.[11,12] In addition, the receiver operator characteristic analysis in the current study revealed encouraging results with an area under the receiver operator characteristic curve of 0.794 for the detection of TP. With regard to the receiver operator characteristic analysis, it has to be considered that the Mannheim Peritonitis Index is an early—if not the earliest—marker for TP. It is accessible immediately during the IO. This renders the Mannheim Peritonitis Index to a diagnostic tool of high potential.

The second parameter was the SAPS II score, initially designed to predict mortality and disease severity of critical ill patients.[13,14] We could demonstrate that SAPS II was significantly higher during the first three postoperative days after initial operation in TP patients (46.0) compared to SP patients (29.7). Interestingly, the curves for TP and SP patients ran completely parallel to each other over the whole period. The receiver operator characteristic analysis on the second day revealed an area under the receiver operator characteristic curve of 0.797, which demonstrates the diagnostic potential of this scoring system for early identification of patients at risk for TP. Our results are consistent with a recent study that reported similar SAPS II scores for TP (45.6) and SP (31.9) patients—underlining the importance of this parameter.[12]

The third parameter tested in our study was the acute phase protein C-reactive protein. Although C-reactive

protein constitutes a routine parameter in patients with abdominal infections, it has hardly been explicitly evaluated in the diagnosis of TP.[5,15] In our study, the time course of C-reactive protein displayed a curve with two peaks: one peak preoperatively and one peak on the second postoperative day after the IO. In between, on the first postoperative day, lower C-reactive protein values were observed, possibly due to an operative clearing effect. Interestingly, although both curves run parallel, C-reactive protein values of TP patients were significantly higher compared to SP patients on the peak of the second postoperative day (265 vs. 217) after the IO. However, the corresponding area under the receiver operator characteristic curve was only 0.696. The main problem of C-reactive protein is the lack of specificity for abdominal infections, as shown in numerous studies.[18–20] A rise of C-reactive protein during the postoperative period may simply be the result of the operative trauma.[21,22] Nevertheless, this study shows a high diagnostic potential of C-reactive protein. This hypothesis has to be addressed in further studies.

Conclusion

In conclusion, due to high mortality of tertiary peritonitis and often delayed diagnosis, it is crucial to identify patients at risk for developing tertiary peritonitis as early as possible: at the initial operation that reveals the diagnosis of peritonitis and during the first postoperative days. Our results indicate that the Mannheim Peritonitis Index assessed at the initial operation and the time course of C-reactive protein and SAPS II during the first days after initial operation are promising diagnostic candidates for the future.

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ORIGINAL ARTICLE

Free Jejunal Graft for Reconstruction of Defects in the Hypopharynx and Cervical Esophagus Following the Cancer Resections

Dean Zhao · Xingqiang Gao · Limei Guan · Wenling Su · Jing Gao · Cunshan Liu · Xianyang Luo · Xiaoyan Li

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Abstract
Objectives The reconstruction of esophagus defects after hypopharyngeal and cervical esophageal carcinoma resection is an ongoing problem. The objective of this article was to investigate the techniques of the free jejunal graft for the reconstruction of hypopharyngeal and cervical esophagus and discuss the outcome related to the procedures.
Subjects and methods From July of 2005 to December 2007, seven patients with hypopharyngeal and cervical esophageal cancer underwent free jejunal graft reconstruction of the hypopharyngeal and cervical esophagus. Their clinical data were retrospectively analyzed. All patients received postoperative radiotherapy and were followed up for 7–24 months.
Results Despite the multistep and time-consuming procedure, free jejunal graft survival was 100%. Operation-induced complications did not occur in six patients. One patient developed pharyngeal fistula.
Conclusion The present experience supports the use of free jejunal grafts in reconstruction of the hypopharyngeal and cervical esophagus defects after exenteration of the central compartment of the neck. A high successful rate with low incidence of complications in reconstruction of the hypopharyngeal and cervical esophagus was obtained in this study.

Keywords Hypopharyngeal · Esophageal cancer · Free jejunal graft · Reconstruction · Microvascular

Introduction

In the restoration of the continuity of the alimentary tract after esophagectomy, the stomach or the colon remain the organs of choice to use.[1] However, when a malignant process arises in the cervical esophagus or in the hypopharynx, the use of those organs carries some problems. Several techniques have been developed, such as the deltopectoral flap[2] and the musculocutaneous flaps,[3] and some disadvantages over those methods have been described, including the long operation time, high rate of flap necrosis, and other complications.

The free jejunal graft, the method described by Miller and Lee,[4] has widely been used for reconstruction of the pharynx and hypopharynx, especially for proximal lesions, whereas gastric pull-up is the technique of choice for reconstruction of the hypopharynx and cervical esophagus when the resection extends below the thoracic inlet.[5–7] The goal of the free jejunal graft is a single stage reconstruction with low morbidity and mortality, short hospital stay, and early restoration of swallowing.

In this article, we present our experience with this technique performed in seven patients and discuss the outcome related to the procedures.

Patients and Methods

From July of 2005 to December 2007, seven patients with the hypopharyngeal and cervical esophageal defects underwent the reconstruction by using a microvascular free jejunal grafts. Mean age of patients was 57.5 years (ranged

D. Zhao (✉) · X. Gao · L. Guan · W. Su · J. Gao · C. Liu · X. Luo · X. Li
Department of Otolaryngology-Head & Neck Surgery,
Xiamen First Hospital Affiliated Fujian Medical College,
55 Zhenhai Road,
Xiamen City, Fujian Province 361003, China
e-mail: xingqiang7211@yahoo.com.cn

from 41 to 75 years). The male–female ration was 5:2. Primary malignancy was located in the hypopharyngeal (five cases) and cervical esophagus (two cases). All patients were examined by X-ray barium meal (Fig. 1), and the diagnosis was confirmed by histological examination of the biopsy tissues. All cancers were the primary squamous cell carcinoma confirmed by the histology. The clinical preoperative staging was according to the tumor-node metastasis classification system of the International Union Against Cancer[8] (Table 1).

All seven patients did not receive any preoperative treatment. For six patients without clinical palpable neck lymph nodes, modified radical neck dissection (excision of the sternocleidomastoid muscle and accessory nerves, but preservation of the internal jugular vein) was performed; for one patient with the primary tumor extending toward the midline and clinical palpable neck nodes on the side of the primary tumor, radical neck dissection (excision of the internal jugular vein, sternocleidomastoid muscle, and accessory nerves) on the side of the primary lesion and modified radical dissection on the contralateral side were performed.

Resection with adequate margin was performed in three dimensions. The resection margin was 15 mm superiorly, 25 mm inferiorly, and 25 mm laterally. The deep margin under both circumstances reached to the prevertebral fascia. For the cervical carcinomas, tumor extirpation to achieve an adequate distal resection margin included the removal of more than 2 cm of the esophagus. Tumor-free margins were confirmed by frozen section during operation.

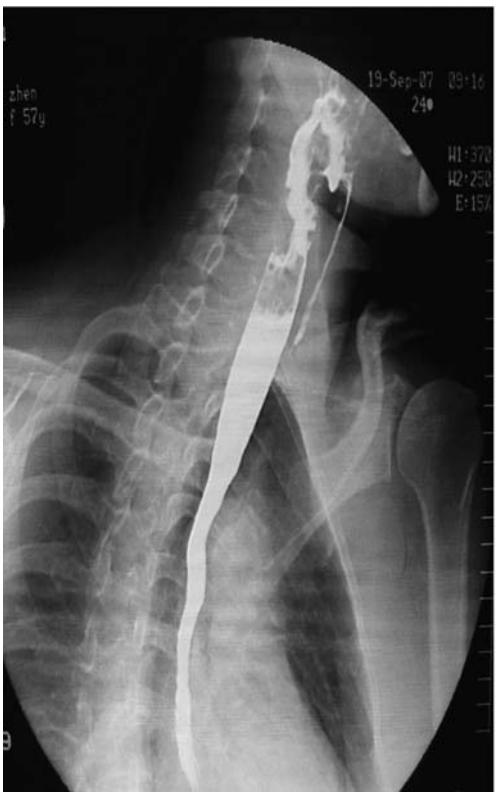

Figure 1 Esophagography reveals left pyriform sinus lesion involving the cervical esophagus.

Table 1 Cancer Staging and Free-grafted Patients

Disease staging	Patient number
Hypopharyngeal cancer	5
Stage 0	0
Stage I	0
Stage II	1
Stage III	1
Stage IV	3
Cervical esophageal cancer	2
Stage 0	0
Stage I	0
Stage IIa	0
Stage IIb	0
Stage III	1
Stage IVa	1
Stage IVb	0

Free jejunal graft for reconstruction was performed by two teams. A team working in the removal of the primary tumor and neck dissection carefully identified the recipient vessels. The internal jugular vein and facial artery were used in most of the patients (Table 2).

Following resection of the lesion, a different team worked in the abdomen. A segment of proximal jejunum (a distance of 20–30 cm from the Treitz ligament) with an appropriate artery, vein, and adequate intestinal arcade was laparoscopically harvested (Fig. 2). The length of intestine harvested was determined by measuring the defect. After the recipient vessels were prepared, the bowel vessels were transected, and the jejunum was transferred to the neck. The upper and lower ends of the intestine were temporally sutured to pharyngeal and esophageal sites, respectively. The microvascular anastomosis was performed first, followed by the enteric anastomosis. The veins first and then the artery were anatomized. The patency of anatomized vessels was characterized with intestinal pink color, peristalsis, and fluid secretion.

Table 2 Anastomotic Vessels

Vessels		Number of cases
Artery	Transverse cervical artery	1/7
	Superior thyroid artery	1/7
	Facial artery	5/7
Vein	Internal jugular vein	6/7
	Common facial vein	1/7

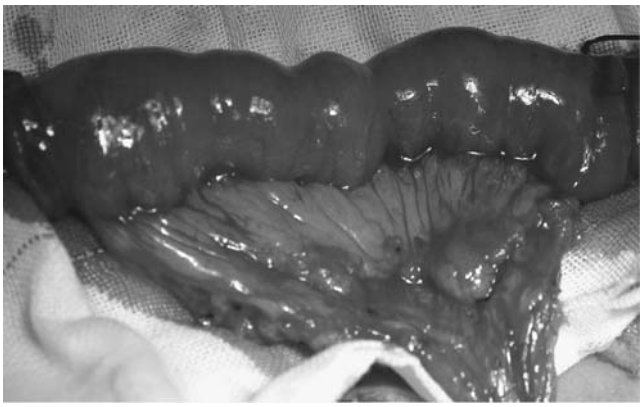

Figure 2 A segment of proximal jejunum (a distance of 20–30 cm from the Treitz ligament) was harvested. The length of intestine required was according to the size of defect.

All patients underwent laryngectomy, total hypopharyngeal, and cervical esophageal resection. Partial oropharyngeal sidewall and tongue root resection were performed in one patient and removal of the involved thyroid gland in three. All patients received postoperative radiotherapy. After a period of 7–24 months (average 13.5 months), follow-up was done. Esophagography was performed 2 months after the operation in all patients.

Results

The entire tumors were removed, and the resection margins were negative in all patients. A harvested jejunal segment was interposed (Fig. 3). All operations were successfully performed without procedure-related complications. The reconstruction of free jejunal graft in all patients survived. Six patients survived well without postoperative complications. One patient developed pharyngeal fistula and recovered with anti-inflammatory treatment and dressing changes. One patient died of heart attack 95 days after the operation.

Figure 3 Free jejunal reconstruction of hypopharyngeal and cervical esophageal defects.

The average time of resumption of feeding was 15 days following the operation (range, 3–20 days). Swallowing was achieved in all patients after recovering from the procedure. Excluding one death of heart attack, all patients survive well until the present data are collected for the report. There was no recurrence of tumor or dysphagia in all surviving patients. There were no late complications such as strictures, and an excellent function of the jejunum was shown by esophagography (Fig. 4).

Discussion

The methods for reconstruction of tissue defects following hypopharyngeal and cervical esophageal cancer resection are diverse.[2,3] With the development and experiences of microsurgical techniques, the free jejunal graft for reconstruction of the esophagus defect has gained wide acceptance.[4] Despite very aggressive therapeutic measures, this technique has many advantages, for example, (1) the first stage of anastomotic procedure shows little impact on the digestive system with low rate of surgical complications; (2) the jejuna with a large and adequate vasculature provides freedom selection for mesenteric vessels to harvest the intestine; (3) free jejunal graft may provide a greater range of security for the tumor resection by a harvest of sufficient

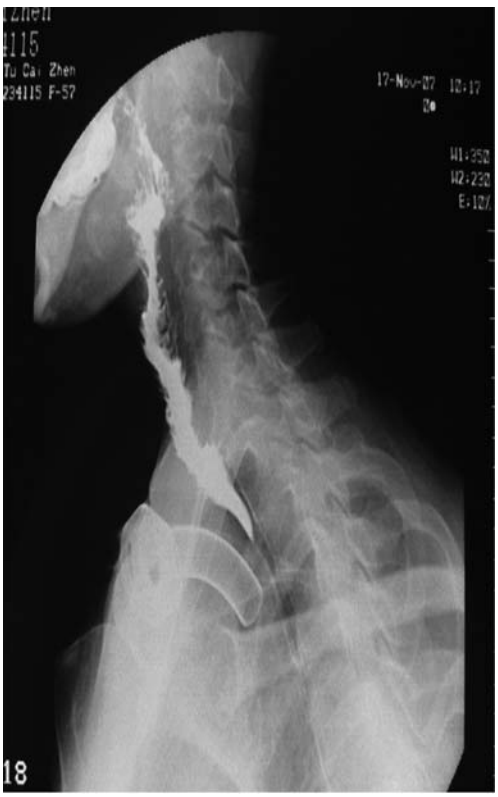

Figure 4 Esophagography reveals a normal peristalsis of free jejunal graft in a patient 2 months after reconstruction.

length of intestinal segment; and (4) the anastomotic jejunum secretes intestinal fluid to moisten the mucous membrane, facilitating the recovery of swallow function.

However, the free jejunal reconstruction has its limitation, for example, the lesion extended or located below the thoracic inlet will be unsafe for anastomosis to transecting margin of the esophagus,[5–7] and this technique is performable only in the condition of disorder free in the thoracic esophagus and intestine.[9] Moreover, free jejunal reconstruction may complicate with wound healing, hemorrhage,[10,11] necrosis,[12] pulmonary infections, and fistula.[13] The incidence of the postoperative complications in our series was low: Only one patient developed pharyngeal fistula. We think that the reason for this problem is because the surgical procedure was performed in a narrow operating field, and the blood flow to the reconstructed bowel was likely to be disordered. To avoid those complications, well-vascularized coverage of the reconstructed cervical esophagus, exposed vessels of the operating filed, and surrounding cutaneous defect are mandatory.

The jejunal free flap is a standard technique in the reconstruction of hypopharyngeal and cervical esophageal defects. Conventional harvest of the jejunal flap is performed with open laparotomy and associated with complications, including wound infection or dehiscence, increased pain, deep venous thrombosis, prolonged ileus, and prolonged hospital stay.[14] These complications significantly influence the outcome of the reconstruction. However, laparoscopic harvest of the jejunum for use in free tissue transfer reconstruction have many advantages such as lower donor site morbidity, shorter operative time, and quicker recovery, particularly in elderly or high-risk patients.[15] Our findings supports the fact that endoscopic harvest of jejunal segments for free tissue transfer is a safe technique, with good postoperative results, and does not possess the inherent risks and complications of a traditional laparotomy harvest.

Technically, it is noteworthy that the upper and lower ends of the intestine must be well identified first, and before the anoastomisis is performed, the two ends are temporally sutured to pharyngeal and esophageal sites, respectively. We feel that these steps are important to avoid the possibility of up-side-down of the intestinal ends, which results in a backflow of intestinal juice, and the risk of vascular pedicle torsion caused by a displacement of anatomized intestinal segment. The hypopharyngeal and cervical esophageal carcinoma located at the postcricoid area or pyriform sinus involved the pyriform sinus tip should be removed without preserving the throat. Our patients reserved no throat, and they recovered quickly from the operation.

Optimal reconstructive procedures should provide the lowest mortality and morbidity and the most rapid return to successful feeding.[14] In this study, the free jejunal grafts in all seven patients survived, and the patients acquired a good quality of life. The most important for survival of free jejunal grafts is to keep the patency of anatomized vessels. This involves many factors, and here we present our successful experience: (1) When harvesting the jejunal segment, more mesenteric tissue should be harvested to allow for coverage of the vessel anastomotic stoma, in a attempt to avoid the obstruction of the blood vessel resulted from scar; (2) because of significant different calibers between the jejunal vein and jugular vein, the anastomosis of the two veins should be performed with an end-to-side anastomosis (the end of jejunal vein was anatomized with the side of the jugular vein), so that the negative pressure of the jugular vein may prevent the possible venous thrombosis; (3) the mesenteric blood vessels should be transected at appropriate length, and this can avoid the tension at the stomal margins. Attention should be paid on the appropriate bowel placement to avoid vascular pedicle torsion, when the jejunal segment is moved to the defect site for anastomosis; (4) two pairs of the artery–vein anastomosis should be performed to ensure the blood supply, if a jejunal segment longer than 13 cm is used; (5) postoperative anticoagulant spasmolytic medication should be administered; and (6) the jejunal graft should be frequently monitored postoperatively by the fiber laryngoscope in order to find the early disorder of blood supply.

In addition to the reconstructive procedures as the principle factors affecting the outcome of reconstruction, curative resection of enough tumor while removing as little normal tissue as possible is a very important factor. A high incidence of submucosal tumor extension along the longitudinal axis of the hypopharynx and the distance of submucosal tumor extension ranging from 10 mm to 25 mm have been reported.[16–19] Therefore, our study suggests that appropriate resection margins in three dimensions are taken into account during surgery for hypopharyngeal carcinomas and that tumor-free margins are further confirmed by frozen section during operation and an appropriate reconstruction followed.

The management of lymph nodes in hypopharyngeal carcinoma has remained a challenging problem. For patients with clinically negative necks, Buckley and MacLennan found that 36% of neck nodes on the side of the primary tumor and 27% of contralateral neck glands contained a metastatic tumor.[20] In consideration of the early and high propensity of metastasis to the contralateral neck, therefore, for the patient with positive neck nodes on the side of the primary lesion, we advocate the modified radical dissection on the contralateral neck nodes, followed by postoperative radiotherapy, even if they may not be clinically detectable. This regime offers a good chance of eradicating the disease.[21]

In view of the extensive spread to the cervical esophagus, Davidge-Pitts and Mannel[22] recommended radical excision of the whole esophagus for adequate distal clearance. However, Ho and colleagues[21] indicated that it was

oncologically feasible not to remove the whole length of the esophagus routinely. The tumor recurrence and overall survival rates did not improve despite a total esophagectomy, and the resection-associated complications were significantly higher in the patients who had undergone an esophagectomy in addition to a pharyngolaryngectomy.[21] In our study, the removal of more than 2 cm of the esophagus was an adequate distal resection margin. The distal margin of the esophagus below the thoracic inlet will be unsafe for anastomosis to the harvested jejunal segment.

On the whole, in our study, satisfied results were obtained by the interposition procedure with fewer postoperative complications, faster refeeding, and better quality. Postoperative radiotherapy were given to all patients in our study, which was a beneficial factor to improve survival;[23] however, a long period of follow-up is needed to explore an actual survival.

Conclusions

The present experience supports the use of free jejunal grafts in reconstruction of the hypopharynx and cervical esophagus defects after exenteration of the central compartment of the neck. A high successful rate with low incidence of complications in repairing the hypopharynx and cervical esophagus was obtained in this study.

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CASE REPORT

High Jejunal Perforation Complicating Tuberculous Abdominal Cocoon: A Rare Presentation in Immune-Competent Male Patient

M. G. Bani-Hani · A. Al-Nowfal · S. Gould

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Abstract
Background Tuberculosis (TB) peritonitis is a rare presentation of TB that is typically insidious, presenting with systemic symptoms and nonspecific abdominal pain. In the majority of the cases, this leads to bowel obstruction and rarely causes abdominal cocoon. The disease process predominantly affects the small bowel with a tendency to involve the terminal ileum, leading to perforation on rare occasions.
Methods We are presenting a case report of multiple small-bowel perforations in immune-competent male patient complicating a TB cocoon and discuss clinical course and therapeutic options.
Discussion TB cocoon is a rare form of TB peritonitis presenting usually in the form of bowel obstruction. However, TB can cause multiple bowel perforations, particularly in children and immune-compromised patients. Such presentation carries a high rate of mortality. With the global increase in TB infections and the emergence of aggressive, multidrug-resistant strains, more severe manifestations are expected to increase. We presented a case of such severe acute manifestation on a background of insidious TB cocoon in a fit immune-competent male. Although primary repair of TB perforation is considered hazardous, it could not be avoided on this occasion. Nevertheless, proximal defunctioning jejunostomy and the early use of anti-TB drugs seemed to facilitate healing in such scenario.
Conclusions TB should be considered in all cases of atypical bowel perforations. Proximal jejunostomy and early use of anti-TB drugs can facilitate primary repair in aggressive TB infection with multiple bowel perforations.

Keywords Tuberculosis · Bowel perforation · Abdominal cocoon · Peritonitis

Introduction

Over the last 20 years, the incidence of tuberculosis (TB) has been steadily rising. It is increasingly encountered with the rise of HIV infection rate worldwide.[1] About one third of HIV-infected persons also harbor mycobacterium tuberculosis. Although the scale of the problem is greater in developing countries, the disease is involving more of the developed countries, possibly due to the increase in intravenous drug abuse, the enlarging old-age population in these countries, and the wave of transglobal emigration. Notably, this is also associated with emergence of aggressive, multidrug-resistant strains of TB.

TB peritonitis is a rare presentation of TB that is typically insidious, presenting with systemic symptoms (fever, anorexia, weight loss, and generalized weakness) and nonspecific abdominal pain. Studies in endemic areas suggest that obstruction is the commonest presentation of TB in the abdomen (~73%)[2] and that the disease process predominantly affects the small bowel with a tendency to involve the terminal ileum. However, jejunum can also be involved especially in children and immune-compromised adults.[3,4] In the majority of cases, the slow inflammation causes strictures, adhesions, and inflammatory masses, but

M. G. Bani-Hani (✉) · A. Al-Nowfal · S. Gould
North West London Hospitals NHS Trust,
Northwick Park Hospital,
Harrow, Middlesex, UK
e-mail: mgbh76@hotmail.com

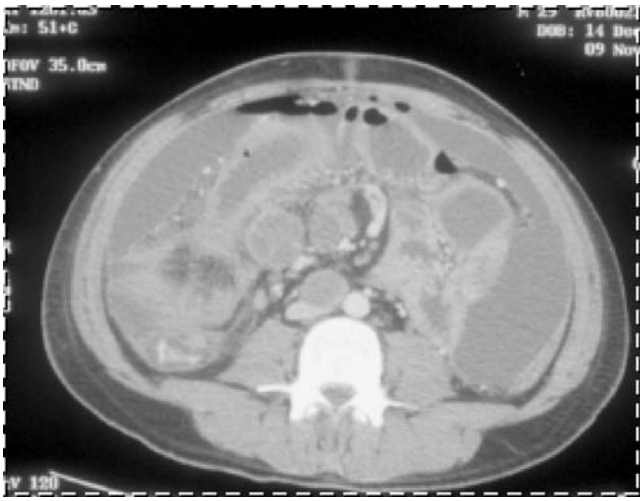

Figure 1 Abdominal CT scan showing intraperitoneal gas and free fluid, multiple fluid-filled small-bowel loops with thickened wall, in addition to enlarged lymph nodes. All abdominal contents encapsulated in a thin fibrinous membrane.

in around 2.5–10% of the cases, it can cause multiple perforations that mandates bowel resection, and this carries a high rate of mortality (up to 29% in some series) especially if the operation was delayed for more than 36 h.[5]

Case Report

A 29-year-old man arrived in the UK from India 5 weeks prior to presenting to Accident and Emergency with sudden onset left flank pain, vomiting, and frank hematurea. Clinically, he was tender in the left flank and was suspected to have renal colic. However, the intravenous urethrogram study performed was inconclusive, and the patient self-discharged before general surgical evaluation. Four days later, the patient presented again to the emergency department with more severe, generalized abdominal pain associated with persistent vomiting and 5 days of constipation. Clinically, he was in shock with severe dehydration. Although he was apyrexial, his heart rate was 130 bpm, and blood pressure was 95/43 mmHg. Abdominal examination revealed a board-like rigidity and generalized peritonism. Urgent computerized tomography (CT) scan showed a large amount of free fluid and free gas in the abdomen with prominent, thickened, fluid-filled small bowel loops and multiple enlarged necrotic lymph nodes in the chest and abdomen (Fig. 1) for which the differential diagnosis included lymphoma, typhoid fever, and tuberculosis. Subsequently, urgent laparotomy showed the presence of 2 l of feculent fluid surrounding an abdominal cocoon. The whole bowel and omentum were encased in a thickened fibrinous membrane with an obvious small-bowel perforation in the left upper quadrant and a large retroperitoneal lymph node mass. As the bowel was very inflamed, the initial management was limited to washout and perforation repair, and the abdomen was left open with a laparostomy. Next day, second-look laparotomy revealed multiple jejunal perforations going as proximal as 20 cm from duodenojejunal (DJ) flexure. The whole bowel was released and all perforations repaired, and this time, a high jejunostomy was formed. Lymph node samples revealed acid-fast bacilli, and anti-TB treatment was started. The postoperative period was complicated by recurrent complex intra-abdominal abscess formation that needed open surgical drainage. Furthermore, the patient developed a vesico-cutaneous fistula which needed further surgical intervention. Despite the hectic recovery period and with adjunct use of anti-TB drugs, the patient made a slow progress to be discharged 7 months after the initial event following surgical closure of jejunostomy.

Discussion

Sclerosing encapsulating peritonitis or abdominal cocoon is a very rare cause of intestinal obstruction described mostly in young adolescent girls[6] diagnosed only intraoperatively. The most common type is idiopathic. However, it has been linked to various pathological processes including: systemic lupus erythematosus, sarcoidosis, endometriosis, ovarian cancer, and rarely, TB. To date, TB abdominal cocoon has been reported in nine cases only with the largest series comprising six cases.[7] In this series, all reported cases presented with intestinal obstruction rather than free perforation and peritonitis with a characteristic delayed initial presentation and prolonged complex recovery pattern taking up to 4 months. Such recovery will depend on the patient health status and the extent of intra-abdominal disease. Unsurprisingly, cases with multiple perforations are associated with more prolonged complicated course.

Although TB perforation is uncommon, it seems to occur more in children and immune-compromised patients. As the disease process seems to predominate in the terminal ileum, most perforations and masses occur in that region. However, jejunal perforations still occur but very rarely in isolation. Even in endemic regions, TB perforation is quite rare. In a series of 167 childhood peritonitis in India, only19 cases had underlying TB enteritis. Jejunum was affected in five cases only, and multiple perforations occurred in three cases. Nevertheless, TB enteritis was associated with a very high mortality (12 of the 19 cases) which is attributed to poor preoperative status associated with the insidious nonspecific symptoms.[3] In another series of 96 histologically proven abdominal TB cases from Ghana, ten cases only presented with perforation.[2]

Because of the encapsulating nature of the abdominal cocoon, it is not usually associated with free perforation,

and if perforation occurs, it is usually contained within the inflammatory mass.

Although our patient was immune-competent, the disease process localized to the jejunal region was quite aggressive with sudden deterioration of an established TB cocoon presenting with acute free intraperitoneal bowel perforation as high as 20 cm from DJ flexure. This is a pattern that has not been reported before. In fact, this multilevel high perforation limited our ability to resect the affected inflamed small intestine and forced us to perform primary repair of perforation despite the high risk of leak and secondary sepsis.[1] However, the adoption of a protective proximal jejunostomy was quite helpful in this particular case.

The lessons we learned from this case include high index of suspicion at all times even in immune-competent previously healthy patients for such a condition with an early administration of anti-TB drugs. Under the umbrella of theses medications, tissue-preserving perforation repair with a protective proximal entereostomy seems to be a safe and effective surgical option despite the initial grim picture on first laparotomy.

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Button-Loop Feeding Jejunostomy

Alejandro R. Ruiz-Elizalde · Jason S. Frischer · Robert A. Cowles

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Abstract
Introduction Post-pyloric feeding via a surgical jejunostomy allows for enteral nutrition in patients that cannot receive oral or gastric feeding. Regardless of the technique used to create a jejunostomy, complications such as tube dislodgement, jejunostomy closure, or bowel obstruction can occur.
Surgical Technique We present a simple and efficient jejunostomy technique that does not require a sewn anastomosis and employs an easily exchangeable feeding button.

Keywords Jejunostomy · Technique · Feeding · Button · Loop · Surgical

Introduction

When oral intake is not possible or when oral intake is not sufficient for maintenance of energy and fluid homeostasis, surgeons must decide how to best provide access to the gastrointestinal tract for feeding. Simple nasogastric or nasoenteric tubes can provide access to the stomach or duodenum for short courses of enteral feeding; however, these tubes are often difficult to secure and uncomfortable for patients over time.[1] The surgical (laparoscopic or open) or percutaneous gastrostomy tube (endoscopic or image-guided) is often the next best option, allowing for physiologic bolus feeding directly into the stomach. Intra-gastric feeding via gastrostomy, however, may not be suitable in certain patients with severe gastroesophageal reflux disease, after major upper digestive surgery, or when the stomach cannot be used.[1–3] In this subset of high-risk patients, jejunostomies have been used for feeding, administration of medications, or to provide drainage since the mid-nineteenth century.[4] Several studies have shown that enteral feeding via a surgical jejunostomy is safe in pediatric and adult patients requiring post-pyloric feeding.[4–7]

Many surgical jejunostomy techniques have been proposed since the first feeding jejunostomy was documented in the literature in 1858.[8] The most common techniques used by surgeons, whether open or laparoscopic, include the Witzel and the Roux-en-Y techniques, each having certain drawbacks. The Witzel jejunostomy is technically simple to perform and is taught to all general surgical trainees. Unfortunately, since the indwelling tube is not held in place by a balloon or other secure mechanism, feeding tubes placed by the Witzel technique are prone to dislodgement with the potential for premature closure and loss of the jejunostomy site.[9] Additionally, placement of a Witzel jejunostomy may result in obstruction at the tunnel site or become a lead point for a small intestinal intussusception.[4,10] While these complications may be avoided by using the Roux-en-Y technique, this procedure is of longer duration and requires the creation of a jejuno-jejunal anastomosis.[5] At our institution, we practice a tube jejunostomy technique that we feel is

A. R. Ruiz-Elizalde (✉) · J. S. Frischer · R. A. Cowles
Division of Pediatric Surgery,
Morgan Stanley Children's Hospital of New York-Presbyterian,
Columbia University Medical Center,
3959 Broadway, CHN-201,
New York, NY 10032, USA
e-mail: arr98@columbia.edu

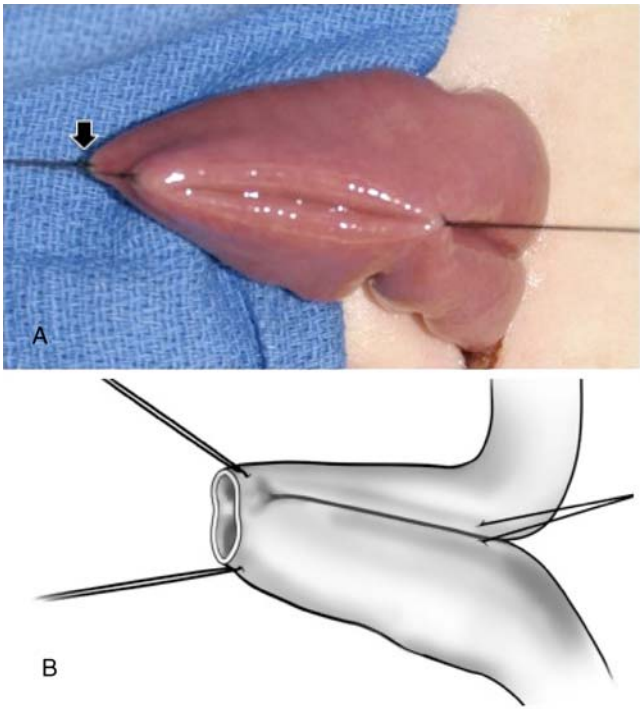

Figure 1 **a**, **b** Delivered segment of jejunum secured at apex (*arrow*) and opposed against itself.

simple and may reduce the risk of bowel obstruction without the need of a sewn anastomosis. In addition, this method utilizes a feeding button which is easily replaceable and comfortable for the patient.

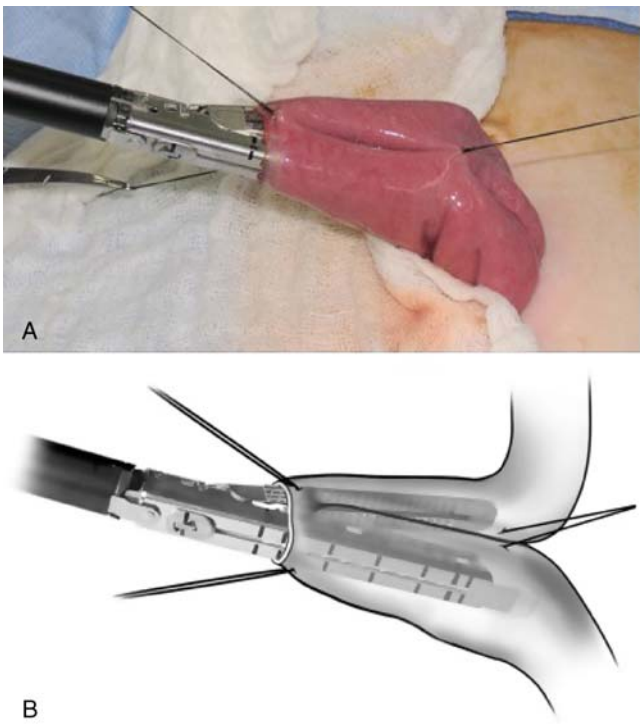

Figure 2 **a**, **b** Endo GIA stapler with individual arms inserted into bowel limbs.

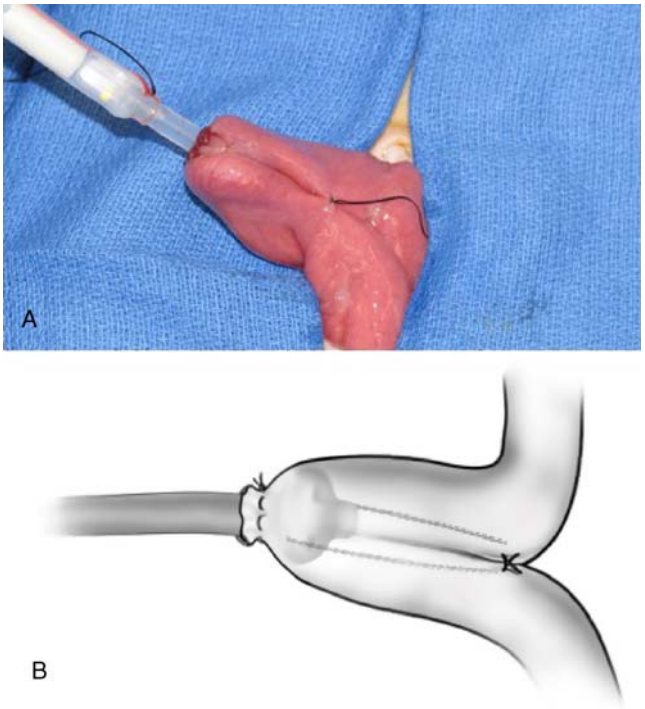

Figure 3 **a**, **b** Button inserted via an apical enterotomy and secured with purse-string stitch.

Surgical Technique

1. General anesthesia is used, and the operation is performed with the patient supine. A modest upper midline abdominal incision is made, and a loop of proximal jejunum, 10–20 cm distal to the ligament of Treitz, is identified and delivered.
2. The loop is opposed against itself and secured at the apex with two silk sutures (Fig. 1a, b), placing the loops of bowel in a side-to-side configuration. Addi-

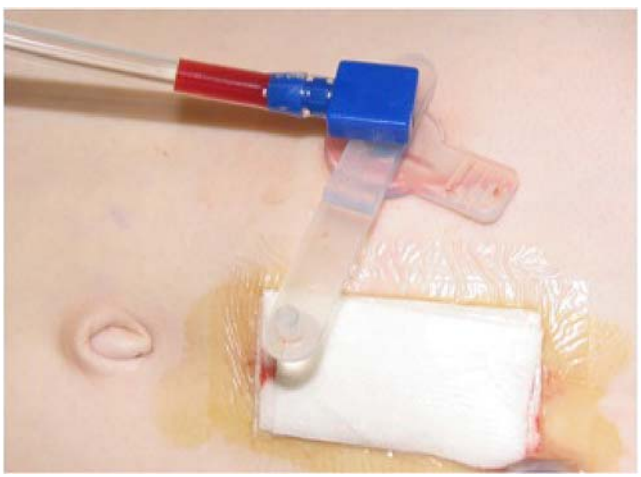

Figure 4 Final appearance of the jejunostomy button, flat against the patient's abdominal wall.

tional sutures are placed at the base in order to optimize side-to-side stabilization.

3. An enterotomy is created with cautery at the apex of this loop between the two apical sutures. An Autosuture ENDO GIA™ stapler is inserted into the bowel loop, making certain that each arm of the stapler enters an individual limb of the loop, as shown in Fig. 2a, b.
4. The stapler is fired and removed, leaving a larger open cavity within the loop. A second load of the Autosuture ENDO GIA™ stapler may be used if a larger cavity is needed. A purse-string suture is placed around the enterotomy site, and the mushroom section of a Boston Scientific EndoVive® Low Profile percutaneous endoscopic gastrostomy device is inserted and secured as the purse-string suture is tied (Fig. 3a, b).
5. A small stab incision is made in the right upper quadrant, and the button is brought through the skin at that location. The loop containing the jejunostomy is anchored to the peritoneum with sutures to prevent dislodgement or volvulus. The midline fascia and skin are closed, and dressings are placed. This tube lies flat on the skin and can be accessed when needed (Fig. 4).

Discussion

Despite its perceived simplicity, creation of a surgical jejunostomy can be associated with bothersome complications.[4] We have described an efficient, simple technique for placement of feeding jejunostomies. The simplicity of this procedure is attractive as it employs the use of the commonly available Endo-GIA stapler to create a side-to-side window between the two opposed limbs of proximal small bowel. The procedure can eliminate certain postoperative problems such as tube dislodgement with site closure, and the "button" device is much less prone to occlusion when compared to longer, narrower red rubber catheters that are used with conventional Witzel jejunostomies. Additionally, since no Witzel tunnel is performed, complications such as bowel obstruction due to the tunnel, large catheter size, or intussusception may be virtually eliminated. These aspects of the procedure make it particularly attractive for use in children, in whom the small bowel lumen may be much narrower. If a Boston Scientific EndoVive® Low Profile tube is not available, other alternatives such as a malecot tube, balloon tube gastrostomy, or a foley catheter can be placed. When non-flanged, longer tubes are used, they would need to be externally secured to the skin in order to prevent inward migration or dislodgement.

In concept, this procedure is similar to the Roux-en-Y jejunostomy. When compared to other descriptions of the Roux-en-Y jejunostomy,[1] however, this technique is simpler and more time efficient as it eliminates the need for a sewn end-to-side jejuno-jejunostomy by replacing it with a more expeditious stapled side-to-side jejuno-jejunostomy. Closure of this type of jejunostomy is similar to closure of other types of feeding sites where simple removal of the tube or a local procedure can be sufficient. In conclusion, the advantages of the procedure illustrated here have led our group to exclusively use this technique for placement of surgical jejunostomy tubes when indicated. While these advantages may appear greater in the pediatric population, where the caliber of the small bowel is diminished, this technique can be easily applied to placement of feeding jejunostomy in any age group.

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REVIEW ARTICLE

Small RNA: A Large Contributor to Carcinogenesis?

Imran Bhatti · Andrew Lee · Jonathan Lund · Michael Larvin

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Abstract
Introduction Homeostasis in normal tissue includes balancing cell proliferation and apoptosis (programmed cell death). Mutations in proto-oncogenes or tumor suppressor genes may lead to disruption of normal cellular function, uncontrolled cell proliferation, and subsequent carcinogenesis.
Discussion Micro-RNAs (miRNAs) are short (19–24 nucleotide) noncoding RNA sequences that inhibit protein translation and can cause the degradation of subsequent messenger RNA, thus playing an important role in the regulation of gene expression. Aberrant expression of miRNAs has been shown to inhibit tumor suppressor genes or inappropriately activate oncogenes initiating the cancer process. Unique miRNA expression profiles have been found in different cancer types at different stages, suggesting a possible diagnostic application. This review summarizes the current evidence supporting a link between aberrant miRNA expression and carcinogenesis and its possible role in improving diagnosis and treatment of cancers, particularly of gastrointestinal origin.

Keywords Micro-RNA · miRNA · Cancer · Carcinogenesis

Introduction

The genetic stability of normal tissue is maintained tightly by mechanisms which regulate cell proliferation and apoptosis (programmed cell death). Proto-oncogenes are genes that are susceptible to mutational activation to oncogenes, which may then promote cell growth and mitosis through cell signaling pathways, and tumor suppressor genes promote DNA damage responses to minimize the tumorigenic effect of mutations. Dysfunction in such genes may lead to disruption of normal cellular function, uncontrolled cell proliferation, and subsequent tumor formation or carcinogenesis.

The precise mechanism for the initiation of cancer remains unclear. Micro-RNAs (miRNAs) are short (19–24 nucleotide) noncoding RNA sequences that are involved in the regulation of human gene expression (noncoding RNA is transcribed from a DNA sequence, but not translated into protein). miRNAs bind to messenger RNA and prevent gene expression by inhibiting protein translation.[1,2] Newly discovered miRNAs are still poorly understood; however, studies performed on animal cells have shown them to be involved in key cellular, immune, and developmental processes.[3]

miRNA was first discovered in the nematode *Caenorhabditis elegans* in 1993 by Lee et al.[4] The gene *lin-4* was transcribed into a 22 nucleotide RNA molecule and found to inhibit protein synthesis.[4] This molecule inhibited the expression of *Lin-14* by directly binding with the 3′ untranslated region of its transcribed messenger RNA molecule.[1] Lee et al.[4] found that this process plays a crucial role in larval development. Furthermore, mutations in *lin-14* miRNA caused abnormalities in the execution of a

I. Bhatti (✉) · A. Lee · J. Lund · M. Larvin
Division of Surgery, School of Graduate Entry Medicine and Health, University of Nottingham Medical School at Derby, Derby City General Hospital,
Uttoxeter Road,
Derby DE22 3DT, UK
e-mail: imran.bhatti@nhs.net

terminal differentiating program, preventing cells from reaching their fully differentiated state.[4]

Since 1993, over 5,000 miRNAs have been discovered in 58 different species (approximately 500 in humans). Each has multiple targets, which are thought to regulate 30% of protein coding genes.[5] Aberrant expression of miRNAs has been shown to inhibit tumor suppressor genes or inappropriately activate proto-oncogenes initiating neoplastic transformation. Unique miRNA expression profiles have been found in different cancer types at different stages, suggesting a possible application in cancer diagnosis and perhaps future treatment strategies.[6]

Biogenesis and Function of Micro-RNA

Formation of mature miRNA follows a three-step process: firstly, miRNA genes are transcribed into primary miRNA (pri-miRNA); secondly, the pri-miRNA is cleaved into pre-miRNA, which is then transported into the cytoplasm; and finally, the pre-miRNA is cleaved and unwound to form mature miRNA (Fig. 1).

MiRNA genes are transcribed into double-stranded pri-miRNA by RNA polymerase II.[7] Pri-miRNA can be found as independent transcripts or incorporated into intronic regions of other genes [4].

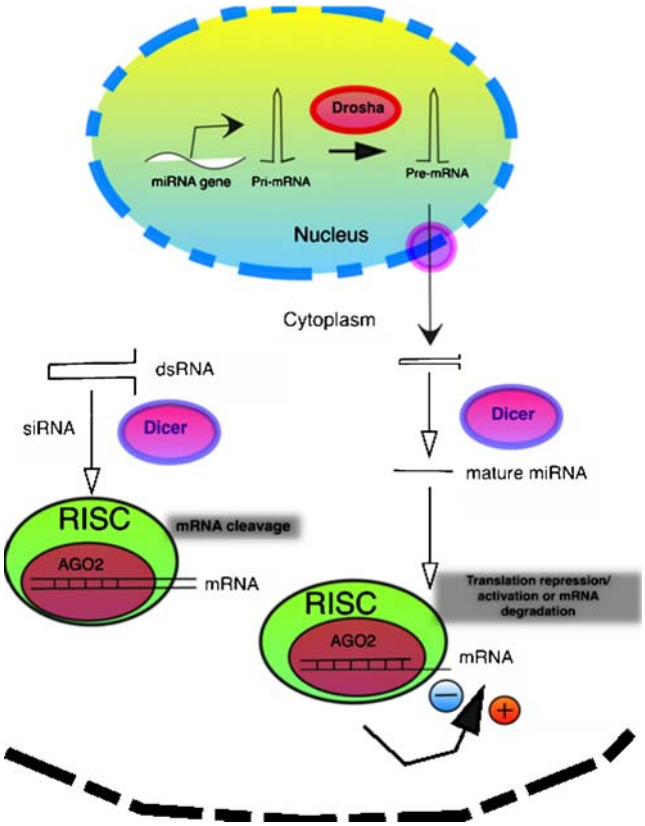

Figure 1 Biogenesis and function of micro-RNA and siRNA. *RISC* RNA-induced silencing complex, *AGO2* Argonaute 2 protein, *siRNA* short-interfering RNA.

pri-miRNA is then cleaved by two distinct complexes: Drosha in the nucleus and Dicer in the cytoplasm, both members of RNase III enzyme family. Drosha cleaves the pri-miRNA into pre-miRNA which is transported out of the nucleus via a nuclear membrane transporter Exportin 5.[8,9] Dicer cleaves the pre-miRNA which is then unwound by helicases to form two mature miRNAs.

MiRNA inhibits messenger RNA (mRNA) translation[10] by a number of mechanisms, including cleaving of the mRNA at the miRNA binding site and by translational repression of the target transcript.[11] Cleavage of the mRNA involves the RNA-induced silencing complex (RISC), which has also been well documented in the short-interfering RNA (siRNA) pathway. This complex associates with Argonaute 2 proteins Gemin 2 and Gemin 3 after it has been charged by the miRNA.[12,13] Translational repression of the mRNA occurs in polyribosomes and involves an as yet unknown mechanism. Some studies have reported localization of mRNA and miRNA to cytoplasmic foci known as processing bodies (p-bodies).[14,15] These p-bodies contain a decapping enzyme (hDcp 1/2), an exonuclease (hXrnl1), and a mRNA degradation protein (LSm 1–7).[14,15]

Kong et al.[16] demonstrated that the mechanism involved in translational repression is determined by the promoter used to transcribe the target gene.[16] They established that transcripts derived from the SV40 promoter are repressed at the initiation stage of translation, whereas mRNAs derived from the TK promoter are repressed at the post initiation stage.[16] Although it was first thought that miRNAs only block translation, it has been suggested that they may also have a role in enhancing or even activating translation at certain points in the cell cycle.[17]

RNA Interference

The discovery of the gene-silencing phenomenon, also known as RNA interference (RNAi), has been further confirmed by exogenously administered or artificially expressed double-stranded RNAs which have been found to selectively inhibit target genes by analogous mechanisms to miRNA.[18] Similar to miRNA, siRNAs undergo processing by Dicer endonuclease producing a single-stranded RNA for the RISC complex (Fig. 1).

Similarities in processing of siRNA and miRNA suggest that functional pathways may cross over because the human genome contains a single specific gene encoding Dicer. The origin of endogenous siRNA is not fully understood. However, it is thought that transposons, viruses, and other repetitive elements in the genome may well play a crucial role in their formation.[19]

The silencing process is highly sequence specific and although it was a believed that effective RNA interference requires almost complete sequence homology, it now appears that as few as seven contiguous complimentary base pairs can mediate gene silencing.[20] RNAi technology could be found useful in the treatment of cancer by knocking down the expression of dominant mutant oncogenes.

Role of Micro-RNA in Carcinogenesis

Dysregulation of miRNAs may be viewed as a consequence rather than a cause of carcinogenesis. However, deletions, local amplifications, and chromosomal breakage in regions of miRNA genes suggest a more direct role of miRNAs in tumorigenesis. Over 50% of miRNA genes are localized in genomic regions known to be associated with cancer or in fragile sites (genomically unstable during replication).[21]

MiRNA profiling studies have revealed abnormal levels in various types of cancer cell lines and tumors.[22] In these studies, multiple deregulated miRNAs have been found, which has assisted in classifying cancer types.[23] The aberrant expression of specific miRNAs has also been associated with prognosis.[24] Manipulating deregulated miRNAs by a process of degradation or miRNA inhibition with RNA interference methods may develop new opportunities for cancer treatment.

miRNAs as Tumor Suppressors

An association between miRNA was first reported by Calin et al.[25] A deletion on chromosome 13 is recognized to be the most frequent abnormality associated with B cell chronic lymphocytic leukemia (B-CLL). It has been demonstrated that in the majority (68%) of B-CLL, the miR-15 and miR-16 gene located within the deletion on chromosome 13 was either unexpressed or down regulated.[25] This study strongly suggests the role of these two miRNAs as tumor suppressors. Although their full target complement is unknown, they appear to mediate their effect by downregulating the anti-apoptotic protein Bcl2 (Fig. 2).[26, 27] Further studies have revealed a seven-base pair mutation downstream from miR-16-1 hairpin in two of 75 CLL patients which correlated with diminished expression of miR-16. It was thought that this mutation caused a defect in the transcription of miR-16. Following on from this, significant progress has been made in specifying the function of miRNAs in a variety of cancers.

The *let-7* family was the first group of miRNAs shown to regulate the expression of Ras protein (proto-oncogene).[28] Ras is a signal transduction protein that

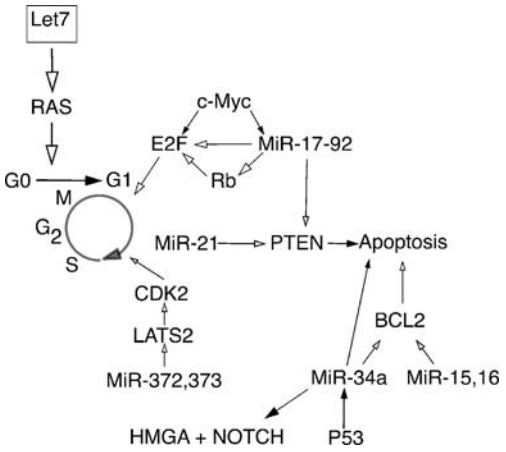

Figure 2 miRNA role in regulating cell cycle and apoptosis. *Clear arrows*—inhibit pathway. *Black arrows*—activate pathway.

control cellular processes such as proliferation, differentiation, and apoptosis. Mutations in *RAS* occur in 15–30% of human cancers, and overexpression of RAS is commonly found in lung cancer.[29] Johnson et al. confirmed that let-7 inhibits *RAS* expression in human cancer cell lines (Fig. 2).[28] Reduction of let-7 in lung cancer led to *RAS* overexpression, resulting in cellular overgrowth and contributing to carcinogenesis.[28]

Conditions of stress activate both p53-induced transcription of several miRNAs including transcription of the *miR-34a* gene.[30,31]. Overexpression of miR-34a was associated with an arrest of the cell cycle and apoptosis and reduced expression of multiple genes responsible for cellular proliferation and angiogenesis. Most of these genes were predicted targets for miR-34a which included the apoptosis inhibitor Bcl-2 (Fig. 2).[31,32] The genetic region of containing the *miR-34a* is often deleted in many types of cancer. Furthermore, the inhibition of miR-34a by antisense oligonucleotides inhibited the p53-dependent apoptosis during DNA damage.[31] Therefore, miR-34a may be considered as another important tumor suppressor.

miRNAs as Oncogenes

miRNAs may act as oncogenes, either by inhibiting tumor suppressor genes or by inhibiting genes that restrict the activity of oncogenes. A recent study suggested that miR-155 (required for functioning of B and T cells) exhibits strong oncogenic properties by interacting with *MYC* oncogene.[33] Its expression is increased in many cancers including Burkitt's lymphoma, Hodgkin's disease, lung cancer, breast cancer, and pancreatic cancer.[34–36] Bioinformatics predict that miR-155 target cytokines, chemokines, and transcription factors.[37] In pancreatic cancer cells, miR-155 inhibits Tp53inp1 (pro-apoptotic protein) causing cellular overgrowth.[36]

Overexpression of miR-372 and miR-373 induced proliferation and malignization of human primary cell culture by increasing the *RAS* oncogene.[38] These miRNAs target *LATS2* to cause suppression and thereby activating *CDK2* (cyclin-dependent kinase) and the cell cycle (Fig. 2).[38]

Cluster/Family miRNAs

A group or cluster of miRNAs with oncogenic or tumor suppressor properties may be located close together. Two independent studies described the relationship between the miRNA cluster, *mir-17-92*, and the *MYC* oncogenic pathway. The *mir-17-92* cluster was found to be located within a region on chromosome 13 (13q31–32) which is commonly amplified in human B cell lymphomas, follicular lymphomas and brain cortex lymphomas.[39] It was further demonstrated that the miRNAs from *mir-17-92* cluster were overexpressed in lymphoma cell lines that carried this amplification, and expression levels correlated with the gene copy number of the *mir-17-92* locus.[40] To test whether *mir-17-92* actively contributed to lymphogenesis, experiments were undertaken on mice that had developed lymphomas due to an overexpression of *MYC* oncogene. He et al.[40] proved that additional expression of the *mir-17-92* cluster accelerated *C-Myc*-induced tumorigenesis in mice. It was therefore suggested that *mir-17-92* was the first noncoding oncogene, recognized as oncomir-1 (Fig. 2).[40] Transformation of mouse hematopoietic stem cells into B cell lymphoma caused by oncogene *C-Myc* was accelerated by transfection of overexpressed cluster fragment lacking the *mir-92-1* gene.[40] Expression of *miR-92-1* cluster also increased the rate of proliferation of lung cancer cells in cell culture.[41]

The predicted targets of such cluster miRNA include tumor suppressors: *PTEN*-inducing apoptosis[42] and *Rb12*-inhibiting E2F (transcription factor that plays a crucial role in the cell cycle and tumor suppression).[43] Interestingly, the miR-17-92 cluster can also be activated by the proto-oncogene *C-Myc* (see Fig. 2).[44]

Cluster miRNAs such as miR-17-5p may also act as tumor suppressors. miR-17-5p can suppress the translation of E2F1 mRNA, resulting in an oncogenic effect.[44] Such observations in miRNA clusters demonstrate the involvement of complex regulatory mechanisms.

miRNA as Tumor Suppressors and Oncogenes

Depending on the type of tumor cell, miR-21 and miR-24 may act as an oncogene or tumor suppressor gene. In HeLa cells (immortal cervical cancer cells), inhibition of miR-21 or miR-24 by the use of anti-miR oligonucleotides resulted in accelerated proliferation.[45] Inhibition of miR-24 in A549 cells (carcinomic human alveolar epithelial cells) caused effective suppression of cell growth, whereas inhibition of miR-21 had no effect.

Many tumors (colon cancer, pancreatic cancer, glioblastomas, or breast cancer) are associated with a high expression of miR-21.[46,47] miR-21 also acts through different mechanism depending on the cancer type. In glioblastoma cell culture, miR-21 causes apoptosis through the activation of caspases (cysteine proteases that play important role in apoptosis),[46] whereas in hepatomas, miR-21 may act as an oncogene by suppressing PTEN (tumor suppressor; see Fig. 2).[47]

Bioinformatic analysis show that many other miRNAs indicate both proto-oncogenic and tumor suppressive activity. However, the false positive prediction rate of these targets is high (approximately 30%).[48]

Global Loss of miRNA Expression

Dysregulation in miRNA expression associated with carcinogenesis is not only caused by chromosomal defects but also due to problems in miRNA processing machinery. Kumar et al.[49] reported for the first time that widespread reduction of miRNA expression was associated with carcinogenesis. By inhibiting the miRNA-processing enzymes Drosha and Dicer in cell lines, the authors were able to produce a global state of miRNA suppression. As a result, these cells demonstrated enhanced cellular growth and proliferation. When injected into nude mice in whom cancer was established, the tumors grew faster and became more invasive.[49] It was also proven that loss of miRNAs led to upregulation of proto-oncogenes such as *RAS* and *C-Myc*. Tumor invasion and metastasis have also been demonstrated to be associated with deregulated miRNAs.[50]

miRNAs in Tumor Diagnostics and Prognosis

The uniqueness of miRNA profiling in particular tumor types could be helpful in cancer diagnostics (Table 1). Several studies have demonstrated that aberrant expression of miRNA exists at the early stage of cancer pathogenesis and that the expression changes as the tumor develops.[22–24,51–53]. This suggests that miRNAs have an important function in the development and differentiation of tested tumors.

Expression analysis of miRNAs in solid tumors resulted in successful classification into subtypes by their origin and stage of differentiation.[23,51]. These results suggest that miRNA profiles may be useful for diagnosis but also for providing prognostic information.[52] However, reproducibility needs to be improved before this technique can be generally applicable. Further studies are required to ascertain the value of miRNAs as diagnostic tools, and

their potential value as prognostic markers by correlating with parameters such as metastatic potential and response to current treatments.

Esophageal Cancer

Feber et al.[53] was able to demonstrate that miRNA profiles distinguish different esophageal tissue types (adenocarcinoma vs. squamous cell carcinoma (SCC)) and also discriminate malignant from normal tissue. miRNA profiles of normal squamous epithelium were more similar to squamous cell cancer than to adenocarcinoma samples. Similarly, miRNA profiles of Barrett's esophagus were more similar to adenocarcinoma than squamous cell cancer,[53] supporting the hypothesis that miRNA is involved in the pathogenesis of esophageal cancer.

In the same study, miR-21 was found to be upregulated in both esophageal adenocarcinoma and SCC. This upregulation of miR-21 has also been observed in breast, lung, prostate, colon, and stomach cancer.[22] MiR-192 showed higher expression in esophageal adenocarcinoma but lower expression of miR-203 was found relative to normal squamous epithelium.[53] Different miRNA profiles were observed between cancer types. A further study demonstrated that prognosis was improved in esophageal cancer expressing lower levels of miR-103/107.[54]

Gastric Cancer

Chan et al.[55] demonstrated that 92% (34/37) of gastric cancer samples were shown to overexpress miR-21; however, the level of expression was not related to prognosis.[55] The high mobility group A2 (Hmga2) is a small protein that can modulate transcription by altering chromosomal structure. Hmga2 levels were significantly higher in gastric cancer compared to normal tissue.[56] High expression levels of Hmga2 were also related to tumor invasiveness and prognosis. The microRNA let-7 families are inhibitors of *HMGA2*. In gastric cancer, the levels of microRNA let-7a were found to be inversely related Hmga2.

Pancreatic Cancer

Expression profiling has identified a large number of miRNAs which are aberrantly expressed in pancreatic ductal adenocarcinoma.[57] Lee et al.[57] also compared profiling of pancreatic endocrine tumors with adenocarcinoma and found that many of the miRNAs that were increased are similar (miR-221, miR-100, miR-125b, and miR-21). MiRNA expression profiling was used to correctly identify 28 of 28 tissue samples as tumor, six of six as normal pancreas, and 11 of 15 of adjacent benign tissue as normal pancreatic tissue.[57]

In another study, the most consistent highly expressed miRNA found in pancreatic cancer was miR-221. MiR-221 expression is also important in thyroid cancer and has a suggested role in angiogenesis.[58] It has also been found to target KIT a cytokine receptor found on stem cells. KIT plays an important role in cell survival, proliferation, and differentiation.

MiR-21 has also been shown to have increased expression in pancreatic cancer. It has been suggested that it plays an important role in preventing apoptosis, therefore functioning in an analogous way to a proto-oncogene.[46] In one study, miR-21 was overexpressed in 79% of pancreatic cancers compared with only 8% ($p<0.0001$) of benign pancreatic specimens and 27% ($p<0.0001$) of chronic pancreatitis samples. Unlike gastric cancer, miR-21 expression levels were not shown to be associated with tumor–node–metastasis (TNM) staging, although high levels did predict a poorer outcome.[59] MiR-196a-2 may also play a role in predicting prognosis in pancreatic cancer.[24]

It has been suggested that chronic pancreatitis may be a premalignant condition. In addition to elevated levels of miR-21 in chronic pancreatitis, seven miRNAs (miR-99, miR-100, miR-125a, miR-125b-1, miR-199a-1, and miR-199a-2) found to be overexpressed in pancreatic cancer were also elevated in chronic pancreatitis.[24]

Colon Cancer

A study performed by Schetter et al.[60] found that levels of five miRNAs were elevated in cancer of the colon (miR-20A, miR-21, miR-106a, miR-181b, and miR-203). They also confirmed that higher expression miR-21 was seen in adenomas compared to normal colonic mucosa ($p=0.006$) and levels correlated with worsening TNM stage ($p<0.001$).[60]

High expression of miR-200c in colon cancer has also been associated with a shorter survival time ($n=15$, median survival=28 months) compared to patients with lower expression ($n=9$, median survival=38 months).[61] Nearly half of the colon cancers in this study contained p53 (tumor suppressor protein) deletions/mutations with concordant high expression of both miR-200c and miR-181b. Yaguang et al.[61] suggested that p53 may mediate miRNA expression to exert its tumor suppressor function.

MiR-let7g and miR-181b have shown to be highly expressed in colonic adenocarcinoma by Schetter et al.[60] Colonic adenocarcinoma cells with a high expression of miR-let7g and miR-181b have also been shown to have a better clinical response to oral 5-flurouracil.[62]

Breast Cancer

Deregulation of miRNAs has also been observed in breast cancer. miR-10b, miR-125b, miR-145, miR-21, and miR-155

are the most consistently deregulated. Both miR-21 and miR-155 are upregulated and the remaining three downregulated.[63] Higher expression levels of miR-21 have been associated with a more advanced tumor stage.[63] Distinct miRNA profiles have been observed in HER+ve compared to HER2−ve and ER+ve compared to ER−ve breast carcinomas.[64]

miRNA Related to Tumor Invasion and Metastasis

The role of miRNAs in tumor metastasis was only recently addressed and remains largely unexplored. Investigating motility of cells is an essential feature in understanding how metastases develop. It is well documented that MCF-7 cells (breast cancer cell line) have a nonmetastatic and nonmigratory phenotype. Enrichment of miR-373, miR-520c, and miR-520e were observed in the migratory phenotype. To determine whether these miRNAs were able to promote metastasis, they were introduced into nonmigratory MCF-7 cells producing a potent migratory phenotype in these cells. Furthermore, miR-373 and miR-520c had no effect on proliferation or cell cycle distribution on cells.[68]

miRNA and Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT) is a well-established embryological process that has been considered to play a vital role in tumor progression.[69–71] EMT is a process which describes the phenotypic change of epithelial cells to form mesenchymal cells which are similar in appearance to fibroblasts.[70,72] This change results in loss of polarity and tight intracellular adhesions maintained by epithelial cells with adheren junctions.[69,70] Recent studies have suggested an association with abnormal induction of EMT in adult epithelia and tumor metastasis.[73,74] In primary tumors, the induction of EMT leads to a structural loss mainly in epithelial cadherin (E-cadherin). E-cadherin is a transmembrane glycoprotein found in epithelial cells that is essential for maintaining structural integrity.[75] Loss of E-cadherin has been associated with several gastrointestinal cancers (esophageal, gastric, pancreatic, and colorectal) and experiments to inhibit its expression show both an increase in invasiveness (i.e., metastatic ability) of cell behavior and a morphological shift of the cells from epithelial to fibroblast type.[76]

Mechanisms by which E-cadherin has been shown to be inhibited include posttranscriptional repression by miRNAs. Three miRNA families (miR-141, miR-200b, and miR-205) play an important role in specifying the cell phenotype and inhibiting the induction of EMT by preventing the expression of translational repressors of E-cadherin such as ZEB1/δEF and ZEB2/SIP1 (Gregory et al. 2008 nature cell biology). Furthermore, the expression of miR-200 is downregulated in cells undergoing EMT to different stimuli.[77]

Transforming growth factor beta (TGF-β) is thought to be a key regulator of EMT in late stages carcinogenesis where it promotes invasion and metastasis. In an important study, the miRNA signature of EMT induced by the TGF-β pathway in normal murine mammary gland epithelial cells was profiled. miR-155 was found to be most significantly elevated. Furthermore, it was found that TGF-β induces miR-155 expression and promoter activity through SMAD4. The knockdown of miR-155 suppressed tight junction dissolution and EMT as well as cell migration and invasion. This study suggested that miR-155 plays an important role in TGF-β induced EMT and indicates its potential therapeutic target in the treatment of breast cancer.

miRNAs as Therapeutic Targets

Normalization of miRNA expression may have a therapeutic effect. Several methods including antisense blocking and miRNA silencing have been used to help normalize miRNA function. Although theoretically possible, the problem with such forms of treatment is that the delivery of these molecules is difficult both locally and systemically. These treatment methods are currently being investigated and need to be comprehensively examined and optimized by further experimentation.

Antisense Blocking

Krutzfeldt et al.[78,79] targeted several miRNAs in mice by the method of antisense blocking using antagonist-miRs

Table 1 miRNA Expression Levels in Different Cancer Types and as Prognostic Markers

Cancer type	miRNAs expression level	Better prognosis	Reference
Esophageal	21↑, 27b↓, 125b↓, 192↑, 194↑, 200c↑	103/107↓	53,54
Gastric	Let 7↓, 21↑, 34↓, 106↑		55,56,65
Pancreatic	21↑, 100↑, 103↑, 107↑, 125b↑, 148a, b↓, 155↑, 181a↑, 221↑, 196a-2↑	196a-2↑	24,36,66,67
Colon	Let7g↑, 20A↑, 21↑, 106a↑, 143↓, 145↓, 181b↑, 200c↑, 203↑	200c↑	60,61
Breast	21↑, 125b↓, 145↓, 155↑	21↓	63

(antagomirs). Interestingly, systemically administered LNA-anti-miR oligonucleotide complimentary to miR-122 led to dose-dependent gene silencing with no hepatotoxicity in mice. Antagomirs are short (21–23 nucleotide) single-stranded RNA molecules that are complimentary to the mature target miRNA, which means that their action is highly specific. Krutzfeldt et al. has shown that antagomirs are highly specific potent tools which have a potential role in cancer treatment.

miRNA Silencing

Silencing is the term used to describe methods that prevent the production of mature miRNA. This is commonly achieved by inhibiting important RNase III enzymes including both Drosha and Dicer. Inhibiting these enzymes would reduce the production of many different miRNAs at once and the final effect is much less specific as compared to antisense blocking.

miRNA and Chemotherapy

Chemotherapy is often the preferred therapeutic approach for the treatment of many tumors; however, tumor response is occasionally limited by drug resistance. Recent work has underlined the involvement of miRNAs with chemotherapy drug resistance.

The involvement of miRNA in tumor cell response to chemotherapy has been suggested in gastric cancer. When miRNA expression profiles from cell lines of human gastric adenocarcinoma and its multidrug-resistant (MDR) variant were compared, it was shown that ten miRNAs were downregulated more than twofold in MDR cell group, including miR-15b and miR-16, which have previously been shown to promote apoptosis by negatively regulating BCL2 (anti-apoptotic gene) in chronic lymphocytic leukemia cells.[27] When miR-15b and miR-16 were transfected into the MDR cell, enhanced sensitivity to chemotherapeutic agents was demonstrated. Similarly, inhibition of these miRNAs in normal gastric adenocarcinoma cells decreased sensitivity to chemotherapy agents. This study provided an insight into the mechanisms of MDR in gastric cancer and may help in developing chemosensitizing strategy through manipulating miRNA expression.[80]

Similar studies have shown that suppression of miR-21 using antisense oligonucleotides (miRNA inhibitor) sensitized breast adenocarcinoma cell lines (MCF7) cells to the chemotherapeutic agent topotecan.[81] Sorrentino et al.[82] showed that six miRNAs (let-7e, miR-30c, miR-125b, miR130a, and miR-335) were always aberrantly expressed in resistant ovarian cancer cell lines. miR-130a was upregulated in ovarian cancer cell lines, while it was downregulated in the resistant cell lines, suggesting its direct involvement in chemoresistance. The downregulation of miR-130a was linked to the overexpression of M-CSF gene, a known chemoresistance factor in ovarian cancer.

Conclusion

miRNA seems to have an emerging role in carcinogenesis and may provide new avenues for diagnosis, prognosis, and treatment. In the future, miRNAs may prove useful in clinical practice. The specific miRNA signature for each cancer type will be valuable in diagnosis and prognosis, especially when identification of tumor type is difficult from histology, adding to immunohistochemical information. miRNA profiling will also help in discriminating between those benign and malignant tumors which would otherwise be difficult to differentiate by routine pathological examination. miRNA profile of a tumor may also provide information to inform choice of adjuvant treatment.

Clearer understanding of the mechanisms of how deregulated miRNAs may lead to cancer has also suggested the possibility of novel therapeutic approaches. In most studies, there has been an overexpression of miRNAs. Therefore, inhibiting these small molecules may influence the behaviour of a tumor. However, delivery of antisense oligonucleotides to specific tissue and minimizing their introduction into non-targeted sites is a significant challenge in the development of novel treatments. Also, multiple miRNAs target the same gene and the mechanisms for this behaviour and sequelae of modification of expression of a particular miRNA would need to be defined in the development of any new treatment. miRNAs seem fundamental to the regulation of gene expression and further knowledge of their actions in cellular pathology may lead to insights into carcinogenesis at least and a new front in cancer therapy at best.

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Thyroid Metastases from Gallbladder Cancer

Jean M. Butte · Luis Marín · Manuel Meneses · Hernán De La Fuente · Rossana Pruzzo · Francisca Redondo · Hugo Parada · Horacio Amaral · Enrique Waugh

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Abstract
Background Gallbladder cancer is an aggressive malignancy and radical resection is the only curative therapy available. Metastatic disease in the thyroid is rarely seen; however, different studies have confirmed that the most common primary tumor source is the kidney.
Case Report Thyroid metastases from tumors originating in the gastrointestinal tract have been reported. We report a patient with gallbladder cancer (T2N1M0) treated with radical resection and postoperative chemoradiation who developed thyroid metastases.

Keywords Gallbladder cancer · Thyroid metastases · Surgical treatment

Case Report

O.C. is a 48-year-old female patient with a previous history of incidental gallbladder cancer diagnosed after a cholecystectomy for gallstones in 2005. After a review of the biopsy specimen, routine laboratory analyses, and abdominal CT scan, we confirmed pT2 gallbladder cancer without systemic disease and a re-exploration and radical resection were carried out that year (R0 resection). The final pathology report demonstrated a pT2 gallbladder cancer, with lymph node metastases identified in one pericoledochal lymph node of a total 13 lymph nodes resected and an absence of tumor involvement in the gallbladder bed (T2N1M0). The patient received adjuvant chemotherapy and radiotherapy, and was then followed with serial abdominal CT scans according to our protocol and for 2 years was without evidence of disease.

J. M. Butte · L. Marín · M. Meneses · H. De La Fuente · R. Pruzzo · F. Redondo · H. Parada · H. Amaral · E. Waugh (✉)
Instituto Oncológico Fundación Arturo López Pérez,
Rancagua 878,
Santiago, Chile
e-mail: ewaugh@mi.cl

In November 2007, an abdominal CT scan showed nonspecific retroperitoneal lymph node. She was asymptomatic and the physical examination was unremarkable. In December 2007, she presented with fatigue, dyspnea, and dysphagia. A physical examination demonstrated bilateral and pathologic cervical lymph nodes, a thyroid mass, and a left axillary mass. A PET-CT scan with 18-fluordeoxiglucose showed multiple and bilateral pathologic cervical lymph nodes, a thyroid mass, a left lymph node axillary mass, pathologic mediastinal lymph nodes, and a retroperitoneal mass suggesting systemic recurrence of gallbladder cancer (Fig. 1). Fine needle aspiration of the thyroid and the retroperitoneal masses were performed. Both demonstrated metastatic adenocarcinoma.

In February 2008, due to an increase of dyspnea, a palliative thyroidectomy was performed. The gross specimen consisted of a total thyroidectomy with the normal parenchyma replaced by white firm tissue measuring 8×5×2.8 cm in aggregate (Fig. 2a). Frozen section diagnosis demonstrated extensive metastatic involvement by adenocarcinoma. The final pathologic report showed moderately to poorly differentiated metastatic adenocarcinoma, involving mainly the lymphatic channels in the thyroid (Fig. 2b). The tumor was negative to TTF-1 and positive for Villin on immunohistochemical stains (Fig. 2c,d).

The patient's symptoms improved, but she died 2 months after palliative surgery due to her disseminated gallbladder cancer.

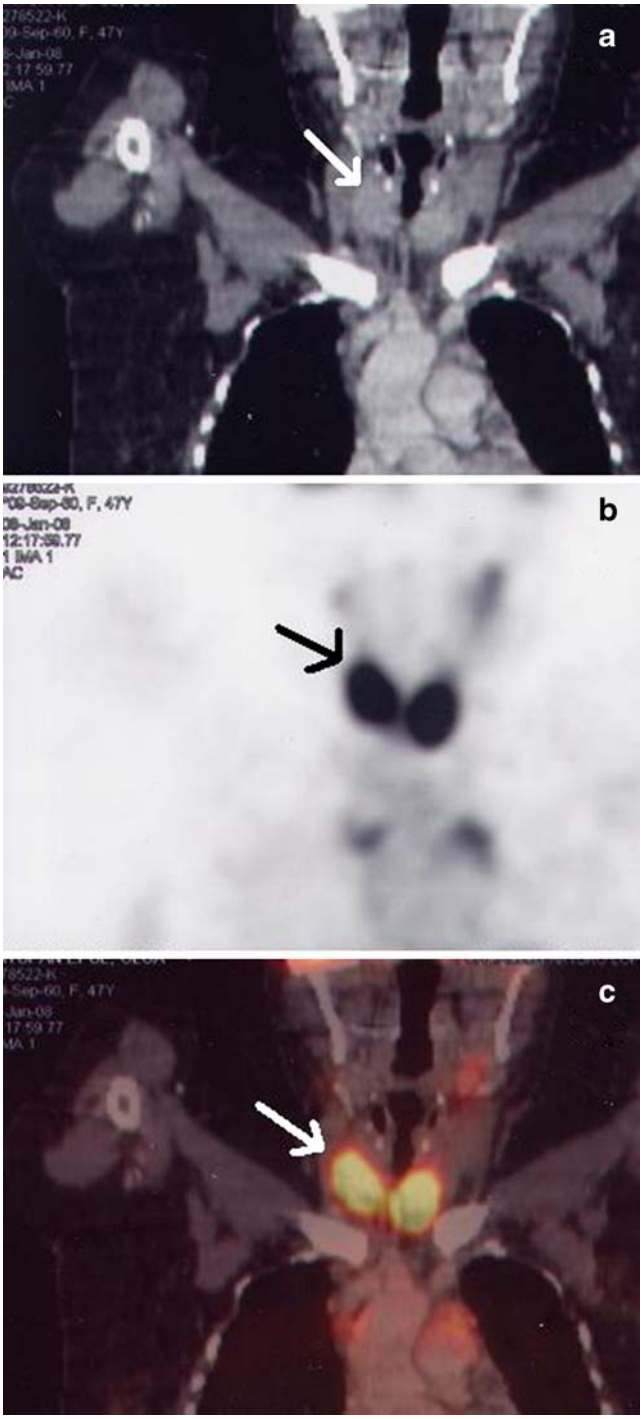

Figure 1 PET-CT coronal images of the neck. **a** CT shows a moderate diffuse goiter (*white arrow*). **b** PET image shows intense and diffuse hypermetabolism in the anterior aspect of the neck (*black arrow*). **c** Fused PET-CT image confirms intense hypermetabolism in the entire thyroid gland (*white arrow*).

Discussion

Gallbladder cancer is an aggressive malignancy, usually diagnosed in an advanced stage; only 0.3% to 2% of patients are diagnosed during or after a cholecystectomy for presumed benign disease, and in the majority of patients the possibility of cure does not exist.[1] Only 15% to 47% of patients are candidates for resection at the time of diagnosis and, despite curative resection, most series quote a long-term survival of only 5% to 12%.[2]

Complete surgical resection is the only treatment modality with curative potential for gallbladder cancer.[3] However, only 25% of patients undergo a potentially curative resection, and residual tumor in the abdominal cavity has been found in 40% to 76% of cases at the time of re-exploration.[4]

At the moment of diagnosis or re-exploration, T1b lesions are associated with lymph node metastases in 15% of cases with T2 lesions having a higher rate of liver and lymph node involvement when compared to T1 tumors.[5] Between 20% and 62% of T2 cancer will have spread to the hiliar and pericholedochal lymph nodes and 20% will have involvement of the peripancreatic and celiac lymph nodes.[6,7] Different studies have shown that lymph node metastases are a prognostic factor in recurrence and distant metastases.[8] The patient presented in this report had metastasis in one pericoledochal lymph node at the time of re-exploration in 2005.

Despite the fact that the reports on adjuvant radiotherapy after resection for gallbladder cancer are limited and controversial, Vaittenim et al.[9] found that the median survival following surgery for gallbladder cancer was improved with adjuvant radiation therapy compared to without adjuvant therapy. The purpose of the complementary chemotherapy and radiotherapy after radical resection in this patient was to improve long-term survival.

After curative intent treatment (surgery and chemo-radiotherapy), gallbladder carcinoma can spread via lymphatic, vascular, perineural, intraperitoneal, and intraductal routes or direct invasion of veins that drain from the gallbladder into the adjacent liver segment. The most frequent postoperative recurrence would be in the regional lymph nodes, liver, and lungs.[10]

Although metastatic disease in the thyroid is not frequently seen, autopsy and clinical series indicate that the problem is more common than generally thought. Different reports suggest that the most common primary sites are the kidneys, lung, breast, and gastrointestinal tract.[11–16] Hematogenous and lymphogenous pathways are considered the route of metastases to the thyroid and have been demonstrated to occur as late as 10 years following resection of the primary tumor.

From the gastrointestinal tract, different authors have reported thyroid metastases from colon, rectal, and primary hepatocellular carcinoma.[14–16] However, thyroid metastases from gallbladder cancer have not been reported previously.

In this patient, the presence of a retroperitoneal mass suggested an abdominal recurrence of gallbladder cancer

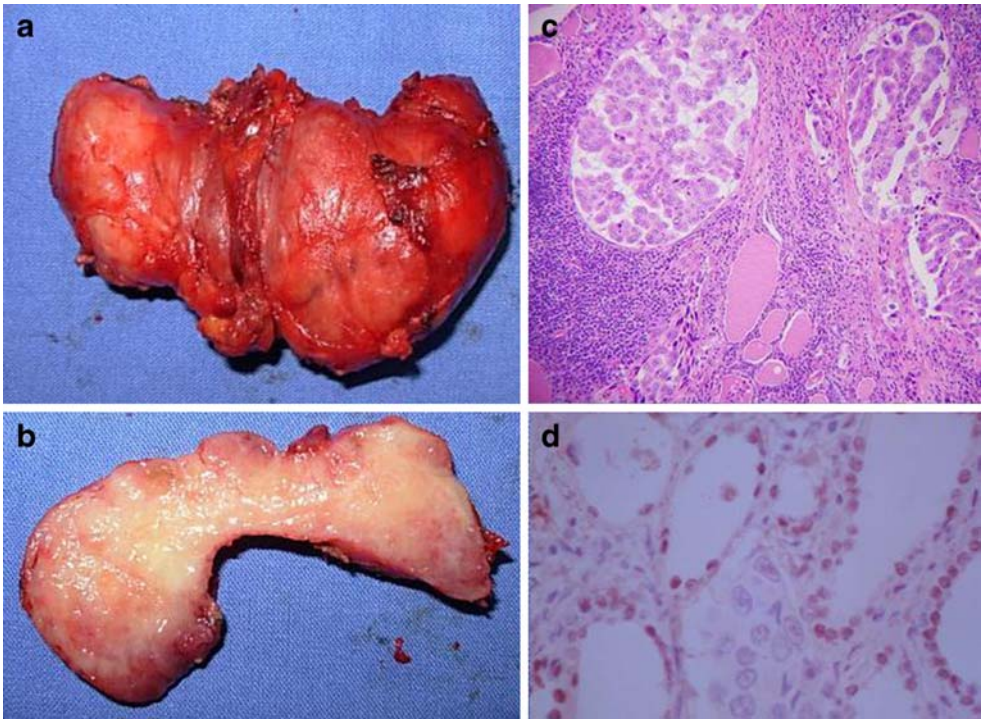

Figure 2 **a**, **b** Thyroidectomy specimen and section of it on the lower left with diffuse enlargement and yellow discoloration. **c** HE stain showing extensive lymphatic involvement by adenocarcinoma. **d** Immunostaining shows negative TTF-1 stain in tumor cell with internal control positive in normal thyroid.

and the physical examination demonstrated bilateral and pathologic cervical lymph nodes, a thyroid mass, and a left axillary mass. A PET/CT scan was useful in establishing the true extent of the disease and a core biopsy confirmed the diagnosis. A total thyroidectomy was necessary as palliative treatment of the disseminated disease and the definite diagnosis was verified with a pathologic study of the entire specimen.

We can conclude and confirm from this case that gallbladder cancer is an aggressive malignancy with a bad prognosis even following radical resection and adjuvant therapy. Systemic recurrence is unpredictable and there is little doubt that more effective systemic adjuvant therapy is needed following radical resection.

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Mechanical Bowel Preparation for Elective Colorectal Surgery: Is it Enough?

Gianpiero Gravante · Riccardo Caruso

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Dear editor,

We recently read with great interest the article of Dr. Peppas and colleagues and strongly favour their approach and concerns about the mechanical bowel preparation of colorectal patients (MBP).[1] In order to give our contribution to the discussion, we would like to focus on some issues that still need to be answered about this time-honoured procedure.

To date, 12 randomised controlled trials (RCT) are present in the literature including 4,919 patients (2,463 in the MBP group and 2,456 in the non-MBP group).[2–13] The overall analysis of the main outcome measures shows that no parameter reaches the statistical significance between MBP vs. non-MBP patients (Table 1).The only exception is represented by the occurrence of cardiac events (acute myocardial infarctions, atrial fibrillations, heart failures, angina pectoris) that seem decreased in the non-MBP group (Table 1). The reasons for this influence could lie in the well-known effects of MBP on body fluids (dehydration) and electrolytes (marked imbalances) that, along with others cardiovascular risk factors (age, comorbid conditions, neoadjuvant treatments, surgical stress and intra-operative blood losses), could further increase the perioperative risk. Taken together, results available confirm the lack of an objective advantage on the use of MBP in elective patients and, in particular cases, would suggest some potential harmful effects.

However, different biases need to be pointed out. Important differences in the protocols adopted render difficult the combination of results in a metanalytic approach. Almost all studies adopted an adequate antibiotic prophylaxis for both groups (MBP vs. non-MBP patients), but in four of them this information was not specified[2,4,9,13] and, when described, different prophylactic regimens were adopted: in three studies, ceftriaxone and metronidazole were used,[5,7–8] in one cephalothin and metronidazole,[3] in one gentamicin and metronidazole,[13] in two neomycin and erythromycin,[6,10] in one sulfamethoxazole–trimethoprim and metronidazole for 46% of patients, cephalosporin and metronidazole for 33% of patients and doxycycline with metronidazole for 14% of patients.[11] Additionally, the mechanical preparation regimen was also different: seven trials adopted the regimen of oral polyethylene electrolyte glycol solution as mechanical bowel preparation,[2,5–8,9–10,12] one the sodium phosphate,[8] two both[11,13] and two did not specify it.[3–4]

The heterogeneity of RCTs involved also the recruitment of patients (one study was conducted on children)[3] and the results presented, including the treatment effect and the precision of its estimate (Fig. 1). When screened with validated quality measures (i.e. the Jadad scale),[14] no RCT scored more than 2 meaning that results presented could be

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G. Gravante (✉)
Department of Colorectal Surgery,
Whipps Cross University Hospital,
Leytonstone,
London E11 1NR, UK
e-mail: ggravante@hotmail.com

R. Caruso
Department of Surgery, University of Tor Vergata,
Rome, Italy

Table 1 Postoperative complications after colorectal surgery

Complications	MBP	%	Non-MBP	%	Odds ratio [95% CI]	*p* value
Wound infections[2–4,6–13]	233/2,381	9.6	207/2,369	8.7	0.87 [0.72–1.06]	NS
Anastomotic leakage[2–13]	101/2,463	4.1	84/2,456	3.4	0.82 [0.61–1.10]	NS
Abdominopelvic abscess[2,5–8,10–13]	40/2,181	1.8	55/2,170	2.5	1.38 [0.92–2.09]	NS
Sepsis[6–8,11]	11/1,115	1.0	9/1,090	0.8	0.84 [0.35–2.03]	NS
Postoperative ileus[6,8,11]	26/1,037	2.5	22/1,015	2.2	0.84 [0.48–1.47]	NS
Cardiac events[5–8,11]	50/1,253	4.0	31/1,219	2.5	0.63 [0.40–0.99]	0.04
DVT/PE[5–8,11]	26/1,253	2.0	33/1,219	2.7	1.27 [0.77–2.09]	NS
Pneumonia[6–8,11,13]	78/1,785	4.4	78/1,774	4.4	0.99 [0.71–1.37]	NS
Urinary infections[6–8,11,13]	102/1,785	5.7	99/1,774	5.6	0.96 [0.72–1.28]	NS
Mortality[6–8,11,13]	36/2,053	1.7	39/2,039	1.9	1.07 [0.67–1.69]	NS

MBP mechanical bowel preparation; *DVT/PE* deep venous thrombosis/pulmonary embolism

overestimated. Finally, no study analysed and stratified outcomes according to the type of surgery (colonic vs. rectal or right-sided vs. left-sided) or the anastomosis conducted. Although some RCT classified patients according to the type of surgery, no sub-classification was performed when results were presented.

In conclusion, we agree with the authors that MBP is probably still abused in colorectal patients on a world-wide basis. However, we believe that future well-conducted and stratified studies could uncover some specific recommendations of this procedure especially on patients at high risk of postoperative complications (i.e. low rectal anastomoses).

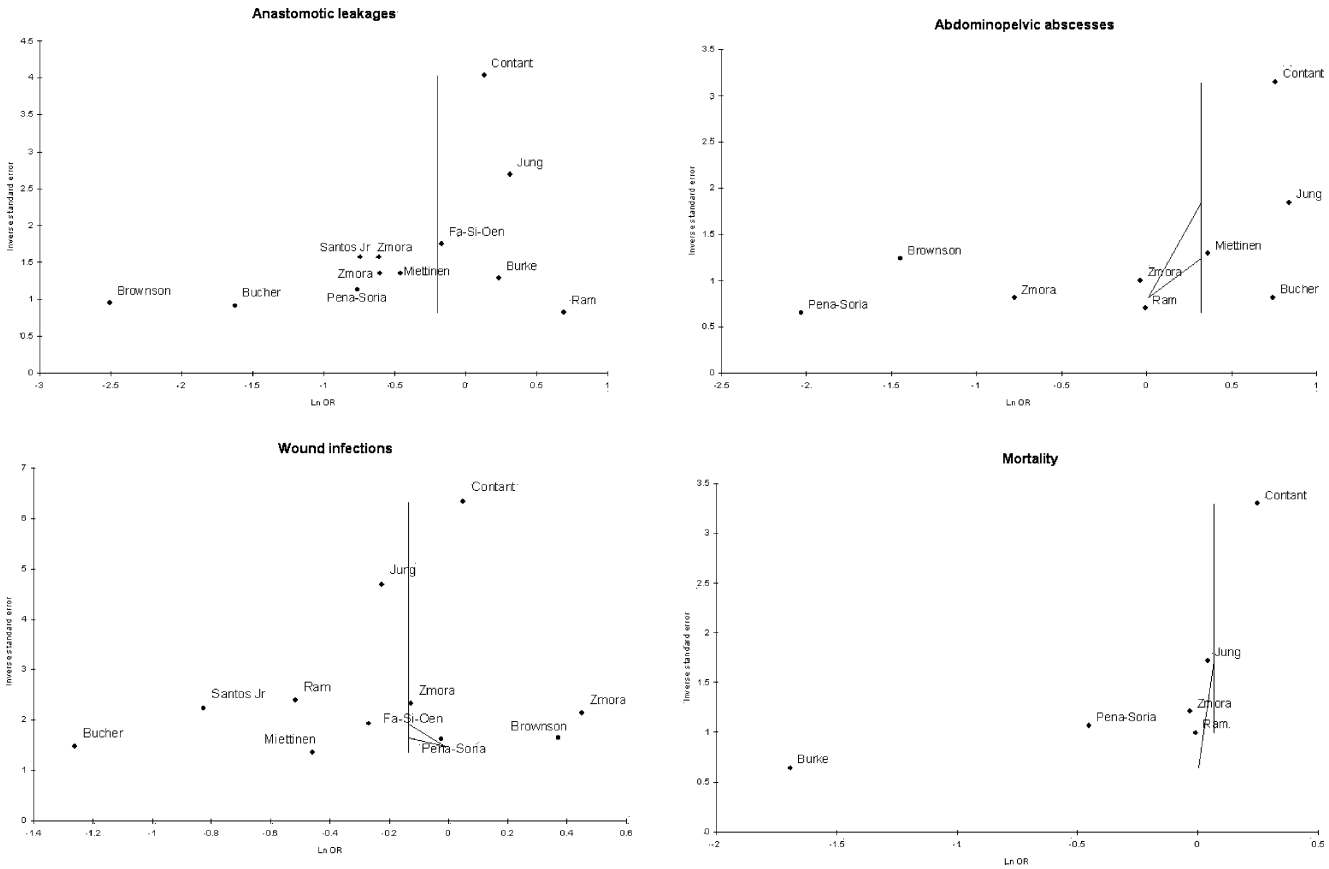

Figure 1 Funnel plots of randomised studies on MBP considering as main outcome measures the anastomotic leakages (*left upper panel*), abdominopelvic abscesses (*right upper panel*), wound infection (*left lower panel*) and mortality (*right lower panel*).

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LETTER TO THE EDITOR

Mechanical Bowel Preparation for Elective Colorectal Surgery: Is It Enough? Reply

George Peppas · Vangelis G. Alexiou · Matthew E. Falagas

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Dear Editor,

We would like to thank Drs. Gravante and Caruso for sharing their thoughts and updated systematic review on this important issue.

We do agree that mechanical bowel preparation/cleansing (MBP) may cause fluid and electrolyte abnormalities. This may be anticipated and corrected, but still, given the available evidence from randomized controlled trials (RCTs), it is preferable to avoid mechanical cleansing. Regarding the heterogeneity of RCTs, it should be acknowledged that the methodology of modern RCTs assures that treatment and control groups are stratified for most characteristics including antimicrobial and MBP regimens.

It is rational to believe that, in particular, colorectal surgical procedures with a high probability of anastomotic leakage, MBP may be useful. Specifically, all procedures with rectal location of the disease (e.g., low anterior resection with total mesorectal excision for rectal cancer) that require more distal anastomoses may have a higher probability of anastomotic leakage. However, we believe that recommendations should be based on evidence and not only medical reasoning. RCTs that stratified the risk of leakage to the site of anastomosis did not find any significant advantage of MBP for surgical procedures with rectal location of the disease.[1–3] As stated in our article,[4] we are confident that current literature provides strong evidence that in elective colorectal surgery, no significant benefit is derived from MBP. This applies to all procedures regardless of the site of anastomosis. Still, we agree that future well-conducted RCTs that are stratified for specific surgical procedures will add further evidence to support more specific recommendations.

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G. Peppas · V. G. Alexiou · M. E. Falagas (✉)
Alfa Institute of Biomedical Sciences (AIBS),
Athens, Greece
e-mail: m.falagas@aibs.gr

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LETTER TO THE EDITOR

Pancreaticojejunostomy with Application of Fibrinogen/Thrombin-Coated Collagen Patch (TachoSil®) in Roux-en-Y Reconstruction after Pancreaticoduodenectomy

Piero Chirletti · Roberto Caronna · Gianfranco Fanello · Monica Schiratti · Franco Stagnitti · Nadia Peparini · Michele Benedetti · Gabriele Martino

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To the Editor

We read with great interest the article by Wellner and colleagues about the comparison between pancreaticogastrostomy (PG) and Roux-en-Y pancreaticojejunostomy (PJ) after pancreaticoduodenectomy (PD) with regard to postoperative pancreatic fistula (POPF) and other complications.[1] The authors concluded that PG was superior to PJ in terms of clinically relevant POPF; although this study is retrospective, the use of a large case number and standardized measures in evaluation of the surgical outcome makes the results not negligible. Instead, the results of our previously described technique of Roux-en-Y reconstruction show that PJ may have a lower prevalence of POPF than that reported by Wellner and colleagues and suggest that outcome after Roux-en-Y reconstruction with regard to POPF can be further improved using fibrinogen/thrombin-coated collagen patch (TachoSil®, Nycomed, UK Ltd.) in carrying out PJ.

Briefly, we reviewed the clinical records of 54 consecutive patients who underwent PD by one surgeon (P.C.) at "La Sapienza" University (Rome, Italy) from January 1995 to December 2008. The underlying diseases were: pancreatic carcinoma in 31 cases; pancreatic serous cystadenoma in six cases; mucinous cystadenoma in one case; pancreatic endocrine tumor in two cases; ampullar carcinoma in seven cases; distal bile duct carcinoma in six cases; and chronic pancreatitis in one case. In all patients, the surgical procedure comprised PD with suprapyloric gastric resection and Roux -en-Y reconstruction with anastomosis of the isolated Roux limb to the stomach and single Roux limb to both the pancreatic stump and hepatic duct.[2] Small catheters were inserted in the main duct, passed through the anastomosed bowel loop and fixed to the abdominal wall (Fig. 1a, b). A drainage tube was placed near to the pancreaticojejunostomy; external biliary drainage was not used. Pancreaticojejunal end-to-end anastomosis was done by simple invagination of the pancreatic stump into the jejunal loop for 2 cm and sutured all around with a single-layer interrupted pledget-supported Ticron stitches between the seromuscularis of the jejunum and the pancreatic capsule. From January 2005, TachoSil® has been layered on suture line of pancreaticojejunal anastomosis (Fig. 1c, d). All 27 consecutive patients had pancreaticojejunostomy without TachoSil® (group A) whereas 27 consecutive patients had pancreaticojejunostomy with TachoSil®. All patients in our study received octreotide during the first six postoperative days.

The postoperative surgical outcome within 60 postoperative days was assessed. POPF, postoperative hemorrhage

P. Chirletti · R. Caronna · G. Fanello · M. Schiratti · N. Peparini · M. Benedetti · G. Martino
Department of Surgery "Francesco Durante",
"La Sapienza" University,
viale Regina Elena, 324,
00161 Rome, Italy

P. Chirletti
e-mail: segreteria.chirletti@uniroma1.it

F. Stagnitti
Department of General Surgery "Fiorini Hospital",
"La Sapienza" University - Polo Pontino,
viale Regina Elena, 324,
00161 Rome, Italy

N. Peparini (✉)
Via Quirina 18,
02032 Passo Corese, Rieti, Italy
e-mail: nadiapeparini@yahoo.it

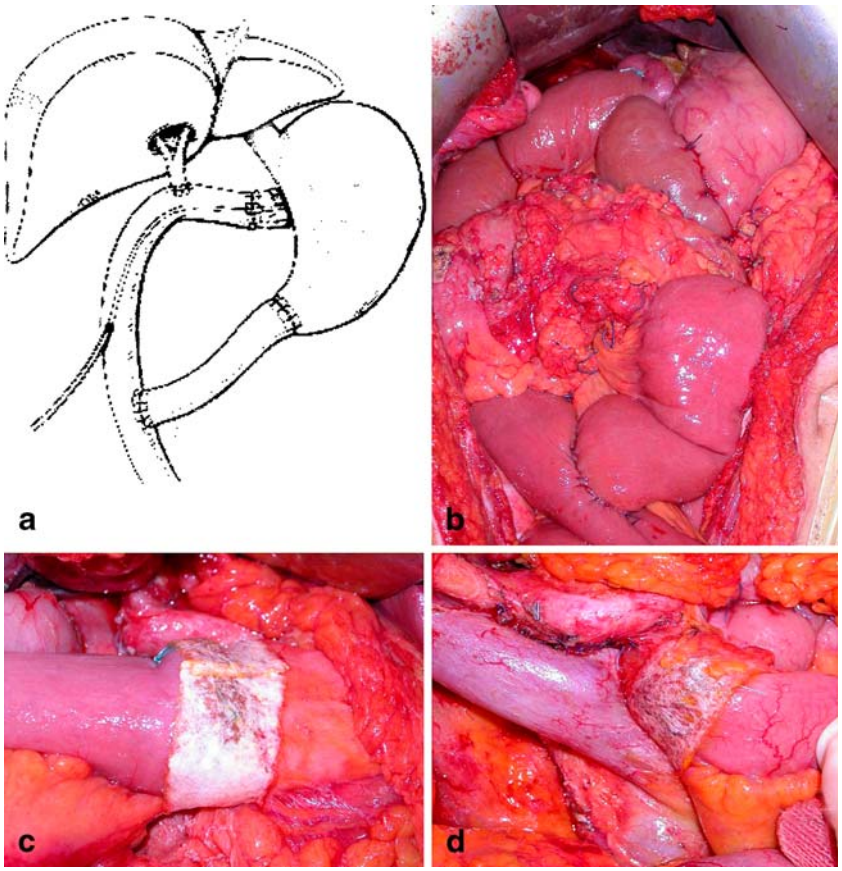

Figure 1 **a**, **b** Roux-en-Y reconstruction with anastomosis of the isolated Roux limb to the stomach and single Roux limb to both the pancreatic stump and hepatic duct; **c**, **d** anterior and posterior aspects of pancreaticojejunal anastomosis after application of TachoSil®.

(PPH), and delayed gastric emptying (DGE) were assessed according to the International Study Group of Pancreatic Fistula and International Study Group of Pancreatic Surgery definitions. POPF occurred in four patients (7.4%): three cases of grade A fistula resolved spontaneously and in one case of grade B fistula percutaneous drainage was necessary. Grade B extraluminal PPH occurred in four (7.4%) of 54 patients; biliary fistula in one case (1.8%); acute pancreatitis in one case (1.8%); and, in one patient with preexisting stenosis of hepatic artery, thrombosis of the hepatic artery (1.8%).

Grade A DGE occurred in eight patients (14.8%), grade C DGE in one patient (1.8%), left pleural effusion in 15 cases (27%), and wound infection in eight cases (14.8%). Postoperative mortality rate was 3.7% (two out of 54 patients: acute myocardial infarction; sepsis due to acute pancreatitis).

No differences were observed between group A and group B as regards clinical data (age, sex) and indications for PD. Three (two grade A and one grade B) out of four POPF occurred in group A and one grade A POPF occurred in group B. Although the differences between groups were not significant (Fisher's exact test: two-tailed $P=0.6104$), our preliminary experience suggests possible advantages of TachoSil® in the prevention of POPF.

Wellner and colleagues reported one case of fatal liver failure due to stent occlusion after stent placement for arrosion of the gastroduodenal artery. The sealing effects of TachoSil® layered on a pancreaticojejunal anastomosis may reduce the risk of the overflow of pancreatic juice from the anastomosis site during the first postoperative days and may minimize the risk of extraluminal PPH due to vessel erosion or development and bleeding of visceral arterial pseudoaneurysms caused by digestion of an arterial vessel wall near a pancreaticojejunal leak by trypsin and elastase.[3] According to Weller and colleagues, we would like to point out that in comparing the results between different studies the variations in operative techniques should be considered. Carrying out PJ by invagination of the pancreatic stump into the jejunum and Ticron-pledgeted sutures makes a homogeneous anastomotic surface that supports the adhesion of TachoSil® and optimizes the sealing effect.

Wellner and colleagues reported more intraluminal PPH and a higher rate of grade B and grade C DGE in the PG group than in the PJ group. Moreover, PG was associated with more severe or equal pancreatic exocrine insufficiency than PJ in different studies but significantly more severe atrophic changes in remnant pancreas were reported in PG group than in PJ group.[4] Minor changes in anastomotic techniques can contribute to improvement of the outcome

of Roux-en-Y reconstruction regarding POPF and, at the moment, PJ cannot be considered inferior to PG.

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LETTER TO THE EDITOR

Answer to Letter to the Editor Pancreaticojejunostomy with Application of Fibrinogen/Thrombin-Coated Collagen Patch (TachoSil ®) in Roux-en-Y Reconstruction after Pancreaticoduodenectomy

Tobias Keck

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To the editor

We thank Dr. Peparini and coauthors for their comment on our recent manuscript and for the demonstration of their own experience with reconstruction after pancreatoduodenectomy in the form of a pancreaticojejunostomy (PJ) with an external guided pancreatic duct drain and the use of a fibrin/thrombin-coated collagen patch.

Even though the results of the presented small series of patients comparing 27 patients with TachoSil ® and 27 patients without the use of fibrin sealant do not show significant differences, the authors demonstrate in their manuscript a very low overall postoperative pancreatic fistula rate (POPF) and therefore conclude that pancreaticogastrostomy (PG) cannot be considered superior to PJ. We have indeed pointed out that PG shows a lower rate of relevant grade B and grade C fistulae after pancreatoduodenectomy. We have as well demonstrated that PG had a higher rate of intraluminal bleeding which was, as described in the manuscript, a problem at the beginning of the introduction of this technique to our surgical armamentarium and is now easily prevented by meticulous hemostasis by 5–0 sutures at the pancreatic remnant. We have as well shown that there is a significantly increased rate of relevant (grade B and C) delayed gastric emptying (DGE). There are, however, several limitations that make a comparison of the results concerning POPF and DGE between our and Peparini's experience and resulting conclusions drawn in their letter difficult.

T. Keck (✉)
Chirurgische Universitätsklinik Freiburg,
Freiburg, Germany
e-mail: tobias.keck@uniklinik-freiburg.de

First, the authors use a completely different perioperative regimen. All patients in the retrospective analysis of Peparini routinely received octreotide, which is known to reduce pancreatic secretion at the early postoperative course. Even though this in many performed trial does not contribute to the rate of relevant fistula, it might well account for the significantly lower rate of early secretion of pancreatic juice as recently shown by Closset and coauthors.[1]

Second, Peparini and coauthors perform a suprapyloric gastric resection in comparison to our classical pylorus-preserving resection (pylorus-preserving pancreaticoduodenectomy, PPPD). Others and we[2,3] have previously reported that the rate of DGE after PPPD is significant and might be increased by pyloric preservation.

Third, the use of fibrin-glue-based sealants has been tested in various clinical trials. The latest and largest prospective randomized clinical trial evaluating the use of fibrin glue for the reduction of pancreatic fistulae after pancreatic head resection to date was performed by Lillemoe and coauthors[4] in 2004. Their analysis showed no statistically different incidence of pancreatic fistulae in both groups with an overall incidence of pancreatic fistulae of 28% (35/124 patients).

In summary, our study demonstrates a significant reduction of relevant postoperative fistulae after PG vs. PJ. Based on this retrospective study, we have started a prospective randomized trial comparing both techniques of reconstruction, which will add to the definite answer of this problem. Based on the high-level evidence of prospective randomized trials, the benefit of the use of fibrin sealant products in reduction of pancreatic fistulae warrants an equally meticulous analysis.

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