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The State of the Highest Level of Evidence: An Overview of Systematic Reviews of Pancreaticobiliary Disease Customized for the Gastroenterologist and GI Surgeon

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Abstract Trends emerged as randomized controlled trials (RCTs) on pancreaticobiliary disease were reviewed by each panel of experts. There were few RCTs. Although studies observed statistical differences between their treatment groups, many of them were underpowered. The studies with the most patients were sponsored by industry—on adjuvant therapy and biliary stents. Two subjects did not have an RCT [necrotizing pancreatitis and intraductal papillary mucinous tumors (IPMN) of the pancreas]. Constant heterogeneity between RCTs was observed. A good example was the 22 variations in study designs noted between the 5 RCTs of the adjuvant chemotherapy panel. Some of these RCTs had no inclusion criteria while a more recent trial utilized very specific measures. Many trials had insufficient follow-up (6 months in one study of chronic pancreatitis surgery). Each randomized controlled trial may have reached a different conclusion than another one on the same topic although they had similar results (adjuvant treatment for resected pancreatic cancer). From this review of the highest level of evidence in the literature for pancreaticobiliary disease, it is apparent that the lack of quantity and quality of the highest level of evidence provides us with a challenge to improve the quality of our literature. Cooperation is required, which might begin by an international consensus on definitions, inclusion criteria, and the minimum length of follow-up.

Keywords Systematic review · Randomized controlled trial · Pancreas · Bile duct · Pancreatitis · Pancreas neoplasms · Gallstones · Chemotherapy · Radiotherapy · Pancreaticoduodenectomy

The terms systematic review and evidence-based medicine are common in today's literature. But what do these terms really mean? In essence, the movement to focus on the highest level of evidence contained in our literature may be one of the most important advances since the printing press. However, perhaps it is just a trendy movement that will in the long run focus on the quality (or lack of) of randomized controlled trials or even the quality and importance of the concept of evidence-based medicine (EBM). With new communication and data transfer technology there has been an explosion of published articles. How does the busy clinician keep up with all of this information? EBM provides a structure to filter and then review just the highest quality of evidence. But if we focused just on the system of "evidence-based medicine" is it capable of providing valuable information? To assess EBM, we would have to know the quality of our highest level of evidence. The EBM proponents describe this as using the "rules of evidence." Therefore, in this postgraduate course, we chose the pancreaticobiliary system and used its most current literature to assess the quality and quantity of the highest level of evidence, i.e., Level 1 evidence. EBM is a simple term, but what is a systematic review?

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Definition of Systematic Review

A traditional literature review differs from a systematic review in that the literature review describes and appraises previous work but does not specify inclusion criteria by

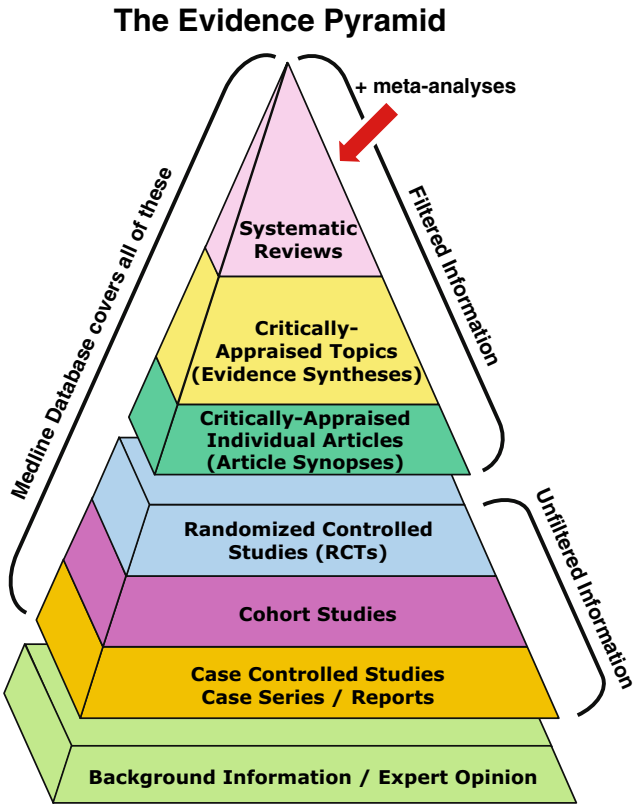

Figure 1 Our literature can be divided into the highest level of evidence with the foundation for our clinical decisions being at the bottom of the pyramid. The level of evidence increases toward the pinnacle which represents the systematic review of randomized controlled trials. All of the published literature is reviewed by Medline and represents unfiltered information. The information can be filtered so we can quickly reach the correct citations among the 15 million articles in the literature. The literature can be self-filtered by using a search engine such as Ovid or PubMed. Some of this information can be filtered for you (or critically appraised) by a number of the organizations mentioned in this article. (Adapted from the EBM Pyramid and EBM Page Generator, with permission, copyright 2006 Trustees of Dartmouth College and Yale University. All Rights Reserved. Produced by Jan Glover, David Izzo, Karen Odato and Lei Wang.).

which the reviewed articles or studies were identified, evaluated, and chosen. A systematic review begins with a comprehensive search of relevant studies, identifies criteria for study inclusion or exclusion, and utilizes established standards to appraise study quality (rules of evidence). This process is time-consuming and only a few pancreaticobiliary disorders have been systematically reviewed by organizations such as the Cochrane collaboration. Whenever possible, the topics of this course were chosen from already existing and the most up-to-date systematic reviews.

To understand the essential factors in clinical decision-making and management of patients with these disorders of the gastrointestinal tract, we must first classify the quality of evidence that supports these decisions. What are the "rules of evidence" to select these studies and then once selected how can they be analyzed using a well-built clinical question?

Course Goals

The course had three goals:

1. To define "levels of evidence" and how to understand the strength of recommendations derived from the confusing taxonomy.
2. To provide the current strength of support for how we treat pancreaticobiliary disorders. To improve our outcomes, we must know the current strength of the evidence, the evolving diagnostic and therapeutic options, and what still needs to be accomplished.
3. To allow the gastroenterologist and gastrointestinal surgeon to hear an analysis of pancreaticobiliary disorders solely oriented toward the highest level of evidence rather than a literature review.

Table 1 An Overview of the Literature for Pancreaticobiliary Disease Based on the Highest Level of Evidence for the Treatments Tested

Panel Topic	Number of RCTs	Patients Studied (*N*)	Europe
1. CBD Stones Discovered During Cholecystectomy: Intraoperative Versus Delayed Endoscopic Removal?	2	166	1/2
2. Early ERCP for Gallstone Pancreatitis: For Whom & When?	5	606	2/5
3. Necrotizing Pancreatitis: Percutaneous, Minimally Invasive, and/or Open Necrosectomy?	0	0	0
4. Chronic Pancreatitis: Treatment with Endo-therapy and/or Surgery	8	380	8/8
5. Progression of IPMN based on Natural History	0	0	0
6. Pancreatic Cancer: Extended Resection, Survival, QOL	4	440	1/4
7. Pancreatic Cancer: Adjuvant Therapy for Resected Lesions	5	1256	3/5
8. Decompression of Malignant Biliary Obstruction: PTBD, Endostents, or Open Biliary Drainage?	23	1634	17/23
Total	47	4482	32/47 (68%)

RCT, randomized controlled trial; *CBD*, common bile duct; *ERCP*, endoscopic retrograde cholangiopancreatography; *IPMN,* intraductal papillary mucinous tumor of the pancreas; *QOL,* quality of life; *PTBD*, percutaneous transhepatic bile duct drainage

Perspective on the Modern Literature

As we entered the summer of 2007, there were 15 million articles in Medline and 2,000 to 4,000 articles were being added daily. There were 5,000 journals providing articles and in 37 languages. These 15 million articles represent the "unfiltered" information in the Evidence Pyramid as shown in Fig. 1. One can filter the publications into randomized controlled trials, cohort studies, and case control studies. Medline also provides another filter in the form of other experts' assessments of the information through a series of critical appraisals. These appraisals concentrate on either a single article or of an entire topic. The highest form of a critically appraised topic is the systematic review. Meta-analysis are part of many systematic reviews and are therefore considered high levels of evidence; however, the quality of these studies as well as the randomized control trials (RCT) vary immensely. After a review of systematic reviews and meta-analyses it becomes apparent that many are not of high-quality and should not be considered high levels of evidence. You are the judge.

Types of Filtered Information

The search engines of Ovid or PubMed allow us to filter this information, i.e., a form of self-filtering. The 50 million articles can be filtered by topic using Ovid's clinical evidence (on the left sidebar after logging on at http://gateway.ovid.com/autologin.cgi) or by reviewing the National Guidelines Clearinghouse, a section of The Agency for Healthcare Research and Quality (http://www.guideline.gov). Specific articles are reviewed by a number of organizations like Bandolier (http://www.jr2.ox.ac.uk/bandolier/), BMJ Updates (http://www.bmjupdates.com/index.asp), and the ACP Journal Club (http://www.acpjc.org).

There is another form of filtered information for the physician which might be best termed a dynamic textbook—a web-based encyclopedia that is constantly being updated. Examples are Up-To-Date, Harrison's Textbook of Medicine, ACS Surgery, and ACP Medicine. All of these "textbooks" are available to you through your library. Make friends with a librarian because that person is the portal to all of this valuable information.

There are even dynamic web-based journals sometimes referred to as "open access journals." The manuscripts are submitted online where they are peer-reviewed whereupon acceptance they are immediately published. BioMed Central (BMC) is a good example (http://www.biomedcentral.com). There is an annual fee to participate with these journals which allow publication of just the introduction and methods portion of an article before the study is ever finished. For example, a randomized controlled trial that is just beginning may decide to publish its methodology. It is unfortunate that Medline filters this information so that it appears as a randomized controlled trial when using a search engine.

Results of the Course—an Overview

A trend emerged as each panel presented the literature it had discovered as the highest level of evidence for their specific topic. In general we found five trends. First, in most panels there were not many randomized controlled trials as summarized for you in Table 1. Of the eight panels dedicated to a specific topic, the last two panels of the day were the most highly studied on adjuvant therapy and biliary stents. The reason was probably that these topics lend themselves to randomized controlled trials by comparing treatments such as using new drugs or devices. They are also industry driven. Second, we discovered that almost all of the other studies contained low patient numbers probably due to difficulties in performing RCTs. Although many of the studies observed statistical differences between their treatment groups, many of the studies were underpowered. Two panels had no studies that met the rules of evidence for high level evidence [necrotizing pancreatitis and intraductal papillary mucinous tumors (IPMN) of the pancreas]. The IPMN panel did present a Level III paper but it was with short follow-up for the natural history of this disease. Third, there was a constant heterogeneity between RCTs. This was particularly true in every panel. A good example was the 22 variations in study designs noted between the 5 RCTs of the adjuvant chemotherapy panel. Another example was a lack of definitions or inclusion criteria for patients receiving treatment for chronic pancreatitis. Some of these RCTs had no inclusion criteria while a more recent trial utilized very specific measures. Fourth, many of the trials had insufficient follow-up (6 months in one study of chronic pancreatitis surgery). Fifth, and not surprising, was that each randomized controlled trial may have reached a different conclusion than another one on the same topic even though they had similar results (Adjuvant Treatment for Resected Pancreatic Cancer, Table 4 of that lecture summary).

From this review of the highest level of evidence in the literature for pancreaticobiliary disease it is apparent that the lack of quantity and quality of the highest level of evidence provides us with a challenge to improve the quality of our literature. Cooperation is required which might begin by an international consensus on definitions, inclusion criteria, and the minimum length of follow-up. Credit should go to Europe for providing 68% of the controlled trials.

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The Rules of Evidence-Based Medicine: Can They Be Generalized to Improve GI Surgical Practice?

Jonathan L. Meakins

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Abstract Evidence-based surgical practice (EBSP) must be integrated into the educational curriculum for all surgeons. Independent of the compelling need for best practice, there are at least three compelling drivers: the exploding cost of health care demands evidence-based practice, patient safety is best supported by best evidence, and the medico-legal environment uses EBSP to pursue its goals.

Keywords Evidence-based surgery · Evidence-based surgical practice · Rules of evidence · EBM · EBSP · PICO · Critical appraisal · Randomized controlled trials

Introduction

"Evidence-based" has entered into the jargon of healthcare. We are here involved with that set of knowledge that relates to surgery and to surgical practice and shall describe evidence-based surgery (EBS) and refer to its application clinically as evidence-based surgical practice (EBSP), incorporating the entire patient journey. Much scorn has been heaped upon EBM(S) proponents most particularly by established clinicians ruffled at the very idea that their clinical practices might not be evidence-based. Most considered themselves to be up to date and some were opinion-leaders in their field. The operative word is, of course, opinion.

Evidence-based surgery could be defined as the integration of *best research evidence* (clinically relevant research, basic science, relating to diagnosis, treatment, prognosis) with *clinical expertise* (skills and experience adapted to a particular patient) and *patient values* (patient preference and attitudes to clinical entity and its overall management).[1–3] The devil is in the details, and the most contentious and difficult is clarifying, defining, or establishing "best research evidence,"[3,4] the methodology for which is iteratively being developed and defined. In reality, the best evidence is usually a summary of all the evidence that will assist in solving the clinical problem with the elimination of bias.[5] The answer to a clinical question in a particular patient is often different from that in a population. The key steps, however, are the same:

- Define the question: Precise formulation of the clinical question to a patient's problem, the proposed intervention, comparative procedure (standard), and outcome is defined as a PICO.
- Search for the evidence: The literature must be accessed. Searching is a *key tool* in our armamentarium.[1,2]
- Critically appraise the literature: Critical appraisal is a second key tool, as relevant as a scalpel, without which bias, validity, quality of design, importance, and relevance to the question at hand cannot be assessed.
- Apply the results: to a patient or a population.
- Evaluate the outcome: Closing the circle – evaluation of outcome – is as important as any of the other steps and leads to "practice-based learning."

A useful concept to calculate from the critical appraisal is the number needed to treat (NNT). The NNT is the

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Table 1 The Levels of Evidence Most Available to Surgeons and Operative Therapy

Grade	Level	Description
A	1c	All or none
B	2a	Systematic review of cohort studies
B	2b	A cohort study
B	2c	"Outcomes" research
C	4	Case series
D	5	Expert opinion

number of patients treated to achieve the primary goal in a patient. For surgeons deciding upon an operation, the number needed to harm (NNH) is as important and ought to be integrated into any clinical or operative decision.[1] When the NNT is high, i.e., clinical benefit is modest, and NNH low, i.e., cost of procedure in complications and mortality are important, a patient-centered approach demands balanced disclosure.

An integral component of EBM/EBSP is the *hierarchy* of *evidence*. The studies are stratified into levels of evidence by their quality, lack of bias, homogeneity, etc. There are five levels. The strongest evidence, 1a, is a systematic review of randomized controlled trials (RCT) with homogeneity. The weakest is expert opinion, however qualified (level 5). The level identifies the quality of the evidence and leads to a grade of recommendation A–D (Table 1). The development of the levels of evidence (http://www.cebm.net) has been iterative.[5]

Much of the surgical literature is case series and has been heavily criticized for the absence of RCTs and well-structured prospective studies.[6] There is, nonetheless, a significant body of information in the literature that has directed therapy of common and uncommon clinical problems, reflecting the corrective nature of much of our clinical practice.

While it is possible to find some support for most therapies, disciplined critical appraisal of the studies may demonstrate significant flaws, structural biases, or failure of adequate follow-up. Critical appraisal, systematic reviews, and meta-analyses will help to identify the value of knowledge we have and that which we require. An additional issue is implementation of the knowledge we have.[7,8]

The Rules of Evidence and Surgical Practice

The criticism that there is no evidence base to the clinical delivery of surgical care is only partly supportable.[6] When considering surgical practice, one generally thinks only of "the procedure." If, however, one examines the patient's pathway, it becomes apparent that there is much more to a satisfactory outcome than the operation itself. The component's parts of the pathway can be isolated and evaluated using the classic tools of RCT. The obvious examples would be:

- Prophylactic antibiotics
- Prevention of thromboembolic events
- Use of drains
- Prevention of respiratory complications
- Postoperative nutrition
- Beta-blockers in noncardiac surgery

These represent just a few of the nonoperative components of surgical care that have been assessed within the RCT methodology. Indeed, most have been studied many times and are suitable for systematic reviews.[7] These reviews have been done by several organizations, e.g., the Cochrane Collaboration, the Scottish Intercollegiate Guidelines Network, the Surgical Care Improvement Project, and the American College of Surgeons. While they all have specific web addresses, they can be accessed via one of the many available search engines. Pubmed gives access to the specific articles and has importance in the search for the primary sources. Many sites will give guidelines based upon properly performed systematic reviews. These are usually graded and give the level of evidence that supports the guideline.

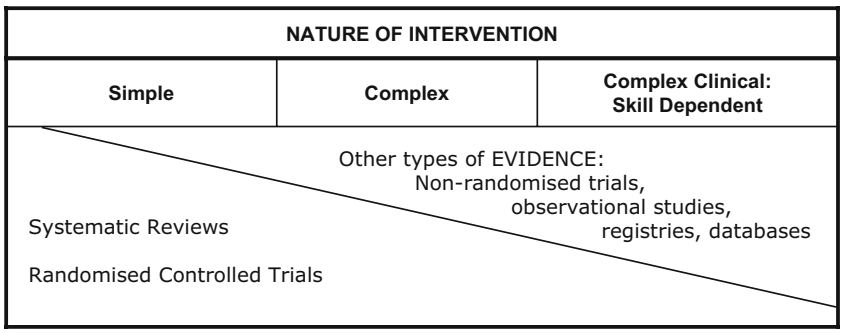

Figure 1 Nature of evaluation of an *intervention* evolves with its complexity The complexity of intervention is divided into three categories. It is hypothesized that the nature of the evaluation technique is different as the clinical therapeutic process becomes more complex. RCT cannot solve all evaluation questions around procedure-based medicine (surgery, endoscopy, radiology, etc.).

As patient journeys become more complex, the use of evidence-based components becomes increasingly important. Complex interventions or protocols, amalgams of evidence-based components, become very difficult to evaluate. Perhaps the best example in GI surgery would be the *fast track* approach to colon resection proposed by Kehlet.[9,10] This integration of preoperative preparation; operative technique; anesthetic management; and postoperative pain control, nutrition, and mobilization is entirely evidence-based. However, it is unlikely that an RCT could be designed to compare to a more traditional delivery care system. Nonrandomized trial designs and observational studies will be required to assess efficacy and validity of the approach. While not considered level-1 evidence (homogeneous RCT), when done well, they can provide grade-A recommendations. This is particularly likely when large improvements in outcome are apparent. Strong recommendations are also made where the study cannot be done (antibiotics and cardiac valve replacement).

The operative intervention is more difficult to evaluate, particularly when it is complex. The technique for appendicectomy or hernia repair is relatively simple, as the procedure has few nonoperative components, which are relatively simple to standardize. Comparing techniques for esophagectomy, transhiatal vs. Ivor-Lewis vs. left thoracoabdominal would be a nightmare because of the complexity of total care. The importance of the operative technique could be lost in the noise of anesthetic technique and the variety of perioperative protocols and hospital systems, which may have little to do with the operation itself (Fig. 1). This is supported by studies looking at volume-outcome relationships. It is usually hospital volume, i.e., systems, not surgeon volume, which is critical. Surgeon training and education as a specialist is related to outcome; however, this may be related to establishing protocols and creating a unified system of management.

These issues are even more difficult when evaluating new procedures or variations on an established operation. The RCT is often not the appropriate tool, and the surgical community has an obligation to develop the instruments to define the evidence base in support of innovative surgical practice.[2,11] In the long run, a major concern must be that if the profession does not utilize the best evidence, external pressures will force the issue. The most obvious change, perhaps the unacceptable one, will be the standardization of pre- and postoperative care. Evidence-based protocols and care maps would be standard operating practice.

There are principally three external drivers to push clinical practice towards a more standardized EBSP, or perhaps the term “best practice” ought to be used. Firstly, the cost of healthcare throughout the western world is increasing almost exponentially, and it needs to be managed. Secondly, issues surrounding patient safety have highlighted the reality that there are vast differences in the management of the same condition. Undoubtedly, some will not matter, but in many areas it is likely that there will be a best-practice approach, and it is up to the medical profession to sort these out. Recognizing that this interferes with physician autonomy, the issues of patient safety will not long tolerate the desire for professional independence vs. continuous quality improvement of evidence-based surgical care. Thirdly, a threatening medico legal environment, increasing in all Organization for Economic Cooperation and Development countries, is utilizing concepts of evidence-based practice and standardized approaches to the management of common problems to support claims. In circumstances where there is an untoward event, failure to have used the best evidence leaves the clinician open to liability. There is a fourth driver. Of the six competencies required for recertification by the American Board of Medical Specialties, at least three touch on EBSP: knowledge, patient care, and systems-based practice.

What are Some of the Solutions?

Driving forces have already been mentioned with respect to the need for EBSP. These drivers will demand from all surgeons an understanding of the principles of EBS and how to implement those in practice. The objective is not the standardization of all aspects of surgical clinical activity but to ensure that patients receive, at all times, optimal surgical care. Therefore, from a surgical career point of view, understanding the issues associated with surgical epidemiology, knowledge management, and EBSP have implications for clinicians in the community, surgeons in large metropolitan hospitals, surgeon scholars, and academic surgeons. All surgeons need to have some understanding of not only the evaluation of the evidence and how to find it but, in addition, application of those concepts, whether derived from randomized or nonrandomized studies, to continuous quality improvement and closing the circle of surgical audit.

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Treatment of Common Bile Duct Stones Discovered during Cholecystectomy

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Abstract
Background Several techniques of laparoscopic bile duct exploration and intraoperative endoscopic sphincterotomy (ES) have been developed to treat patients with common bile duct (CBD) stones in one session and avoid the complications of ES. With all these options available, very few randomized controlled trials (RCTs) have been undertaken. This review analyzes those studies.
Methods We searched PubMed. Four RCTs and a Cochran Database Systematic Review were found.
Results Two RCTs compared preoperative ES and laparoscopic CBD exploration (E) for known CBD stones. Laparoscopic CBDE had shorter length of hospitalization. Two RCTs compared immediate and delayed treatment and found that length of stay was less with laparoscopic CBDE, but clearance rates and morbidity/mortality were similar.
Conclusions Studies suggest that CBD stones discovered at the time of cholecystectomy are best treated during the same operation. The transcystic approach is safest if applicable. Individual surgeons must be aware of their own capabilities and those of the available endoscopists and perform the safest technique.

Keywords Choledocholithiasis · Cholecystectomy · Laparoscopic choledochotomy · Bile duct stones · Common bile duct exploration · CBD stones

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The incidence of choledocholithiasis in patients undergoing cholecystectomy varies with age, ranging from 6% in patients less than 80years old to 33% in patients more than 80 years of age.[1] It is estimated that 5% to 12% of patients with choledocholithiasis may be completely asymptomatic and have normal liver function tests.[2–4] The vast majority of common bile duct (CBD) stones originate from the gallbladder, and only a small percentage of patients will develop CBD stones de novo. Choledocholithiasis is diagnosed during cholecystectomy under two scenarios: 1.) Intraoperative cholangiography (IOC) performed on patients with a high suspicion of CBD stones based on history, ultrasound or other imaging, and liver function tests; and 2.) IOC performed on patients as part of a protocol of routine cholangiography.

The treatment of common bile duct calculi was uniform before the adoption of laparoscopic cholecystectomy (LC). In the prelaparoscopic era, patients suspected of harboring CBD stones underwent intraoperative cholangiography. If CBD calculi were discovered, choledochotomy, stone extraction, and T-tube placement were performed. The introduction of therapeutic laparoscopy altered the surgical

approach to CBD stones. In the 1990s, preoperative endoscopic retrograde cholangiography (ERC) became the standard approach for patients suspected of having choledocholithiasis to avert subsequent intraoperative conversion to open common bile duct exploration (CBDE). Postoperative endoscopic sphincterotomy (ES) became the preferred approach to treat CBD stones encountered during LC or discovered afterwards. In some communities, ERC/ES increased 243%.[2]

In an effort to treat patients with CBD stones in one session and avoid the potential complications of ES (especially in younger patients with small-diameter CBD), several techniques of laparoscopic transcystic common bile duct exploration (LTCBDE) and laparoscopic choledochotomy were developed. Also, intraoperative ES has been advocated. With all of these options available, only a few randomized controlled trials (RCTs) have been undertaken to define the best treatment algorithms for patients with CBD stones. This review analyzes those studies, i.e., the highest level of evidence.

Methods

A search of PubMED (a service of the U.S. National Library of Medicine; www.pubmed.gov) was performed. The search terms used for the review include "common duct stones," "common duct," "common duct exploration," "common bile duct exploration," "endoscopic sphincterotomy," "transcystic," "choledochotomy," and "bile duct stones." The primary search was then distilled to include randomized controlled trials (RCT). Two RCTS were found that compared treatment for preoperatively known CBD stones and two RCTs compared treatments of intraoperatively discovered CBD stones. A Cochrane Database Systematic Review was also found. This Level I evidence along with other relevant studies are analyzed here.

Results and Discussion

Laparoscopic techniques of CBDE were developed in the early 1990s to decrease the need for preoperative ERC and treat patients in one session. Two RCTs compared the treatment of known CBD stones—preoperative ES vs. laparoscopic CBDE.[5,6] The results are described in Table 1. The results of the two approaches are similar, although the length of hospital stay is shorter with LCBDE in the Cuscheiri, et al. study. The weakness inherent in these studies is that they fail to include the morbidity of negative preoperative ERC.

During the early experience with LC, many patients underwent preoperative ERC/ES. Freeman presented a multicenter 30-day outcome study of ES at the 1994 World GI Congress in Los Angeles. This study, which included 1,494 patients, revealed an overall complication rate of 7.4%, procedure-related mortality of 0.5%, and all-cause mortality of 2.2%.[7] Although the days of routine preoperative ERC are over, laparoscopic techniques of CBDE still have not been widely embraced.

Several options are available when confronted with CBD stones during cholecystectomy: open CBDE, laparoscopic CBDE, and intraoperative ES. Laparoscopic CBDE involves either transcystic CBD stone extraction (fluoroscopic guided wire basket or choledochoscopy) or laparoscopic choledochotomy and stone extraction. Several cohort studies have shown that two thirds of the stones detected by intraoperative cholangiography can be removed via the transcystic approach.[8] For patients in whom transcystic extraction of CBD stones fails, laparoscopic choledochotomy and stone extraction may be performed. However, this approach requires experience in laparoscopic suturing and a CBD of adequate diameter.

Alternative management options have been described, but have not been subjected to RCT. For example, intraoperative ES has been reported in a number of centers.

Table 1 Endoscopic Sphincterotomy (ES) vs. Laparoscopic Cholecystectomy (LC) Plus Laparoscopic Common Bile Duct Exploration (LCBDE)

Category	Cuschieri[6]			Sgourakis[5]		
	Preop ES n=150	LC+ LCBDE n=150	P Value	Preop ES n=36	LC + LCBDE n=42	P Value
Morbidity (% of patients)	12.8	15.8	0.54	13	17	<0.87
Mortality (% of Patients)	1.5	0.75	NS	2	2	NS
Common Duct Stone Clearance (% of operations)	84	84	0.96	86	84	NS
Length of hospital stay (mean days)	9	6	<0.05	7.4	9	0.07

NS=Not significant

Table 2 Intraoperative Randomized Controlled Trials for Management of Common Duct Stones Discovered during Laparoscopic Cholecystectomy

Category	Nathanson[8] (n=86 patients)			Rhodes[12] (n=80 patients)		
	LCBDE (choledochotomy) n=43	Postop ES n=43	P Value	LCBDE (trancystic) n=40	Postop ES N=40	P Value
Primary Ductal Clearance (%)	100	74	0.20	75	75	NA
Final Ductal Clearance (%)	100	100	NS	100	93	NA
Morbidity (%)	17 (14.6 bile leak)	13	NS	0	0	NA
Mortality (%)	0	0	NS	0	0	NA
Length of hospital stay (mean days)	6.4	7.7	0.57	1	3.5	NA

LCBDE=Laparoscopic Common Bile Duct Exploration
ES=Endoscopic Sphincterotomy
NA=Not available
NS=Not significant

This approach is wholly dependent on the availability of endoscopic expertise in the operating room. Available results, although limited, show high clearance rates in excess of 90%, with minimal morbidity and no increase in the length of hospital stay over that of laparoscopic cholecystectomy alone.[9,10]

The other alternative to immediate treatment of CBS stones discovered at surgery is delayed treatment. Surgeons can insert a biliary stent through the cystic duct into the CBD and through the sphincter of Oddi.[11] This procedure ensures access to the bile duct for postoperative ES.

When CBD stones are discovered intraoperatively, what is the best treatment option? Two prospective randomized studies (Table 2) have evaluated the merits of immediate versus delayed treatment for bile duct stones. Rhodes et al. (1995)[12] randomized 80 patients at the time of diagnosis by cholangiography to either laparoscopic exploration or delayed postoperative ES. Patients were excluded if they had preoperative ES, cholangitis, or acute pancreatitis. The laparoscopic approach entailed transcystic exploration (n=28) of the duct followed, if necessary, by laparoscopic choledochotomy (n=12) in those patients with CBD exceeding 6 mm in diameter. This study showed that both techniques were associated with a 75% successful bile duct clearance rate at the time of first intervention. Final duct clearance was not significantly different, although there was a trend toward better clearance with the laparoscopic approach. The length of hospital stay was significantly shorter with the single-stage approach (1 day, 3.5 day; $p<0.001$). There was no significant difference in morbidity (18%, 15%; p=NS) or mortality (0%, 0%). However, the authors concluded that the transcystic approach was preferred.

Nathanson et al. (2005)[8] conducted a more focused study. Patients were included only if the transcystic approach failed to clear the intraoperatively discovered CBD stones. Eighty-six patients were randomized to laparoscopic choledochotomy or delayed postoperative ES. There were no differences between the two approaches in terms of bile duct clearance rates, morbidity, or length of hospital stay. However, the patients undergoing choledochotomy experienced a significantly higher rate of bile leak (14.6%) from the choledochotomy. The authors conclude that both techniques are efficacious, while recognizing that the laparoscopic approach may be limited in less experienced centers.

A Cochrane systematic review by Martin et al. (2006)[13] concluded that a single-stage treatment of bile duct stones via the cystic duct approach was recommended for intraoperatively discovered CBD stones. In patients where it is not possible to clear the duct by this approach, a delayed postoperative ES would be the preferred option in most centers. However, it was also noted that the reported experience is limited, and larger randomized trials are warranted to compare these therapeutic options.

A potential study when transcystic exploration fails might be the use of open CBDE in younger patients versus postoperative ES in older people. Open CBDE has been shown in RCTs to result in morbidity ranging from 11% to 14% and mortality of 0.6% to 1%. Interestingly, Morgenstern et al.[14] reported on 220 open CBDE before the laparoscopic revolution. Their results revealed no mortality in patients under 60 years of age and 4.3% mortality in those over 60. This suggests that patient age could affect the treatment algorithm, and that ES should be strongly considered in patients above the age of 60.

Other deficiencies in our literature must be considered in addition to the paucity of RCTs. First, we have few data on the natural history of small or "silent" stones and the true morbidity of retained CBD stones. One recent study from the United Kingdom reported a series of patients undergoing laparoscopic cholecystectomy with routine cholangio-

Table 3 Proposed Randomized Control Trials

Proposed Trials
1. Preoperative ES vs. Postoperative ES in patients with + MRCP
2. Preoperative ES vs. LCBDE vs Postoperative ES
3. Interoperative ES vs. Postoperative ES
4. Open CBDE vs. LCBDE vs. Postoperative ES
5. Technique of LCBDE: Transcystic fluoro, wire basket vs. transcystic endoscopy, wire basket vs. choledochotomy (t tube, endostent)

CBDE=Common Bile Duct Exploration, ES=Endoscopic Sphincterotomy, MRCP=Magnetic Resonance Cholangiopancreatography, LCBDE=Laparoscopic Common Bile Duct Exploration

gram. In patients discovered to have CBD stones, a transcystic catheter was left in place for postoperative cholangiogram. Fifty percent of these patients were discovered to be stone-free after 6 weeks.[15] Next would be the methodology of future trials. In the aforementioned RCTs, there were numerous exclusion criteria that changed the management of some patients. These exclusion criteria included acute pancreatitis, acute cholangitis, anatomy precluding ERCP, ASA status 3–4, and the need for a drainage procedure of the CBD. Also, the issue of operative experience must be considered.

Over the past 30 years, the number of cholecystectomies performed annually in the United States has increased from approximately 400,000 to 750,000 per year. On the other hand, the rate of CBDE has dropped dramatically from approximately 20% to 2%. In total, only approximately 15,000 CBDEs are performed each year. Experience is therefore limited in the performance of laparoscopic removal of CBD stones. Although the results are generally excellent in the published reports, these usually originate from centers of excellence, and there are no data on the outcomes of procedures performed by less experienced surgeons. Clearly, the incidence of surgical CBD exploration has diminished over the past few decades. A recent report from the national inpatient database suggested that only 7% of CBD stones are treated surgically, with the remainder being managed by endoscopic techniques.[16] Furthermore, the number of CBD explorations reported by finishing chief surgery residents has decreased from a mean of 10 in 1990 (all "open") to means of 1.5 open and 0.8 laparoscopic CBD explorations in 2006. Thus, it is clear that trainees are not gaining adequate hands-on experience in CBD exploration.

Finally, the indications for a surgical drainage procedure or an endoscopic sphincterotomy must be considered. A Roux-en-Y hepaticojejunostomy, a choledochojejunostomy, or a surgical sphincteroplasty may be indicated for sphincter of Oddi stenosis/dysfunction, primary CBD stones, patients with duodenal diverticula, multiple CBD stones, or intrahepatic stones. Similarly, ES is indicated for patients with CBD stones with severe preoperative cholangitis or pancreatitis, and for sphincter of Oddi stenosis/dysfunction. When

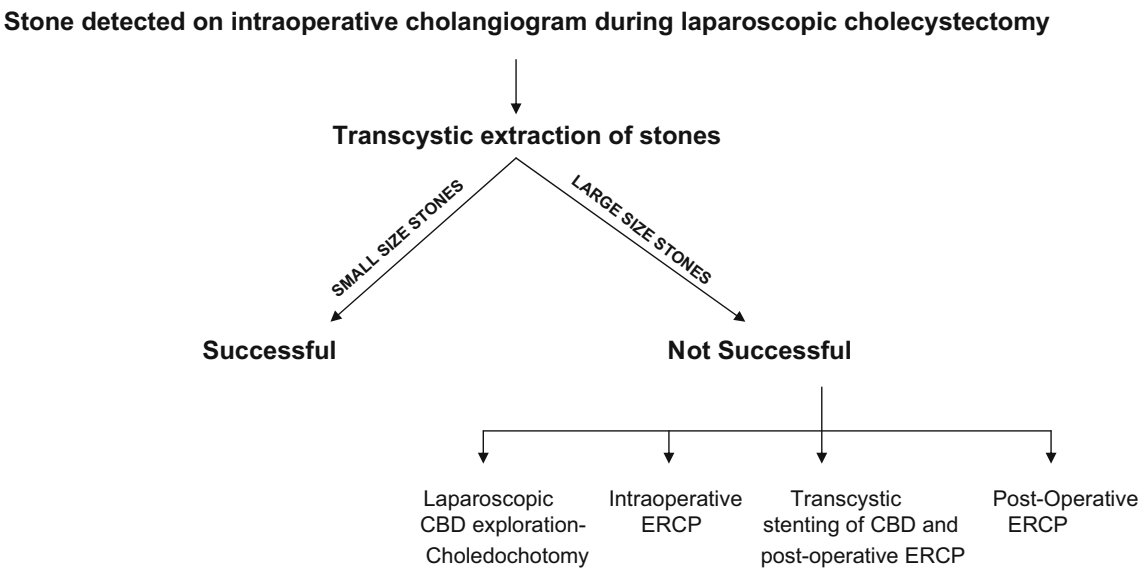

Figure 1 Algorithm for common bile stones detected on intraoperative cholangiogram during laparoscopic cholecystectomy.

these indications overlap, open CBDE and ES are often complementary. However, open CBDE remains the "gold standard" for selected, rare patients such as those with Mirizzi syndrome, Billroth II anatomy, and those requiring a drainage procedure. Because experience is now limited, these procedures should be performed by a hepato-pancreato-biliary (HPB) surgeon with advanced training.

Conclusion

The results of studies over the last decade suggest that stones detected in the CBD at the time of LC are best treated via a transcystic laparoscopic approach during the same operation. If this fails, alternate approaches such as intraoperative or postoperative ES, laparoscopic choledochotomy or open CBDE may be used. Alternatively, a stent may be placed through the cystic duct and across the sphincter of Oddi to facilitate postoperative ES. These data reveal areas that require future study that will help clinicians treat their patients with CBD stones (Table 3).

Figure 1 illustrates a proposed algorithm for treating CBD stones detected on intraoperative cholangiography during laparoscopic cholecystectomy. However, it is unrealistic to extrapolate standards of care based on the available RCTs given the wide variation in skills and resources available in different communities. Individual surgeons must recognize their own limitations and the limitations of available endoscopists and perform the safest approach.

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Early ERCP for Gallstone Pancreatitis: For Whom and When?

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Abstract The indications for early endoscopic retrograde cholangiopancreatography (ERCP) in gallstone pancreatitis are unclear, and the examination is often requested or performed without substantial supporting evidence. Several trials have been performed to determine the benefit of early ERCP in pancreatitis, yet the results of these studies are inconsistent. To more closely analyze these studies, we performed an evidence-based review of the outcomes of early ERCP in gallstone pancreatitis. To obtain the best available evidence, a PubMed search using the MeSH terms "gallstones" and "pancreatitis" was performed and further refined to identify appropriate studies. We included five randomized trials, a meta-analysis, and a Cochrane Database Systematic Review in our detailed examination of the pertinent literature. Collectively, these studies suggest that early ERCP does not alter mortality in gallstone pancreatitis. In addition, few patients with mild pancreatitis benefit from the procedure, whereas some studies indicate that patients with severe pancreatitis or documented biliary obstruction may experience fewer complications if ERCP is performed. The data in the studies are confounding because of heterogeneity of the patient population and the inability to confirm gallstones in up to one third of patients. In conclusion, ERCP is not indicated for patients with mild pancreatitis. In select patients with severe disease or biliary obstruction, ERCP may be indicated. A multicenter trial designed to study the effect of early ERCP in severe pancreatitis only may provide additional useful information in patients with documented gallstones.

Keywords Gallstone pancreatitis · Cholangiopancreatography · Gallstone

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Introduction

At the inception of the twentieth century, a medical student and subsequent pathologist at Johns Hopkins Hospital postulated that pancreatitis was the result of gallstone impaction in the distal common bile duct. This student, Eugene Opie, surmised that gallstones could leave the gallbladder, traverse the common bile duct, and become impacted at the union of the distal common bile duct and pancreatic duct with impaired pancreatic secretion and reflux of bile into the pancreatic duct.[1,2] This pathogenesis of gallstone pancreatitis, known as the "common channel theory" of biliary pancreatitis, has been challenged, but the concept of gallstone-induced pancreatitis with subsequent pancreatic inflammation remains intact.

Acosta and Ledesma[3] provided further rationale for the concept of gallstone-induced pancreatitis when they demonstrated that the strained stool of patients with pancreatitis contained gallstones. In addition, patients with severe pancreatitis tended to have stones impacted in the ampulla,

and early (≤48 h) operative decompression of the obstructed biliopancreatic ducts by sphincterotomy and stone extraction decreased mortality rates from 16 to 2%.[4] However, the retrospective study design combined with the use of a historical control group made interpretation of this study difficult. Ranson[5] demonstrated that cholecystectomy within the first week of onset of symptoms of pancreatitis was accompanied by an unacceptable mortality of 67%. Further evidence supporting an increased risk of morbidity and mortality for early surgery in pancreatitis was produced by Kelly and Wagner,[6] who performed a prospective randomized trial of early (≤48 h of admission) versus delayed (more than 48 h after admission, but before discharge) surgery in biliary pancreatitis. This study found that the timing of surgery had little effect in patients with mild pancreatitis, but early surgery resulted in significantly more complications (83 versus 18%) and mortality (48 versus 11%) in patients with severe pancreatitis. As a result, early operation to remove an impacted stone to theoretically decrease the extent of pancreatitis was abandoned.

At the time when the effect of early operation on gallstone-induced pancreatitis was studied, the techniques and equipment requisite for endoscopic retrograde cholangiopancreatography (ERCP) were both developed and advanced.[7] For the purposes of this study, ERCP is defined as associated with the possibility of papillotomy. The introduction of this new diagnostic and therapeutic technique paved the way for reassessment of the treatment paradigm for patients with biliary pancreatitis. In addition, at the 1992 International Symposium of Acute Pancreatitis held in Atlanta, the care and study of patients with acute pancreatitis was enhanced by improved communication within the medical field, in conjunction with the standardization of terms related to acute pancreatitis and its complications.[8] The convergence of standardized medical language and less invasive techniques for removal of bile duct stones inciting pancreatitis has facilitated a change in practice and the publication of numerous papers examining the benefits and risks of ERCP in the treatment of pancreatitis. However, the indications for ERCP and a plus or minus papillotomy for stone extraction in patients with acute biliary pancreatitis remain controversial 20 years or more after the introduction of the technique.

At the 2007 Society for Surgery of the Alimentary Tract Postgraduate Course, the published evidence for early ERCP in the treatment of patients with gallstone-induced pancreatitis was reviewed in an attempt to develop an evidence-based understanding regarding patients that may benefit from ERCP and when this procedure should be performed relative to the onset of symptoms. The aim of this review was to present and critique the best available evidence and, thereby, develop strategies for care of patients with acute biliary pancreatitis.

Materials and Methods

To capture the best available evidence published on the use of ERCP in gallstone pancreatitis, a search of Pub-Med (National Center for Biotechnology Information; http://www.pubmed.gov) was performed with a closing date of February 1, 2007. Although the intent of the review was to confine the search to the last 10 years, two seminal papers that met the study criteria were identified outside of the designated time period and were included in the review. The initial MeSH search terms were "gallstones" and "pancreatitis", which yielded 788 citations. The search was further restricted by adding the MeSH term "cholangiopancreatography, endoscopic retrograde", which reduced the number of citations to 235. From these search results, only studies that met the criteria for level 1 evidence were selected. Therefore, the search produced five randomized controlled trials, a meta-analysis, and a Cochrane Database Systematic Review that examined the role of ERCP in gallstone pancreatitis. For uniformity in terminology throughout this report, endoscopic retrograde cholangiopancreatography with or without sphincterotomy or papillotomy will be designated "ERCP" under the caveat that pancreatic duct cannulation and sphincterotomy were performed as indicated in the individual studies.

Results

The randomized control trials, meta-analysis, and systematic review were examined chronologically to preserve the sequence of findings over the nearly 20-year period of evidence review.

In a 1988 paper published in *Lancet*, Neoptolemos et al.[9] were the first to examine the role of early (≤72 h) ERCP in gallstone pancreatitis. In a controlled trial, 121 patients were randomized to treatment by early ERCP (ERCP; N=59) versus conventional therapy (N=62) alone. The study demonstrated that only patients predicted to have severe disease by the modified Glasgow criteria benefited from ERCP. Although mortality was not impacted by the study intervention, overall complications were significantly decreased in the ERCP group (24%) compared to those patients that received conventional treatment (61%). In addition, the hospital stay was shorter for patients with severe disease that underwent ERCP compared to those patients with severe disease treated with conventional therapy. Although this study showed that patients with severe pancreatitis that underwent ERCP had decreased complications and a shorter hospital stay, only 12 of 19 patients (63%) with gallstone-induced pancreatitis had common bile ducts stones documented. Furthermore, 15% of all patients in this study did not have gallstones

confirmed by imaging or ERCP, and patient enrollment for early ERCP was from the time of admission rather than at the onset of symptoms. Therefore, some patients may not have been identified early in the onset of pancreatitis. Interestingly, the average age of patients with severe pancreatitis was 75 years, which is somewhat older than other patient populations. Finally, 25% of patients with severe pancreatitis had cholangitis and were treated with antibiotics; thus, differentiating a treatment benefit from antibiotic therapy or ERCP may be difficult.

Subsequently in 1993, Fan et al.[10] from Queen Mary Hospital, Hong Kong, published an important work that randomized 195 patients to either early ERCP (within 24 h; N=97) versus conservative treatment (N=98). Severity of pancreatitis was stratified by serum urea and plasma glucose concentrations and Ranson's criteria. Twenty-one and 24 patients in the ERCP and conservatively managed groups, respectively, had severe disease. Mortality did not differ between the groups, and overall morbidity was similar. However, if the analysis was confined only to patients that had documented biliary tract stones, morbidity in the ERCP group was significantly decreased compared to patients managed by conservative therapy (16 vs 33%; p=0.03). Mortality in this subset of patients also tended to be decreased (2 vs 8%; p=0.09). In addition, biliary sepsis was more common in patients with severe pancreatitis who did not undergo ERCP. The authors concluded that ERCP was indicated in acute pancreatitis regardless of the severity because it was effective in reducing biliary sepsis. Like the Neoptolemos et al.[9] study, a substantial number of patients in this study did not have gallstones confirmed, and cholangitis was a frequent confounding condition. Finally, the conclusion suggests that all patients with suspected biliary pancreatitis should undergo ERCP, but biliary sepsis, the only parameter improved by ERCP, was decreased after ERCP only in patients with severe disease.

In a 1997 publication in the *New England Journal of Medicine*, the German Study Group on Acute Biliary Pancreatitis conducted a prospective multicenter study in which 126 patients were randomized to early ERCP (72 h) and 112 patients that were managed with medical therapy.[11] Severity of disease was assessed by the modified Glasgow criteria. Sixteen patients in each group had severe disease. No difference in mortality or overall morbidity was noted between the study groups. However, the patients in the ERCP group sustained more severe complications, and respiratory failure was also more common in these patients. The authors concluded that ERCP was not beneficial in patients with acute biliary pancreatitis that did not have obstructive jaundice. In this multicenter study, three centers enrolled 20 or more patients, and the remaining 19 centers contributed fewer than two patients per year on average. In addition, the number of patients with severe disease was low (<15%) in this study. Surprisingly, patients in the ERCP treatment arm had an increased incidence of respiratory failure of unknown cause. Finally, 12 patients were excluded from the analysis because of a serum bilirubin greater than 5 mg/dl, but these patients may have benefited from ERCP.

In 1999, Sharma and Howden[12] published a meta-analysis of controlled trials of ERCP for acute biliary pancreatitis. This study included four randomized controlled trials in which the data were analyzed by both an individual study and pooled assessment. The authors noted that each trial demonstrated a numerical reduction in the complication rate for ERCP, but in only two of the studies was the difference statistically significant. When the data from these studies were pooled, a statistically significant decrease in complications in patients treated by early ERCP was noted (25 vs 38%; p<0.001). Furthermore, Sharma and Howden suggested that eight patients would need to be treated by ERCP to prevent one complication. Similarly, with pooled data, the mortality rate decreased in the ERCP group (5.2 vs 9.1%; p<0.01), and 26 patients would require ERCP to prevent one death. Unfortunately, this meta-analysis included only four studies, one of which has been published in abstract form only. Importantly, this latter study had the most patients and, therefore, the meta-analysis may have been skewed by data that have not been adequately peer-reviewed.

A Cochrane Database Systematic Review was updated in August 2005, and this publication reviewed three randomized controlled trials including 511 patients.[13] The studies were subjected to rigorous statistical criteria and met the standards for inclusion. In this review, patients with severe disease that were treated by ERCP had a reduced risk of complications. In patients with predicted mild disease, morbidity was not affected by ERCP. Mortality was not significantly reduced in patients with mild or severe disease regardless of treatment. Importantly, this review adjusted for the presence of cholangitis, which is a confounding condition in several published studies. However, the methods used to control for this variable are not adequately delineated.

In the January 2006 issue of the *Annals of Surgery*, Acosta et al.[14] reported a randomized prospective trial of 61 patients with gallstone pancreatitis and persistent ampullary obstruction. In this trial, patients with evidence of persistent (>24 h) ampullary obstruction underwent ERCP within 48 h (N=30) or conservative treatment with selective ERCP (N=31). No patients died in this study, but only 10% of the patients had severe disease. Patients that underwent early ERCP had a shorter period of obstruction and a coincident decrease in immediate complications. If ampullary obstruction was less than 48 h in any treatment arm, the risk of complication was decreased compared to patients in whom

obstruction persisted longer than 48 h. The authors surmise that ERCP is indicated in patients with acute biliary pancreatitis and ampullary obstruction of 48-h duration. The crux of this study was identification of patients with ampullary obstruction, which was defined as persistent severe epigastric pain, bile-free gastric aspirate, and increased serum bilirubin determined every 6 h. These criteria are subjective, open to interpretation, and do not provide succinct classification of patients that may benefit from ERCP.

One year later, in the January 2007 issue of the *Annals of Surgery*, Oria et al.[15] performed a single center randomized trial that focused on patients with biliary obstruction, but excluded patients with evidence of acute cholangitis. Patients were deemed at risk for biliary obstruction if they had a distal bile duct ≥8 mm combined with a serum bilirubin ≥1.2 mg/dl. Patients that met these criteria were randomized to ERCP (72 h; $N=51$) or conservative therapy ($N=52$). Severity of disease was determined by the APACHE II scoring system with a score of 6 or greater indicating severe disease. At ERCP, 72% of the patients in the early ERCP group had biliary stones. The mortality, overall morbidity, and local and systemic complications were similar between those randomized to early ERCP or conservative management. Therefore, this study failed to provide evidence supporting early ERCP in patients deemed at risk for biliary obstruction early in the course of gallstone pancreatitis. Much like the Acosta et al.[14] study, this paper used relatively the non-specific criteria of a dilated bile duct and a modestly increased serum bilirubin as evidence for biliary obstruction. Therefore, the criteria for patients at risk vary among studies, and a uniform approach to patients with biliary pancreatitis has not been readily adopted.

A summary of the findings in the above-reviewed papers is shown in Table 1. Clearly, early ERCP did not decrease mortality in patients with a variety of mild to severe gallstone pancreatitis. Moreover, overall morbidity appears to be decreased by early ERCP only in select patients with severe disease or biliary obstruction. Local complications were unaffected by biliary intervention, and too few data are reported to determine an impact on hospital length of stay.

Discussion

This evidence-based review on the use of early ERCP in patients with gallstone pancreatitis overwhelmingly suggests that ERCP does not improve mortality or overall complications, especially in patients with mild pancreatitis. Although five randomized trials have addressed this important clinical topic and have not identified a major benefit of ERCP, caution should be exercised because collectively, these studies are without homogeneity. They are heterogeneous with various enrollment criteria, and these studies were performed, in some cases, nearly 20 years apart. Furthermore, the endoscopic community is hampered by a lack of a strict definition of biliary pancreatitis. Each of the studies includes a substantial number of patients that do not have confirmed cholelithiasis or choledocholithiasis. Therefore, while the preponderance of evidence suggests that early ERCP is not warranted in gallstone pancreatitis, some evidence suggest that patients with severe pancreatitis or biliary obstruction may benefit from biliary intervention.

Review of these studies suggests that a multicenter trial enrolling only patients with severe disease determined by a standardized definition may be warranted. Furthermore, the issue of biliary obstruction in patients with acute pancreatitis may be a confounding factor, but a standard definition of biliary obstruction should be determined and used as a criterion for early ERCP in a trial setting.

Table 1 Summary of Study Outcomes with Early ERCP in Biliary Pancreatitis

	Mortality Increased	Decreased Overall Morbidity	Decreased Local Complications	Increased Systemic Complications	LOS
Neoptolemos et al.[9]	No	Yes	No	No	Yes
Fan et al.[10]	No	No[a]	No[a]	No	NR
Folsch et al.[11]	No	No	No	No	NR
Sharma and Howden[12]	Yes	Yes	NR	NR	NR
Ayub et al.[13]	No	No[a]	NR	NR	NR
Acosta et al.[14]	No	Yes	Yes	No	Yes
Oria et al.[15]	No	No	No	No	NR

Local Complications = Complications arising from ERCP treatment, bile duct stones, or pancreatitis, depending on specific study; Systemic Complications = Non-localized complications arising from treatment paradigms

LOS Length of stay, *NR* not reported

[a] Decreased complications in patients with severe disease only

Conclusion

In conclusion, the question "For whom and when should early ERCP be performed in patients with gallstone pancreatitis?" is answered using the best available evidence suggests that early ERCP is not indicated in patients with biliary pancreatitis. However, the clinical presentation and course should guide the pancreatologist, and early ERCP and possible papillotomy should be kept in mind for those patients with severe disease and biliary obstruction who are not improving with medical therapy. In addition, other imaging modalities such as MRCP and endoscopic ultrasound may serve as useful screening adjuncts in patients that have clinical evidence of biliary obstruction.

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Intervention in Necrotizing Pancreatitis: An Evidence-based Review of Surgical and Percutaneous Alternatives

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Abstract Interventional therapy in necrotizing pancreatitis is evolving. Efforts to modify or prevent pancreatic necrosis by intra-arterial infusion of antibiotics and antiproteases have been described. Moreover, traditional approaches to the surgical management of infected pancreatic necrosis are being challenged by a host of endoscopic and percutaneous techniques. While these approaches are potentially valuable additions to interventional therapy in necrotizing pancreatitis, few evidence-based studies are available to support their supplanting more traditional approaches at this time. Cooperative evidence-based multiinstitutional studies will be required to address the validity of these proposals.

Keywords Pancreatic necrosis · Surgical debridement · Minimally invasive · Laparoscopy · Infected necrosis · Guided percutaneous drainage · Continuous regional intraarterial protease infusion

The surgical management of acute necrotizing pancreatitis has been controversial ever since the issues were first debated by Fitz and Senn at the turn of the 19th century. Fitz, a Harvard anatomist and pathologist, was convinced that surgery had no place in the management of necrotizing pancreatitis.[1] On the other hand, Senn, a surgeon from the Chicago school, argued that survival could not be expected without surgical intervention,[2] although no evidence exists that he actually attempted to remove a necrotic pancreas. As is often the case in polarized debates, future events established that the truth lay between the extremes.

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Methodology

Similar searches for evidence-based articles were used for each of the four topics covered in this review. Searches of the Pub Med data base with the OVID search engine using pertinent key words (acute pancreatitis, necrotizing pancreatitis, infected pancreatic necrosis) served to generate the first layer of articles. Additional filtering with "English", "humans", and "last 10 years" further reduced the number of articles, and all abstracts were reviewed. After further eliminating small case studies and duplicate reporting, the remaining papers constituted the material analyzed in this paper.

Traditional Open Surgical Approaches

Of the 1,967 articles identified by the initial search, only 20 articles concerned with traditional surgical approaches to infected pancreatic necrosis (note indication) remained after the final filtering process. Only one Level I RCT (randomized controlled trial) was found in the literature search for this

Table 1 Traditional Open Surgical Approaches to Infected Pancreatic Necrosis

Author (reference)	Procedure (debridement plus)	IPN (*N*)	APACHE II (mean)	Organ Failure (%)	Reoperations/ P.O. Drainage (%)	P.O. Days (mean)	M.R. (%)
Fernandez et al[4]	Closed drainage	31	9	31	38	41	11
Rau et al[5]	LSL	140	11	68	51	64	27
Bradley[6]	Open packing; secondary closure, and LSL	96	12	41	NA	37	14

LSL=Lesser sac lavage, IPN=Infected pancreatic necrosis, NA=Not applicable

topic. Mier and his colleagues[3] found that surgical exploration within the first week after the onset of necrotizing pancreatitis resulted in significantly higher surgical morbidity and mortality, when compared to debridement delayed until the second or third week of the illness.

Three generic approaches to open surgical debridement of infected pancreatic necrosis (note indication) were evident: (a) debridement with conventional drainage,[4] (b) debridement with immediate continuous lesser sac lavage,[5] and (c) debridement with planned reexplorations and subsequent secondary closure with lesser sac lavage[6] (Table 1). Numerous minor technical modifications of these three generic approaches have been reported; i.e., zipper closure for repetitive explorations, retroperitoneal approaches to the retroperitoneum, drain configurations, etc.

Evidence-based comparisons of results between the three generic open surgical techniques are not possible, as multiple variables known to be important to the results from surgery of necrotizing pancreatitis have not been similarly controlled between the three procedures. As a result, we do not currently know the optimal open surgical approach to patients with infected pancreatic necrosis.

Minimally Invasive Techniques

Of the 687 articles identified by the generic search, 24 met the specific final inclusion criteria: five were case reports, and seven were from three treatment units that published sequential reports on their cumulative experience covering the same patients. Only the last clinical experience from these units was used, leaving 14 qualifying publications.[7–20] The majority of these articles dealt with minimally invasive approaches to infected necrosis. It became apparent that these publications could be further classified under three general headings: (a) video-assisted retroperitoneal debridement (VARD), (b) laparoscopic transperitoneal necrosectomy, and (c) endoscopic drainage (Tables 2 and 3).

The primary differences between these three types of alternative surgical approaches are the methods used to obtain retroperitoneal access, and the specific instrumentation used for debridement.

All publications regarding minimally invasive techniques consist of small, single institutional case series, qualifying for Level 4 evidence, at best. Proponents of these alternative "minimally invasive" surgical approaches cite the potential benefits from a blunted physiologic response from these procedures when compared to open abdominal surgery,[7,9,14] although hard data to support these assertions are not available. Moreover, the majority of these alternative surgical approaches require multiple separate interventions to obtain complete removal of the necrotic material, and to deal with persistent or recurrent infection.[7,12,20]

The VARD approach has the advantage of avoiding peritoneal contamination, but is limited in detecting colonic ischemia, performing simultaneous cholangiography or cholecystectomy, or establishing a feeding jejunostomy at the time of debridement.[7,11] In addition, the technique of necrosis extraction is limited to the amounts of debris retrievable through the operating channel of a nephroscope or endoscope.[9] Laparoscopic transperitoneal necrosectomy, with or without use of a hand access device, has the advantage of simultaneous access to the peritoneal cavity (gallbladder, bowel), but the potential drawback of trans-

Table 2 Minimally Invasive Approaches to Infected Pancreatic Necrosis

Procedure (ref #s)	Access Route	Instrumentation	Mean No. of Procedures	Limitations
VARDS (7–13)	Retroperitoneal	Nephroscope	3	Abdominal access
LD (14–16)	Transperitoneal	Grasper forceps	1	Intraperitoneal Contamination
ED (17–21)	Transgastric	Biopsy forceps	4	Abdominal access

VARDS=video-assisted retroperitoneal débridement, LD=laparoscopic débridement, ED=endoscopic débridement

Table 3 Cumulative Outcomes; Minimally Invasive Procedures for Infected Necrosis

	Patients (N)	Success rate	Morbidity	Mortality
VARDS	111	71 (64%)	52 (47%)	16 (14%)
LD	24	19 (79%)	8 (33%)	0
ED	64	44 (69%)	22 (34%)	1 (2%)

VARDS=video-assisted retroperitoneal débridement, LD = laparoscopic débridement, ED = endoscopic débridement

peritoneal contamination with infected necrosis.[14–16] Necrotic debris is removed by laparoscopic instruments and suction-irrigation catheters. Endoscopic drainage methods employ a transenteric access route (gastric or duodenal), extraction of necrotic debris into the gastrointestinal tract, and subsequent alimentary tract passage.[17–20] Endoscopic stenting is frequently used to maintain patency of the transenteric egress route.[17] The principal advantage of the endoscopic approach is avoiding the potential problem of an external pancreatic fistula. Its limitations are that it can only be applied to well walled-off necrosis anatomically confined to the pancreas, and cannot perform any necessary intraperitoneal procedures. However, if necessary, an endoscopic biliary sphincterotomy with clearance of the bile ducts can be accomplished at the time of endoscopic debridement.[17,19]

Currently, there are no randomized clinical trials by which to evaluate one minimally invasive surgical approach versus another. However, a prospective, multi-institutional randomization between a "step-up" minimally invasive approach utilizing VARD versus open laparotomy and maximal necrosectomy (PANTER Study), is currently undergoing enrollment through the Dutch Acute Pancreatitis Study Group. This study has the potential to clarify some of the important concepts regarding alternative surgical approaches to the treatment of infected pancreatic necrosis.

Guided Transcutaneous Techniques

Despite the existence of an extensive body of literature regarding percutaneous drainage of pancreatic pseudocysts and abscesses, publications on percutaneous drainage of infected pancreatic necrosis (note indication) are notably limited. When the initial search was combined with "interventional radiologic drainage", and the other filters used in this study, only 37 articles remained. Each of these articles was reviewed, finding only five dealing with percutaneous radiologic drainage (PCD) of infected pancreatic necrosis[21–25] Four of the articles dealt with the immediate results of PCD (Table 4). None of these four articles rose above an evidence-based Level 4. The fifth article studied pancreatic function in nine patients at a mean interval of 30 months after undergoing PCD for infected pancreatic necrosis.[23] In the latter study, new onset diabetes mellitus developed in 50% of patients not previously diabetic. Seven of eight patients suffered from pancreatic insufficiency, and only one of the nine patients studied was entirely normal. Similar degrees of pancreatic dysfunction are seen after surgical intervention, and are not thought to be procedure specific, but rather reflect the extent of the underlying necrosis.

There are several observations in Table 4 that are worthy of consideration. First, as has already been mentioned, is the small number of studies that have been conducted regarding PCD of infected pancreatic necrosis. Secondly, there is little doubt that PCD can result in the cure of many patients without the necessity for backup surgical intervention. Nevertheless, the patient best suited for PCD has not been defined, as many of the variables known to be important to survival in these cases were not controlled in these studies. Thirdly, the rate of complications is not insignificant, being primarily composed of hemorrhage along the drain tract, and drain-induced intestinal fistulization. Mortality, however, is low and comparable to other drainage approaches. Furthermore, guided PCD can often be of benefit to both patients and physicians by serving as a "bridge" to surgical debridement, even when it is unsuccessful per se.[26] A decrease in clinical toxicity from PCD may permit postponing surgical debridement until the third week of illness, a period thought to be technically optimal for pancreatic debridement.

Intra-arterial Anti-Protease Therapy

Activation of pancreatic protease enzymes is considered to play a critical role in the pathogenesis of severe acute

Table 4 CT-guided Percutaneous Drainage (PCD) of Infected Pancreatic Necrosis

Author (ref)	# Patients	Cured By PCD	Surgical Rescue	Complications	Catheter Duration	M.R.
van Sonnenberg et al 1997[24]	59	86 %	13%	22%	33 days	10%
Freeny et al 1997[22]	34	47%	53%	26%	85 days	15%
Echenique et al 1998[21]	20	100%	0%	50%	83 days	0%
Cheung et al 2005[25]	8	37%	62%	50%	NS	12%

M.R.=Mortality rate, NS = Not stated

pancreatitis. The current thinking is that activated proteolytic enzymes, in conjunction with vascular endothelial changes, are responsible for pancreatic necrosis and autodigestion of the gland.[31,32] Inhibition of this pathologic process appears to be a logical step in treatment. Despite several recent claims for efficacy, this approach to patients with sterile necrotizing pancreatitis has not as yet been subjected to an evidence-based review.

After the initial search of the PubMed data base, 537 study titles were identified. Of these, 21 were found to be concerned with intravascular protease infusion. After the final filters, nine articles remained. The single Level I RCT compared intravenous administration of gabexate mesilate vs. placebo in patients with acute pancreatitis,[33] failing to find a significant difference in the morbidity or mortality of patients with this therapy. Similarly, a Level II RCT in 42 patients with acute pancreatitis treated with and without intravenous gabexate mesilate again failed to show any significant difference in outcomes between the two groups.[34] Because of the limited half life of antiproteases, however, intraarterial infusion of protease inhibitors has been claimed to be more effective for administration of antiproteases into the pancreatic tissue than intravenous administration.[35,36]

At the present time, unfortunately, there are no published randomized clinical trials with appropriate controls for evaluating the treatment of sterile necrotizing pancreatitis with continuous regional arterial infusion (CRAI) of protease inhibitors. Many Level 4, single-institution, non-randomized studies describing intravascular administration of antiproteases exist in the literature.[37–40] In one of these reports, Takeda et. al.[37] studied 53 patients with acute necrotizing pancreatitis divided into three groups: Group I (16 patients) received intravenous infusion of nafamostat and antibiotics; Group II (22 patients) received continuous regional arterial infusion (CRAI) of nafamostat (120–240 mg/day) for 3–5 days as well as intravenous antibiotics, and Group III (15 patients) received CRAI of nafamostat and intraarterial infusion of imipenem (500 mg every 12 h) for 3–5 days. The mortality rates were 43.8%, 13.6%, and 6.7% in groups I, II, and III, respectively ($P<0.05$; Table 5). This study was later expanded to include collaborative patients from multiple institutions and published as a cooperative study.[38] Interestingly, in this later study, there was no significant difference in morbidity or mortality between groups who received intravenous antibiotics, compared to those receiving intraarterial antibiotics. A recent nonrandomized study by Imaizumi et. al.[40] compared CRAI of Nafamostat and Imipenem (23 patients) to intravenous administration of both drugs (28 patients). The survival rates were 87% in CRAI group compared to 49% in the non-CRAI group ($P<0.002$).

In preparing this article, it was difficult to ignore the predominance of studies advocating the use of CRAI of protease inhibitors originating from Japan, and a comparative lack of such studies in European and North American publications. Moreover, recent comprehensive review articles regarding the treatment of acute pancreatitis in many western journals fail to even mention CRAI of protease inhibitors as potential therapy. Whereas older studies using protease inhibitor infusion for treatment of severe acute pancreatitis have largely been discounted, the more recent Japanese studies using the continuous intraarterial approach show promise and warrant further investigation. A randomized clinical trial of continuous pancreatic-arterial infusion of protease inhibitors is already underway in Japan. The results of this trial could clarify the role of CRAI protease inhibition in the treatment of necrotizing pancreatitis.

Conclusions

From this discussion, we may conclude that within the past two decades significant progress has been made in the interventional approach to infected pancreatic necrosis, (note indication) but that the evidence for many of today's recommendations for invasive therapy remains at a lower level of proof than we might wish. Moreover, although anecdotal recommendations for noninvasive management of infected necrosis exist, in the opinions of the authors such an approach is limited in frequency, and currently uncertain in its indications.

Table 5 Continuous Regional Intraarterial Infusion of Antiproteases in IPN

Author	Patients (*n*)	Method	Mortality	Resolution of Sepsis	Surgical Intervention
Takeda et al. 1989[36]	16	Nafamostat IV w/o ABX	44%	50%	75%
	22	Nafamostat IA w/ IV ABX	14%	87%	27%
	15	Nafamostat IA w/ IA ABX	7%	100%	26%
Komoriyama et al. 2001[38]	30	NS	13%	NS	NS
Imaizumi et al. 2004[39]	28	Nafamostat IV w/ IV ABX	51%	NS	32%
	23	Nafamostat IA w/ IA ABX	13%	NS	9%

IPN=Infected pancreatic necrosis, IV=Intravenous, ABX=Antibiotics, IA=Intra-arterial, NS=Not stated

However, the principal limitation to an evidence-based approach and the optimization of future therapy lies in the difficulty for single institutions to timely accumulate the numbers of patients with pancreatic necrosis that are sufficient to satisfy the requirements for meaningful randomization. In most cases, this means that multiinstitutional studies will be necessary to address current and future issues in necrotizing pancreatitis. To facilitate the development of future multiinstitutional research, the authors call upon our relevant societies and their members to make a concerted effort to facilitate such studies. The Society for Surgery of the Alimentary Tract, the American Pancreatic Society, The Society of Gastrointestinal Radiology, and the International Association of Pancreatology contain the manpower necessary to accomplish such studies, given the encouragement of their officers and members. Considering the importance of sufficiently large randomized studies to the establishment of future evidence-based clinical practice, Federal, Industrial, and Foundation support should be attainable.

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Treatment of Chronic Pancreatitis with Endotherapy or Surgery: Critical Review of Randomized Control Trials

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Abstract The goal of this Society for Surgery of the Alimentary Tract postgraduate course was to review critically the highest level of published evidence focused on treating the disabling chronic abdominal pain due to chronic pancreatitis. Just eight randomized controlled trials (RCTs) have been reported since 1995. All are from Europe. These eight RCTs utilized 380 patients to compare a diverse variety of surgical resections, surgical drainage vs. endotherapy (trans-ampullary pancreatic stents for drainage), or endotherapy with or without shock wave lithotripsy. Therefore, these trials contained a paucity of patients for each treatment compared. Heterogeneity was evident after analysis of the study designs because they used a diverse set of inclusion and exclusion criteria usually not based on objective criteria such as ductal anatomy. All but one had short follow-up. Because of the lack of homogeneity for these study designs that were somewhat underpowered, the RCTs on the treatment of chronic pancreatitis to relieve disabling abdominal pain must be read carefully. In addition to RCTs, the case series still remains a valuable part of our literature.

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Introduction

Chronic pancreatitis (CP) is a complex inflammatory disease of the pancreas that causes recurrent severe abdominal pain and evolves towards exocrine and endocrine insufficiency. The view that pain will disappear in the majority of patients as CP progresses to the point of pancreatic "burnout" is widely accepted, but this process usually takes many years, or it may never occur.[1,2]

Ductal obstruction (and resulting tissue hypertension) plays a major role in pancreatic pain, mainly by inducing ischemia and the resulting inflammatory cascade. Pancreatic ductal decompression is considered a cornerstone of pain therapy by many surgeons. In the group of CP patients with enlargement of the head of the pancreas, pancreatic resection in conjunction with or without upstream main

ductal decompression may be more valuable, according to the theory of the pancreatic head pacemaker.[3] No randomized controlled trial is available comparing surgery of any kind vs. placebo or sham procedure, but it is obvious that surgical intervention relieves pain in the majority of patients and that the response is reasonably durable, lasting for years. Recurrence of pain after head resection may be due to continued smoldering CP in the pancreatic remnant.

Another problem has been the lack of objective anatomic selection criteria for treatment or anatomic factors that predict the best treatment to relieve the chronic pain of CP. Indeed, without these objective indications, some studies may include patients where surgery is not indicated because they do not truly have CP. Rather, they suffer from chronic abdominal pain of another etiology, e.g., sphincter of Oddi hypertension, mesenteric ischemia, or somatoform disorders.

Over the last 20 years, endoscopic ductal decompression (endotherapy), associated with extracorporeal shock wave lithotripsy (ESWL) to fragment stones in the main pancreatic duct (MPD), has been proposed as an alternative method for treating pain in patients with a dilated MPD due to intraductal stones.[4] In uncontrolled studies, it offers long-term pain relief in approximately two-thirds of patients, and it may identify those who will benefit from surgical decompression.[5] However, similar to surgery, endotherapy is typically performed in highly specialized "high-volume" centers with all the appropriate tools available, including ESWL and a dedication for follow-up of the patient. Indeed, the pattern of pain relief after endotherapy has been observed to be different from that seen after surgery. Relapses after endotherapy often occur within the first 2 years after initial treatment and become unusual later on, whereas surgery is more effective in the first few years, with the pain relapse seen after a delay of 5 to 7 years.[6]

The goal of this Society for Surgery of the Alimentary Tract postgraduate course was to critically review the highest level of published evidence focused on treating the disabling chronic abdominal pain due to CP with either surgery (drainage ± resection) or endotherapy (drainage via transampullary pancreatic stents ± shock wave lithotripsy). We found the published randomized controlled trials (RCTs) concerning the management of pain in CP to be fraught with low numbers of patients and a diverse set of nonstandardized indications, and most were without an adequate follow-up time. These studies are fascinating and underline where progress can be made in our literature of pancreaticobiliary disease.

Literature Search

Using medical subject headings (MeSH) of "pancreatitis" and "chronic" in the PubMed search engine of the National Library of Medicine, an inquiry yielded 12,686 citations. Further limits were applied for English, the last 10 years, humans, age ± 19 years, and RCTs. The latter yielded just 35 citations. The abstracts of these 35 citations were examined by the authors and some were found to be duplicate or not applicable. Two references were added as per the recommendations of the authors to yield just eight RCTs examined in this study. They were all European and contained a total of 380 patients. The RCTs can be divided into three groups—those that compared surgical techniques (mainly resection), surgical techniques (mainly drainage) to endotherapy, and endotherapy ± shock wave lithotripsy.

RCTs (n=5) Comparing Surgical Techniques (Mainly Resection)

Two trials have compared the pylorus-preserving pancreaticoduodenectomy (PPPD) vs. duodenum preserving pancreatic head resection (DPPHR, the "Beger" procedure) in patients with head-dominant disease. As shown in Table 1, these trials have small numbers of patients (although some

Table 1 Comparison of Pain Relief Observed in the RCTs for CP Treatments

Year	Location	Group 1	Group 2	Pain Relief	Follow-up	Patients
1995	Bern/Ulm	PPPD (n=20)	Beger (n=20)	Beger better 75 vs. 40%	6 months	40
2006	Szeged, Hungary	PPPD (n=20)	Beger (n=20)	Same ~85%	12 months	40
1998	Hamburg	PPPD (n=30)	Frey (n=30)	Same ~95%	24 months	60
1995	Hamburg	Beger (n=20)	Frey (n=22)	Same ~100%	36 months	NA
2005	Hamburg	Beger (n=38)	Frey (n=36)	Same ~90%	9 years	74
2003	Brno, Czech Rep	EndoTx, no ESWL (n=36)	Mixed surgeries (36)	Surgery better 85 vs. 61%	5 years	72
2007	Amsterdam	ESWL then EndoTx (n=19)	LPJ only (n=20)	Surgery better 75 vs. 53%	24 months	39
2007	Brussels, Rome	ESWL then EndoTx (n=29)	ESWL only (n=26)	Same ~55%	50 months	55
Total						380

All European studies—total 380 patients
EndoTx = endotherapy, NA = not applicable as the 2005 report included the 1995 patients

reached statistical significance), have short follow-up, and do not reach consensus on pain relief after resection. In addition, indications for resection were not clearly stated.

Büchler et al.[7] demonstrated, in two groups of 20 patients each randomly allocated to DPPHR or PPPD, significantly better results for DPPHR in terms of complete pain relief (75 vs. 40%) and weight gain (4.1 vs. 1.9 kg). The follow-up time was 6 months. Hospital stay and morbidity (around 15%) were similar while the mortality was nil in both groups. A subsequent report with longer follow-up has not yet been published.

Farkas et al.,[8] using a similar small number of patients (n=20 in each group), observed different rates of pain relief than the Büchler study. There was an impressively high rate of complete pain relief for both operations at 1 year after operation (85 and 90% after DPPHR and PPPD, respectively), whereas morbidity was reported to be 0% in DPPHR and 40% in PPPD. Quality of life in these studies favored the DPPHR. With their limitations, these two trials suggest that DPPHR is superior to PPPD, while more work needs to be done (more patients and a follow-up longer than 6 or 12 months) before adopting either procedure as the procedure of choice for head-dominant CP.

The Frey procedure[9] is a hybrid of resection and drainage. It combines a subtotal ventral head resection or local resection (LR) with a drainage procedure, i.e., the longitudinal pancreaticojejunostomy (LPJ) described by Partington and Rochelle.[10] The LR–LPJ, or Frey, procedure was described by Frey and colleagues as a partial head resection in a coronal (frontal) plane through the head of the pancreas, and its depth "involves excision of the pancreas overlying the ducts of Wirsung and Santorini and the duct to the uncinate process along with its tributary ducts, and opening of the main duct in the body and tail of the pancreas."[9] This less complex surgical technique has been prospectively compared to PPPD[11] with each group comprised of 30 patients and with a median follow-up of 24 months. The early morbidity was significantly higher in the PPPD group (53 vs. 19%), whereas the long-term results were similar for both groups in terms of pain control. The less complex Frey procedure, however, was associated with a greater increase in quality of life and a better preservation of exocrine and endocrine function.

Finally, the Frey and Beger procedures have been compared in a prospective RCT. The first report of this trial by Izbicki and colleagues was in the German language, but it was also reported in the *Annals of Surgery*.[12] The early results showed that the LPJ with partial head resection (n=22) was equally effective to the head resection of Beger (n=20), not only in terms of pain relief at 1.5 years (89 vs. 95%, respectively) but also for control of complications arising from adjacent organs, preservation of exocrine and endocrine function, and improvement of quality of life. The rate of in-hospital complications was significantly lower with the Frey procedure than with the Beger procedure.

A follow-up report of this trial[13] compared the procedures in a larger group of patients (Frey n=36, Beger n=38) and a sufficiently long-term follow-up of almost 9 years. The two operations were equally effective in pain relief and improvement of quality of life. The rates of exocrine insufficiency and endocrine insufficiency were also similar, whereas the need for reoperation was slightly but not significantly higher in surviving patients (Frey 0/25, Beger 3/26).

These three trials involving the Frey (LR–LPJ) procedure suggest that it has potential for management of pain (Table 1). It may be more suitable than the PPPD, as it is less complex and associated with lower morbidity, we expect, especially in centers without a high volume for the PPPD. The Frey procedure may be equivalent or perhaps slightly better than the duodenum preserving pancreatic head resection (DPPHR) of Beger in terms of hospital morbidity and need for reintervention in the long term. However, the trials were insufficient in patient numbers to find significance other than for immediate complications. The indications for any type of surgery (resection, drainage, or hybrid) have yet to be examined in a controlled trial.

RCTS (n=2) Comparing Endotherapy and Surgery (Mainly Drainage)

Endotherapy has been compared to "surgical therapy" in two RCTs. The first trial[14] contained a modest number of cases and sufficient follow-up but with a diverse surgical treatment group. Here, the authors compared a group of 36 patients treated with endotherapy (endoscopic transampullary extraction of pancreatic duct stones ± stents) to another group of 36 patients treated with a variety of surgical procedures consisting of 80% resections and 20% drainage procedures. In this trial, similar efficacy was reported with both procedures for short-term pain control, but surgery was better for long-term pain control at 5 years after treatment. Complete or partial pain relief was observed in 85% after surgical techniques vs. 61% after endotherapy. One significant feature of this study is that extracorporeal shock wave lithotripsy (ESWL) was not available for stone fragmentation. In our experience, this might render adequate stone extraction impossible in approximately 40% of the cases.

A recently published RCT of endotherapy ± ESWL (n=19) vs. surgical drainage (lateral pancreaticojejunostomy, n=20)[15] compared patients with fairly specific inclusion and exclusion criteria for "severe chronic pancreatitis" with anatomic changes of stenosis ± calcifications. Most of these

39 patients already had exocrine insufficiency at the time of presentation. The morbidity of endotherapy and lateral pancreaticojejunostomy were comparable, but pain relief using Izbicki scores at a median of 24 months was significantly better for surgery (75 vs. 32%). Interestingly, four patients from the endotherapy group were converted to surgery and only one of them had pain relief after operation, questioning the indications for treatment. From an endoscopic point of view, a major concern with this study was that the majority of patients had persisting stenosis after stone removal, and the authors opted for a policy of short-term stenting (mean 6 months), which has been shown by others[16] to be ineffective in establishing adequate long-term caliber, i.e., prevention of stenosis. This study of a small group of patients with modest follow-up was terminated early by the safety committee after an unscheduled interim analysis favored surgical drainage.

Besides the limited number of cases in each trial, the heterogeneity for indications; follow-up; and the definition of endotherapy, surgical drainage, and resection provide a limited amount of useful information. Taken together, these two trials might suggest to the reader that surgical therapy was more effective than endoscopic therapy for pain due to chronic calcific pancreatitis. However, information obtained from noncontrolled studies should be considered when designing a prospective trial, namely, the need for ESWL for stone disintegration when endotherapy is planned and the need for prolonged calibration of the duct (approximately 2 years) by maintenance of stenting when strictures are observed. In addition, long-term follow-up is important in objectively comparing endotherapy to surgery because the pattern of pain relapse after endotherapy appears to be different from that after surgical therapy, the former having most of the reoccurrences of pain within 2 years after the initial treatment.[17]

RCT (n=1) ESWL Alone

Finally, a recent trial tested the observation that the application of ESWL alone might provide pain relief after short- and long-term follow-up in patients with pancreatic ductal stones causing upstream obstruction of the MPD.[18] In such patients, ESWL alone had been observed to eliminate pancreatic stones. A RCT utilized painful CP patients with obstruction of their MPD with stones. This European study compared the application of ESWL alone (n=26) and ESWL combined with endoscopic removal of stone fragments (n=29) as initial treatment. Two years after intervention, the percentage of those with pain was 38% (10/26) in the ESWL-alone group vs. 45% (13/29) in the group with ESWL and endoscopic removal of stone fragments. The percentages with pain at the end of follow-up (50 months) were 42 and 45%, respectively (no significant difference). Body weight increase was also similar (3.9 vs. 3.5 kg). Therefore, about 55% of patients might expect relief of pain with endotherapy after 4 years of follow-up.

The total duration of hospital stay for management of pain during the entire follow-up period was reduced in the group treated initially only by ESWL (3.1 vs. 8.6 days). Only 31% of the patients in the group treated initially with ESWL alone required supplemental endotherapy during follow-up. In patients with MPD obstruction caused by stones, this study suggests that ESWL alone should be proposed as the initial treatment. Removal of stone fragments with its increased hospital days and cost might be avoided in almost 60% of such patients.

Summary

The algorithm for treatment of patients with abdominal pain thought to be due to CP has not been adequately studied with the highest level of evidence because just eight RCTs have been reported since 1995. We do not have prognostic factors that predict pain relief after a large variety of treatment options—endotherapy ± ESWL, surgical drainage, or the variety of head resection techniques. At this time, we cannot provide guidelines in the treatment of this disease. Subsequent trials require a more international source of patients, a standardized set of inclusion and exclusion criteria based on objective criteria such as ductal anatomy (although the Cahen methodology[15] would be a good template), and an adequate length of follow up (5 years). Because of the paucity of patients in the available RCTs, physicians and surgeons must rely on their own experience with a variety of therapies and subsequent outcomes. Careful interpretation of case series still remains the bastion of our literature. These studies, as well as the RCTs, must be read carefully because of the lack of homogeneity of study design among them.

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Natural History of Intraductal Papillary Mucinous Neoplasms (IPMN): Current Evidence and Implications for Management

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Abstract Intraductal papillary mucinous neoplasms (IPMNs) show varying degrees of dysplasia throughout the neoplasm that can range from adenoma to invasive carcinoma, with dysplastic changes of borderline neoplasms and carcinoma in situ in between. An understanding of the natural history, and especially the required time to transform into either carcinoma in situ or an invasive adenocarcinoma, is critically important for management policy. This topic serves as the rationale for the present analysis. At the beginning of February 2007, using the key word "IPMN" in PubMed, we initially selected 119 publications using the principal criteria as defined by the WHO classification. We identified 20 appropriate original reports and one consensus paper. Neither randomized control trials (RCT) or systematic reviews of RCTs (level 1 evidence) nor cohort studies or reviews of cohort studies (level 2 evidence) have been published. Only one report fit the criteria for level 3 evidence (case control study). Nineteen papers satisfied criteria for level 4 (cases series) and two for level 5 (expert opinion publication). After additional review and analysis, we considered only six reports to be "cornerstone papers" of merit for the final review. Clues to the natural history of IPMNs can be gained by using several methods to examine the articles: (a) to verify different prognoses between main and side branch duct subtypes; (b) to compare the average age of patients with benign vs. malignant IPMNs; (c) to summarize the findings of nonoperative, observational studies based on follow up by clinical, biochemical, and imaging techniques without operative resection; (d) to determine the prognostic importance of the status of the resection margin; and (e) to follow patients clinically after surgical resection. Although important aspects of the natural history of IPMN are still unknown, the following conclusions can be drawn: (1) Branch-duct IPMNs are less aggressive than main-duct IPMNs. (2) Malignancy is more common in older patients. (3) Malignancy (invasive or carcinoma in situ) is found in about 70% of resected main-duct IPMNs. (4) After resection of noninvasive IPMNs (branch- and main-duct varieties), recurrence is rare (<8%). (5) After resection of invasive IPMN, recurrence occurs in 50–65% of patients.

Keywords Pancreas · Pancreatic neoplasm · Pancreatic ducts · IPMN

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Introduction

The first description of intraductal papillary mucinous neoplasms (IPMNs) was made in 1982 by Ohashi et al.[1] They described this neoplasm as a "mucin-producing" cancer of the pancreas. More than a decade passed before IPMN was recognized clearly as a distinct entity and, until then, a number of confusing terms were used to describe these lesions (e.g., mucinous ductal ectasia, IPMT, mucin-secreting neoplasm, etc.). Since the 1980s, with the widespread use of cross-sectional imaging, both IPMNs and mucinous cystic neoplasms (MCNs) have been diagnosed with increasing frequency.[2,3] Confusion between IPMN and MCN used to occur often, but in 1996, the World Health Organization (WHO) introduced the term IPMN and proposed clear criteria for diagnosis that distinguished IPMN from MCNs. We now recognize that IPMNs are connected to the ductal system, while the MCNs are not. MCNs also typically contain ovarian stroma. Both of these neoplasms are lined by a mucinous epithelium that, like adenomatous polyps in the colon, has the potential to progress to the eventual development of carcinoma. Thus, they are both considered to be premalignant.

IPMNs are subclassified as main- and branch-duct types and as a mixed type that contains elements of both.[4] Main-duct IPMN is characterized by involvement of the duct of Wirsung, which is dilated to more than 1 cm in diameter. Branch-duct IPMN originates in the side branches of the pancreatic ductal system and appears as a multilobular cystic lesion communicating with a *nondilated* main pancreatic duct. Typically, branch-duct IPMN occurs in the uncinate process-head of the gland, but it can also be seen in the neck and distal pancreas. If the main duct is dilated with synchronous involvement of the branch ducts, it is described as mixed IPMN.

Histologically, IPMNs often show varying degrees of dysplasia throughout the neoplasm that can range from adenoma to invasive carcinoma, with dysplastic changes of borderline neoplasms and *carcinoma in situ* in between. These findings suggest an aggressive, premalignant epithelium. An understanding of the natural history of these neoplasms, and especially the time required for them to transform into either carcinoma in situ or an invasive adenocarcinoma, is critically important in arriving at recommendations about their management. This topic serves as the rationale for this analysis.

Methods

The vast majority of studies on IPMNs have dealt with the diagnosis and surgical outcome of affected patients rather than with the natural history of these neoplasms.[2,3,5–30] At the beginning of February 2007, using the key word "IPMN" in PubMed, we initially selected 119 publications using the principal criteria as defined by the WHO classification. Because this classification was published in 1996 (categorizing IPMN into four groups—adenoma, borderline, carcinoma in situ, and invasive tumors), it is only since that time that pathologists had a standard definition to utilize that allowed comparisons across different institutions.[4] As a consequence, the present review has largely been restricted to reports published after 1996. Other factors used to select pertinent reports involved the requirement that the report identified a communication of the lesion with the main pancreatic duct and required the absence of ovarian stroma to exclude MCN. We identified 20 original reports[2,3,5–11,13,14,17,20,24,29–34] and one consensus paper[35] that we considered appropriate. Neither randomized control trials (RCT) or systematic reviews of RCTs (level 1 evidence) nor cohort studies or reviews of cohort studies (level 2 evidence) have been published. Only one report[32] fit the criteria for level 3 evidence (case control study). Nineteen papers[2,3,5–11,13,14,17,20,24,29–31,33,34] satisfied criteria for level 4 (cases series) and two[35,36] for level 5 (expert opinion publication). After additional review and analysis, we considered only six reports to be "cornerstone papers" of merit for the final review.[13,17,24,31,32,35]

Clues to the natural history of IPMNs can be gained by using several methods to examine the articles:

(a) To verify different prognoses between main and side branch duct subtypes
(b) To compare the average age of patients with benign vs. malignant IPMNs
(c) To summarize the findings of nonoperative, observational studies based on follow up by clinical, biochemical, and imaging techniques without operative resection
(d) To determine the prognostic importance of the status of the resection margin
(e) To follow patients clinically after surgical resection

Results

To Verify a Different Prognosis Between Main- and Side Branch-Duct Subtypes

No studies fulfill the criteria for level 1, 2, or 3 evidence; all are level 4 or 5 evidence-based studies. In the early 1990s, there was no clear distinction between main-duct and branch-duct IPMNs; they were all considered to have the same biologic behavior. The rate of malignancy (i.e., carcinoma in situ or invasive cystoadenocarcinoma) was stated to be up to 70%. In 1999, Kobari et al.,[31] and then

Terris et al.,[34] demonstrated that branch-duct IPMNs exhibited a less aggressive biology, observations that were confirmed later by several other authors.[12,16,20,22,27,37] These combined data established convincingly that branch-duct IPMNs are associated with a lesser rate of malignancy than the main duct counterpart and that branch-duct IPMNs less than 3 cm in size, with no mural nodules, and in asymptomatic patients, they rarely harbored malignant epithelial changes of either carcinoma in situ or invasive carcinoma. Tanaka et al. summarized existing data and showed that main-duct and branch-duct IPMN were associated with malignancy in 70% and 25% of all reported cases, respectively.[35] The rate of invasive carcinoma was 43% for main-duct IPMN and 15% for branch-duct IPMN. In conclusion, it is now widely accepted that main-duct IPMN have a greater chance of harboring a malignancy than branch-duct IPMN.

To Compare the Average Age of Patients with Benign vs. Malignant IPMNs

No studies fulfill the criteria for level 1, 2, or 3 evidence; all are level 4 and 5 evidence-based studies. Bernard et al.[12] found that, in patients <60 years old, 45% had a malignant form of IPMN, while in those ≥60 years old, 73% had a malignant form ($p=0.04$). Sohn et al.[17] confirmed this trend of age in main-duct and branch-duct IPMNs, with main-duct IPMN occurring more frequently in older patients, while Salvia et al.[24] found a similar trend in main-duct vs. branch-duct neoplasms.

By combining the experience of the Verona University and the Massachusetts General Hospital, Salvia et al.[24] analyzed a series of 140 patients who underwent operative resection for main-duct IPMN. This study reported a greater proportion of males, malignancy in 60% (42% of which were invasive carcinoma), and the average age of patients with malignant main-duct IPMN to be 6.4 years older than patients with adenoma or borderline IPMN. In a series of 136 resected IPMNs from the Johns Hopkins Hospital,[17] the rate of invasive carcinoma was 38%. The patients with cancer were also significantly older than those with adenoma.

Similarly, Yamao et al.[16] compared patients with IPMN who had hyperplasia only with those who had invasive neoplasms and observed that the latter patients were 5.3 years older. The studies by Sohn et al.[17] and Salvia et al.[24] provide similar evidence; patients with adenoma were about 5 years younger than those with invasive neoplasms. The difference in age between benign and malignant IPMN and the presence of different degrees of dysplasia within the same lesion (in some cases varying from adenoma to invasive cancer) are consistent with the possibility of progression to malignancy, at least in main-duct IPMN. In conclusion, patients with malignant IPMN are likely to be about 5 years older than those with benign forms of the lesion.

To Summarize the Findings of Nonoperative, Observational Studies Based on Follow up by Clinical, Biochemical, and Imaging Techniques without Surgery

No studies fulfill the criteria for level 1 or 2 evidence, and only one study involves level 3 evidenced-based data; all others are level 4 or 5 evidenced-based studies. Seven case series[19,25–28,37,38] have followed about 500 patients with presumed IPMN without resection; 90% of these cystic lesions were presumed branch-duct IPMN rather than main-duct IPMN, presumably because main-duct IPMN is regarded as high risk for malignancy and therefore treated more aggressively by resection. Therefore, the current trend in these centers is that main-duct IPMN is not managed by a surveillance program but rather treated by resection in most patients who are operative candidates. This approach has been adopted because of the coexistence of malignancy in 70% (based on the WHO criteria) at the time of resection and because of their *presumed* aggressive behavior. The result is that the estimated risk for degeneration into malignancy for main-duct IPMN has not been well studied. The work of Levy et al.[28] suggests that the majority of main-duct IPMN will manifest malignancy within 2 years of the diagnosis.

Most of the patients reported in these observational studies did not have a tissue diagnosis (although a few had benign cytology). In them, the most common criterion for the diagnosis of IPMN was that the patient had imaging evidence of a cystic pancreatic mass that communicated with the main pancreatic duct. The average duration of follow-up with cross-sectional imaging varied from 28 to 42 months. Overall, about 15% of these lesions were observed to enlarge (up to 60% in diameter) over that time. In a Japanese multicenter trial[25] during a 40-month (0–225) average follow-up period, 12% of the branch-duct IPMN increased in size vs. 19% of the main-duct IPMN. On the basis of these findings showing a lesser rate of malignancy of branch-duct IPMN and the evidence that malignancy was rare in asymptomatic patients with small branch-duct neoplasms without nodules, one of us (CB) began a prospective study at the University of Verona in January 2000. The purpose was to evaluate the safety of a surveillance program for the management of asymptomatic patients with a diagnosis of branch-duct IPMN of less than 3.5 cm in size without nodules and with a serum CA 19.9 value within normal limits.[32] This study met the criteria for level 3 evidence. The diagnosis of branch-duct IPMN was based on the combination of magnetic resonance imaging with cholangiopancreatography (MRCP). A cohort of 89

patients was followed prospectively for a median of 32 months. During this time, five IPMNs (6%) showed progression in size and, per protocol, were treated by operative resection; none had cancer in the resected specimen. The conclusion of this study was that a strategy of nonoperative management was safe in selected patients with branch-duct IPMN.

Currently, then, based on available literature (primarily level 4 evidence and one level 3 evidence-based study), the best guidelines[35] suggest that asymptomatic branch-duct IPMN of less than 3 cm in diameter with no mural nodules can be followed with periodic, high-resolution cross-sectional imaging; in contrast, main-duct IPMN should be resected whenever possible because of the high prevalence of malignancy.

To Determine the Importance of Status of the Resection Margin

No studies meet the criteria of level 1, 2, or 3 evidence; all are level 4 or 5 evidence-based studies. For main-duct IPMN, the status of the main pancreatic duct at the margin of transection has received considerable attention.[7,9,12–17,20,21,23,29,30,35] The role of frozen section analysis and the criteria for a "positive margin" remain controversial. Similarly, the concept of a local field defect (segmental involvement only) vs. a global field defect (potential multicentricity—i.e., the entire pancreatic ductal epithelium "at risk") continues to be debated. Studies addressing results of resection (see below; "To Follow Patients After Resective Surgery") suggest that recurrence rates are extremely low in all the categories of noninvasive main-duct IPMNs, arguing against a global field defect and multicentricity. In contrast, branch-duct IPMN can be multicentric.

The importance of changes at the resection margin suggestive (or diagnostic) of IPMN such as mucinous ductal hyperplasia, areas of denuded epithelium, mucinous adenoma, or findings of dysplasia within a mucinous epithelium are unknown. One study suggested that local recurrence could occur in the setting of a positive margin.[20] Common sense and most authorities (level 5 evidence) would suggest that all reasonable attempts to obtain a remnant margin free of IPMN in the main duct should be the goal. For multicentric branch-duct disease, total pancreatectomy assures removal of all epithelium at risk but also subjects the patient to considerable morbidity.

To Follow Patients after Resective Surgery

No studies meet the criteria of level 1, 2, or 3 evidence; all are level 4 or 5 evidence-based studies. The review of the literature is confounded by the fact that the majority of reported series with at least 5 years follow-up (and almost all prior to 2000) did not distinguish adequately between branch-duct and main-duct IPMN.

Chari et al.[13] followed 113 patients for a mean of about 3 years after resection of IPMN. For the 40 invasive malignancies, recurrence occurred in 65% of patients, usually within 3 years and usually in the form of distant disease. In contrast, for the 60 noninvasive IPMN (including carcinoma in situ), recurrence occurred in 8% (three as invasive carcinoma and two as noninvasive lesions, and only one of these five patients had a definitely positive margin).

Recurrences occurred in half of the invasive IPMN cases reported by Sho et al.;[30] their patients had a median disease-free survival of 38 months. In the report by Paye et al.,[23] all of the ten invasive IPMNs recurred. Of the 43 patients reported by Terris et al.,[34] seven of 11 recurrences were limited to the pancreatic remnant at a mean of 26 months.

In our recent experience with follow-up of 137 resected main-duct IPMN, 5-year disease-specific survival for 80 patients with adenoma, borderline dysplasia, and carcinoma in situ was 100%; indeed, there were no clinical recurrences in these patients. In contrast, for 57 patients with invasive carcinoma, the 5-year survival was 50%. Of 145 resected branch-duct IPMN collected from both the Massachusetts General Hospital and the University of Verona, 5-year disease-specific survival for 129 patients with adenoma, borderline dysplasia, and carcinoma in situ was 100%, while it was 60% for the 16 patients with invasive carcinoma.[12]

We conclude that, while published case numbers are still insufficient, recurrences occur in at least 50% of resected invasive branch-duct *and* main-duct IPMNs. Recurrences after resection of noninvasive IPMNs are rare.

Summary of Results

Although important aspects of the natural history of IPMN are still unknown, the following conclusions can be drawn:

1. Branch-duct IPMNs are less aggressive than main-duct IPMNs.
2. Malignancy is more common in older patients.
3. Malignancy (invasive or carcinoma in situ) is found in about 70% of resected main-duct IPMN.
4. After resection of noninvasive IPMNs (branch- and main-duct varieties), recurrence is rare (<8%).
5. After resection of invasive IPMN, recurrence occurs in 50–65% of patients.

Discussion: Interpretation and Implications for Management

Although it is hard to escape the conclusion that main-duct IPMN is more aggressive and more likely to harbor invasive cancer at the time of diagnosis, compared to branch-duct IPMN, one feature of the data that led to this conclusion should be mentioned. The data are based largely on patients who have undergone resection. The probability is, therefore, that these patients already had clinically important symptoms at the time of presentation and, for that reason, may have had more advanced disease. Nevertheless, it would seem prudent to recommend resection for all patients who present with main-duct IPMN because at least 60% of the neoplasms have evidence of malignancy (either carcinoma in situ or invasive cancer) in the resected specimen. Patients with mixed duct disease should also be managed in the same way. Of course, some patients with clinically significant comorbidities may not be operative candidates, and they represent exceptions. Those with asymptomatic, branch-duct IPMN, <3–3.5 cm in diameter, and without mural nodules or abnormal cytology of cyst fluid, may be managed more conservatively. The data suggest that this latter group has a <20% chance of harboring invasive malignancy, so surveillance may be a more reasonable option. Again, the decision must be individualized based on a variety of considerations. These include patient age, patient compliance for a surveillance program, and the *quality* of a surveillance program, which can vary according to available resources.

The evidence that IPMNs undergo a progression from a benign adenoma to a dysplastic process that eventually transforms into an invasive malignancy is circumstantial but quite convincing. This evidence leads naturally to the conclusion that all patients with IPMN, whether they have been resected or are not operated on, require surveillance. In the former resected group, the goal is to detect any evidence that the remaining pancreas will develop recurrent IPMN that requires treatment. For patients with resected *invasive* IPMN, at least half will develop evidence of recurrent (? persistent) disease, some only in the pancreas. If the pancreas is the only site, it probably makes sense to resect the remaining pancreas. For patients with resected, *noninvasive* IPMN, the likelihood of recurrence is <10%, but surveillance still seems appropriate. Of course, there is the group of patients who are managed initially with surveillance, usually because they had branch-duct IPMN that seemed unlikely to harbor malignancy.

If benign adenomas can progress to invasive malignancy, at the time of pancreatic resection, it is logical to strive for a negative resection margin. However, the definition of what constitutes such a negative margin is somewhat vague. Most surgeons would resect more of the pancreas if the margin contained evidence of PanIN 3 lesions, severe dysplasia, carcinoma in situ, or invasive cancer. With main-duct IPMNs (not thought to be multicentric), ideally, we should strive to achieve a main-duct resection margin that shows no evidence of *any* IPMN, even adenomatous change, because the main-duct lesions *may* be more likely to transform into an invasive neoplasm. With branch-duct IPMN, the question of whether these lesions are associated with a field defect that involves the entire pancreas is important but unanswered. While removing the entire pancreas would settle the issue, the decision to do so requires mature judgment and must be individualized because a total pancreatectomy is associated with considerable long-term morbidity. Consideration must be given to the patient's life expectancy, the patient's ability to manage the apancreatic diabetic state, and the likelihood that invasive malignancy is present or will develop in the pancreatic remnant. In the absence of a total pancreatectomy, we would resect more if the margin revealed evidence of severe dysplasia or anything more advanced.

There are two important questions that the literature review did not address, although we are unaware of any relevant information that has been published. The first relates to the frequency and kind of surveillance that should be preferred. In patients who had resected invasive main-duct IPMN, we currently favor CT or MR imaging two times per year for a period of 5 years, with endoscopic ultrasound (EUS) yearly to investigate questionable areas. In patients with noninvasive IPMNs, yearly CT or MR may be more reasonable. EUS may be valuable to follow-up CT or MR findings. The status of the resection margin should also be taken into account in estimating the frequency and duration of follow-up. In nonoperated patients with branch-duct IPMN, a similar two-times-per-year surveillance seems reasonable for 5 years and once yearly thereafter.

The second question concerns the efficacy of surveillance that is performed with the goal of detecting an invasive neoplasm at a stage when it is still curable. While this is at the heart of any surveillance program, we are unaware of any evidence that this is a realistic goal.

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The Role of Extended Lymphadenectomy for Adenocarcinoma of the Head of the Pancreas: Strength of the Evidence

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Abstract With improvements in the safety of Whipple resection in recent decades, surgeons have continued to explore the role of more extensive lymphadenectomy in hope of improving long-term survival. A systematic literature search of level I evidence addressing the role of the extent of lymphadenectomy was undertaken. Only reports of prospective, randomized controlled trials comparing pancreaticoduodenectomy with standard lymphadenectomy to pancreaticoduodenectomy with extended lymphadenectomy where information regarding survival, morbidity, mortality, the number of resected lymph nodes in each group and detailed operative technique were included. Four prospective, randomized trials comprising some 424 patients and one meta-analysis were identified. In aggregate, these studies confirmed that the number of resected lymph nodes was significantly higher in the pancreaticoduodenectomy with extended lymphadenectomy group. Morbidity and mortality rates were comparable. Postoperative diarrhea in the early months after operation was problematic in patients undergoing extended lymphadenectomy. In none of the studies was a benefit in long-term survival demonstrated. Standard pancreaticoduodenectomy continues to be the operation of choice for adenocarcinoma of the head of the pancreas.

Keywords Pancreatic cancer · Pancreaticoduodenectomy · Extended lymphadenectomy

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Introduction

With improvements in the safety of the Whipple operation in recent decades, surgeons have continued to explore the role of more extensive resections in the hope of improving long-term survival. The regional pancreatectomy, first described by Fortner in 1973,[1] was innovative, complex and not adopted by Western pancreatic surgeons. In contrast, Japanese surgeons were influenced by Fortner's concept of extended lymph node dissection and soft-tissue clearance for resectable pancreatic head cancer. The rationale for a more extensive procedure was based upon the observation that standard Whipple resection does not encompass nodal groups often involved with microscopic disease.[2–7] and that many patients frequently experienced local recurrence after resection.[8]

In the 1980s several Japanese surgeons reported survival rates after pancreatic head resection superior to those achieved in the Western hemisphere. These reports were criticized due to use of historical controls and lack of prospective randomization.[2,5,8–13] Nevertheless, their results were not easily dismissed, and a number of groups became interested in evaluating the role of extended

lymphadenectomy in the surgical management of resected pancreatic head cancer. In this report, we review current pertinent literature in an effort to arrive at evidence-based recommendations relative to the extent of lymphadenectomy to complement a resection of an adenocarcinoma of the head of the pancreas.

Methods

A systematic literature search of the following data bases was undertaken: National Center for Biotechnology Information, National Library of Medicine (PubMed and Ovid; Jan 1997–Jan 2007). We selected only reports of prospective, randomized, controlled trials (RCTs) comparing pancreatoduodenectomy with standard lymphadenectomy (PD) to pancreatoduodenectomy with extended lymphadenectomy (PD/ELND) where information regarding survival, morbidity, mortality, the number of resected lymph nodes in each study group and detailed operative technique was included. In addition, pertinent systematic reviews and meta-analyses were sought in an effort to improve the statistical power of available data from RCTs. Using this methodology, four RCTs and one systematic review were found and they comprise the data analyzed in this report. Only patients with pancreatic head carcinoma were included.

Results

The first RCT was reported by Pedrazzoli et al.[14] in 1998 and comprised 81 patients undergoing pancreatoduodenectomy for potentially curable pancreatic head adenocarcinoma from March 1991 to March 1994. The patients were randomized in this multicenter study to standard PD (n=40) or PD/ELND (n=41). Standard PD included removal of anterior and posterior pancreatoduodenal, pyloric, biliary duct, superior and inferior pancreatic head and body lymph nodes (first order nodes: N1). In the PD/ELND, additional nodes from the hepatic hilum, and along the aorta from the celiac trunk to the inferior mesenteric artery and laterally to both renal hila, and circumferentially from the hepatoduodenal ligament, the celiac trunk and superior mesenteric artery (SMA) were removed (second order nodes: N2). The nodal dissection was performed en bloc. Pylorus preservation was used in the majority of patients. Mean lymph node harvest was 13.3±8.3 for PD and 19.8±15.1 for PD/ELND (p<.03) and duration of the surgery was 30′ longer in the PD/ELND group (Table 1). Adjuvant chemoradiotherapy was not employed. Neither morbidity nor mortality was found to differ. A validated quality of life tool was not employed. In spite of circumferential dissection of the SMA in the PD/ELND, disabling diarrhea was rare. The difference in morbidity, mortality, and 4-year actual survival was not statistically different in the two groups (Table 1). Actuarial survival curves for the two study groups overall did not differ. An a posteriori analysis, not planned at study design, was performed for node-positive patients and suggested a significant (p<.05) survival benefit for the PD/ELND group (Fig. 1).

Table 1 Operative Time, Morbidity, Mortality and 4-year Actual Survival in Pedrazzoli's Study

Parameter	Standard (n=40)	Extended (n=41)	p Value
Operative time	6 h 12′	6 h 37′	
Morbidity	35%	45%	NS
Mortality	5%	5%	NS
4-year survival (actuarial)	12%	6%	NS

In 1999, Yeo et al.[15–18] published the first of four reports describing the results of their single institution RCT ultimately enrolling 299 patients with pancreatic head or periampullary adenocarcinoma from March 1996 to June 2001. There were 81 patients with pancreatic head adenocarcinoma randomized to standard PD and 82 to PD/ELND. Pylorus preservation was preferred in the standard group. For the PD group, nodes removed en bloc included anterior and posterior pancreaticoduodenal, nodes in the lower hepatoduodenal ligament, and nodes along the right lateral aspect of the SMA and superior mesenteric vein (SMV) (N1 nodes). For the PD/ELND group, distal gastrectomy was added, and sequential retroperitoneal lymphadenectomy from the right renal hilum to the left lateral border of the aorta in the horizontal axis and from the portal vein to the inferior mesenteric artery (IMA) in the vertical axis was undertaken (N2 nodes). Circumferential dissection of hepatic, SMA, and celiac trunks was not performed, although a celiac node was sampled. Mean lymph node harvest was 17.0±0.6 for the PD group and 28.5±0.6 for the PD/ELND group (p=.001). Calculation of nodal harvest was based upon all 297 evaluable patients in the trial.

Adjuvant chemoradiotherapy was used in both groups. Positive second-order nodes (N2) were present in 15% of patients in the PD/ELND group. While operative mortality was similar for the two groups, the rates of delayed gastric emptying, pancreatic leak, and wound infection were higher and duration of surgery and length of stay longer in the PD/ELND group (Table 2). Evaluating 105 patients a mean of 2.2 years after operation using a validated instrument [Functional Assessment of response to Cancer Therapy—General (FACT-G) and Functional Assessment of response to Cancer Therapy—Hepatobiliary (FACT-Hep)] revealed no difference in quality of life between study and control

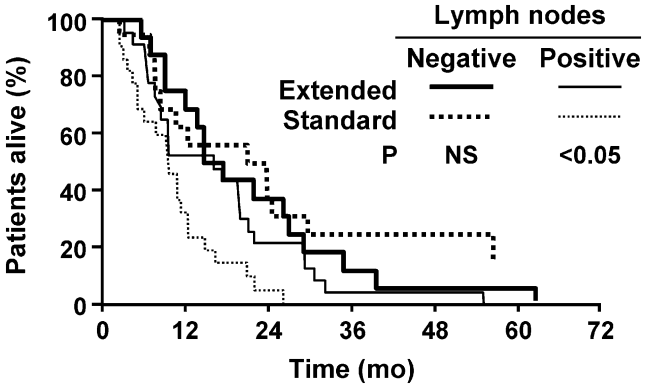

Figure 1 Actuarial survival curves (Kaplan–Meier) according to lymphadenectomy (standard or extended) in patients who survived pancreatoduodenectomy. There appears to be a trend toward a better long-term survival rate in patients with positive lymph nodes who underwent an extended rather than a standard lymphadenectomy. In particular, using a posteriori analysis, the long-term survival rate in patients who were node positive was significantly ($p<0.05$) better after undergoing an extended rather than a standard lymphadenectomy. Indeed, the survival curve of patients who were node positive after an extended lymphadenectomy mimicked the survival curve of patients who were node negative. Survival in patients who were node negative was not affected by the extent of lymphadenectomy.[14]

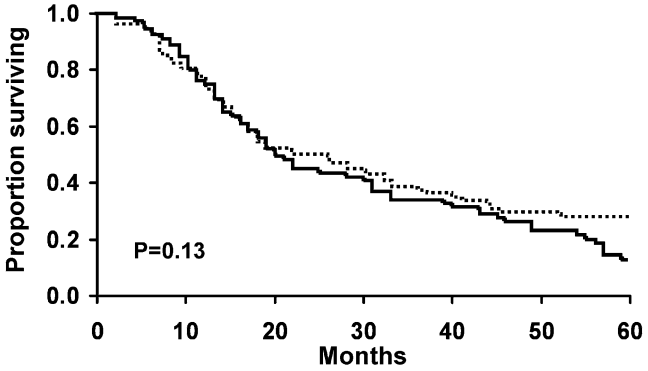

Figure 2 The actuarial survival curves for all patients with pancreatic adenocarcinoma who survived the immediate postoperative period, comparing the standard resection group ($n=80$, *solid line*) to the radical group ($n=82$, *dashed line*). The 1-, 3-, and 5-year survival rates were 75, 34, and 13% for the standard group and 73, 38, and 29% for the radical group ($p=0.13$), respectively.[18]

patients. Limiting the survival analysis to patients with pancreatic head cancer, there was a trend toward improved survival in the PD/ELND group (Fig. 2). The authors noted a higher incidence of positive margins in the PD group (21%) than in the PD/ELND group (5%; $p=0.002$), which may have accounted for the survival trend.

The next trial was published by Nimura et al.[19] in 2004 in abstract form. This was a multicenter RCT conducted in Japan from March 2000 to March 2003. Fifty-one patients underwent standard PD and 50 PD/ELND. The ELND was performed en bloc after the technique of Ishikawa[8] and is similar to that described in the Pedrazzoli study. The mean number of lymph nodes harvested in the PD group was 13 and 40 in the PD/ELND group. Operative mortality was similar in the two groups. None of the patients received adjuvant therapy. The mean operative time and intraoperative blood loss were significantly higher in the PD/ELND group (Table 3). Overall survival for node-positive and node-negative patients at 1, 2, and 3 years was not significantly different for the PD and the PD/ELND groups (Fig. 3). The incidence of severe postoperative diarrhea in the PD/ELNP group was 25, 9, and 4% at 3, 6, and 12 months, respectively; the difference in incidence of severe diarrhea between the PD and the PD/ELND group at 3 months was significant. Quality of life was similar for the control and study groups, although a validated assessment tool was not used. Similarly, the two groups showed no difference in weight loss, enzyme use, or number of bowel movements per day.

In 2005, Farnell et al.[20] reported the results of an RCT which included 40 in the PD group and 39 patients in the PD/ELND group enrolled between May 1997 and July 2003. Pylorus preservation was not allowed with both groups undergoing distal gastrectomy. The extent of the ELND was similar to that reported by Pedrazzoli but was performed in a sequential manner. Positive second-order (N2) lymph nodes were found in 29% of the patients in the PD/ELND group. The mean number of lymph nodes harvested was 15 in the PD group and 36 in the PD/ELND group ($p=.001$). Adjuvant radiochemotherapy was employed in both groups. When comparing PD with PD/

Table 2 Operative Time, Morbidity, Mortality, 3- and 5-year Actuarial Survival in Yeo's Study

Parameter	Standard ($n=146$)	Extended ($n=148$)	p Value
Operative time	5.9 h	6.4 h	
Morbidity	29%	43%	NS
Mortality	4%	2%	NS
Survival ($n=167$)			
3-year (actuarial)	36%	38%	NS
5-year (actuarial)	10%	25%	NS

Operative time, mortality and morbidity figures apply to the entire cohort of patients, including patients with non-pancreatic periampullary cancers, while survival data apply only to patients with adenocarcinoma of the pancreas

Table 3 Operative Time, Morbidity, Mortality, and 3-year Actuarial Survival in Nimura's Study

Parameter	Standard ($n=51$)	Extended ($n=50$)	P Value
Operative time	7 h	9 h	<0.0001
Morbidity	12%	20%	NS
Mortality	0%	2%	NS
3-year survival (actuarial)	28.5%	16.6%	NS

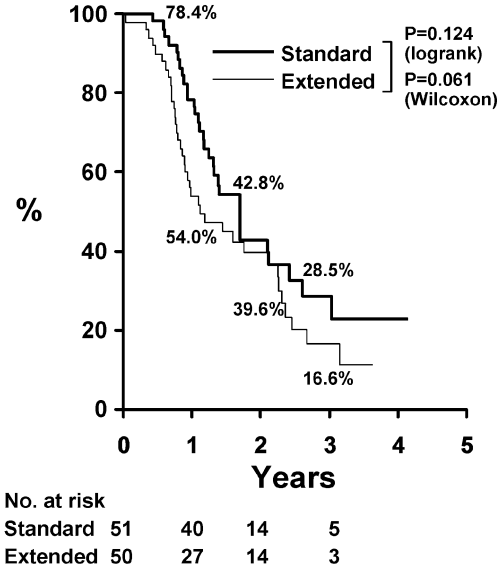

Figure 3 Actuarial survival curves for patients undergoing standard pancreatoduodenectomy (n=51) compared to those patients undergoing pancreatoduodenectomy with extended lymphadenectomy (n=50). The curves were derived from data presented at the 2004 International Hepato–Biliary–Pancreatic Association meeting in abstract form (Survival curve provided by Yuji Nimura, M.D., President, Aichi Cancer Center, Nagoya, Japan).

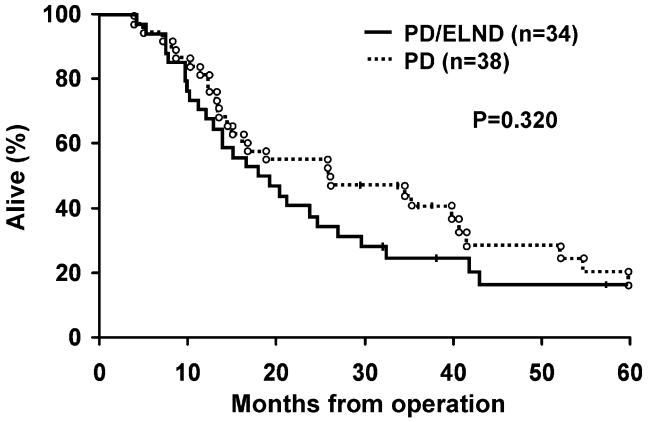

Figure 4 Overall survival (Kaplan–Meier technique) for 34 patients undergoing pancreatoduodenectomy with extended lymph node dissection (PD/ELND) and 38 patients undergoing standard pancreatoduodenectomy (PD). There is no difference in survival. The 1-, 3-, and 5-year survival estimates for the PD/ELND group were 71, 25, and 17%; for the standard PD group, they were 82, 41, and 16%, respectively.[20]

ELND, the median operating time was less for the PD group (6.2 vs 7.6 h; p<.01) and blood transfusion less likely (22 vs 44%; p<.05). Morbidity and mortality rates were comparable. Median duration of stay was 10.5 and 11 days (p=NS), respectively. There were no significant differences in 1-year (82 vs 71%), 3-year (41 vs 25%), 5-year (16.4 vs 16.5%), and median (26 vs 19 months) survival (p=.32; Table 4). Actuarial survival curves are shown in Fig. 4. At 4 months postoperatively, diarrhea, body appearance, and bowel control scored lower on the Functional Assessment of Response to Cancer Therapy specific to the pancreas after PD/ELND (p<.05). Forty-two percent of patients in the PD/ELND group experienced "very much diarrhea" compared to 8% of patients in the PD group. At 8 and 14 months, the incidence of diarrhea in the PD/ELND group decreased to 11 and 15% vs 11 and 0%, respectively, in the PD group. These differences were not statistically different. In addition, 53% of the patients in the PD/ELND group had "no control" or "a little bit of control of their bowels" compared to 9% in the PD group at 4 months. Over time, this difference became less pronounced with 22 and 15% of patients in the PD/ELND group experiencing decreased "bowel control" at 8 and 14 months, respectively, in comparison to 16 and 6% in the PD group.

A systematic review and meta-analysis of standard and extended lymphadenectomy in pancreatoduodenectomy for pancreatic head cancer was recently published.[21] The systematic review identified the four RCTs noted above, three of which were included in a meta-analysis of survival totaling 323 patients. The number of resected lymph nodes was significantly higher in the PD/ELND groups (p<.001). Morbidity and mortality rates were comparable, with a trend toward higher rates of delayed gastric emptying for PD/ELND. The weighted mean log hazard ratio for survival overall for the three studies was 0.93 (95% confidence interval 0.77 to 1.13), revealing no difference between PD and PD/ELND (p=0.48). The authors concluded that PD/ELND does not benefit survival, and there may be a trend toward increased morbidity (Fig. 5).

Table 4 Operative Time, Morbidity, Mortality and 4-year Actuarial Survival in Farnell's Study

Parameter	Standard (n=34)	Extended (n=31)	P
Operative time	6.2h	7.6h	<0.0001
Morbidity	35%	45%	NS
Mortality	0%	2.6%	NS
3-year survival (actuarial)	41%	25%	NS

Discussion

In the late 1980s, two retrospective studies from Japan[8,9] suggested that improved long-term survival could be achieved by associating an extended lymphadenectomy to a pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas. In both studies, the difference in survival between patients undergoing a regular lymphadenectomy and patients undergoing an extended lymphade-

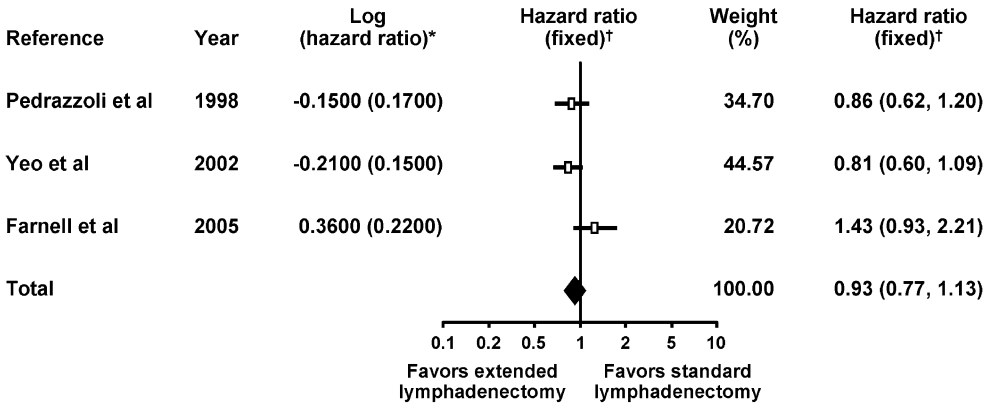

Figure 5 Hazard ratios on survival data in patients with pancreatic cancer from three trials. Overall data were analyzed using hazard ratios and SEs. The hazard ratios for all trials were pooled using the inverse variance method. No significant differences in overall survival were found (p=0.480). Test for heterogeneity: χ^2=4.91, 2 *df*, p=0.090, I2=59.3%. Test for overall effect: Z=0.71, p<0.001. *asterisk*: *values in parentheses* are SEs; *dagger*: *horizontal bars and values in parentheses* are 95% confidence intervals.[21]

nectomy was statistically significant. In addition, patients undergoing an extended lymphadenectomy achieved a 5-year actuarial survival rate between 30 and 35%.

These results, obtained in a retrospective fashion, awaited confirmation by randomized, controlled, prospective studies. In the last decade, the results of four prospective and randomized studies have been published. Two of the studies were multi-institutional[14,19]; one from Japan and the other mainly Italy. Neither used adjuvant therapy. The two United States studies were from single large institutions.[15,20] Both employed adjuvant therapy. Three studies included only patients with adenocarcinoma of the head of the pancreas,[14,19,20] while one study included also ampullary, distal bile duct and duodenal adenocarcinoma.[15] The extended lymphadenectomy was performed en bloc in two studies[14,19] and sequentially in two,[15,20] and its extent was similar in three studies[14,19,20] and less encompassing in the study performed by Yeo et al.[15] In the aggregate, these studies showed that performance of an extended lymphadenectomy added an average between 25 min and 2 h to the length of the operation, carried similar perioperative morbidity and mortality as a standard lymphadenectomy and conferred no improved long-term survival.

In an attempt to calculate the number of patients who would benefit from an extended lymphadenectomy in association with a pancreaticoduodenectomy for adenocarcinoma of the pancreas, Pawlik et al.[22] offered a mathematical equation based on three assumptions. The author postulated that an extended lymphadenectomy would be of benefit only to patients with N2 disease (i.e., the lymph node stations not harvested in a standard lymphadenectomy but removed with an extended one), in whom a pancreaticoduodenectomy was performed with negative circumferential margins (R0 resection) in the absence of distant metastatic disease (M0). By assigning percentages to these three categories (M0 disease 5%, N2 disease 10%, R0 resection 80%), Pawlik calculated that only 1 in 250 patients would benefit from an extended lymphadenectomy.

Postoperative quality of life was studied to a different extent in all of these four RTCs. Two studies[15,20] employed validated instruments to assess postoperative quality of life, and the other two[14,19] reported on the incidence of severe postoperative diarrhea. None of the four studies commented on the preoperative and postoperative incidence of diabetes, and only one[17] assessed need for postoperative pancreatic enzyme replacement therapy. Two of these studies reported severe diarrhea in a high percentage of patients after a PD/ELND,[15,20] while in the other two, the incidence of postoperative severe diarrhea was low or not reported. It is likely that the difference in incidence of disabling severe postoperative diarrhea reported by these studies may be due to the intensity with which patients were questioned about this adverse outcome, the use of a validated tool, and the timing when this parameter was evaluated. In the aggregate, available data from these studies point to the fact that severe diarrhea may occur postoperatively due to circumferential clearance of the superior mesenteric vessels with severance of parasympathetic nerve fibers and that it improves within the first postoperative year.

Conclusions

Available data from controlled randomized prospective trials indicate that PD/ELND confers no survival advantage over PD and may be associated with disabling diarrhea and malnutrition postoperatively. Therefore, standard PD continues to be the operation of choice for adenocarcinoma of the head of the pancreas.

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Strength of the Evidence: Adjuvant Therapy for Resected Pancreatic Cancer

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Abstract Pancreatic cancer remains one of the greatest challenges within oncology. Among resected patients, 5-year survival is typically only 10–25%. Among eight major randomized trials for resected pancreas cancer, five (GITSG, EORTC, ESPAC-1, RTOG 9704, and CONKO-1), containing a total of over 1,200 patients, have shaped world opinion on this subject. These trials have many significant methodological differences. Major conclusions that can be drawn from these trials in composite are (1) adjuvant chemotherapy is superior to observation following pancreaticoduodenectomy for pancreatic cancer, (2) gemcitabine is superior to 5-FU as adjuvant chemotherapy, and (3) the benefit of adjuvant chemoradiation is uncertain. Additional randomized trials are needed to address significant areas of controversy within available data.

Keywords Pancreatic cancer · Adjuvant therapy · Postgraduate course · Pancreatic neoplasms

Introduction

Pancreatic cancer remains one of the greatest challenges within oncology. Over 37,000 people in the USA were diagnosed with pancreatic cancer in 2005; only 2–3% can expect to live 5 years using present treatment techniques.[1] Virtually all long-term survivors come from among the approximately 5,000 people who will undergo definitive surgical resection of their pancreatic cancer this year. However, 5-year survival even for this relatively favored group of patients is typically only 10–25%.

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The Evidence

There have been eight major randomized trials for the adjuvant treatment of pancreatic cancer worldwide (Table 1).[2–9] Five of these trials have largely shaped world opinion on the treatment of this condition because they were completed by major organizations that tested widely used chemotherapy or chemoradiation therapy protocols.[2–6] These five trials contained over 1,200 patients and included the Gastrointestinal Study Group (GITSG) trial (1985, 1987),[2] the European Organization for Research and Treatment of Cancer (EORTC) trial (1999),[3] the European Study Group for Pancreatic Cancer (ESPAC-l) trial (2004),[4] the Radiation Therapy Oncology Group (RTOG) 9704 trial (presented in abstract form in 2006)[5] and the Charité Onkologie (CONKO-1) trial (2007).[6]

The GITSG trial initially contained 43 patients; 30 patients were subsequently treated according to the study arm. In this trial, patients in the control group were

Table 1 Randomized Clinical Trials in Resected Pancreatic Cancer

Author	Name	Year	Region
Kalser et al.[2]	GITSG	1985	USA
Klinkenbijl et al.[3]	EORTC	1999	Europe
Neoptolemos et al.[4]	ESPAC-1	2004	Europe
Regine et al.[5]	RTOG	2006	USA
Oettle et al.[6]	CONKO	2007	Germany, Austria
Bakkevold et al.[7]		1993	Norway
Lygidakis et al.[8]		2002	Greece
Kosuge et al.[9]	JSAP	2006	Japan

compared with patients who received radiotherapy 40 cGy in two 2-week, 20-cGy sequences separated by a 2-week break. 5-Flurouracil (5-FU) was given as an intravenous bolus at a dose of 500 mg/m^2 on days 1–3 of each radiation course and then given weekly for up to 2 years or until disease progression. With chemoradiation, patients experienced improvement in median survival as compared to patients receiving surgery only (18 vs. 11 months, $p=0.05$) and 2- and 5-year survival (43 vs. 18% and 19 vs. 0%, respectively). This study claimed efficacy for the experimental approach and formed the basis of subsequent adjuvant studies in resected pancreatic cancer.

The EORTC study sought to recapitulate the results of the GITSG study in 114 patients with pancreatic head lesions (observation $n=54$ and adjuvant treatment $n=60$) recruited from 29 European centers. However, chemotherapy (5-FU) given during radiation was given as a continuous infusion (rather than via bolus) during each radiation sequence, depending on toxicity, for up to 5 days. No chemotherapy was given postchemoradiation. Fifty-six percent of patients received the intended chemotherapy dose during radiation. Patients in the chemoradiation arm had a median survival of 17.1 months vs. 12.6 months in the observation arm ($p=0.099$); 2- and 5-year overall survivals were 37 and 20%, respectively, for the experimental arm and 23 and 10%, respectively, for the control arm. Mean follow-up time was not provided. This study concluded that the addition of chemoradiation to surgery did not produce an overall benefit in resected pancreatic cancer.

The ESPAC-1 trial published in 2004 analyzed 289 patients recruited from 53 hospitals in a 2×2 factorial design. The four study groups included (1) surgery only ($n=69$); (2) chemotherapy only ($n=73$) consisting of 5-FU, 425 mg/m^2, and leucovorin, 20 mg/m^2, given daily for 5 days every 4 weeks for six cycles of treatment; (3) radiation therapy and 5-FU given ($n=75$) according to the original GITSG method; and (4) both treatments ($n=73$, chemoradiation followed by chemotherapy). After a mean follow-up time of 47 months, local recurrence was noted in 62% of patients. The major study conclusions were the 5-year overall survival comparisons between patients who received chemotherapy vs. those that did not (21 vs. 8%, $p=0.009$) and those that received radiation therapy vs. those that did not (10 vs. 20%, $p=0.05$). The authors concluded that adjuvant chemotherapy had a beneficial effect in resected pancreas cancer, whereas chemoradiation had a deleterious effect. A quality-of-life questionnaire showed no difference between those that received chemotherapy and those that did not and those that received chemoradiation and those that did not.

The RTOG 9704 trial, presented in abstract form in 2006, contained 442 eligible patients (from an unknown number of centers) who received adjuvant chemoradiation (5040 cGy) given as continuous fractions with 5-FU 250 mg/m^2 continuous infusion given daily during radiotherapy. The comparisons were with the addition of either three cycles of 5-FU (one prechemoradiation, two postchemoradiation for 12 weeks) vs. four cycles of gemcitabine (one prechemoradiation, three postpostchemoradiation) at a dose of 1,000 mg/m^2 3 weeks out of every 4 weeks. The incidence of grade 3/4 toxicity was approximately 60% in the 5-FU arm and nearly 80% in the gemcitabine arm. Although the study showed no overall difference in aggregate survival, when pancreatic head lesions only were considered (eliminating study results from resected lesions in the pancreatic body or tail), both median survival (16.7 vs. 18.8 months) and overall survival at 3 years (21 vs. 31%) favored the gemcitabine arm ($p=0.047$). Follow-up time was not provided. The ability to complete chemoradiation and chemotherapy (both between 85 and 90%) was similar between the two arms. The study concluded that the addition of adjuvant gemcitabine to postoperative 5-FU chemoradiation was superior to the addition of 5-FU.

The CONKO-1 trial, conducted in Germany and Austria, represented a randomization of 368 patients (from 88 centers) following R0 or R1 resection to either observation or an experimental arm of gemcitabine—six cycles with each cycle consisting of three weekly infusions at 1,000 mg m^{-2} week^{-1}, 3 weeks out of every 4 weeks. The location of the tumor was not provided in the report, and 11 patients did not have adenocarcinoma. Approximately 10% of study patients never received chemotherapy; 62% were given the full six cycles of treatment. The incidence of grade 3/4 toxicity during 1,116 cycles of gemcitabine was 7.7%, in comparison with a 2.5% grade 3/4 toxicity rate in the control group who received no chemotherapy. After a median follow-up time of 53 months, the median *disease-free survival* was 13.9 months in the gemcitabine arm vs. 6.9 months in the observation arm ($p<0.001$). There was no difference in overall survival for the gemcitabine arm vs. the control group—median survival was 22 vs. 20 months, estimated 1-, 2-, 3-, and 5-year survivals were 58, 31, 24, and 17% vs. 31, 15, 8, and 6% in the observation arm. Quality of life as measured by the Spitzer questionnaire was

Table 2 Randomized Trials in Resected Pancreatic Cancer—Areas of Variation

Area
Patient accrual
Patient eligibility
Pathology review
Statistical design
Statistical analysis
Surgical standardization
Surgical quality control
Radiotherapy dose
Radiotherapy schedule
Radiotherapy field design
Radiotherapy quality control
Postoperative staging
Radiology imaging
Radiology quality review
Use chemoradiation
Chemotherapy agent
Chemotherapy dose
Chemotherapy schedule
Method follow-up
Frequency follow-up
Toxicity analysis
Study conclusion

similar in both groups. Although survival was not different, the authors concluded that postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone and, thus, was supported as adjuvant therapy in resectable pancreatic cancer.

Despite studying the same patient population, the five studies cited above contain at least 22 variations in study design, execution, and analysis (Table 2). Perhaps not surprisingly, they also came to divergent conclusions despite rather similar survival results (Tables 3 and 4). The question thus exists as follows: how do we interpret these results in composite?

Interpretation

Among the five major RCTs dealing with adjuvant therapies for pancreatic cancer, three issues have been examined—(1) the value of adjuvant chemotherapy (ESPAC-1, CONKO-1), (2) the value of adjuvant chemoradiation (GITSG, EORTC, ESPAC-1), and (3) the choice of chemotherapeutic agent when administering adjuvant chemoradiation (RTOG-9704).

Table 3 Results of Randomized Controlled Trials—Surgery Only

Study	Median Survival (months)	2-Year Overall Survival (%)	5-Year Overall Survival (%)
GITSG	11	18	0
EORTC	13	23	10
ESPAC-1	17	Not stated	11
CONKO	20	42	12

Table 4 Survival After Randomized Controlled Trials Testing Adjuvant Therapy

Study	Median Survival (months)	2-Year Overall Survival (%)	5-Year Overall Survival (%)
GITSG	18	43	19
EORTC	17	37	20
ESPAC-1 Chemo	20	40	21
ESPAC-1 CRT	16	29	10
RTOG 5-FU	17	21 (3-year)	Not available
RTOG gemcitabine	19	31 (3-year)	Not available
CONKO	22	48	23

Both trials evaluating adjuvant chemotherapy found significant benefit. One may conclude that there is concordant level-one evidence supporting the use of adjuvant chemotherapy. The trials examining adjuvant chemoradiation have led to very discordant findings. One trial found benefit (GITSG), one found no benefit (EORTC), and one actually found that chemoradiation worsened results (ESPAC-1). Based on these findings, no firm conclusion is possible regarding benefit of adjuvant chemoradiation other than that benefit or harm is yet to be proved convincingly. The conclusion of RTOG-9704 that gemcitabine is superior to 5-FU for the chemotherapy portion of chemoradiation treatment is based on level-one evidence, and there is little controversy in accepting the added value of gemcitabine over 5-FU in this situation.

Interpretation of why discordant results occur and what may be done to avoid them in the future may be of value. There is a spectrum of difference between two treatments. At one end of the spectrum is the all-or-none (or all-or-some) findings. This type of difference gives rise to level-1c evidence. To meet the criteria to fit into the level-1c category, a treatment must lead to some survivors when there previously were none or to survival of all when previously some died. An extreme example of this category is the parachute. While reductive, this is a useful example because it illustrates two important points beside the fact that mere demonstration on *one* occasion of the effectiveness of a parachute in preventing death in a fall from a great height is level-1c evidence. Also, a randomized trial of such a treatment is unnecessary and, in fact, unethical. Finally, systemic variability will have little effect on the ability to gather level-one evidence to support the value of the parachute. In other words, it will not matter if the parachute is big or small or dome- or wing-shaped or if the parachutist is male or female, old or young, or thin or obese as long as the parachutist is alive after touching down. This type of proof has been used in certain areas of surgery. For

instance, there has been no need to perform randomized trials to prove the value of liver resection for metastatic colorectal cancer to the liver because all untreated patients die within 5 years, whereas some surgically resected patients survive.

At the other end of the treatment difference spectrum are treatments that have a real but small benefit (or harm). Can a RCT observe these differences? Obviously, such treatments will require a comparative trial of large numbers of patients to prove benefit. Besides failure to include large enough cohorts, there are additional problems that may lead to the inability of a study to see small but real differences and therefore cloud the results. These other problems are systemic variability, selection of optimal therapy, or a presence of a selection bias although the study is randomized. Adjuvant treatment of pancreatic cancer is such a treatment, and discordant results arise from some of these sources. In terms of systemic variability, the main sources of error are carrying out the trial over many years during which other aspects of care change, failure of large numbers of patients to receive the therapy in the arm in which they were enrolled, and failure to administer the therapy in a standard fashion from center to center (lack of quality assurance). The latter usually focuses on quality assurance of the radiation and chemotherapy treatments but should also include standardization of the surgical treatment prior to the adjuvant therapy.

Critics of the available trials have cited the (1) lack of power (GITSG, EORTC), (2) long intake period (GITSG), (3) lack of standardization of treatment (the surgical margins of EORTC, RTOG-9704; the radiation and chemotherapy treatments of EORTC, ESPAC-1) and failure of patients to receive treatment (GITSG, EORTC, ESPAC-1), (4) selection of suboptimal treatment (the lack of maintenance chemotherapy in chemoradiation arm of EORTC and ESPAC-1; the suboptimal radiation therapy of GITSG, EORTC, ESPAC-1), and (5) selection bias (ESPAC-1).

One notable finding in the ESPAC-1 trial is that chemoradiation actually worsened outcome. Critics of chemoradiation suggest that the use of radiation may delay initiation of effective chemotherapy,[10] but others note that many patients in the chemoradiation arm did not actually complete radiation treatment.[11] An important question is whether the shortcomings (heterogeneity) in trial design and execution invalidate the conclusions of these studies. There is no quantitative way to answer this question. The objections do not seem to exclude the conclusion that chemotherapy is beneficial; however, they do seem to exclude the conclusion that chemoradiation is either beneficial or harmful.

The way forward in adjuvant therapy for pancreatic cancer would include trial designs that weed out the significant criticisms. These studies have required a huge effort, and their shortcomings have provided guidance in further trial design. Surgeons need to be involved to standardize the procedure, especially in terms of extent of node dissection and development of planes of proposed margins, especially along the superior mesenteric artery. Furthermore, every specimen should be inked in a standard fashion soon after excision to guide the pathological examination. There is a real need for a trial to examine the value of chemoradiation, and it would seem that the effort should be spearheaded by the radiotherapy community. Currently, the use of adjuvant chemoradiation outside of a trial may be questioned. Finally, and perhaps most importantly, new effective agents are required. The past 25 years have made pancreatic cancer surgery safe. Now it has to be made effective—a truly effective agent will squelch any problems with trial design.

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Indications for Sleeve Gastrectomy as a Primary Procedure for Weight Loss in the Morbidly Obese

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Abstract
Background Single-stage laparoscopic sleeve gastrectomy (LSG) may represent an additional surgical option for morbid obesity.
Methods We performed a retrospective review of a prospectively maintained database of LSG performed from November 2004 to April 2007 as a one-stage primary restrictive procedure.
Results One hundred forty-eight LSGs were performed as primary procedures for weight loss. The mean patient age was 42 years (range, 13–79), mean body mass index of 43.4 kg/m^2 (range, 35–75), mean operative time of 60 min (range, 58–190), and mean blood loss of 60 ml (range, 0–300). One hundred forty-seven procedures (99.3%) were completed laparoscopically, with a mean hospital stay of 2.7 days (range, 2–25). A 2.7% major complication rate was observed with four events in three patients and no deaths. Four patients required readmission; mild dehydration in two, choledocholithiasis in one, and a gastric sleeve stricture in one.
Conclusion Laparoscopic SG is a safe one-stage restrictive technique as a primary procedure for weight loss in the morbidly obese with an acceptable operative time, intraoperative blood loss, and perioperative complication rate.

Keywords Bariatric surgery · Laparoscopy · Morbid obesity · Roux-en-Y-gastric bypass · Sleeve gastrectomy

Abbreviations

BPD-DS	biliopancreatic diversion with duodenal switch
BMI	body mass index
GE	gastroesophageal
LAGB	laparoscopic adjustable gastric banding
LRYGB	laparoscopic Roux-en-Y gastric bypass
LSG	laparoscopic sleeve gastrectomy
POD	postoperative day
SG	sleeve gastrectomy

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Introduction

Worldwide, the incidence of morbid obesity has increased dramatically. Surgery has been proven to be the most effective long-term treatment option for sustained weight loss and improvement in comorbidity in the morbidly obese.[1] Although a number of surgical techniques exist, laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic adjustable gastric banding (LAGB) are currently the most commonly performed bariatric procedures.[2]

The sleeve gastrectomy (SG) was first described by Hess in 1988 and subsequently by Marceau as a modification of Scopinaro's technique of biliopancreatic diversion (BPD) with distal gastrectomy and gastroileostomy.[3–5] Hess substituted a SG to function as the restrictive component

of the BPD, replacing the need for a distal gastrectomy and thus avoiding the serious complications of stomal ulceration and bleeding. The new BPD–duodenal switch (BPD–DS) procedure combined a vertical SG with a gastric volume of approximately 100 to 150 ml and a duodenal switch with a common channel of 100 cm and an alimentary limb of 150 cm.[3] This approach resulted in comparable weight loss in the long term with reduced morbidity compared to the original Scopinaro BPD procedure.[5–7] As well as reduced rates of ulcerogenicity, the effects of severe malabsorption including hypoproteinemia, hypocalcemia, and the dumping syndrome were attenuated.[6] More importantly, maintenance of greater than 50% excess weight loss (EWL) has been reported by Hess in the majority of patients who underwent BPD–DS with long-term follow-up of more than 10 years.[6]

With the advent of minimally invasive techniques, Gagner performed the first laparoscopic BPD–DS in 1999, and the role of the SG continued to evolve.[8,9] To attempt to reduce morbidity and mortality, and to facilitate the laparoscopic approach, SG was recommended as a staged procedure in the super and super–super morbidly obese or in those patients with high operative risk because of excessive comorbidity.[10–12] A more definitive procedure in the form of a laparoscopic BPD–DS or LRYGB was deferred for approximately 6 months to allow for an initial weight loss.[10–12] This approach was used successfully by several groups as a bridge to a future laparoscopic bariatric surgical procedure with acceptable weight loss and reduction in comorbidity.[10,12] Because of the relative technical ease of performance compared to other bariatric procedures, acceptable operative time, low complication rate, and reports of average EWL of 51–83% at 1 year with improvement in comorbidity, many began to consider laparoscopic SG (LSG) as a primary single-stage restrictive procedure.[11–14]

We and others have adopted the technique as an additional procedure in the surgical management of our morbidly obese patients.[15–19] We wished to examine our series of morbidly obese patients who have undergone LSG as a single-stage primary procedure for weight loss and propose a series of guidelines to assist in the identification of patients who may benefit from this approach.

Methods

A retrospective review of a prospectively maintained database and patient medical record review of all morbidly obese patients presenting to our institution for LSG as a primary restrictive one-stage procedure over a 29-month period from November 2004 to April 2007 was performed. There were no cases where LSG was performed as a bridge to a second bariatric procedure. Laparoscopic SG was offered in the presence of the following criteria: patient preference, contraindications for LRYGB including extensive previous surgery and Crohn's disease, elderly patients with significant comorbidity, adolescents, patients on antocogulant medications, recalcitrant smokers, and patients with low body mass index (BMI) of 35–40 kg/m^2 with comorbidity. All patients had routine laboratory investigations including nutritional parameters, Helicobacter serology, chest X-ray, electrocardiogram, abdominal ultrasound, and additional investigations as deemed necessary determined by their comordid conditions. All patients with positive Helicobacter serology were treated with eradication doses of triple therapy.

All procedures were carried out by two surgeons (S.S. and R.J.R.) in accordance with the National Institute of Health consensus criteria for morbid obesity.[20] Permission for the study was obtained from the Institutional Review Board. All patients had a routine gastrograffin upper gastrointestinal contrast study (GUGI) on postoperative day (POD) 1. If normal, patients were commenced on oral fluids. A preoperatively placed foley catheter was removed on POD 2, and all surgical drains were removed before discharge. Proton pump inhibitors were continued for 3 months. After discharge, patients were reviewed at 1, 3, 6, 12 months and yearly thereafter. All data pertaining to each patient including demographic data, weight, body mass index (BMI), comorbidities, preoperative investigations, previous surgical procedures, perioperative complications, and postoperative outcomes included morbidity, readmission rate, weight loss, and comorbidity status were analyzed from a prospectively maintained bariatric database.

Surgical Technique

Prophylactic heparin and a single dose of a broad spectrum antibiotic were administered at induction. A seven-trocar technique was used as previously described (Fig. 1).[17] After induction of anesthesia and endotracheal intubation, the abdominal cavity was accessed through a 1-cm supraumbilical incision using an Optiview trocar™ (Ethicon EndoSurgery, Cincinnati, OH, USA). The abdominal cavity was insufflated with carbon dioxide to a pressure of 15 mmHg. The operating trocars were inserted under direct vision. The liver was retracted cranially and the gastroesophageal (GE) junction exposed. A point on the greater curvature approximately 6 cm proximal to the pylorus was identified as the distal extent of the resection. The Harmonic scalpel™ (Ethicon EndoSurgery) was used to divide the vessels along the greater curve up to the angle of His. A 44–52 Fr bougie was inserted transorally to the level of the distal stomach and across the pyloric channel. Linear cutting staplers (Endopath®, Ethicon EndoSurgery) were used to vertically transect the stomach, creating a narrow

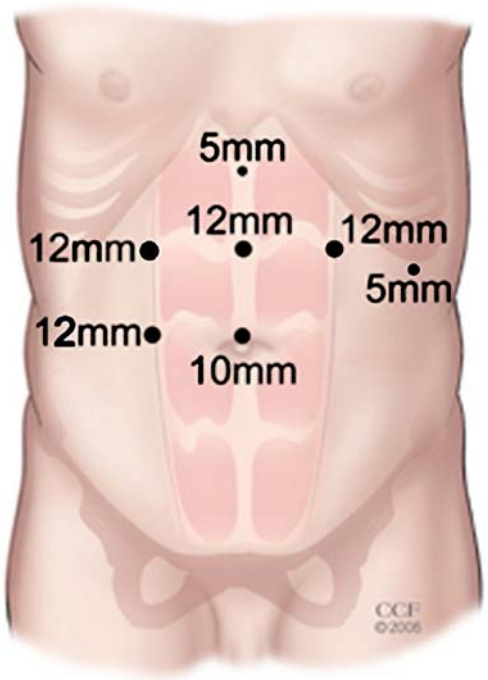

Figure 1 Trocar placement for laparoscopic sleeve gastrectomy.

gastric tube with an estimated capacity of less than 150 ml. The staple line was oversewn with a running 2/0 silk suture (Fig. 2). A large bore drain was placed in the subhepatic space adjacent to the stomach tube. The resected stomach was placed in a specimen bag and extracted through the supraumbilical port site. All trocar sites were closed with a subcuticular suture. Fascial sutures were not inserted routinely.

Results

Over a 29-month period from November 2004 to April 2007, 164 patients underwent LSG as a single-stage restrictive procedure for morbid obesity. Laparoscopic SG was performed as a primary restrictive procedure in 148 patients (90.2%) and as a revisional procedure in 16 patients (9.7%) with prior failed bariatric surgery. Patients who underwent LSG as a revisional procedure were excluded from further analysis.

Of the patients who had LSG as a primary restrictive procedure, the majority were female with a male to female sex ratio of 1:3. The mean age was 42 years (range, 13–79), and mean weight was 270 lbs (range, 168–453), with a mean BMI of 43.4 kg/m^2 (range, 35–75). The procedure was completed laparoscopically in 147 cases (99.3%). One procedure was converted to an open approach after an iatrogenic colotomy in the presence of dense adhesions related to previous surgery. The mean duration of surgery in the 148 patients was 60 min (range, 58–190), with a mean blood loss of 60 ml (range, 0–300). As expected the operative time in the patient who was converted was prolonged at 129 min, with an intraoperative blood loss of 100 ml. The mean operative time was 60 min (range, 58–190) in the laparoscopic group with a mean blood loss of 20 ml (range, 0–300). There were no perioperative deaths. One patient developed a staple-line leak, which was detected on POD 1 on the routine GUGI study and underwent laparoscopic primary repair of the site of leak high on the greater curvature with omental patchplasty. A second patient required laparoscopic exploration for postoperative hemorrhage because of a liver laceration from a retractor-induced injury. A pelvic abscess requiring percutaneous drainage developed in the patient with the iatrogenic colotomy. Three patients (2%) developed umbilical port site infections that responded to oral antibiotics and local wound care. The mean length of hospital stay was 2.7 days (range, 2–25).

In the first 3 months after LSG, four patients required readmission (2.7%). The majority were related to dehydration from inadequate oral intake or vomiting, related to transient gastric dysmotility, choledocholithiasis in one, and a gastric sleeve stricture in one. The patient with the gastric sleeve stricture (0.7%) presented 3 weeks postoperatively with dysphagia and vomiting. A 44-Fr bougie had been used to size the gastric tube at the time of LSG. A single

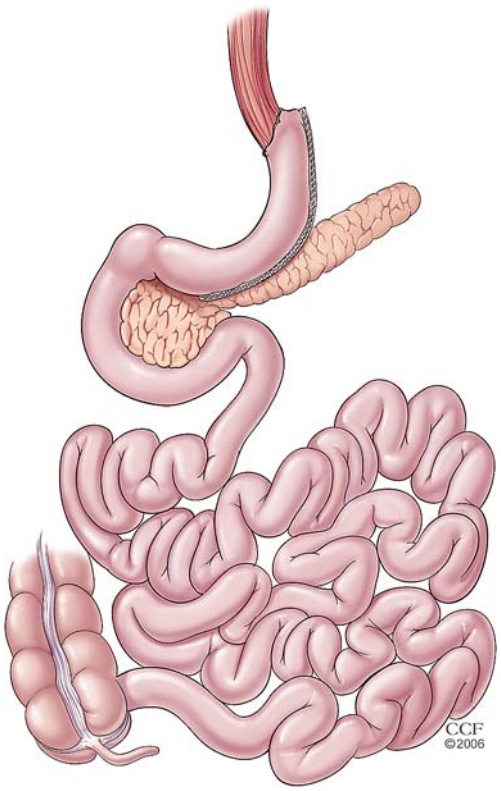

Figure 2 Laparoscopic sleeve gastrectomy.

endoscopic dilation with a through-the-scope endoscopic balloon was sufficient to produce symptomatic relief. An additional two patients developed symptomatic cholelithiasis.

Discussion

Laparoscopic SG results in weight loss not only from the restriction of oral intake but also because of significantly reduced ghrelin levels after resection of the gastric fundus, which is the predominant area of ghrelin production.[21–23] As the first part of the duodenum, pylorus, antrum, lesser curvature, and vagal nerve integrity are maintained, moderate restriction is created while allowing a relatively normal eating behavior. The concept of LSG as a single-stage primary restrictive procedure has not been widely accepted by the bariatric surgical community as published outcome data remains limited. Previous studies of LSG as a single-stage procedure report varying complication rates of 0–23%.[11,18,24,25] Some of the more significant complications after LSG include leaks and hemorrhage, with leak rates of 1.5–2.4%.[10,17,18,25] In a previous report of our early experience with LSG, we observed an acceptable perioperative complication rate with satisfactory short-term weight loss.[17] However, data was presented on only 30 patients who had undergone LSG as a primary or revisional procedure. Our current report evaluates our single center experience of one-stage LSG in 148 patients over a 29-month period and represents the largest series of one-stage LSG performed as a primary procedure for morbid obesity. All patients who underwent LSG as a revisional procedure were excluded. Operative complexity has been evaluated by conversion rates, mean operative time, and mean blood loss. Perioperative morbidity and mortality data are reported with additional data on mean hospital stay, readmission rates, and management of short-term complications. In our experience, LSG had a low conversion rate of 0.7%, with an acceptable intraoperative blood loss and mean operative time. A major complication rate of 2.7% was observed, with four adverse events in three patients. There were no patient deaths. These results compare favorably with other published reports of LSG. In our series, surgical intervention was required for a leak in one patient (0.7%) and bleeding in another (0.7%). All cases were recognized in the early postoperative period with immediate surgical intervention. One patient developed a leak during the early phase of our learning curve. This leak occurred high on the greater curve just distal to the angle of His. This complication emphasizes the importance of meticulous dissection to clearly identify the GE junction and angle of His. We now routinely leave a narrow cuff of tissue at the most superior aspect of the greater curve just below the angle of His, which is imbricated with a running 2/0 silk suture. This suture is continued down to the level of the distal extent of resection. Meticulous attention to oversewing the staple line is the main factor contributing to our extended operative time, but we believe this time is essential to reduce the risk of a staple-line leak and/or hemorrhage. To validate our current findings, similar conversion, perioperative complication, and readmission rates were observed in our initial 28 patients who underwent primary one-stage LSG.[17] Encouragingly, although there was a trend toward a nonstatistically significant increase in mean patient BMI, we observed reduced mean

Table 1 Indications for Primary Laparoscopic Sleeve Gastrectomy in the Morbidly Obese

Procedure	Characteristics
Two-stage procedure	
First step in super–super morbidly obese patient	Followed by RYGB or BPD
First step to a non bariatric second procedure	Low BMI of 35–40
	Followed by hip replacement, recurrent incisional hernia, pull through procedure for ulcerative colitis, renal/liver transplantation
Single-stage procedure	
Final step in ASA IV Morbidly Obese Patient	Low EF, Heart/Liver/Kidney transplant recipient
Final step in poor candidate for LRYGB or BPD-DS	Smoker
	Warfarin
Final step in extremes of age	Adolescents
	Elderly age ≥70 yrs
Final step in a high risk stomach	Chile, Colombia, Japan: high incidence of gastric cancer
Final step in Crohn's disease	
Patient preference	
Low BMI of 35–40 with comorbidity	
BMI 30–35 with the metabolic syndrome	

operative time and mean hospital stay compared to our early experience.

Although our series suggests that LSG may be a safe alternative option for the morbidly obese, it does have several limitations. Late complications of weight regain, gastric sleeve dilatation, and long-term resolution of comorbid conditions were not addressed. In addition, a number of key questions remain unanswered. Will the long-term results be as good as other restrictive procedures such as the LAGB? Will the percentage of excess weight loss at 10 to 15 years be comparable to LRGBP? What is the best bougie size to achieve maximal restriction and therefore optimal weight loss without creating an excessive narrow sleeve causing dysphagia, vomiting, and reflux symptoms? Currently, there is no consensus on the optimal size of the gastric tube. We routinely use a 44- to 52-Fr bougie to size the gastric tube, which has resulted in satisfactory weight loss and a stricture rate of 0.7%, which compares favorably to other published studies.[10,18] Will the gastric tube dilate over time and result in weight gain? Langer et al. demonstrated a single case of an asymptomatic radiologically detected gastric sleeve dilation in 14 patients at 1 year after LSG.[26] A dilated sleeve may be caused by intraoperative use of an excessively large bougie, true gastric tube dilation over time, or inadequate resection of the posterior gastric folds. Will sleeves need to be resleeved, and if so, how often? In a large series of BPD–DS procedures, Gagner et al. reported further weight reduction in one patient with inadequate weight loss after a resleeve.[27] Will the physiological advantage of reduced ghrelin production be lost over time? Will ghrelin levels remain low or will other sites of ghrelin production, such as the duodenum or brain, compensate to *normalize* levels? What percentage of one-stage LSG will eventually be converted to LRYGB or LPBD–DS? And finally, who should undergo LSG?

We believe LSG has a role in the management of the morbidly obese but in highly selected cases. At our institution, LRYGB, LAGB, and LSG are offered to all patients. Laparoscopic SG is performed under an Institutional Review Board-approved protocol while further data is awaited on long-term outcome. We continue to recommend LRYGB as the procedure of choice in patients with a BMI of $\geq$50 kg/m^2 with comorbidity. As our experience increases, we are attempting to define indications for primary LSG in our patient population (Table 1). We currently perform LSG in the presence of contraindications to LRYGB, including extensive previous surgery and Crohn's disease, and in poor candidates for LRYGB or LBPD–DS such as heavy smokers and those taking anticoagulants because of the risk of postoperative anastomotic ulceration and bleeding. We perform LSG in patients at the extremes of age, in high risk elderly patients aged >70 years with significant comorbidity, and in adolescents where a LRYGB and its metabolic consequences may be problematic. Other indications include LSG as a first step to another nonbariatric procedure such as joint replacement, organ transplantation, or incisional hernia repair where an initial weight loss would facilitate the required secondary intervention (Table 1). We also offer LSG to patients with a low BMI of 35–40 kg/m^2 with comorbidity and according to patient preference. Other indications for LSG include as a first step to a staged procedure in the super–super morbidly obese and as a primary procedure in endemic regions at risk of stomach cancer where ongoing endoscopic surveillance is required. More controversially, LSG may have a role in patients with a low BMI of 30–35 kg/m^2 with the metabolic syndrome.

In conclusion, we believe LSG is a safe and effective one-stage restrictive procedure in the short term to achieve weight loss as a primary procedure in the morbidly obese. In our experience, primary LSG is associated with an acceptable operative time, intraoperative blood loss, and perioperative morbidity (0.7% leak rate), with no mortality (0%). Prospective studies are required to evaluate the long-term outcome after LSG, specifically effective weight loss, maintenance of weight loss, resolution of comorbidity, and the potential for gastric tube dilation with weight regain.

Acknowledgment Competing Interests Declared: None

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Complications and Functional Results after Ileoanal Pouch Formation in Obese Patients

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Abstract
Objective Ileoanal pouch formation (IPAA) can be technically challenging in obese patients, and there is little data evaluating results after the procedure in these patients. We compare outcomes for patients with a body mass index (BMI) ≥30 undergoing IPAA when compared with those for patients with BMI <30.
Methods Retrospective analysis of prospectively accrued data for patients with BMI ≥30 undergoing IPAA. Patient and disease-related characteristics, complications, long-term function, and quality of life (QOL) using the Cleveland Global Quality of Life scale (CGQL) were determined for this group of patients (group B) and compared with those for patients with BMI <30 (group A). Kruskal–Wallis and Wilcoxon rank sum tests were used to compare quantitative or ordinal data and chi-square or Fisher's exact tests for categorical variables. Long-term mortality and complication rates were estimated using the Kaplan–Meier method with group comparisons performed using log rank tests.
Results There were 345 patients (median BMI 32.7) in group B and 1,671 patients in group A. When the cumulative risk of complications over 15 years was compared, group B patients had a significantly higher chance of getting a complication (94.9% vs 88%, $p=0.006$). The rates of pelvic sepsis (6.7% vs 5.3%, $p=0.3$), pouchitis (58.1 vs 54.4%, $p=0.9$), pouch failure (6% vs 4.5%, $p=0.9$), and hemorrhage (5.6% vs 4.8%, $p=0.7$) were similar for group B and group A. Group B patients, however, had a significantly higher risk of the development of wound infection (18.8% vs 8.1%, $p<0.001$) and anastomotic separation (10.4% vs 5.4%, $p<0.001$), whereas group A patients had a higher rate of development of obstruction over time (26.7% vs 22.3%, $p=0.02$). Long-term outcome including QOL and function after 15 years was comparable between groups.
Conclusions Although technically demanding, IPAA can be undertaken in obese patients with acceptable morbidity. Good long-term functional results and QOL that is comparable to nonobese patients may be anticipated.

Keywords Ileoanal pouch formation · Obese patients · Complications · Long-term function · Quality of life

Introduction

The ileoanal pouch (IPAA) offers long-term continence and quality of life (QOL) for patients with ulcerative colitis (UC) undergoing restorative proctocolectomy (RP).[1,2] Indications of the technique have been broadened to include its use in indeterminate colitis (IC),[3,4] familial adenomatous polyposis (FAP),[5] and selected patients with Crohn's disease (CD)[6] desiring maintenance of continence. The prevalence of obesity among US adults has doubled since 1990.[7] Although previous studies have demonstrated that obesity by itself does not correlate with adverse outcomes in general surgical operations,[8–10] there is a paucity of available literature on outcomes in obese patients undergoing IPAA. The relevance of this data is especially important as IPAA may be technically challenging in obese patients. As there have been few reports in the literature examining the application of this technique in this group, we evaluate

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the differences in the preoperative and perioperative factors of patients with BMI ≥30 and of patients with BMI <30 and compare the long-term functional results and QOL in the two groups.

Methods

All patients undergoing IPAA at our institution are prospectively accrued into an institutional review board (IRB)-approved pouch database. Patients with a body mass index (BMI) ≥30 (group B) in the database were retrospectively identified from the database and compared with patients with BMI <30 (group A). Differences in demographics, preoperative factors, indication for surgery, final pathological diagnosis, and surgical factors including type of anastomosis, use of defunctioning stoma, and configuration of the pouch were determined. The two groups were also compared to determine any differences in the incidence of complications, function, and QOL over time. Complications, long-term functional outcome, and QOL for this group of patients at 5, 10, and 15 years were analyzed.

The function of the pouch was determined by evaluation of the number of daytime and nighttime bowel movements, incontinence, urgency, and pad usage as reported by patients at each follow-up. Incontinence and urgency were graded as never, rarely, sometimes, mostly, and always. Complications, long-term functional outcome, and QOL for this group of patients at 5, 10, and 15 years were analyzed.

QOL was assessed by the Cleveland Global Quality of Life scale (CGQL), which has been previously described in patients undergoing restorative proctocolectomy.[11] Patients rated each of three items (current QOL, current quality of health [QOH], and current energy level [CEL]) on a scale of 0–10, 0 being the worst and 10 the best. The sum of the three scores divided by 30 gave the CGQL score (possible range 0–1). The three components of CGQL and the overall CGQL score at different time points were evaluated.

The availability of long-term functional and QOL data varies greatly among the patients in the database. Among patients with available data, patterns with respect to the timing of data collection also varied greatly. To overcome the inconsistencies and assess these outcomes at specified times after surgery of 1, 5, 10, and 15 years, we defined windows around these time points of 3 months, 1 year, 2 years, and 2 years, respectively, and for each patient, we captured the measurement taken closest to the target time point and still within the defined window. Within any time point and its acceptable window, only a fraction of the patients had data available.

Statistical methods Only patients with complete data pertaining to BMI were included in the analysis. Data that were missing for some patients were excluded during the particular analysis. Data is reported as the mean±standard deviation (SD) for parametric data and as the median (interquartile range [IQR]) for nonparametric data. With respect to quantitative or ordinal data, groups were compared using Kruskal–Wallis and Wilcoxon rank sum tests. Comparisons with respect to categorical variables were performed using chi-square, or alternatively, Fisher's exact test when chi-square assumptions were of questionable validity based on low frequencies or group sizes. For long-term functional and QOL data, selected time points were analyzed separately because of inconsistencies in the sets of patients with data available for analysis. Long-term mortality and complication rates were estimated using the Kaplan–Meier method with group comparisons performed using log rank tests. p values for individual comparisons are reported. A level of $\alpha=0.05$ was used to define significance; although with several group comparisons performed, some false-positive tests are to be expected. For analyses of functional and QOL outcomes that include four time points, Bonferroni-corrected significance levels of 0.0125 were applied.

Results

There were 345 patients with BMI ≥30 in the database with a median BMI of 32.7 and 1,671 patients in group A (median BMI 23.8). Although all patients who were overweight were advised to lose weight before surgery, data pertaining to the amount and weight lost, if any, in these patients is not available.

Baseline characteristics for groups A and B are given in Table 1. As a number of patients have more than one indication for surgery, the predominant indication for surgery was listed as primary and any additional indications as secondary. The most common primary indications in group B were desire for continence after prior colectomy (35.7%), steroid dependency or toxicity (34.8%), presence of dysplasia (12.5%), and failure of medical therapy (9.9%). Patients in groups A and B had similar primary and secondary indications for surgery ($p=0.09$). Final pathological diagnosis ($p=0.14$) was also similar between groups. The subset with a final pathologic diagnosis of Crohn's disease includes patients who developed a secondary diagnosis of Crohn's disease after IPAA. Based on a review of our experience in this group of patients,[12] we also currently consider IPAA in a select group of patients with isolated colonic Crohn's disease who have no evidence of perianal and small bowel involvement.

Table 1 Comparison of Patients with BMI <30 and ≥30

Variable		BMI <30 (n=345)	BMI ≥30 (n=1,671)	p value
Age (mean±SD)		36.8±13.1	42.3±12.3	<0.001*
Female gender, n (%)		742 (44.5)	144 (40.6)	0.2
Previous steroids and immunosuppressive medication, n (%)		1,179 (70.5)	272 (77.3)	0.01*
Comorbidity, n (%)		600 (35.9)	261 (74.1)	<0.001*
Resection, n (%)	Completion proctectomy	604 (36.1)	126 (35.8)	0.9
	Total proctocolectomy	1,069 (63.9)	226 (64.2)	
Pouch configuration, n (%)	J	1,437 (85.9)	310 (88.6)	0.19
	S	235 (14.1)	40 (11.4)	
Anastomosis, n (%)	Handsewn	276 (16.5)	35 (10.1)	0.003*
	Stapled	1,394 (83.5)	313 (89.9)	
Proximal diversion, n (%)	False	250 (14.9)	50 (14.2)	0.72
	True	1,423 (85.1)	302 (85.8)	
ASA class, n (%)	Class I	5 (5.7)	2 (4.5)	0.53
	Class II	61 (70.1)	26 (59.1)	
	Class III	20 (23)	15 (34.1)	
	Class IV	1 (1.1)	1 (2.3)	
Intraoperative transfusion, n (%)		269 (16.1)	57 (16.2)	0.96
Postoperative transfusion, n (%)		104 (6.2)	24 (6.8)	0.7
Final pathological diagnosis, n (%)	MUC	995 (59.5)	208 (59.3)	0.14
	Indeterminate colitis	251 (15)	49 (14)	
	Indeterminate favoring Crohn's	44 (2.6)	3 (0.9)	
	Indeterminate favoring MUC	182 (10.9)	46 (13.1)	
	Crohn's	62 (3.7)	8 (2.3)	
	FAP	121 (7.2)	31 (8.8)	
	Cancer	6 (0.4)	4 (1.1)	
	Not documented	2 (0.1)	0 (0)	
	Other	8 (0.5)	2 (0.6)	

MUC: mucosal ulcerative colitis
*p<0.05

Pouch configuration, use of proximal diversion, and use of intraoperative or postoperative blood transfusion was similar in groups A and B. A significantly higher proportion of group B patients was on steroids and immunosuppressive medication preoperatively, and as may be expected, had associated comorbidity. However, the ASA class distribution was similar in the two groups. A significantly lower proportion of group B patients had a handsewn anastomosis when compared with group A patients. The preferred technique is a stapled anastomosis at our institution. Mucosectomy is performed when a handsewn anastomosis is performed and in patients with FAP with rectal cancer and UC patients with dysplasia or cancer in the lower rectum.

Complications The estimated cumulative risk of any complication occurring for group B was 82.1% after 5 years of follow-up, 85.3% after 10 years of follow-up, and 94.9% after 15 years of follow-up. At 5 years after the procedure, the commonest complications were pouchitis and anastomotic stricture. After 15 years of follow-up, pouchitis continued to be the most common complication but obstruction became more common. The cumulative risk of pouchitis, fistula, and intestinal obstruction continued to rise after 10 years, whereas the other complications remained constant. The cumulative risk of developing a complication for group A and B patients are in Table 2. Group B patients had a significantly higher risk of the development of wound infection and anastomotic separa-

Table 2 Estimated Cumulative Risk of Complications for the Two Groups

Variable	BMI <30	BMI 30	p value
Pouchitis[a]	54.4	58.1	0.9
Obstruction[a]	26.7	22.3	0.02
Anastomotic stricture	23.7	17.2	0.1
Fistula[a]	11.4	13.4	0.3
Wound infection	8.1	18.8	<0.001
Pouch failure[a]	6	4.5	0.9
Pelvic sepsis	5.3	6.7	0.3
Hemorrhage	4.8	5.6	0.7
Any complication[a]	88	94.9	0.006

[a] Cumulative risk over 15 years of follow-up.

Table 3 Daytime and Nighttime Frequency of Bowel Movements in the Two Groups

Variable		BMI <30	BMI ≥30	*p* value
1 year	Day	5.7±2.2	6.6±5.2	0.06
	Night	1.8±1.6	2.3±2.8	0.03
5 years	Day	5.6±3.7	5.9±2.6	0.08
	Night	1.7±1.7	1.8±1.4	0.12
10 years	Day	5.3±2.3	5.8±2.7	0.15
	Night	1.7±1.3	1.9±1.6	0.2
15 years	Day	5.7±4.4	5.5±4.5	0.35
	Night	4.8±5.2	1.9±1.1	0.19

Data are presented as the mean±SD. $p<0.0125$ (Bonferroni-corrected significance level).

tion whereas group A patients had a higher rate of development of obstruction over time.

Functional outcome Results relating to function of the pouch were assessed at 1, 5, 10, and 15 years of follow-up by the mean number of bowel movements during the day and night (Table 3), incontinence, pad usage during the day and at night (Table 4), and urgency.

The mean number of bowel movements both during the day and at night was similar between groups at 1, 5, 10, and 15 years of follow-up. The proportion of patients using pads during the day and night and with urgency at 1, 5, 10, and 15 years of follow-up was also similar between groups. Overall, continence for the two groups over the duration of follow-up was hence similar.

QOL All the components of CGQL and the overall CGQL score 1 year after surgery improved considerably from the baseline and remained high after 5, 10, and 15 years of follow-up for group B. A significant number of patients (97%) continued to remain satisfied with their operation after 15 years of follow-up and stated that having undergone the procedure, they would be willing to undergo IPAA again if they were given the option. A significant proportion (97.9%) also continued to state their willingness to recommend the procedure to other patients in a situation similar to theirs (Table 5).

The two groups continued to maintain a high QOL as determined by CGQL during the duration of follow-up. Group B patients had significantly lower CEL than group A patients at 5 and 10 years after surgery. However, there was no significant difference in the other components of CGQL and overall CGQL score. All the components of CGQL and the overall CGQL score were similar between groups at 1 and 15 years after surgery.

Table 4 Daytime and Nighttime Pad Usage in the Different Groups

Variable		BMI <30, *n* (%)	BMI ≥30, *n* (%)	*p* value
1 year	Day	109 (21.6)	20 (20.6)	0.68
	Night	140 (28)	25 (26)	0.16
5 years	Day	148 (17.7)	31 (20.4)	0.43
	Night	185 (22.3)	38 (25)	0.46
10 years	Day	119 (19)	19 (21.1)	0.64
	Night	143 (23.1)	26 (28.6)	0.25
15 years	Day	62 (21.1)	11 (25.6)	0.5
	Night	75 (25.7)	10 (23.8)	0.79

Data are presented as the mean±SD. $p<0.0125$ (Bonferroni-corrected significance level).

Discussion

Although the ileoanal pouch is an established technique for the treatment of ulcerative colitis and familial adenomatous polyposis and has been shown to be useful in patients with indeterminate colitis and carefully selected CD patients, there is little data in the literature looking at the role of the procedure in obese patients.[13] Obesity has previously been reported to lead to increased operating room time and resource utilization in general surgical operations.[14] There are also data supporting adverse outcomes after surgery in obese patients undergoing gynecologic and orthopedic operations.[15,16] Poor long-term function has also been

Table 5 QOL in Groups A and B

Variable		BMI <30	BMI ≥30	*p* value
Baseline	QOL	6.8±2.1	6.9±2.5	0.8
	QOH	7±2.2	7.3±−2.1	0.8
	CEL	6.6±2.4	6±2.1	0.5
	CGQL	0.7±0.2	0.7±0.2	0.8
1 year	QOL	8.4±1.6	8.2±1.8	0.4
	QOH	8.4±1.6	8.1±1.8	0.2
	CEL	7.7±1.9	7.4±2	0.1
	CGQL	0.8±0.2	0.8±0.2	0.2
5 years	QOL	8.6±1.5	8.4±1.8	0.3
	QOH	8.4±1.7	8.1±1.9	0.09
	CEL	7.8±2	7.3±2	0.002*
	CGQL	0.8±0.2	0.8±0.2	0.02
10 years	QOL	8.6±1.6	8.4±2	0.3
	QOH	8.4±1.7	8.1±2	0.2
	CEL	7.8±1.9	7.2±2.3	0.008*
	CGQL	0.8±0.2	0.8±0.2	0.03
15 years	QOL	8.6±1.6	8.6±1.2	0.6
	QOH	8.3±1.8	8±1.4	0.06
	CEL	7.7±1.9	7.4±2.1	0.3
	CGQL	0.8±0.2	0.8±0.1	0.2

Data are presented as the mean±SD.
QOL: quality of life, *QOH*: quality of health, *CEL*: current energy level, *CGQL*: Cleveland Global Quality of Life
*$p<0.0125$ (Bonferroni-corrected significance level)

described after surgery for some other general surgical conditions.[17] A previous study that examined the impact of obesity on surgical outcomes after colectomy reported that the risk of complications may be worsened in patients undergoing left colectomy and proctectomy.[18] For patients undergoing IPAA, associated additional significant intraoperative technical challenges may be expected. In addition to difficulty with intraabdominal, pelvic, and perineal exposure, the bulky mesentery in obese patients may serve as a deterrent for the reach of the pouch to the pelvic floor. The creation of an ileostomy in obese patients is also often attendant with operative difficulties because of the presence of a foreshortened, bulky mesentery and a thick abdominal wall.

BMI is a measure of an individual's weight in relation to height and is calculated as weight in kilograms divided by the square of height in meters. The World Health Organization has adopted the weight classifications developed by the National Institutes of Health (NIH) that recommend the use of BMI >30 as a definition of obesity. We chose to evaluate outcomes in patients with obesity and hence selected patients with BMI ≥30.

There is a dearth of information on the risk of pouch surgery, long-term complications, functional outcomes, and QOL in this select group of high-risk patients. A previous study compared outcomes after IPAA in 31 obese patients (BMI ≥30) with those for the same number of nonobese patients matched for age, gender, steroid use, and diagnosis.[13] This study reported higher perioperative morbidity in obese patients but the long-term functional outcome after restorative proctocolectomy was similar to that of the nonobese patients. The study, however, included a small number of patients matched to a control group of nonobese patients with a mean follow-up of 50.7 months. In contrast, our study evaluates outcomes in a large group of obese patients, the largest reported in the literature thus far, and compares them to all the nonobese patients included in the pouch database.

Despite the expected difficulties with the formation of a stoma in obese patients, most patients in our series underwent a defunctioning stoma. The patients were found to have an acceptable risk of complications, and this risk was comparable to that expected for IPAA based on current reports.[19–21] The pouch failure rate over 15 years of follow-up was 4.5%. Thus, the long-term results of IPAA in the obese group are very encouraging and suggest that obesity should not be a deterrent to patients being offered the procedure.

Studies have shown that QOL after IPAA is rated as excellent by patients with minimal deterioration in pouch function with time.[11] Although there was some deterioration in function with time, the function of the pouch in the obese patients remained acceptable as manifested in the high QOL. The mean number of daytime and nighttime bowel movements, urgency, daytime and nighttime pad usage, and incontinence remained acceptable over the duration of follow-up. The functional outcome was similar to that of reports in the literature based on studies examining outcomes for patients (obese and nonobese patients not separately examined) undergoing IPAA.[22,23] In our study, patients with BMI ≥30 had an appreciable increase in QOL from the baseline as measured by an elevation in CGQL. All the components of CGQL including QOL, QOH, and CEL, and the overall CGQL score were found to increase from the baseline value 1 year after surgery, continued to rise after 5 years, and continued to be sustained even after 15 years after surgery. Most patients said they would have the procedure again and would recommend the procedure to others. The percentage of patients with this response continued to increase with increasing duration of follow-up.

We compared patients with BMI ≥30 with those <30 BMI to determine any differences in the preoperative and perioperative factors between the two groups of patients and evaluated whether the former group would have adverse outcomes when compared with the nonobese patients. Group B patients were significantly older than group A patients but both groups had comparable age, gender, diagnosis, and indication for surgery. However, group B patients had a significantly higher proportion of patients with associated comorbidity and on steroids and immunosuppressive medication, thus suggesting that these patients were sicker than group A patients.

Despite similar indications for surgery and diagnosis in the two groups, a greater proportion of group B patients underwent a stapled anastomosis. This may be related to the fact that a handsewn anastomosis is technically more demanding in obese patients. As our preference is for a stapled anastomosis at this institution and as both groups had comparable diagnoses and indication for surgery, a handsewn anastomosis would be indicated when a stapled anastomosis failed because of technical reasons. Thus, it can be surmised that the incidence of intraoperative technical problems may have been lower in the obese group of patients when compared with the others despite the increased challenges. A previous study reported that a higher proportion of obese patients underwent mucosectomy,[13] although this difference did not reach statistical significance between groups in this study.

The incidence of complications such as pouchitis, sepsis, hemorrhage, and anastomotic stricture was similar in group A and group B patients. Although group B patients had a higher incidence of immediate complications such as wound infection and anastomotic separation when compared with group A patients, the incidence of pouch failure over a long duration of follow-up was similar in the two

groups. In contrast, group B patients had a significantly lower incidence of obstruction than group A patients. The increased risk of wound infection in obese patients has previously been described in general surgical operations.[8–10] A previous study on IPAA also noted a higher incidence of complications in obese patients.[13]

Patients in the obese group had similar function as evaluated by the frequency of daytime and nighttime bowel movements, pad usage, urgency, and incontinence at 1, 5, 10, and 15 years of follow-up.

Previous studies have demonstrated that IPAA patients have a good QOL after surgery.[24–26] We found that QOL as determined by QOL, QOH, CEL, and CGQL remained high in both groups after surgery. A significantly lower CEL was noted at 5 and 10 years after surgery in group B patients when compared with group A. However, the other components of CGQL and the overall CGQL score were comparable over the duration of follow-up and at the different time frames of comparison.

By asking patients about their decision to have undergone IPAA and of their willingness to recommend the procedure to other patients in their situation at each follow-up, we gave them an opportunity to reevaluate their decision to undergo surgery. The response of patients at this time would be expected to take into account their QOL, functional results, complications, and freedom from illness. A high proportion of patients (97.9%) continued to state that they would undergo the procedure again and would recommend the procedure to other patients even after 15 years of follow-up.

Restorative proctocolectomy in obese patients is associated with a significantly higher incidence of wound infection and anastomotic separation. The proportion of patients retaining a functional pouch is, however, high and is comparable to that of nonobese patients. Long-term functional outcome and QOL is acceptable and patients are happy with their decision to undergo the procedure. IPAA may hence be offered to patients with a BMI ≥30 after assessing the risks associated with the procedure. As they are more likely to suffer potentially serious complications than patients with BMI <30, when possible, postponing surgery until weight loss is achieved merits due consideration.

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Umbilical Herniorrhapy in Cirrhosis: Improved Outcomes with Elective Repair

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Abstract
Objective This study was undertaken to examine the effect of cirrhosis on elective and emergent umbilical herniorrhapy outcomes.
Methods Procedures were identified from the Veterans' Affairs National Surgical Quality Improvement Program at 16 hospitals. Medical records and operative reports were physician abstracted to obtain preoperative and intraoperative variables.
Results Of the 1,421 cases reviewed, 127 (8.9%) had cirrhosis. Cirrhotics were more likely to undergo emergent repair (26.0% vs. 4.8%, $p<0.0001$), concomitant bowel resection (8.7% vs. 0.8%, $p<0.0001$), return to operating room (7.9% vs. 2.5%, $p=0.0006$), and increased postoperative length of stay (4.0 vs. 2.0 days, $p=0.01$). Best-fit regression models found cirrhosis was not a significant predictor of postoperative complications. Significant predictors of complications were emergent case (OR 5.4; 95% CI 3.1–9.4), diabetes (OR 2.1; 95% CI 1.2–3.8), congestive heart failure (OR 4.0; 95% CI 1.4–11.4), and chronic obstructive pulmonary disease (OR 2.0; 95% CI 1.1–3.6). Among emergent repairs, cirrhosis (OR 4.4; 95% CI 1.3–14.3) was strongly associated with postoperative complications.
Conclusion Elective repair in cirrhotics is associated with similar outcomes as in patients without cirrhosis. Emergent repair in cirrhotics is associated with worse outcomes. Early elective repair may improve the overall outcomes for patients with cirrhosis.

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Introduction

The prevalence of umbilical hernias in cirrhotic patients with ascites is as high as 20%, with recurrence rates after repair in those patients as high as 60%.[1,2] Obesity, chronic cough, smoking, and ascites are contributing factors to the development of umbilical hernias in adults.[3] The increased intra-abdominal pressure associated with ascites is thought to predispose cirrhotic patients to the development of umbilical hernias.

Cirrhotic patients are considered to be high surgical risk, with increased perioperative morbidity and mortality.[4,5] Among good risk patients, umbilical herniorrhaphy is a relatively straightforward operation with low morbidity and

mortality. Complications of umbilical hernias in cirrhotic patients include leakage, ulceration, rupture, and incarceration.[2] Repair of umbilical hernias in the cirrhotic patients has been associated with elevated morbidity, mortality, and recurrence rates.[6] Surgery in cirrhotic patients is considered by many surgeons to be high risk, and there is a tendency to reserve umbilical hernia repair (UHR) until bowel-related complications develop, such as incarceration, strangulation, rupture, ulceration, and leakage of ascitic fluid.[7] The development of incarceration, strangulation, ulceration, and rupture further elevate the risk of surgical repair. Additionally, surgical repair of incarcerated hernias in cirrhotic patients is associated with an elevated morbidity and mortality rate.[2,7,8]

Prior studies have documented increased morbidity and mortality among cirrhotic patients undergoing emergent surgical procedures.[9,10] The aim of this study is to describe the effect of cirrhosis on short-term UHR outcomes. We examine the effect of preoperative comorbidities obtained from the Veterans' Affairs National Surgical Quality Improvement Program (VA NSQIP) data and surgery specific variables obtained from operative note abstraction. We specifically focus on the effect of emergent or elective case status on UHR outcomes, especially postoperative complications and hospital resource allocation.

Materials and Methods

Study Design

This is a retrospective cohort analysis of subjects undergoing UHR at 16 VA Medical Centers (VAMC) affiliated with surgical residency programs across the USA between 1998 and 2002. Institutional review board approval and waiver of informed consent was obtained at all participating VAMCs. Eligible procedures were identified by querying the VA NSQIP database by Current Procedure Terminology (CPT) codes for ventral hernia repair (49560, 49561, 49565, 49566, 49568, 49570, 49572, 49580, 49585, 49587, 49590, and 49659). Individual operative notes obtained from each site were physician abstracted to identify the type of hernia repair, method of repair, intraoperative enterotomy or bowel resection, and other operative variables. Outcome variables were obtained from the VA NSQIP, the VA National Patient Care Database, and the computerized patient record system (CPRS).

Study Databases

The VA NSQIP prospectively collects data from all 123 VA facilities that perform surgery and includes preoperative, intraoperative, and postoperative outcome variables. The VA NSQIP accrues the CPT code and date of procedure on all non-cardiac cases performed in the VA system. Additional risk variables are collected on a subset of patients based on a sampling algorithm that minimizes bias from high-volume centers and roughly includes 70% of all major operations performed.[11,12] Thirty-day morbidity and mortality data, operative time, and length of stay were obtained from the VA NSQIP database.

The VA National Patient Care Database is comprised of the Patient Treatment File (PTF) and the Outpatient Care Files (OPC).[13] The PTF is a national VA database that includes all admissions to VA hospitals along with up to ten ICD-9 diagnostic and procedure codes. The OPC is a national VA database that contains information on all ambulatory contacts with VA staff.

The CPRS is the comprehensive electronic medical record available through web access. Chart abstraction for patients with cirrhosis identified from the PTF and the OPC was performed to confirm the diagnosis of cirrhosis.

Study Population

Based on VA NSQIP query, we identified all patients at the 16 VA hospitals with CPT codes listed above. Patients were excluded if the repair was not an umbilical hernia repair (i.e., incisional hernia repair or ventral hernia repair), if there was a same site concomitant procedure (i.e., cholecystectomy or planned colectomy), if their operative note was not available for abstraction, or if the case had one or more missing NSQIP preoperative risk variables.

Study Variables

The main variable of interest, cirrhosis, is not included in the VA NSQIP dataset. Cirrhosis was defined by the presence of an associated ICD-9 code in the medical record. The PTF and OPC were queried with ICD-9 codes for chronic liver disease and cirrhosis (571), alcoholic cirrhosis of liver (572.2), cirrhosis of liver without mention of alcohol (571.5), and biliary cirrhosis (571.6). The presence of ascites is a VA NSQIP variable defined as the presence of fluid accumulation within the peritoneal cavity noted on physical examination or abdominal imaging within 30 days before the operation.

Additional variables of interest were patient-level demographics (age and gender), preoperative comorbid conditions, technique of repair, history of prior repair, and intraoperative variables. The presence of any full-thickness bowel-wall injury recorded in the operative note was considered an enterotomy. The occurrence of a bowel resection documented in the operative record that was not planned before operation was included in this analysis. The presence of bowel strangulation or obstruction recorded in the operative note was considered an indication of

compromised bowel. Preoperative risk factors were defined using the VA NSQIP definitions. A dichotomous variable was constructed for technique of repair to classify repairs as either suture or mesh.

The effect of cirrhosis on UHR outcomes was examined. Dichotomous outcomes of interest were the occurrence of one or more postoperative complications or return to operating room within 30 days of the original operation. Continuous

Table 1 Study Demographics, Patient Comorbidities, and Procedure Variables by Presence of Cirrhosis

Variable		Number of Patients	Percent	+ Cirrhosis		− Cirrhosis		Odds Ratio	95% CI	*p* Value
				N	Percent	*N*	Percent			
Overall		1,421		127	8.9	1,294	91.1			
Sex[a]										
Male		1,370	97.7	121	98.4	1,249	97.7	1.5	0.3–6.2	0.6
Female		32	2.3	2	1.6	30	2.4			
Race[b]										
White		976	68.9	98	77.2	878	68.1			0.1
Black		140	9.9	9	7.1	131	10.2			
Other		301	21.2	20	15.8	281	21.8			
Age										
<55		750	52.8	57	55.1	693	46.5	0.7	0.5–1.0	0.06
≥55		671	47.2	70	44.9	601	53.6			
Preoperative risk factors										
Smoke	Y	459	32.3	60	47.2	399	30.8	2.0	1.4–2.9	0.002
	N	962	67.7	67	52.8	895	69.2			
Alcohol abuse	Y	150	10.6	24	18.9	126	9.7	2.2	1.3–4.5	0.001
	N	1,271	89.4	103	81.1	1,158	90.3			
Chronic steroid use	Y	35	2.5	5	3.9	30	2.3	1.7	0.7–4.5	0.3
	N	1,386	97.5	122	96.1	1,264	97.7			
CHF[c]	Y	20	1.4	3	2.4	17	1.3	1.8	0.5–6.3	0.3
	N	1,401	98.6	124	97.6	1277	98.7			
Diabetes	Y	152	10.7	16	12.6	136	10.5	1.2	0.7–2.1	0.5
	N	1,269	89.3	111	87.4	1,158	89.5			
COPD[d]	Y	150	10.6	13	10.2	137	10.6	1.0	0.5–1.8	0.9
	N	1,271	89.4	114	89.8	1,157	89.4			
ASA Class [e]										
1–2		750	52.8	16	12.6	734	56.7	9.1	5.3–15.5	<0.0001
≥3		671	47.2	111	87.4	560	43.3			
Case status[f]										
Elective		1,325	93.3	94	74.0	1231	95.2	7.0	4.3–11.2	<0.0001
Emergent/urgent		95	6.7	33	26.0	62	4.8			
Bowel status[g]										
Compromised bowel	Y	31	2.2	13	10.3	18	1.4	8.1	3.9–17.0	<0.0001
	N	1,385	97.8	113	89.7	1,272	98.6			
Repair history[h]										
Primary		1,302	92.5	112	88.2	1,190	93.0	1.8	1.0–3.2	0.05
Recurrent		105	7.5	15	11.8	90	7.0			
Anesthetic										
General		1,221	85.9	116	91.3	1,105	85.4	1.8	1.0–3.4	0.07
Other		200	14.1	11	8.7	189	14.6			

[a] Sex missing for 19 procedures
[b] Race missing for four procedures
[c] Congestive heart failure
[d] Chronic obstructive pulmonary disease
[e] American Society of Anesthesiologists' Class
[f] Case status missing for one procedures
[g] Bowel status missing for five procedures
[h] Repair history missing for 14 procedures

outcomes of interest were operative time and postoperative length of hospitalization.

Statistical Analysis

Univariate analysis of demographics and operative variables were performed to describe the study population. Chi-square tests were performed to examine differences in proportions between cases based on the diagnosis of cirrhosis and the occurrence of one or more postoperative complications. Multivariable logistic regression models were used to examine the effect of cirrhosis on postoperative complications by case status. Those variables with $p<0.1$ in testing of univariate association with complications were used as main effects in logistic regression analysis. Stepwise backward elimination was employed to achieve a best-fit logistic regression model. All statistical tests were performed using Statistical Analysis Software (SAS version 9.1; SAS Institute Inc., Cary, NC).

Results

Of the 1,421 procedures available for analysis, 1,370 (97.7%) were on men, and the median age was 55 years old. Overall,

Table 2 Patient Comorbidities and Procedure Variables by Occurrence of One or More Postoperative Complications

Variable		Number of Patients	Percent	+ Complication		− Complication		Odds Ratio	95% CI	*p* Value
				N	Percent	*n*	Percent			
Overall		1,421		86	6.1	1,335	94.0			
Preoperative risk factors										
Cirrhosis	Y	127	8.9	12	9.5	115	90.6	1.7	0.9–3.3	0.09
	N	1294	91.1	74	5.7	1,120	94.3			
Smoke	Y	459	32.3	35	7.6	424	92.4	1.5	0.9–2.3	0.09
	N	962	67.7	51	5.3	911	94.7			
Alcohol abuse	Y	150	10.6	11	7.3	139	92.7	1.3	0.6–2.4	0.5
	N	1,271	89.4	75	5.9	1,196	94.1			
Chronic steroid use	Y	35	2.5	4	11.4	31	88.6	2.1	0.7–6.0	0.2
	N	1,386	97.5	82	5.9	1,304	94.1			
CHF[a]	Y	20	1.4	7	35.0	13	65.0	9.0	3.5–23.2	<0.0001
	N	1,401	98.6	79	5.6	1,322	94.4			
Diabetes	Y	152	10.7	19	12.5	133	87.5	2.6	1.5–4.4	0.0004
	N	1,269	89.3	67	5.3	1,202	94.7			
COPD[b]	Y	150	10.6	19	12.7	131	87.3	2.6	1.5–4.5	0.0003
	N	1,271	89.4	67	5.3	1,204	94.7			
Ascites	Y	72	6.1	12	16.7	60	83.3	3.4	1.8–6.7	0.0001
	N	1,349	94.0	74	5.5	1,275	94.5			
ASA class[c]										
1–2		750	52.8	23	3.1	727	96.9	3.3	2.0–5.4	<0.0001
≥3		671	47.2	63	9.4	608	90.6			
Case status[d]										
Elective		1,325	93.3	63	4.8	1,262	95.3	6.4	3.8–10.9	<0.0001
Emergent/urgent		95	6.7	23	24.2	72	75.8			
Bowel status[e]										
Compromised	Y	31	2.2	10	32.3	21	67.7	8.2	3.7–18.0	<0.0001
	N	1,385	97.8	76	5.4	1,309	94.5			
Repair history[f]										
Primary		1,302	92.5	76	5.5	1,226	94.2	1.7	0.9–3.4	0.1
Recurrent		105	7.5	10	9.5	95	90.5			
Anesthetic										
General		1,221	85.9	77	6.3	1,144	93.7	1.4	0.7–2.9	0.3
Other		200	14.1	9	4.5	191	95.5			

[a] Congestive heart failure
[b] Chronic obstructive pulmonary disease
[c] American Society of Anesthesiologists' Class
[d] Case status missing for one procedures
[e] Bowel status missing for five procedures
[f] Repair history missing for 14 procedures

Table 3 Continuous Outcomes Overall and Stratified by Case Status

	Operative Time			Postoperative Length of Stay		
	Median	IQR	*p* Value	Median	IQR	*p* Value
Overall						
Cirrhotic	1.2	1.1	0.02	4.0	5.0	0.01
Non-cirrhotic	1.0	0.9		2.0	5.0	
Elective	1.0	0.9	0.1	4.0	8.0	0.0007
Emergent	1.1	0.9		2.0	4.0	
Elective						
Cirrhotic	1.1	1.0	0.07	3.0	4.0	0.2
Non-cirrhotic	1.0	0.9		2.0	4.0	
Emergent						
Cirrhotic	1.2	0.9	0.2	5.0	9.0	0.04
Non-cirrhotic	1.1	0.8		3.0	6.0	

there was documentation of cirrhosis in 127 (8.9%) UHR procedures. History of ascites was documented within 30 days before operation in 53.5% (n=68) of patients with cirrhosis. The study population is comprised of 1,302 (92.5%) primary and 105 (7.5%) recurrent umbilical hernia repairs. Elective procedures accounted for 93.3% of the study population. There were no differences in patient gender, race, age, chronic steroid use, congestive heart failure (CHF), diabetes, or chronic obstructive pulmonary disease (COPD) based on the presence of cirrhosis (Table 1). There was a higher prevalence of smoking and alcohol abuse among cirrhotic patients. A higher proportion of cirrhotic patients underwent emergent repair (26.0% vs. 4.8% p<0.0001) and repair of a recurrent hernia (11.8% vs. 7.0% p=0.05) compared to patients without cirrhosis. A higher proportion of cirrhotic patients had indications of compromised bowel at the time of UHR (10.3% vs. 1.4% p<0.0001). Recent history of ascites was documented in 22.1% (n=28) of cirrhotics who underwent emergent repair.

Postoperative complications occurred in 6.1% (n=86) of patients undergoing UHR (Table 2). There were six deaths documented within 30-days of the operation, one of those patients had cirrhosis. Overall, patients with cirrhosis, alcohol abuse, tobacco, or chronic steroid use were no more likely to develop postoperative complications within 30 days. There was an increased incidence of complication among patients with ascites, CHF, diabetes, and COPD. Complications were more likely after emergent repair (24.2% vs. 4.8%, p<0.0001) and repair with indications of compromised bowel (32.3% vs 5.4%, p<0.0001). There was a significant association between cirrhosis and the occurrence of bowel resection (8.7% vs. 0.8%, p<0.0001), as well as emergent case status and occurrence of bowel resection (19.0% vs. 0.2%, p<0.0001). Additionally, patients with cirrhosis were more likely to return to the operating room within 30 days of UHR (7.9% vs. 2.5%, p= 0.0006). Patients who underwent emergent repair, compared to elective repair, were no more likely to return to the operating room within 30 days of UHR.

There was a significant difference in operative time and postoperative length of stay in patients with cirrhosis versus those without cirrhosis (Table 3). Additionally, postoperative length stay was greater in emergent compared to elective UHR. However, comparing only elective UHR in patients with and without cirrhosis, there was no difference in operative time or postoperative length of stay. Whereas patients with cirrhosis undergoing emergent UHR had a longer length of stay compared to non-cirrhotics undergoing emergent repair.

Best-fit logistic regression models of predictors of postoperative complications demonstrated that cirrhosis was not a significant predictor of complications in the overall study group or among elective UHR patients. However, cirrhosis was a predictor of a greater than threefold increase in complications among emergent UHR patients (Table 4). The overall model incorporates age, case status, indications of bowel compromise, smoking status, diabetes, COPD, CHF, cirrhosis, and hernia repair history. The elective and emergent models incorporates age, indications of bowel compromise, smoking status, diabetes, COPD, CHF, cirrhosis, and hernia repair history.

Table 4 Best-Fit Regression Models of Morbidity After Umbilical Hernia Repair by Case Status

Variable	Odds Ratio	95% CI
Overall model		
Emergent/urgent case	5.4	3.1–9.4
History of CHF[a]	4.0	1.4–11.4
Diabetes	2.1	1.2–3.8
History of COPD[b]	2.0	1.1–3.6
Elective model		
Diabetes	2.2	1.2–4.2
History of COPD	2.1	1.1–4.0
Emergent model		
History of CHF	11.8	1.7–81.7
Cirrhosis	4.4	1.3–14.3
History of COPD	3.7	1.0–14.2
Diabetes	3.7	0.9–15.1

[a] Congestive heart failure
[b] Chronic obstructive pulmonary disease

Discussion

In this multi-site study, we found that elective UHR in cirrhotics is safe and associated with similar outcomes as in patients without cirrhosis. We found that patients with cirrhosis were more likely to undergo emergent UHR. Patients with cirrhosis had poor outcomes after emergent UHR, and cirrhosis is a significant predictor of postoperative complications after emergent UHR.

Our data demonstrates that cirrhosis is not a significant predictor of postoperative complications for the overall study population or patients undergoing elective UHR. Prior studies have documented increased morbidity and mortality among cirrhotic patients undergoing emergent surgery.[5,9,10] A previous study demonstrated an increased incidence of emergent hernia repair among cirrhotic patients, as well as increased complications, hospital resource utilization, and mortality.[8] Our data demonstrates that cirrhosis is a significant predictor of postoperative complications after emergent UHR only. Other studies have demonstrated that cirrhotic patients tolerate elective hernia repair, especially if ascites is controlled preoperatively.[14,15] Our study supports elective repair of umbilical hernias among cirrhotic patients.

We found a significant association between cirrhosis and bowel resection, likely due to the incidence of strangulation, incarceration, and obstruction leading to the emergent UHR. We have previously shown that the occurrence of an enterotomy or bowel resection in elective incisional hernia repair is associated with increased postoperative complications, rate of return to the operating room, operative time, and postoperative length of stay.[16]

Our models of postoperative complications illustrate the role of diabetes and COPD on the development of complications regardless of case status. Previous studies have found that hyperglycemia is an independent predictor of short-term infectious complications.[17,18] Among critically ill patients, intensive insulin therapy (glucose level less than 110 mg/dl) is associated with decreased incidence of blood stream infections, acute renal failure, blood transfusion, ventilator support, intensive care utilization, and reduced overall in-hospital mortality.[19] Other studies have shown COPD to be an independent risk factor for the development of surgical site infections.[20,21] Our data reinforces the importance of optimizing medical comorbidities before UHR.

Our study has several limitations. The incidence of cirrhosis was ascertained from administrative data and likely underestimates the true incidence. Similarly, the mortality data was ascertained from administrative data and may underestimate the mortality rate. Unfortunately, a number of cirrhotic patients are missing preoperative lab values, which limits our ability to classify the degree of hepatic impairment among the cirrhotic patients. Finally, the incidence of postoperative complications in elective umbilical hernia repair is low, and we may lack power to detect a difference in complications between patients with and without cirrhosis in the elective subgroup.

Conclusion

We found that elective UHR in cirrhotics is safe and associated with similar outcomes as in patients without cirrhosis. However, emergent repair of UHR in patients with cirrhosis is associated with worse outcomes. Early elective repair of umbilical hernias may improve the overall outcomes for patients with cirrhosis.

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^{32}P as an Adjunct to Standard Therapy for Locally Advanced Unresectable Pancreatic Cancer: A Randomized Trial

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Abstract This prospective randomized trial was undertaken to determine the added efficacy of ^{32}P in treating locally advanced unresectable pancreatic cancer. Thirty patients with biopsy proven locally advanced unresectable adenocarcinoma of the pancreas were assessable after receiving 5-fluorouracil and radiation therapy with or without ^{32}P, followed by gemcitabine. Intratumoral ^{32}P dose was determined by tumor size and volume and was administered at months 0, 1, 2, 6, 7, and 8. Tumor cross-sectional area and liquefaction were determined at intervals by computed tomography scan. Tumor liquefaction occurred in 78% of patients receiving ^{32}P and in 8% of patients not receiving ^{32}P, although tumor cross-sectional area did not decrease. Serious adverse events occurred more often per patient for patients receiving ^{32}P (4.2±3.1 vs. 1.8±1.9; p=0.03) leading to more hospitalizations. Death was because of disease progression (23 patients), gastrointenstinal hemorrhage (4 patients), and stroke (1 patient). One patient not receiving ^{32}P and one receiving ^{32}P are alive at 28 and 13 months, respectively. ^{32}P did not prolong survival (7.4±5.5 months with ^{32}P vs. 11.5±8.0 months without ^{32}P, p=0.16). ^{32}P promoted tumor liquefaction, but did not decrease tumor size. Intratumoral ^{32}P was associated with more serious adverse events and did not improve survival for locally advanced unresectable pancreatic cancer.

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Introduction

Pancreatic cancer is diagnosed in more than 33,000 people per year in the USA, with nearly all dying of the disease.[1] Median survival in patients with unresectable pancreatic cancer is 5 to 6 months, with a 5-year survival of less than 1%.[3] The lethality of pancreatic cancer is a result of patients presenting late in the course of the disease and the biologically aggressive nature of the cancer. Patients present late because most symptoms and signs of pancreatic cancer are nonspecific. Ultimately, at the time of the diagnosis, excessive local invasion and/or distant metastases have occurred in more than 95% of patients, making their cancers unresectable.[2]

Marginal improvements in survival have occurred with development of a variety of chemotherapeutic regimens.[4] Survival of patients with locally advanced pancreatic cancer

is still very limited with median survival in the range of 7 to 12 months.[6] Although no standard treatment for locally advanced unresectable pancreatic cancer is established, therapy for this stage of pancreatic cancer often involves 5-fluorouracil (5-FU) and radiation therapy, followed by chemotherapy, generally gemcitabine. With combination chemoradiation, tumor response is seen in a small number of patients, and median survival remains disappointing.[4,5]

Conventional chemotherapy seems hopelessly inefficacious in treating pancreatic cancer. The dose and, thereby, efficacy of external beam radiation therapy is limited by the vulnerability of surrounding organs and structures to radiation. In attempts to improve survival with locally advanced pancreatic cancer with high-dose radiation while limiting radiation to surrounding organs and structures, trials of brachytherapy utilizing radionucleotides of iodine, gold, and iridium have been undertaken.[7–10] Brachytherapy with these agents has been abandoned because of toxicity without notable benefit. Conversely, Order et al. and others have demonstrated in Phase I trials that ^{32}P when combined with macroaggregated albumin could be used safely and efficaciously in patients with locally advanced unresectable pancreatic cancer, achieving doses as high as 1,700,000 cGy.[11–17] In uncontrolled trials, Order documented relatively extended survival (e.g., more than 12 months) for patients with locally advanced unresectable pancreatic cancer undergoing intratumoral ^{32}P injections with or without concomitant chemoradiation. The promise of extending survival for patients with safe efficacious brachytherapy utilizing ^{32}P lacks support from a controlled prospective trial.

This study was undertaken to determine the beneficial impact intratumoral ^{32}P contributes to a standard chemoradiation regimen for locally advanced unresectable pancreatic cancer. We hypothesized that adding intratumoral ^{32}P injections to standard chemoradiation therapy would improve survival without adding significant morbidity.

Methods

After receiving an Institutional Review Board approval, 80 patients with locally advanced unresectable pancreatic cancer were to be entered into a trial to determine the impact of ^{32}P on a standard regimen of radiation and chemotherapy. All patients were to receive external beam radiation therapy and concomitant 5-FU, followed by gemcitabine. Utilizing a computerized randomization program, patients would be randomized so that half of the patients would additionally receive intratumoral injections of colloidal chromic ^{32}P. Interim analysis was to be undertaken after the 40th patient was enrolled to evaluate the added efficacy and morbidity of ^{32}P, if any.

Adenocarcinoma of the pancreas was confirmed in all patients by cytology or histology. All patients had locally advanced cancers that were unresectable because of contiguous invasion into major adjacent blood vessels (i.e., the portal or superior mesenteric veins or the superior mesenteric artery) by intravenous contrast-enhanced computed tomography (CT) or operative exploration. No patients had detectable distant metastases or detectable cancer beyond the field of a conventional resection for pancreatic cancer. All patients had a Karnofsky performance status $\geq$ 60%[18] and had adequate bone marrow,[3] renal and hepatic function. Patients could not have received prior therapy for pancreatic cancer or prior therapy with ^{32}P. In addition, patients with prior malignancies except for curatively resected basal cell carcinoma, cervical cancer, breast cancer in situ, or early stage prostate cancer must have been disease free for at least 5 years before randomization.

Patients with obstructive jaundice underwent biliary decompression with stent placement and normalization of serum bilirubin before randomization. Pain management was a priority during the trial, and percutaneous celiac plexus blocks were liberally applied to limit pain.

Before beginning therapy in the trial, patients underwent bidimensional measurement and estimation of tumor volumes of their pancreatic tumors utilizing CT scanning. In addition, potential sites of tumor metastases were evaluated by CT and positron-emission tomography (PET) scans (Table 1). After initiation of therapy, subsequent tumor measurements were undertaken using CT scans. All scans were reviewed by the principal investigator.

Concomitant with external beam radiation therapy, 5-FU was administered intravenously at 350 mg/m^2 via continuous infusion 5 days per week for 6.5 weeks. External beam radiation was administered utilizing immobilization devices to ensure accurate repositioning for daily treatments. Treatment volumes consisted of the image-guided tumor volume plus the immediate peri-pancreatic nodal drainage volume plus a 1.5-cm margin to allow for setup variation and patient movement. Treatment was delivered utilizing high-energy linear accelerators with the use of multiple photon energies between 6 and 18 MV to allow for homogenous treatment distributions. Daily treatment consisted of 1.8 Gy fractions 5 days per week for a total of 9.0 Gy per week. The total dose to the initial treatment volume including the nodal basin was 45 Gy. A cone-downed field to encompass the pancreatic tumor volume only was administered to an additional 14.4 Gy. The total treatment dose to the pancreatic volume was, therefore, 59.4 Gy and was administered in divided doses 5 days per week for 6.5 weeks.

After chemoradiation, gemcitabine was administered intravenously at 1,000 mg/m^2 once per week for 7 weeks

Table 1 Description of Patients with Locally Advanced Unresectable Pancreatic Cancer Treated with Standard Chemoradiation Followed by Gemcitabine, With or Without ^{32}P

Where appropriate, data are presented as median (mean ± SD)

	With ^{32}P	Without ^{32}P
Number of patients	18	12
Percent male	56%	58%
Age (years)	70 (68±11.8)	60 (61±10.1)
KPS	90% (87%±9.5)	80% (78%±5.0)
Pancreas tumor location	89% head	67% head
Patients who underwent celiotomy	44%	50%
Patients who underwent PET scans	94%	100%

with a 1-week rest during the eighth week. All subsequent cycles were of 4 weeks: three weekly administrations of gemcitabine with a 1-week rest. Gemcitabine was continued until prohibited by drug toxicity, disease progression, or death. Body surface area was calculated at baseline using weight and height; this was recalculated before dosing if the patient experienced a significant (>10%) change in weight.

Half of the patients were randomized to receive intratumoral injections of colloidal chromic ^{32}P while receiving chemoradiation. Chromic [^{32}P] phosphate suspension (Mallinckrodt Inc., St. Louis, MO, USA) was available in a concentration of up to 370 MBq (10 mCi) per milliliter. ^{32}P was injected intratumorally utilizing CT guidance on the first day of months 0, 1, 2, 6, 7, and 8. ^{32}P emits β particle radiation and the radiation from ^{32}P, thereby, penetrates only millimeters into the surrounding tissues.

^{32}P dose was determined by tumor size (0.5 Ci/g tissue) and volume (1 ml suspension/4 cm^3 tumor) with tumor volume estimated in three dimensions using CT (1 cm^3 = 1 gm). ^{32}P was dosed consistent with approved guidelines from the manufacturer (i.e., the package insert) at 0.5 mCi/g of tissue, to a maximum dose of 20 mCi. The ^{32}P was diluted with saline to produce a volume of ^{32}P equal to one-fourth the tumor volume.

A nuclear medicine physician oversaw all dosimetry and ^{32}P administration. ^{32}P was injected percutaneously under CT guidance by experienced interventional radiologists. All injections were undertaken with local anesthesia; sedation was not required. To ensure dissemination of the colloid throughout the tumor, the needle containing the ^{32}P was redirected once inside the tumor, so that injections occurred in a grid-like manner through one percutaneous site. Nuclear images were obtained after the first ^{32}P injection and before and after each subsequent ^{32}P injection to measure the activity of ^{32}P in the pancreatic tumor (Fig. 1). Single photon emission computerized tomography (SPECT) scanning documented the radiation emitted by the injected ^{32}P.

All patients were monitored for objective tumor response, duration of response, toxicity of therapy, time to disease progression, time to treatment failure, and overall survival, as well as physical performance.

Patients were to be removed from the study only by opinion of the investigators or upon patient request. Patients removed from the study for either disease progression or toxicity were to receive best supportive care. Patients who required discontinuation of 5-FU, external beam radiation, gemcitabine, or ^{32}P radiopharmaceutical therapy because of specific toxicity could continue to receive the partner drugs, as recommended by their oncologist. Regardless of the reason for removal from the study, each patient was to be followed after therapy termination to monitor tumor response, duration of survival, and toxicity of therapy.

Toxicity was graded based upon the National Cancer Institute Common Toxicity Criteria.[19] Where toxicity was attributed to one or more agents (chemotherapy ± external beam radiation ± ^{32}P), dose reduction of appropriate therapies was undertaken. For 5-FU-related toxicities, patients with grade I or II toxicity had their subsequent dosage decreased by 25%. Grade III or IV toxicity resulted in missing a dose and decreasing the next dose by 50%. For toxicities related to external beam radiation, treatment was interrupted for white blood cells < 1.0 million cells/mm^3 or platelet counts < 50,000 per mm^3. For gemcitabine-related toxicities, dose reduction was based on manufacturer guidelines.[20] Toxicities associated with ^{32}P that led to dose reduction were transitory radiation sickness, bone marrow suppression, pleuritis, peritonitis, nausea, and/or abdominal cramping. Patients with complete liquefaction of their tumors had their ^{32}P injection withheld. Patients with areas of solid tumor in addition to areas of tumor liquefaction had only the solid portion of the tumor injected.

Compliance with 5-FU, external beam radiation, and gemcitabine therapy was verified through source documentation. ^{32}P radiopharmaceutical therapy was prepared in nuclear medicine and administered in interventional radiology. Compliance was verified through source documentation.

All medications were recorded in the database from day 0 until death or study termination. Patients may have received concomitant therapy, such as myelosuppression support, but no investigational agents or other anticancer therapy were provided during the study.

Patients were determined to be assessable if they completed 66% of the prescribed chemoradiation or, if randomized to receive it, two doses of ^{32}P.

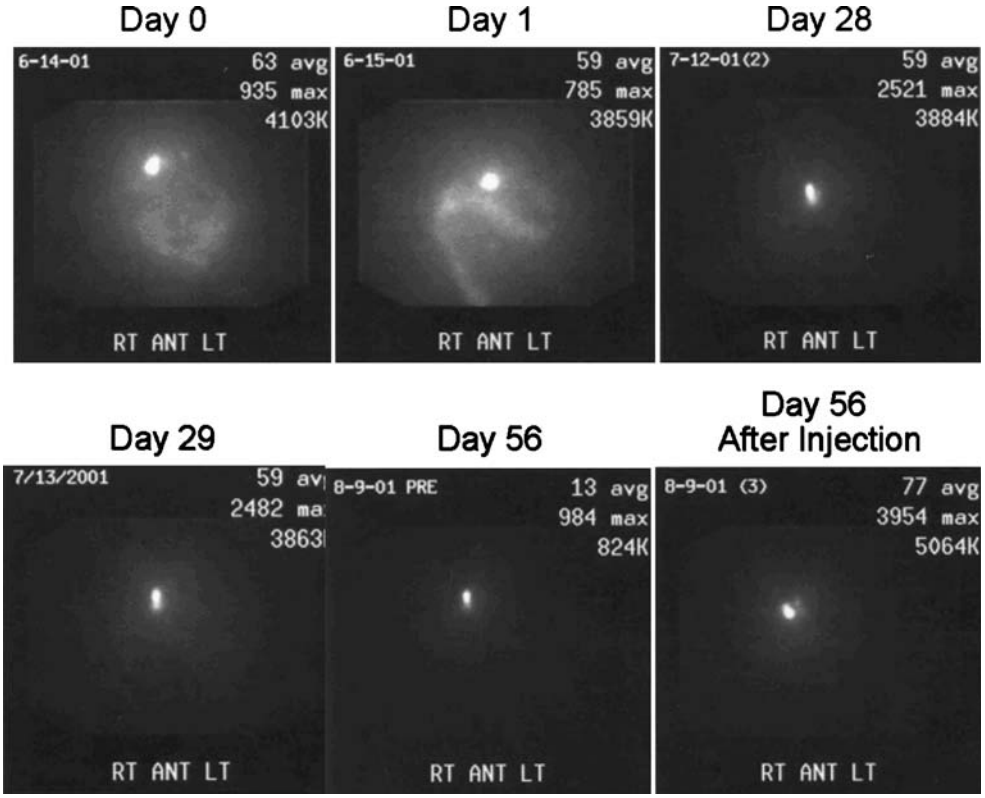

Figure 1 Consecutive nuclear images of a patient receiving ^{32}P in addition to standard chemoradiation. The scans document radioactivity in the pancreas just after the first injection of ^{32}P (Day 0), the day after the first injection of ^{32}P (Day 1), just before the second injection of ^{32}P (Day 28), 1 day after the second injection of ^{32}P (Day 29), and just before (Day 56), and just after (Day 56—after injection) the third injection of ^{32}P. Radioactivity in the bowel seen after the first injection prompted us thereafter to purge the gastrointestinal tract after each injection of ^{32}P.

Data were stored in Microsoft Excel (Microsoft Corp, Redmond, WA, USA) files. Statistical analysis utilized Graphpad Instat version 3.06 (Graphpad Software Inc., San Diego, CA, USA). Survival curve analysis was undertaken on Microsoft Excel, using the additional software XLSTAT-Life (Addinsoft SARL, New York, NY, USA), which permitted the log-rank, Wilcoxon, and Tarone–Ware tests on the survival curves. Where appropriate, data are presented as median, mean±standard deviation.

Results

Informed consent for this trial was obtained from 43 patients; four patients did not undergo randomization as part of this study despite signed informed consent because of reasons unrelated to the protocol or their cancer. Thirty-nine patients were randomized to receive 5-FU and radiation therapy followed by gemcitabine with or without ^{32}P. Nine of 39 patients were not assessable because five patients experienced rapid symptomatic deterioration and declining health, three patients died of other causes, and one patient was removed from the study because of late recognition of a mediastinal metastasis present before therapy was initiated. Thirty patients were assessable: 18 (60%) patients received ^{32}P in addition to standard chemoradiation, and 12 (40%) patients received standard therapy alone.

Patients receiving or not receiving ^{32}P were demographically similar (Table 1). All patients underwent either PET scanning or celiotomy before initiating therapy.

Single SPECT scanning documented the β-radiation emitted by the injected ^{32}P. Immediately after the initial dose, the median radiation was 1,255.34 Gy (1,227.02±486.88).

Four (33%) patients receiving standard therapy alone and two (11%) patients treated with ^{32}P did not experience any serious adverse events (SAEs). Sixteen (89%) patients receiving ^{32}P experienced a total of 75 SAEs, whereas eight (67%) patients not receiving ^{32}P experienced 22 SAEs (Table 2). Each SAE caused or significantly contributed to the need for hospitalization. For patients receiving ^{32}P, 34 hospitalizations were required as a consequence of their SAEs, whereas for patients receiving standard therapy alone, ten hospitalizations were required. Patients receiving ^{32}P required more hospitalizations for their SAEs (1.0, 1.8±1.4 versus 1.0, 0.8±0.7, p=0.05, Mann–Whitney U-test). Overall, SAEs were more frequent with ^{32}P therapy (3.5 SAEs, 4.2±3.1) than with standard therapy alone (1.5 SAEs, 1.8±1.9, p=0.03, Mann–Whitney U-test). SAEs were grouped for illustrative purposes (Table 2).

Particularly serious were the occurrences of gastrointestinal (GI) bleeding, which for eight patients was directly

Table 2 Total Serious Adverse Events (SAEs) Experienced by Patients with Locally Advanced Unresectable Pancreatic Cancer Treated with a Standard Program of Chemoradiation Followed By Gemcitabine, With or Without ^{32}P

Serious adverse events (SAEs)	With ^{32}P	Without ^{32}P
Gastrointestinal		
GI bleeding	13	2
Abdominal pain	4	0
Ascites	3	2
Constipation	0	1
GI outlet obstruction	1	0
Chronic diarrhea	1	0
Hematologic		
Pancytopenia	1	0
Leukocytopenia	1	0
Anemia	5	4
Thrombocytopenia	5	0
Major DVTs		
SVC obstruction	0	1
Deep venous thrombosis	2	0
Pulmonary		
Acute hypoxia	1	0
Pneumothroax	1	0
Pleural effusion	1	0
Constant hiccups	1	0
Jaundice/cholangitis		
Fever/chills	1	0
Obstructive jaundice	4	1
Cholangitis	1	0
Metabolic/nutritional		
Hypoproteinemia	1	0
Fatigue	2	1
Malnutrition	4	0
Hypotension	0	1
Syncope	0	1
Inanition	3	1
Vomiting/dehydration		
Vomiting	5	3
Hyponatremia	2	0
Dehydration	3	1
Distal Limb Edema	1	0
Nausea	6	2
Weakness	2	1
Patients without SAEs	2	4

attributable to their pancreatic tumor eroding into their duodenum. Of these eight patients, seven had received ^{32}P, which may have contributed to the bleeding. Other notable SAEs included nausea and vomiting leading to dehydration, myelosuppression, ascites, jaundice, and malnutrition. Patients experiencing significantly limited intake and/or progressive malnutrition received a feeding tube, a gastrojejunostomy, or parenteral nutrition. Patients with medically intractable ascites underwent paracenteses, and one patient had a Denver® peritoeovenous shunt placed. Patients with obstructive jaundice underwent biliary decompression through endo-biliary or percutaneous stent placement.

For patients receiving ^{32}P versus standard therapy alone, there were no differences in the number of doses of 5-FU received, in the number of days of external beam radiation therapy, or in the number of doses of gemcitabine received (Table 3). Patients receiving ^{32}P had a median of two doses of ^{32}P.

Tumors did not significantly decrease in cross-sectional area whether the patients were receiving ^{32}P (16.1 cm^2, 19.7±10.5 to 13.3 cm^2, 17.4±10.8, p=0.18, Wilcoxin matched-pairs test) or standard therapy alone (20.0 cm^2, 24.1±16.8 to 12.4 cm^2, 17.4±13.1, p=0.19, Wilcoxin matched-pairs test). Decreases in tumor cross-sectional area were not different for patients receiving ^{32}P versus standard therapy alone (1.4 cm^2, 2.2±5.8 versus 6.6 cm^2, 6.6±8.1, p=0.31, Mann–Whitney U-test).

Of 30 assessable patients, 28 (93%) have died. Of patients dying, 23 (82%) died because of progressive disease, 13 of which received ^{32}P. Four (14%) patients receiving ^{32}P died from GI hemorrhage, and one (4%) patient not receiving ^{32}P died because of a stroke.

Patients receiving ^{32}P in addition to standard therapy survived 5.2 months, 7.4±5.5, whereas patients receiving standard therapy alone survived 12.2 months, 11.5±8.0, p= 0.16, Mann–Whitney U-test. The addition of ^{32}P to standard therapy did not improve survival. Survival curve analysis confirms that ^{32}P did not confer a survival advantage (Fig. 2).

Discussion

Survival with pancreatic cancer continues to disappoint. Whereas this is most obviously true with widely metastatic disease, it is also true after resections of curative intent. Intuitively, patients with locally advanced yet unresectable pancreatic cancer would expect survival notably better than patients with widely metastatic pancreatic cancer. Presumably, with aggressive local antitumor therapy, combined with systemic therapy, long-term survival should be possible. This trial was designed to test this presumption. Although brachytherapy trials have been undertaken in the past, this trial employs modern technology, such as CT scans and PET scans, to improve the accuracy of staging and radiopharmaceutical delivery. This trial represents the first brachytherapy trial to evaluate radiopharmaceutical therapy for locally advanced unresectable pancreatic cancer in many years and is the first controlled trial evaluating the ability of ^{32}P to improve survival with standard chemoradiation for locally advanced unresectable pancreatic cancer.

Table 3 Doses Or Days of Therapy Received by Patients per Treatment Protocol

Therapy	With ^{32}P	Without ^{32}P	*p* value
5-FU	30 days (25±9.6)	30 days (30±4.3)	0.46
External beam radiation therapy	31 days (27±8.6)	31 days (31±2.0)	0.60
Gemcitabine	1 dose (5±10.8)	5 doses (11±13.2)	0.11
^{32}P	2 doses (2±1.4)	N/A	N/A

Data presented as median (mean±SD), where appropriate.

The patients in this trial were a generally homogenous group. All patients had locally advanced unresectable pancreatic cancer without discernable metastatic disease beyond the immediate vicinity of the pancreas.

Consent for this trial was obtained from 43 patients. Interim analysis conducted after enrolling 39 patients led us to abandon further trial enrollment because of dismal survival outcomes for patients receiving ^{32}P. When the interim analysis was first undertaken, ^{32}P was associated with a significant survival disadvantage, which was lost with ongoing follow-up of enrolled patients. Nonetheless, ^{32}P cannot be associated with a survival advantage with further follow-up, or even further enrollment, unless future patients have incredibly different experiences than the patients enrolled to date. Stopping enrollment after the interim analysis seems justified.

This trial involves a small number of patients. Although 43 consented patients are a considerable number, less than three quarters of these patients completed a prospectively defined threshold of therapy and were determined to be assessable. Notably, this threshold was quite modest. This illuminates a significant issue for patients with locally advanced unresectable pancreatic cancer. These patients are often deconditioned and in ill-health. They are often old and suffer significant medical comorbidities, and the impact of their locally advanced pancreatic cancer renders them often unable to withstand the implications and "baggage" of external beam radiation therapy and systemic chemotherapy, let alone the added impact of ^{32}P. Interestingly, more patients receiving standard treatment alone "dropped out" of the trial. Although this might be interpreted as abandoning the trial because of randomization away from the study drug, review of the data supports that patients generally withdrew because of rapidly declining health that presaged death.

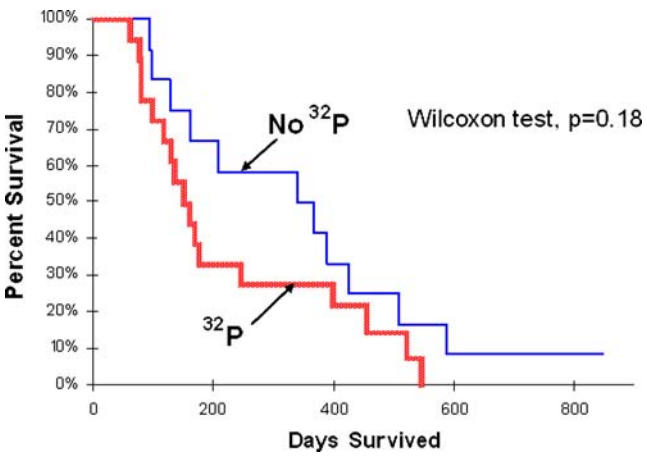

Figure 2 Patient survival with vs. without ^{32}P.

In some preclinical studies, ^{32}P was not prone to staying where injected.[21] Order circumvented this by concomitantly injecting microaggregates of albumin. In preclinical studies, we were able to get ^{32}P to "stick" by having the colloids manufactured uniformly larger (unpublished work). The nuclear medicine scans that we used to measure ^{32}P radioactivity after injection confirmed that the ^{32}P stayed, essentially, where it was injected and that the retained radiation was very substantial.

^{32}P caused tumor liquefaction without decreasing tumor size. Although tumor size detected by CT may not have decreased because of ^{32}P, the ^{32}P obviously had antitumoral activity. Most reasonably, ^{32}P caused central tumor liquefaction, while cancer persisted at the periphery of the injection sites, thus limiting the ability of ^{32}P to cause a decrease in radiologic tumor size. The patients died with progressive disease, but generally not with measurable metastatic disease. Without objective evidence, we postulate that tumor or cancer-related hematogenous factors almost certainly contributed to ill-health and patient demise. In any event, it seems that the risks and consequences associated with ^{32}P outweighed the benefits of its antitumoral activity, however limited.

The half-life of ^{32}P is 14 days. Monthly injections led to an accumulation of radiopharmaceutical. Nuclear scanning confirmed high levels of radioactivity in the tumors. Certainly, the patients were not under dosed with ^{32}P. The failure of ^{32}P to promote survival was not a result of underdosing, although the converse could be argued given the range and severity of SAEs.

Earlier trials failed to support radiopharmaceutical brachytherapy. Although it was tempting in initiating this trial to presume that better clinical staging and radiopharmaceutical delivery would lead to a survival advantage with ^{32}P, the presumption proved to be incorrect. Although future studies with radiopharmaceuticals might involve lower doses of radiation or different delivery systems, it seems to us that future work should focus on more promising approaches for locally advanced unresectable

pancreatic cancer. We have utilized TNFerade™ Biologic[1] in this manner and view it as better tolerated and less toxic to the patient. Furthermore, gene directed therapies, vaccines, anti-angiogenesis therapies, viral vectors carrying tumoricidal therapies, and monoclonal antibodies to tumor-specific antigens are being evaluated and seem much more promising. There seems to be no role for intratumoral radiopharmaceuticals in the treatment of locally advanced unresectable pancreatic cancer at this time.

Conclusions

Although the timing of a trial investigating brachytherapy with intratumoral radiopharmaceutical ^{32}P for locally advanced unresectable pancreatic cancer seemed appropriate given advances in staging and delivery, ^{32}P did not improve survival beyond standard chemoradiation therapy while significantly increasing therapy-related morbidity. There seems to be no role for intratumoral radiopharmaceuticals in the treatment of locally advanced unresectable pancreatic cancer at this time.

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[1] Product of GenVec, Inc., Gaithersburg, MD, USA.

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Clinical Significance of Tumor Location in Remnant Gastric Cancers Developed after Partial Gastrectomy for Primary Gastric Cancer

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Abstract We sought to elucidate the clinical value of tumor location of the remnant gastric cancer developed after partial gastrectomy for gastric cancer to determine the disease characteristics and surgical outcome. Fifty-two patients underwent a second operation with a curative intent because of remnant gastric cancer after undergoing partial gastrectomy for gastric cancer between 1995 and 2005. The clinicopathological features of their primary and recurrent diseases, surgical results, and survivals according to tumor sites within the remnant stomach were examined. Tumors that developed at the anastomotic site (n=27) in remnant stomach favored a female gender, younger age, and unfavorable histological characteristics of primary and recurrent diseases and were also associated with lower tumor resectability than those that developed in the non-anastomotic site (n=25). The overall 5-year survival rates of patients that experienced an anastomotic recurrence and non-anastomotic recurrence were 36.9 and 95.8% (p=0.001), respectively, and the overall 5-year survival rates of patients with stage I primary gastric cancer were 83.3 and 100% (p=0.018) for anastomotic and non-anastomotic recurrence. Tumor location of remnant gastric cancer is an important factor for predicting surgical outcome, but it also reflects the characteristics of primary and recurrent diseases. It is hoped that these results will assist surgeons establishing the treatment plan for remnant gastric cancer.

Keywords Remnant gastric cancer · Tumor location · Surgery · Prognosis

Introduction

Local recurrence is a commonly encountered cause of treatment failure in gastric cancer patients.[1–3] However, the increased use of diagnostic endoscopy and advances in follow-up program methodologies after surgical treatment for primary gastric cancers have increased the detection of remnant gastric cancers with an operable status. The treatment of remnant gastric cancers, especially deemed to be recurrence, is one of the most difficult problems in clinical oncology because of the low rate of resectability, the need for the concomitant resection of adjacent organs, and high rates of postoperative morbidity and mortality. However, surgical removal probably offers the best chance of cure. Nevertheless, even when careful preoperative examinations allow an estimation of tumor resectability and exclude the possibility of metastatic disease, it is often difficult for surgeons to perform safe surgery with curative intent intraoperatively.

In a previous report, we suggested that the operative curability and prognosis of remnant primary gastric cancer, which are newly developed cancers in remnant stomach 10 years after initial gastric resection for benign or malignant lesions, are similar to those of upper one-third cancers.[4] It is difficult to differentiate whether remnant

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gastric cancer developing within 10 years after gastric cancer surgery is a recurrent or residual lesion, even given comprehensive information on the primary lesion.[5] However, tumor location within the remnant stomach might provide a clue as to whether the disease is recurrent or residual cancer.[6] Therefore, in the present study, we selected patients who underwent an initial operation for primary gastric cancer and a second operation for remnant gastric cancer at our institute. We examined the clinicopathological features of primary and recurrent diseases, the resectability of remnant gastric cancers, and survival according to tumor locations within the remnant stomach to find out the clinical value of the tumor location within the remnant stomach.

Patients and Methods

Patients

Between 1995 and 2005, a total of 9,284 patients with gastric adenocarcinoma underwent surgical treatment at the Samsung Medical Center. Of these, 52 patients that had undergone partial gastrectomy with a D2 lymph node dissection at the initial operation underwent a second operation with curative intent because of recurrent disease within the remnant stomach. All of the patients underwent R0 resection, and proximal and distal resection margins were evaluated intraoperatively to confirm freedom from disease at the initial surgery.

Diagnosis

Periods between initial surgery and the development of remnant gastric cancer were less than 10 years in all patients. During routine postoperative follow-ups after initial surgery, an endoscopic examination, abdominal computed tomography (CT), complete blood count, chemistry, biological markers (e.g., carcinoembryonic antigen, cancer antigen [CA] 19-9, and CA 72-4), and a chest X-ray were evaluated every 6 months. Local recurrence was defined as tumor development within remnant stomach and was detected during routine follow-up examinations after partial gastrectomy for gastric adenocarcinoma, usually by endoscopy with pathological confirmation and CT. No patients showed distant metastasis in the preoperative examinations.

Evaluation

The tumor locations were dichotomized into the non-anastomotic site and the anastomotic site. The clinicopathological characteristics of recurrent and primary diseases, recurrent tumor resectability, and survival rates were retrospectively reviewed with respect to recurrent tumor location. The tumors were staged according to the sixth edition of the International Union Against Cancer classification.[7] Tumor histology was dichotomized as 'differentiated', which included papillary adenocarcinoma and well or moderately differentiated adenocarcinoma, and as 'undifferentiated', which included poorly or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma.

Statistical Analysis

A Mann–Whitney U test was used to compare the differences in the continuous variables between the two groups. Statistical analysis of the proportions was evaluated using either a chi-square test or Fisher's exact test. The survival curves were plotted using the Kaplan–Meier method and were compared with the log rank test. p value <0.05 was considered significant.

Results

Tumor Locations within the Remnant Stomach and Primary Disease Characteristics

Table 1 summarizes the clinicopathological characteristics of the 52 patients at initial operations according to location of remnant gastric cancer. The male-to-female ratio of patients with a non-anastomotic recurrence showed approximately an 11-fold male predominance, whereas that of those with an anastomotic recurrence was 1.7:1 ($p=0.02$). Mean ages in the non-anastomotic and anastomotic groups were 58.7 and 48.4 years, respectively, which was significantly different ($p=0.001$). Types of initial operation and primary tumor sizes were similar in both groups.

Disease stage distributions, including depth of wall invasion and lymph node status, were significantly different in the two groups; the non-anastomotic group showed a higher rate of early gastric cancer than the anastomotic group (56.0 versus 7.4%). In addition, although 64% of the non-anastomotic group were included in N0 (no evidence lymph node metastasis), only 18.5% of the anastomotic group were included in N0. Histological differentiation and Lauren's classification revealed significant differences between the two groups; the non-anastomotic group showed higher levels of a differentiated histology (52%) and of the intestinal type (60.9%) as compared with the 14.8 and 21.1% of the anastomotic group.

Overall, tumors that developed at anastomotic sites had several features in their primary diseases, i.e., predilections for a female gender, younger age, less

Table 1 Characteristics of the Primary Gastric Cancer According to the Location of Recurrence in the Remnant Stomach

	Non-anastomotic site (n=25)	Anastomotic site (n=27)	p value[a]
Gender			0.020
Male	23 (92.0)	17 (63.0)	
Female	2 (8.0)	10 (37.0)	
Age (years)	58.7±11.3	48.4±8.5	0.001[b]
Primary operation			0.173
STG, B-I[c]	15 (60.0)	11 (40.7)	
STG, B-II[d]	9 (36.0)	16 (59.3)	
PG	1 (4.0)	0 (0.0)	
Tumor size (cm)	4.1±2.4	5.1±2.1	0.097[†]
Resection margin			
Proximal	4.7±2.9	4.8±3.0	0.992[b]
Distal	5.8±4.1	3.9±2.9	0.056[b]
Primary disease			<0.001
EGC[e]	14 (56.0)	2 (7.4)	
AGC[f]	11 (44.0)	25 (92.6)	
Depth of invasion			0.001
T1	14 (56.0)	2 (7.4)	
T2	4 (16.0)	15 (55.6)	
T3	7 (28.0)	9 (33.3)	
T4	0 (0.0)	1 (3.7)	
LN metastasis			0.002
N0	16 (64.0)	5 (18.5)	
N1	5 (20.0)	9 (33.3)	
N2	3 (12.0)	9 (33.3)	
N3	3 (12.0)	4 (14.8)	
Stage of disease			0.025
I	15 (60.0)	6 (22.2)	
II	4 (16.0)	4 (14.8)	
III	5 (20.0)	12 (44.4)	
IV	1 (4.0)	5 (18.5)	
Histology			0.007
Differentiated	13 (52.0)	4 (14.8)	
Undifferentiated	12 (48.0)	23 (85.2)	
Lauren			0.006
Intestinal	14 (60.9)	4 (21.1)	
Diffuse	7 (30.4)	15 (78.9)	
Mixed	2 (8.7)	0 (0.0)	
Borrmann			0.631
I	0 (0.0)	0 (0.0)	
II	2 (18.2)	3 (12.0)	
III	9 (81.8)	22 (88.0)	
IV	0 (0.0)	0 (0.0)	

Values in parentheses are percentages.
[a] Fisher's exact test
[b] Mann–Whitney U test
[c] Billroth-I reconstruction
[d] Billroth-II reconstruction
[e] Early gastric cancer
[f] Advanced gastric cancer

favorable histological type, and more advanced tumor stage.

The Characteristics of Remnant Gastric Cancers According to the Tumor Location

The clinicopathological variables of remnant gastric cancers were examined with respect to recurrent tumor locations (Table 2). Mean intervals between initial and second operations in the non-anastomotic and anastomotic groups were 37.6 and 35.2 months, respectively. The tumor resection rate was greater in the non-anastomotic group (96 versus 55.6%). Curative resection (R0) was performed in 84% of patients in the non-anastomotic groups and in 51.9% patients in the anastomotic group. Exploration without definitive palliative treatment was performed in 1 (4%) patient in the non-anastomotic group and in 12 (44.4%) patients in the anastomotic group. The major causes that made tumor resection impossible were multiple adjacent organ invasion and peritoneal seeding. The anastomotic group had higher rates of adjacent organ invasion, lymph node metastasis, and higher proportions of patients with an undifferentiated histological type and a diffuse type (Lauren's classification), and these group differences were significant.

Survival Analysis According to the Tumor Stage

Mean follow-up durations were 56.8 months after first operation and 20.4 months after second operation. The survival data was calculated from the point of first gastrectomy in all cases. Overall 5-year survival rates in the non-anastomotic and anastomotic groups were 95.8 and 36.9%, respectively (p=0.001). Overall 5-year survival rates in the non-anastomotic and anastomotic groups by each stage were 100 and 83.3% for stage I (Fig. 1, p= 0.018), 100 and 75% for stage II (p=0.450), and 66.6 and 45% for stage III (Fig. 2, p=0.317), respectively. Each patient with stage IV disease in the non-anastomotic and anastomotic groups were alive at 24.2 and 12.1 months, respectively, after second operations with no evidence of recurrence or distant metastasis.

Discussion

Despite a substantial decline in mortality because of early diagnosis, radical surgery, and the development of adjuvant therapies, gastric cancer remains a prominent cause of death because of cancer in Korea, and these deaths almost invariably follow tumor recurrence.[3,8] Remnant gastric cancers that occur after gastric cancer surgery are divided into three subgroups: remnant primary cancers detected at

Table 2 Characteristics of Remnant Gastric Cancers According to *the Second Tumor Location*

	Non-anastomotic site (n=25)	Anastomotic site (n=27)	p value[a]
Interval from first to second operation (months)	37.6±27.8	35.2±27.0	0.783[b]
Second operation			0.001
Resectable	24 (96.0)	15 (55.6)	
Unresectable	1 (4.0)	12 (44.4)	
Curability			0.042
R0	21 (84.0)	14 (51.9)	
R1	0 (0.0)	1 (3.7)	
R2	4 (16.0)	12 (44.4)	
Secondary disease			0.080
EGC[c]	12 (48.0)	6 (22.2)	
AGC[d]	13 (52.0)	21 (77.8)	
Depth of invasion[a]			0.012
T1	12 (48.0)	6 (22.2)	
T2	9 (36.0)	6 (22.2)	
T3	0 (0.0)	0 (0.0)	
T4	4 (16.0)	15 (55.6)	
Lymph node metastasis			0.011
Negative	16 (64.0)	7 (25.9)	
Positive	9 (36.0)	20 (74.1)	
Distant metastasis			0.296
M0	22 (88.0)	20 (74.1)	
M1	3 (12.0)	7 (25.9)	
Histology			<0.001
Differentiated	17 (68.0)	2 (7.4)	
Undifferentiated	8 (32.0)	25 (92.6)	
Lauren classification			0.002
Intestinal	16 (66.7)	2 (13.3)	
Diffuse	8 (33.3)	13 (86.7)	

Values in parentheses are percentages
[a] Fisher's exact test
[b] Mann–Whitney U test
[c] Early gastric cancer
[d] Advanced gastric cancer

10 years or more after initial gastric resection, regardless as to whether the primary lesion was benign or malignant; remnant residual cancers detected at non-anastomotic sites in the remnant stomach within 10 years after initial gastric resection for a malignant lesion; and remnant recurrent cancers detected at anastomotic sites within 10 years after initial gastric resection for a malignant lesion.[6] Although remnant recurrent and remnant residual cancers could be categorized by tumor location, it is difficult to determine whether a remnant cancer is recurrent or residual even given comprehensive information on the primary lesion. In the present study, because all patients underwent a second operation within 10 years of initial gastrectomy for gastric cancer, sites of tumor recurrence could be considered indicative of the recurrent or residual nature of a given tumor. In other words, tumors developed in the anastomotic site may indicate the local recurrence of gastric cancer, and those developed in the non-anastmotic site within the remnant stomach may indicate the other primary gastric cancer that was not detected at the initial surgery. Our results provide clinical clues regarding the relation between the characteristics of primary or recurrent disease and tumor location and, thus, help predict tumor resectability and prognosis in patients with remnant gastric cancer.

Tumors that developed in anastomotic sites occurred more so in women, and at a younger age, and tended to be associated with primary diseases with unfavorable histological characteristics. On the other hand, tumors that developed in non-anastomotic sites followed primary diseases with more favorable histological characteristics. These results suggest that the remnant gastric cancers with an anastomotic location are more likely to be because of recurrence, whereas those that develop at non-anastomotic sites are more likely to have been because of residual carcinomas not detected at initial treatment. Tumor cells may remain in remnant stomach, although resection margins are deemed histologically free of tumor involvement at primary surgery. The incidence of multiple primary gastric carcinomas has been reported in 5.1–5.8% of patients with gastric carcinoma, and it is reported more commonly in early than advanced gastric carcinomas.[9,10] In addition, multifocal gastric carcinoma has been reported to develop in elderly patients and to show the intestinal type of gastric carcinoma more frequently than solitary carcinoma.[10] These are in agreement with our results, and therefore, the remnant gastric cancer developed in the non-anastomotic site should be regarded as rather residual gastric cancer than recurrent carcinoma.

Although many reports have been issued on gastric stump carcinomas that have developed after benign ulcer resection, relatively few studies have evaluated the resectability of remnant gastric cancer developed after gastric cancer surgery.[11–13] This might be because of the recurrence patterns of gastric cancer; that is, distant metastasis to the liver, peritoneum, lung, and others is more common than loco-regional recurrence only.[3,14] The resectability of remnant gastric cancer is ultimately determined by the local aggressiveness of the disease. However, it is difficult to determine disease extent in such cases before surgical mobilization, because of postoperative adhesions, fibrotic changes, and the effects of adjuvant chemotherapy and radiotherapy. Surgeon's preference and experience and postoperative morbidity and mortality rates may also influence management plans. Authors have reported resection rates ranging from 14.1 to 53% for recurrent gastric cancer.[2,3] However, no evaluation of risk factors, such as primary disease status and site of recurrence, was undertaken. In the present study, the resection rate of remnant gastric cancer was 96.0% for tumors that developed at non-

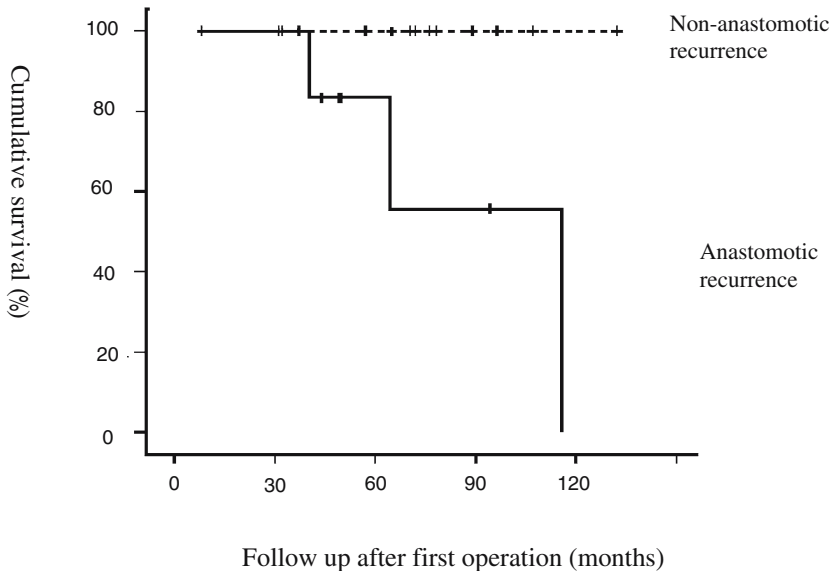

Figure 1 Kaplan–Meier survival curves for patients with stage I gastric cancer (p value=0.018).

anastomotic sites and 55.6% for those at anastomotic sites. Moreover, 41% of patients with tumor resection underwent a combined adjacent organ resection, i.e., spleen (13), pancreas (5), transverse colon (4), and left lateral segment of the liver (1), with no postoperative mortality or significant morbidity. These results indicate that tumor location within the remnant stomach should be noted, because tumor location is closely related to the possibility of surgical resection that, in turn, determine the patients' prognosis. It is worth emphasizing that an aggressive surgical approach to remnant gastric cancer in a non-anastomotic site can achieve a satisfactory outcome, despite technical difficulties.

The overall 5-year survival rates of patients in the anastomotic and non-anastomotic groups from the first operation were 36.9 and 95.8%, respectively (p=0.001). Considering the higher incidence of early stage tumor in the non-anastomotic group, these results are a matter of course. Therefore, the comparison of survival at the same stage is important, and survival curves of patients with stage I primary lesion showed a significant difference between these two groups favoring the non-anastomotic group. For more advanced stage, patient prognosis also tended to be better in the non-anastomotic group even if there was no significant difference probably because of low patient numbers. Despite the selection bias caused by the enrollment of only patients who were operable according to preoperative evaluations, tumor location within the remnant stomach, a key factor for determining whether recurrent or residual lesions, appears to be associated with patients'

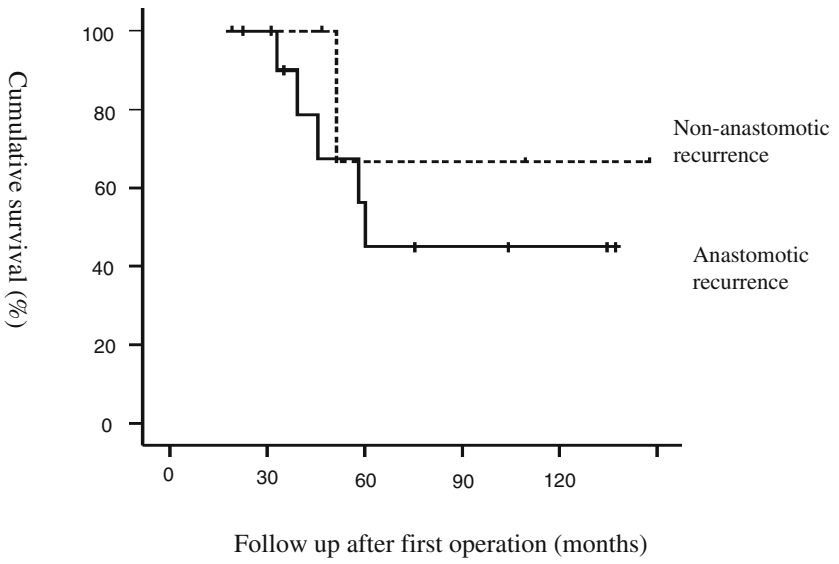

Figure 2 Kaplan–Meier survival curves for patients with stage III gastric cancer (p value=0.317).

prognosis. It is hoped that these findings assist surgeons in establishing the treatment plan for remnant gastric cancer.

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Gasless Laparoscopy-Assisted Subtotal Gastrectomy for Early Gastric Cancer: A Novel Minimally Invasive Surgery

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Abstract
Background Due to the highly invasive nature of traditional surgery and the limitation of gas-filling laparoscopic surgery in gastric cancers, we developed a new method of gasless laparoscope-assisted subtotal gastrectomy (GLASG). This study investigated the technique and clinical results of this procedure and compared it with traditional radical subtotal gastrectomy (TRSG) for early gastric cancers.
Methodology From December 2004 to January 2006, 41 patients diagnosed with early gastric cancer were included in the study. All cases underwent subtotal gastrectomy with standard radical lymph node dissection. Twenty patients underwent GLASG, whereas the other 21 patients underwent TRSG. In the GLASG group, we performed our newly developed method using three working ports created at the bilateral subcostal and umbilicus, which provided a 3-dimensional sensation by direct vision through a minilaparotomy and laparoscopic view simultaneously. B-II gastrojejunostomy reconstruction was performed by intracorporeal anastomosis using an endostapler. The TRSG group underwent the standard open method used for gastric cancer. Preoperative characteristics and postoperative recovery between the two groups were compared.
Results The operative time was comparable between the two groups, but the bleeding was significantly less severe in the GLASG group. Postoperative pain was significantly less in the GLASG group, as well as body temperature from post-operative day 2 to 7. The number of days to first flatus, first oral intake, and discharge were all significantly less in the GLASG group. No major complications were noted in either group.
Conclusions GLASG may be a feasible and safe procedure for early gastric cancer. Gasless laparoscopic gastrectomy has the advantages of less pain, better cosmetic outcome, and earlier recovery. The newly developed gasless environment may hybridize the advantages of open method and pure laparoscopic method.

Keywords Gasless laparoscopy · Subtotal gastrectomy · Gastric cancer · Minimally invasive surgery

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Introduction

Over the last decade, an increasing number of surgeons have been performing laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer by creating a pneumo-peritoneum using carbon dioxide.[1,2] This gas-filling system allows for the inflation of the abdominal cavity, which widely expands the operative space to allow for improved visualization and access to the operative site. However, the creation of a pneumo-peritoneum also increases cardiac pre-load and afterload, cardiac index, and systemic vascular resistance, all of which might adversely affect the heart function in susceptible patients to a clinically significant

degree.[3,4] Moreover, in such an airtight space, manipulation is restricted and tactile sensation is lost, a combination that may significantly prolong the operating time. Port site seeding of cancer cells caused by the pneumo-peritoneum has also been reported as a concern regarding this method.[5]

Recently, a novel technique has been developed by our team that combines the benefits of laparoscopy with the benefits of an open procedure. This procedure is gasless laparoscopy-assisted gastrectomy using an abdominal wall lift. We investigated this procedure in the treatment of early gastric cancer of the antrum, which is highly technically demanding, and compared it with a traditional radical subtotal gastrectomy (TRSG).

Methodology

Patients

From December 2004 to January 2006, 41 consecutive patients at the National Taiwan University Hospital who were diagnosed with early gastric cancer in the antrum were included in this study. All of the patients had abdominal computed tomography for cancer staging, and none exhibited any evidence of lymphadenopathy or distant metastasis indicative of late-stage disease.

Twenty patients underwent gasless laparoscope-assisted subtotal gastrectomy (GLASG) combined with radical lymph node dissection, whereas the other 21 patients underwent TRSG. Characteristics recorded for each patient included age, gender, and comorbidities, if any. The number of lymph nodes dissected, operative time, quantity of blood loss, depth of cancer invasion, and size of the lesion were investigated.

In addition, all of the patients were asked to estimate their postoperative pain daily on a standardized visual analog scale. The postoperative temperatures were likewise recorded. Peak daily temperatures, as well as the day of first postoperative flatus and the day of first oral intake, were recorded. The length of hospitalization was calculated as the date of discharge minus the date of surgery.

Surgical Procedure: Gasless Laparoscopic Subtotal Gastrectomy

All of the patients underwent panendoscopy to locate and mark the tumor preoperatively using surgical clips. A minilaparotomy was made (5 cm, called a three-finger port) in the upper midline of the abdomen. A wound protector was positioned over the minilaparotomy to avoid contamination or cancer cell implantation. Palpation of the tumor and clip location was performed using one or two fingers through the minilaparotomy to ensure the position of the clips and the tumor.

The abdominal wall was then elevated by specially designed self-retaining retractors (Fig. 1). Three working ports were created at the bilateral subcostal region and periumbilicus. The laparoscope was inserted either through the minilaparotomy or through any of the ports for thorough examination of the whole peritoneal cavity and the various abdominal organs. A 3-dimensional sensation was obtained efficiently by direct viewing through the minilaparotomy and the laparoscopic image simultaneously.

The dissection was accomplished using laparoscopic devices, such as a Harmonic scalpel (Ethicon, Cincinnati, OH, USA), Ligasure (Tyco, Valleylab, Boulder, CO, USA) and endoclips through the minilaparotomy or the ports. The omentectomy or bursectomy was carried out first partially extracorporeally through the minilaparotomy. The dissection of lymph nodes located in the perigastric area and at the celiac trunk, the common hepatic artery, the left gastric artery, and the hepato-duodenal ligament was accomplished mainly via the minilaparotomy by direct vision. The other dissections were made via laparoscopic view when the operation field was far away from the minilaparotomy. The

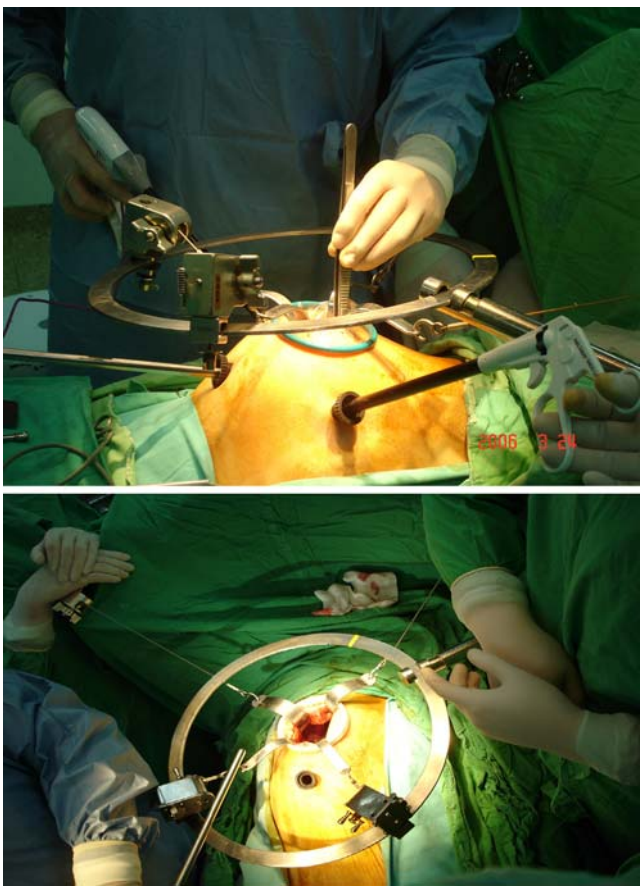

Figure 1 A minilaparotomy is made at the beginning of the procedure. Three accessory ports were made at para-umbilicus and left and right abdomen. Abdominal wall is then left up by self-retractors. Dissection can be performed through the laparotomy and accessory ports.

abdominal wall could be elevated by self-retractors mentioned above or lowered down according to the location or depth of the dissection area. The specimen was removed through the minilaparotomy after transection from the remnant stomach by stapler (Endo GIA, Tyco, Valleylab) inserted through either the minilaparotomy or ports. After that, B-II gastrojejunostomy was performed by intracorporeal anastomosis using Endo GIA. The laparoscopic instruments could be inserted more freely into the peritoneal cavity through the minilaparotomy or the ports to perform anastomosis depending on the level of the remnant stomach. The anastomosis could be reinforced by hand suture by traditional instruments either by direct view through the minilaparotomy or by intracoporeal suture with laparoscopic instruments under laparoscopic inspection or both. The procedures made through the minilaparotomy could also be reassured by laparoscopy. Direct control of the bleeding could be made easily if needed through the minilaparotomy, and vigorous suction could be accomplished through the ports or the minilaparotomy.

Statistical Analysis

The nonpaired t test and Fisher's exact test were used to compare the two surgical groups (GLADG vs. TRSG) with respect to all continuous or ordinal variables. A p value< 0.05 was considered statistically significant.

Results

Patient characteristics were comparable between the two groups. In the GLASG group, the mean age was 59.3 years (range: 45–84 years). In the TRSG group, the mean age was 61.78 years (range: 36–88 years). The male/female ratio was 22/19 (GLASG, 11/9; TRSG, 11/10). The body mass indices were 27.54±2.78 kilograms per square meter (kg/m^2) in the GLASG group and 26.99±2.21 kg/m^2 in the TRSG group. No significant difference was noted between these two groups (Table 1).

There was no difference in the number of lymph nodes dissected (D2 dissection). All of the specimens were sent for pathology examination and all of the lesions were confirmed to be limited to the submucosal layer, consistent with the preoperative diagnosis of early gastric cancer. The operative time was 208.38±23.21 min for GLASG, which was not significantly different compared to the traditional procedure (206.11±13.99 min). Blood loss was significantly less in the GLASG group ($p<0.001$).

The number of days to first flatus (2.63±0.52 vs. 3.50± 0.79), first oral intake (5.0±0.93 vs. 6.44±1.04), and discharge (11.3±1.36 vs. 14.39±2.93) were all significantly less in the GLASG group (all $p<0.05$). The mean follow up time was 20.4±3.5 months in the GLASG group and 21.2± 3.1 months in the TRSG group. No recurrence was noted during follow up in both groups (Table 2). Postoperative pain, assessed using a visual analog scale, was less in the GLASG group in the first 3 days, but the two groups converged by days 4 through 7 (Fig. 2). The peak daily temperature was significantly lower from postoperative days 2 to 7 in the GLASG group ($p<0.05$) (Fig. 3).

Postoperative morphine was used less in the GLASG group, especially on postoperative day 2 ($p=0.007$) (Fig. 4). No major complications, such as anastomostic leakage or major organ dysfunction, were noted in either group. As to minor complications, two cases of wound infection in the GLASG group were noted with mild discharge, compared to one case of wound infection in the TRSG group. No significant difference was noted.

Table 1 Demography of Patients

	GLADG	Traditional Surgery	p Value
Number of patients	20	21	
Gender (female/male)	9/11	10/11	NS
Age (years)	59.25±12.3	61.78±12.40	NS
Comobidities			
DM (+/−)	4/16	5/16	NS
Hypertension (+/−)	5/15	3/18	NS
CAD (+/−)	4/16	3/18	NS
CVA (+/−)	2/18	0/20	NS
BMI (kg/m^2)	27.54±2.78	26.99±2.21	NS

No significant between two groups was noted
NS = nonsignificant, DM = diabetes mellitus, CAD = coronary artery disease, CVA = cerebral vascular accident

Discussion

Gas-filling laparoscopic gastrectomy has been used for early gastric cancer and has demonstrated some postoperative benefits, including faster recovery and less postoperative pain than open procedures. However, due to the potential, largely cardiovascular disadvantages, this procedure generally has been considered relatively contraindicated in patients with cardiopulmonary disease.[3,4] Port-site cancer seeding due to pneumo-peritoneum has also been reported.[5–8] In this newly developed setting, gas is not needed to inflate the peritoneum and, therefore, such possible adverse effects secondary to gas-filling surgeries are eliminated.

Moreover, difficulty in control of accidental massive bleeding and a steep learning curve are still the major concerns in gas-filling laparoscopic surgeries. Intraoperative bleeding has been encountered in various fields of laparoscopic surgeries. The incidence of bleeding complications ranges from 0.05 to

Table 2 Perioperative Data

	GLADG	Traditional Surgery	*p* Value
Number of LN at dissected (group 7, 8, 9, 11, 12, 13)	12.63±7.76	19.67±7.64	NS
Number of LN metastasis	2	2	NS
Days to first flatus	2.63±0.52	3.50±0.79	<0.05
Days to oral intake (day)	5.0±0.93	6.44±1.04	<0.05
Days to discharge after surgery	11.3±1.36	14.39±2.93	<0.05
Operative time (min)	208.38±23.21	206.11±13.99	NS
Estimated blood loss (ml)	95.63±31.33	207.22±73.31	0.001
Depth of invasion (number)			
Mucosa	9	7	
Submucosa	11	14	
Wound length	4.64±0.74	16.61±1.54	0.000
Tumor size	1.83±0.57	1.74±1.07	NS
Complications[a]			
Wound infection	2/18	1/20	NS
Time of follow up (months)	20.4±3.5	21.2±3.1	NS
Recurrence	0/20	0/21	NS

NS = nonsignificant, LN = lymph node

[a] No major complication was noted as to anastomostic leakage or postoperative organ sever dysfunction

4%.[9,10] Although major vascular injuries are rare, they are one of the most serious complications and a major cause of conversion. Through the minilaparotomy made at the beginning of our procedure, the surgeon can perform dissection similar to traditional methods through direct vision. Major bleeding can be controlled more easily by the surgeon's fingers or traditional instruments. Vigorous suction could be accomplished fast without the limitation of space collapse due to decreased intra-abdominal pressure in the gas-filling environment. In our series, no cases were converted to TRSG. The Ligasure coagulation system was also used to help save time in ligating vessels, which significantly reduced blood loss in our patients.[11–14]

Nonetheless, although technical limitations related to lymph node dissection and gastrectomy have gradually decreased with technological advancements in laparoscopic instruments, the procedure remains highly technically dependent and more time-consuming than traditional surgery. Lymph node dissections through the minilaparotomy made in our procedure were much easier and faster. Due to familiar dissection procedures such as traditional laparotomy, the possibility of injury to vital structures may be decreased. For those groups located far from the minilaparotomy, the lymph node dissections were accomplished with the aid of laparoscopy. The lymph node harvest, thus, may be adequately performed with our method. Comparing this new procedure with TRSG, data reveal no difference in the number of lymph nodes dissected (D2 dissection), which is an outcome that is considered to be very important in early gastric cancer surgeries.[15–18] The oncological results seemed satisfactory

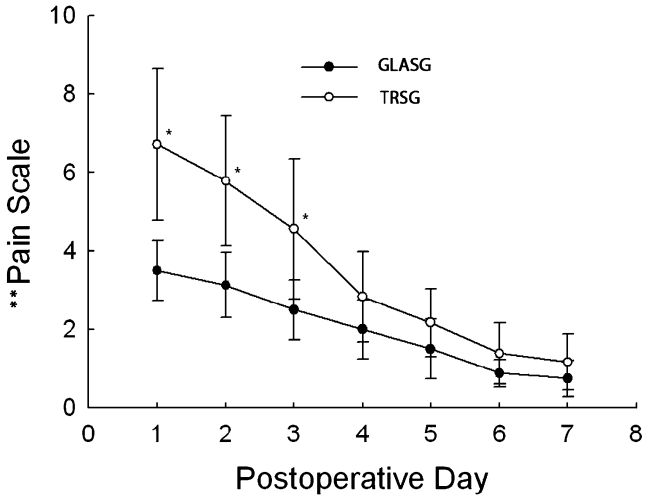

Figure 2 Postoperative pain scale showed less severe pain in the minimal-invasive group (GLADG) than in the traditional radical gastrectomy group, especially in the first three postoperative days. *Single asterisk* $p<0.05$, *double asterisks* visual analog scale.

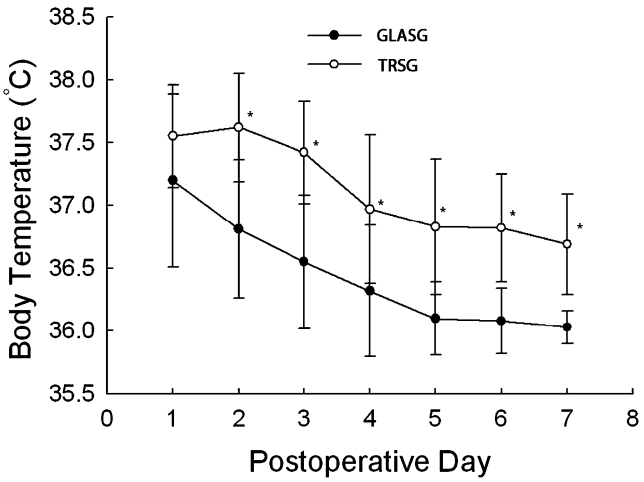

Figure 3 Postoperative daily highest body temperature curve shows significant lower temperatures from days 2 to 7 in the minimal-invasion group (GLADG) than in the traditional surgery group (TRSG). *Asterisks* $p<0.05$.

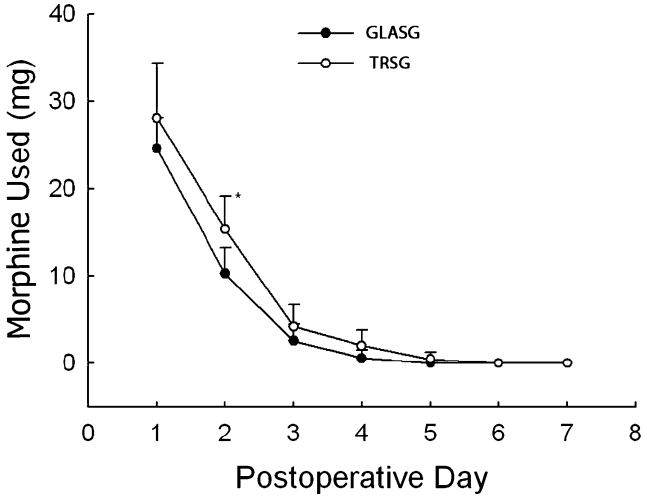

Figure 4 Postoperative morphine use is less in the GLASG group. Significant difference is noted at postoperative day 2. *Asterisk* $p<0.05$.

during the early follow up of our patients, with no nodal or other cancer recurrence being noted during follow up in both groups.

The learning curve was speedy and no major complications were noted compared to other series of reports in gastric operations. It takes only a few cases for surgeons to get familiar with the operative environment, and thus, the D2 dissection of lymph nodes is feasible.[19–21] The dissection and anastomosis of stomach and intestine can be performed intracoporeally with the assistance of traditional instruments and laparoscopic instruments simultaneously. In our experience, it only takes more operative time in the first five cases. The overall operative time decreased rapidly in the following cases. The mean operative time was significantly shorter than TRSG for the last 15 cases. Based on our experience, GLASG requires less time than gas-filling laparoscopic procedures reported.

In our patients receiving GLASG, the average basic mass index (BMI) was 27.54±2.78 kg/m^2 and the maximum BMI was 32.8 kg/m^2. In these moderately obese cases, GLASG could also be done successfully. However, the operative field was limited due to thick abdominal walls. The average length of minilaparotomy may need to be extended for 2 to 3 cm in these moderately obese patients to overcome the limited operative field. The maximum wound size was 6.8 cm in our GLASG group. GLASG, in our experience, is somewhat difficult but not contraindicated for obese patients.

A better cosmetic effect is another benefit of laparoscope-assisted surgery. In this study, our method provided the same results as previous laparoscopic studies. With GLASG, the number and size of incisions are no greater than those of gas-filling laparoscopic procedures reported.[22] However, unlike the latter, where minilaparotomy incisions are created later in the procedure to remove the specimen from the body, our minilaparotomy incision is created first in the procedure to allow for easier visualization and for dissection, in addition to aiding final specimen removal.

Postoperative pain was less with GLASG as compared to TRSG, although the same quantity or less (on day 2) of analgesics was used. Decreased postoperative pain has also been noted. This may be related to the smaller incision size compared to TRSG.[23] The absence of any pneumoperitoneum-induced postoperative pain may be an additional benefit of GLASG as compared to gas-filling laparoscopic procedures.[24,25]

In addition to the advantages of improved cosmetics and less pain with GLASG, GI function appears to resume faster in GLASG than in TRSG, as evidenced in this study by the earlier first flatus and resumption of oral intake. This may be due to less vigorous bowel manipulation. The mechanism behind the earlier return of GI motility has been discussed by Schippers et al. in laparoscopic cholecystectomy. These investigators showed that the time to first myoelectrical activity was 5.5±1.0 h with laparoscopy, which was much shorter than the 46±5 h observed with conventional cholecystectomy.[26] With laparoscopic colectomy, the median time of restoring normal digestive pattern of myoelectrical activity is 60% shorter than that observed with open colectomy.[27] The same effect of faster recovery of gastro-intestinal function is noted in our study. With earlier recovery of GI function, less pain, and a smaller incision, the time to discharge was likewise shortened by about 3 days in GLASG.

Peak daily body temperature was lower from postoperative days 2 through 7 in the GLASG group. Hayashi et al. reported decreased serum IL-6, C-reactive protein, and white blood cell count, all suggesting less inflammation in patients who undergo laparoscopic-assisted distal gastrectomy.[28] Serum IL-6 levels reflect tissue trauma and postoperative themoregulation.[29–31] It is therefore likely that GLASG patients experienced less inflammation because of the smaller incisions and less bowel manipulation, resulting in lower-level release of cytokines and other thermoregulatory compounds, leading to lower body temperatures. In addition, less pain and the absence of pneumo-peritoneum may result in less fever secondary to pulmonary ectasis.

Conclusions

Early gastric cancer patients were treated with a newly developed procedure for laparoscopy-assisted radical subtotal gastrectomy and found that few difficulties are encountered, even for D2 lymph node dissection and GI reconstruction. The result includes faster recovery, less postoperative pain, fewer adverse cosmetic effects, and yet the same removal of malignant tissue compared with TRSG. Our gasless procedure

enjoys virtually all the benefits of gas-filling laparoscopic surgery but preserves tactile sensation, allows for the use of traditional instruments, potentially allows for better visualization, and prevents potential adverse effects from pneumoperitoneum. Although the follow up time was not long enough in our study, there have been no recurrences noted during follow ups to date. In the view of oncological results, longer-term studies are warranted to compare this to other procedures in terms of long-term cancer remission and survival rates.

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Pancreatic Adenocarcinoma: The Actual 5-Year Survivors

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Abstract
Background Most reports of patients undergoing resection for pancreatic adenocarcinoma report estimated (actuarial) 5-year survival rates. Actual 5-year survival is rarely described, and factors associated with long-term survival are not well described.
Methods Review of a prospectively maintained database identified 618 patients who underwent resection for pancreatic adenocarcinoma between 1/1983–1/2001. Patient, tumor, and treatment-related variables were assessed for their association with 5-year survival.
Results There were 75 patients who survived >5 years after resection (75 out of 618, 12%), and 18 patients who survived >10 years (18 out of 352, 5%). Patient age, gender, and tumor location were not associated with 5-year survival, whereas early American Joint Committee on Cancer (AJCC) stage ($p<0.001$) and negative margins ($p=0.001$) were associated with 5-year survival. Patients with stage IA disease had an actual 5 year survival of 26%. Median follow-up was 108 months. Recurrent disease developed in 38 patients (51%) and all died from disease. Adjuvant therapy was received by 21% (16 out of 75), and tumors were moderately differentiated in 58% (42 out of 75) and had a median size of 2.8 cm (0.8–13 cm).
Conclusions Actual 5-year survival after resection of pancreatic adenocarcinoma was 12%. AJCC stage and negative margins were the only significant predictors of long-term survival. Early detection and intervention for patients with pancreatic cancer is crucial.

Keywords Pancreatic adenocarcinoma · 5-Year survivors

Oral presentation at AHPBA 2007 Las Vegas.

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Introduction

The American Cancer Society predicts 37,170 new cases and 33,370 deaths from pancreatic adenocarcinoma in 2007.[1] Fewer than 15% of patients diagnosed with pancreatic adenocarcinoma will undergo resection. Both the advanced stage at presentation and the lack of effective non-operative treatment modalities contributes to the poor prognosis of this disease. Despite advances in adjuvant therapy, operative resection offers the only chance for long-term survival. A recent study by Imamura et al.[2] randomized patients with resectable pancreatic cancer to operative resection or radiochemotherapy with 5-FU/5040cGy. Patients who underwent resection had an improved 1-year survival and mean survival compared to patients who underwent chemoradiation (62 vs 32%, $p=0.05$; >17 vs 11 mo, $p<0.03$).

Since 1941, when Brunschwig reported the first pancreaticoduodenectomy for cancer, the operative mortality

has decreased significantly.[3] However, even at high volume centers, the current reported morbidity and mortality of pancreatic resection are approximately 35–51% and 1–6%, respectively.[4–6] Despite continuous improvements in perioperative mortality and adjuvant chemotherapy, pancreatic adenocarcinoma continues to carry a dismal prognosis.[7] Lymph node metastases, depth of invasion, resection margin, and adjuvant therapy are known to be prognostic factors in pancreatic cancer.[8,9] However, because the majority of the patients die within two years, it is difficult to assess determinants of long-term survival. Most reports on patients undergoing pancreatic resection for pancreatic adenocarcinoma report estimated (actuarial) 5-year survival rates. Actual 5-year survival is rarely described, and factors associated with this long-term survival are not well known.

The purpose of this study was to identify the actual 5-year survival at a tertiary referral center. Clinicopathologic factors associated with actual 5-year survival were assessed and which of these factors were associated with survival beyond 5 years were investigated.

Methods

A review of a prospectively maintained database of patients undergoing resection for periampullary neoplasms identified 618 patients who underwent resection for pathologically confirmed pancreatic adenocarcinoma between 1/1983–1/2001. Patients who presented with metastatic disease or locally advanced disease precluding pancreatic resection were excluded. This study includes 12 5-year survivors previously reported by our institution.[10]

Patient, tumor, and treatment-related variables were retrieved from the database and confirmed by chart review. Follow up was obtained through office records, phone conversations, and the social security death index. Patient factors evaluated included age, gender, and medical comorbidities. Treatment factors included the date of operation, type of operation, the estimated blood loss, length of stay (LOS), status at last follow up, and whether adjuvant therapy was administered.

Histological confirmation was determined at a monthly multi-disciplinary conference attended by surgeons and pathologists. Pathologic factors determined at this conference included tumor, nodes, and metastases (TNM) stage, margin (positive or negative), and differentiation (well, moderate, or poor). Maximal tumor size was determined and defined as the maximum diameter at pathological analysis. Margins assessed included the pancreatic resection margin, biliary margin, posterior margin, retroperitoneal margin, and mesenteric margin.

Utilizing Statistical Package for the Social Sciences and SAS 9.1 software univariate and multivariate analyses were performed. Continuous variables were expressed as median or mean ± standard deviation and were compared using an independent samples T test. Categorical variables were compared using a χ^2 test. Overall survival was computed from the time of operative resection to the date of last follow-up. A p value of <0.05 was considered significant.

The institutional internal review board approved this study, and none of the authors have any conflict of interest.

Results

Between January 1983 and January 2001, 2,342 patients were operatively explored for the diagnosis of pancreatic adenocarcinoma. A complete gross resection (R0/R1) was

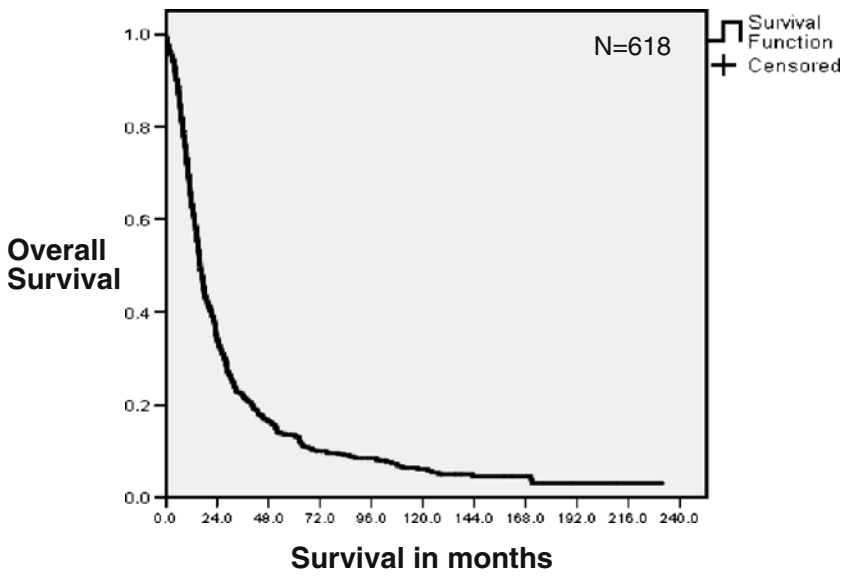

Figure 1 Estimated survival for 618 undergoing resection for pancreatic adenocarcinoma between 1983 and 2001.

performed in 618 patients. Overall survival for the entire cohort is demonstrated in Fig. 1. The clinicopathologic features are listed in Table 1. The actual 5-year survival was 11.8% (75 out of 618). Death from disease occurred in 81% (501 out of 618), 1.1% (7 out of 618) died within 30 days from postoperative complications, 6% (35 out of 618) died of another cause, and 2.6% (16 out of 618) were lost to follow-up. Ten-year survival was experienced by 18 of 352 patients (5%) who had potential 10-year follow-up (1982–1995).

The median survival for the 5-year survivors was 7.6 years. Age, gender, operation performed, total number of lymph nodes pathologically assessed, median estimated blood loss, median LOS, and the use of adjuvant therapy did not differ between those who survived 5 years and those who did not. Adjuvant therapy was documented in 21% (16 out of 75) of the 5-year survivors. Perineural and lymphovascular invasion was documented in 69 and 24%, respectively. Poorly differentiated tumors were documented in 20% (15 out of 75) of the patients. Favorable variants of adenocarcinoma were seen in 8 of the 75 patients; 5 with a mucinous component, 1 with clear cells, 1 anaplastic, and 1 papillary tumor. The only significant clinicopathologic factors associated with 5-year survival were early American Joint Committee on Cancer (AJCC) stage and negative margins, with 26% (6 out of 23) of the stage Ia patients surviving beyond 5 years compared to 9% (30 out of 334) of the stage IIb patients (Fig. 2).

Within the group of 75 patients who survived 5 years, 38 patients were dead of disease and 2 patients were dead of another cause at the time of last follow-up. The site of first recurrence for the 38 patients who died of disease after 5 years could be determined in 19 patients. Within this group of patients, 47% were found to have local recurrence as the site of first recurrence. The site of first recurrence for the 53% of patients who were identified as having failed initially at a distant site was the lung in 32% (6 out of 19) and the liver in 11% (2 out of 19).

Five year survival unfortunately does not represent cure, with 26% (19 out of 75) of the patients dying of disease within the fifth year. Higher AJCC stage was associated with death in the fifth year. Within this group of 19 patients, a single patient who had stage Ia disease died, 9 patients had stage Ib disease, and 9 patients had stage IIb disease. No clinicopathologic factors (perineural invasion, lymphovascular invasion, poor differentiation, or adjuvant chemotherapy) were associated with death within the fifth year.

Survival beyond 10 years was experienced by 18 of the 353 patients (5%) who had potential 10-year follow-up. Early AJCC Stage was the only factor associated with actual 10-year survival (Table 2). Survival beyond 10 years was documented in 10% of the patients with stages I and

Table 1 Clinicopathologic Factors of Patients with Pancreatic Adenocarcinoma Who Underwent Curative Resection

Clinicopathologic Characteristics	Overall (<5-Year Survival), $N = 543$	Five-Year Survivors, $N = 75$	P Value
Median age	68 (range 34–92)	66 (range 38–84)	NS
Female	267 (49%)	42 (56%)	NS
Tumor location			NS
Head	487 (90%)	65 (88%)	
Body	28 (5%)	5 (6%)	
Tail	28 (5%)	5 (6%)	
Operation			NS
Pancreaticoduodenectomy	463 (85%)	62 (83%)	
Distal pancreatectomy	56 (10%)	8 (11%)	
Total pancreatectomy	24 (5%)	5 (7%)	
Stage of resected patients			<0.001
IA	17 (3%)	6 (8%)	
IB	120 (22%)	30 (40%)	
IIA	61 (11%)	9 (12%)	
IIB	334 (62%)	30 (40%)	
III	0	0	
IV	11 (2%)	0	
Margin			<0.001
Positive	158 (29%)	7 (10%)	
Negative	385 (71%)	68 (90%)	
Follow-up			<0.001
NED	(0%)	28 (37%)	
AWD	(0%)	4 (5%)	
DOD	503 (93%)	38 (51%)	
DOC	40 (7%)	5 (7%)	

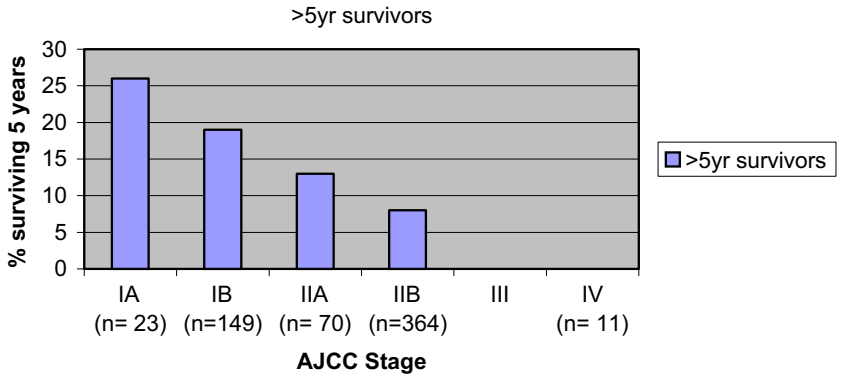

Figure 2 Percent of patients who survived more than 5 years.

Table 2 Clinicopathologic Factors of 5- and 10-Year Survivors Who Underwent Curative Resection of Pancreatic Adenocarcinoma

Clinicopathologic Characteristics	Five-Year Survivors, $N = 57$	Ten-Year Survivors, $N = 18$	P Value
Median age	66 (38–84 years)	64 (43–78 years)	NS
Female	32 (56%)	10 (56%)	NS
Tumor location			NS
Head	50 (91%)	15 (83%)	
Body	4 (7%)	1 (6%)	
Tail	3 (5%)	2 (11%)	
Operation			NS
Pancreaticoduodenectomy	48 (84%)	14 (78%)	
Distal pancreatectomy	5 (9%)	3 (17%)	
Total pancreatectomy	4 (7%)	1 (5%)	
Stage of resected patients			<0.001
IA	6 (11%)	10 (56%)	
IB	20 (35%)	2 (11%)	
IIA	7 (12%)	0	
IIB	24 (42%)	6 (33%)	
Margin			NS
Positive	4 (7%)	3 (17%)	
Negative	53 (93%)	15 (83%)	
Perineural invasion			NS
Yes	33 (58%)	7 (39%)	
No	13 (23%)	3 (17%)	
Unknown	11 (19%)	8 (44%)	
Perivascular invasion			NS
Yes	14 (24%)		
No	33 (58%)	10 (56%)	
Unknown	10 (18%)	8 (44%)	
Adjuvant chemotherapy			NS
Yes	12 (21%)	4 (22%)	
No	33 (58%)	10 (56%)	
Unknown	12 (21%)	4 (22%)	
Adjuvant Radiation			NS
Yes	9 (16%)	4 (22%)	
No	35 (61%)	10 (56%)	
Unknown	13 (23%)	4 (22%)	
Follow-up			<0.001
NED	15 (26%)	11 (61%)	
AWD	3 (5%)	1 (6%)	
DOD	35 (62%)	5 (27%)	
DOC	4 (7%)	1 (6%)	

IIA tumors and in 4% of patients with stage IIB tumors. There are currently two patients who have experienced 20-year survival; 1 was resected for a stage IB tumor and the other for a stage IIA tumor. Similar to the 5-year survivors, 22% (4 out of 18) of patients who survived 10 years had documentation of having received adjuvant therapy.

Discussion

Despite improvements in adjuvant therapy for pancreatic adenocarcinoma, surgical resection offers the only hope for long-term survival. A recent prospective randomized study by Imamura et al.[2] randomized patients with resectable pancreatic cancer to operative resection or radiochemotherapy with 5-FU/5040cGy. Patients who underwent resection had an improved 1-year survival and mean survival compared to patients who underwent chemoradiation (62 vs 32%, $p=0.05$; >17 vs 11 months, $p<0.03$).

Most studies reporting patient survival after pancreatic resection for pancreatic adenocarcinoma report estimated survival (actuarial). Since actual 5-year survivors are few in number, the reporting of an estimated 5-year survival results in widely disparate survival estimates that are highly dependent on the median length of follow-up. Because of the desire to accurately predict who will experience long-term survival from this disease, we sought to determine the actual 5-year survival for patients undergoing resection at a high volume tertiary care center and to further describe the course of disease after 5 years of survival has been achieved.

In the current study of 618 patients resected for pancreatic adenocarcinoma between 1983–1995, the actual 5-year survival rate was 12%. The factors found to be associated with this survival endpoint were the stage of disease at presentation and the margin of resection. Actual 5-year survival, however, was not found to be equivalent to cure as 38 of the 75 5-year survivors recurred and eventually died of disease. The pattern of disease recurrence in those who recurred of disease more than 5 years after resection was more often local than distant, and when distant, it was more likely to be identified in the lung than in the liver. This pattern of recurrence may reflect a different biology of disease.

These results are similar to other reports of actual 5-year survival (Table 3). Most series have suggested 5-year survival rates of 10–15%, and the factors associated with 5-year survival have been typically stage related. The study by Han et al. did suggest that long-term survival may be limited to histologic variants such as mucinous non-cystic carcinoma (colloid carcinoma). Reports from our institution and others have also found that patients with colloid carcinoma may experience long-term survival even in the setting of advanced T and N stage.[11] In this series, 4% (24 out of 618) of the patients had a favorable morphology. Positive nodes were documented in 13 out of 24 patients, and 4 out of 8 had positive nodes and survived beyond 5 years.

Analysis of the clinicopathologic variables in the group of 5-year survivors demonstrates the difficulty in prognostication for an individual patient. Only early AJCC Stage and negative margins were significant prognostic factors for 5-year survival. AJCC Stage was also a significant prognostic factor for the Hopkins and Toronto cohorts,[12,13] and Han et al. also reported margin status as a significant prognostic marker.[14] Despite these associations, 40% of the 5-year survivors and 33% of the 10-year survivors were resected in the setting of node-positive disease.

Some consider the extent of nodal dissection and margin status as surrogates for the completeness of the tumor resection. Extent of nodal dissection is confounded by the number of nodes pathologically assessed. Because there was no difference in the median number of nodes evaluated between patients who survived 5 years and those who did not, it is likely that staging was consistent between groups. Margin status is likely associated with the location and size of the tumor, and the subsequent difficulty in obtaining a negative margin for uncinate and head lesions that approximate the superior mesenteric artery. A negative resection margin was a significant prognostic factor. Median tumor size was 3.5 cm (range, 1–10 cm) for patients with positive margins, compared to 3.2 cm (range, 0.5–13 cm) for patients with negative margins.

Table 3 Comparison of Other Series with Actual 5-Year Survivors Post-Resection of Pancreatic Adenocarcinoma

	Number of Patients	Female	Whipple	Median Survival (Months)	Actual 5- and 7-Year Survival	Predictors of Survival
Ahmad et al.[17]	116	54%	95%	16	19 and 11%	Adjuvant therapy
Cleary et al.[13]	123	43%	91%	14	15 and 4% (10 years)	AJCC stage grade
Winter et al.[12]	1175	46%	100%	18	18 and 11% (10 years)	Tumor size, lymph node, margin, histological grade, COPD, bile leak, adjuvant therapy
Han et al.[14]	123	29%	81%	15	12%	AJCC Stage Margin
Present (2007)	618	309	525		12 and 5%	Negative margins, AJCC stage

Preoperative comorbidities and postoperative complications affect not only a patient's 30-day mortality but may also affect their long-term disease-specific survival.[15] There was no significant difference in LOS for the 5-year survivors. LOS has been reported as a surrogate for both the degree of preoperative morbidity as well as the number and severity of postoperative complications. Therefore, it is unlikely that the 5-year survivors survived because of fewer preoperative comorbidities or postoperative complications. Postoperative complications are difficult to gather retrospectively; however, LOS is reported consistently and may represent the most accurate indicator of overall morbidity of a procedure when obtaining data retrospectively. Although LOS has been shown to be influenced by non-clinical factors such as discharge destination, socioeconomic status, and type of insurance, these variables probably play less of a role in cancer patients than they do in trauma patients.[16]

In the current study, patients resected for pancreatic adenocarcinoma experienced a 5-year survival of 12% and a 10-year survival of 5%. Five-year survival, however, was not consistent with cure as an additional 26% (19 out of 75) patients died of disease within the fifth year and an additional 19 patients died of disease at the time of last follow-up. Only AJCC stage and margin status were significant predictors of long-term survival. These data support the position that surgical resection is a woefully inadequate treatment for the majority of patients with pancreatic adenocarcinoma even in the favorable minority with resectable disease and highlights the need for improved screening for early detection and better neo-adjuvant and adjuvant systemic therapies.

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Laparoscopic vs. Open Resection of Noninvasive Intraductal Pancreatic Mucinous Neoplasms

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Abstract
Required resection margins for noninvasive intraductal papillary mucinous neoplasms (IPMNs) are a controversial issue. Over a 10-year period we have resected IPMNs from the entire pancreatic gland with minimally invasive techniques and compared our survival and complication rates with open controls to see if any difference in resection margins and outcomes could be observed. Data were collected retrospectively, including our first cases of advanced laparoscopic resections. Five-year Kaplan–Meier curves were calculated and statistical analysis was performed using the log rank and Student's *T* test for continuous variables. Chi square and Fisher's exact tests were used for analyzing categorical variables. From March 1997 to Febuary 2006, we operated on 22 patients with noninvasive IPMNs, of which 9 (41%) were operated on laparoscopically and 13 (59%) using open techniques. Three patients underwent laparoscopic duodenopancreatectomy, compared to five in the open group. All resection margins were negative, but two patients required total pancreatectomy, both of which were performed laparoscopically. One of these was converted to open (11%) because of difficulty in reconstructing the biliary anastomosis. The overall complication rates were 56% for the laparoscopic group and 85% for the open group. Twenty-two percent of the laparoscopic group required reoperation and 11% required percutaneous drainage, compared to 15 and 23% in the open group, respectively. All patients are alive after a mean of 20 months (range=2–43) in the laparoscopic group and 37 months (range=1–121) in the open one ($p>0.05$). Laparoscopic resection of noninvasive IPMNs of the entire pancreatic gland has similar complication and survival rates as open procedures. As a result, the laparoscopic approach is appropriate for noninvasive IPMNs of the entire pancreatic gland; however, larger cohorts are needed to see if any approach has superior outcomes. Because of these favorable results, studies are currently underway to see if the minimally invasive approach is also appropriate for invasive IPMNs.

Keywords IPMN · Intraductal · Pancreatic · Mucinous · Neoplasm · Laparoscopic

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) were first recognized over three decades ago and subsequently reported by varying names.[1,2] Recognizing the need for a unifying nomenclature, a classification system for mucinous tumors of the pancreas was described by the World Health Organization in 1996, differentiating IPMNs from other mucinous cystic tumors of the pancreas.[1] Since this time, IPMNs have been reported with greater frequency, but difficulties in differentiating these lesions from mucinous cystic neoplasms (MCNs) have persisted.[3–5] As a result, international consensus guidelines for the management of IPMNs and MCNs were published in 2006 to help physicians properly diagnose and treat these lesions. The current definition of IPMN is an intraductal, mucin-producing neoplasm with tall, columnar, mucin-containing epithelium with or without papillary projections. The pancreatic ducts are extensively involved, and as opposed to MCN, IPMNs lack ovarian-type stroma.[1,3,4] As with mucinous cystadenocarcinomas, invasive IPMNs have been reported to recur after margin negative pancreatic resec-

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tions; however, unlike benign MCNs, noninvasive IPMNs have also been reported to recur after R0 pancreatic resections.[3] The potential multifocality and late recurrence of invasive and noninvasive IPMNs has made surgical management particularly troublesome.

Since Gagner's first reports of pancreatic resections, pancreatic surgeons have concomitantly been making advances in the field of minimally invasive hepato-pancreato-biliary surgery. Currently, conventional indications for pancreatic resections include benign pancreatic tumors that are small and confined to the body and tail of the pancreas. Controversy currently exists as to the need for negative margins in noninvasive IPMNs and the suitability to perform these resections laparoscopically. Because of concerns with adequacy of oncological margins via the minimally invasive approach, we compared our laparoscopic IPMN outcomes and complication rates with our open experience.

Methods

Data were reviewed retrospectively during a 10-year period when IPMNs of the entire pancreas were removed laparoscopically. Survival and complication rates were then compared with open controls. Statistical analysis was performed using Student's *T* test for continuous variables and chi square and Fisher's exact tests were used for analyzing categorical variables (Excel, Microsoft, Redmond, WA, USA).

All patients presenting with symptoms of either jaundice, abdominal pain, or diarrhea were considered for surgery. Preoperative work-up included an echo-endoscopy and cholangiogram via endoscopic retrograde pancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP). Preoperatively, tumors were stratified into main duct, branch duct, or combined variants preoperatively because the rate of malignancy seems very different (15% for lateral ducts, 70% for the main pancreatic duct), despite the absence of clear differences in survival for others.[3] The operative approach for main duct and combined variants was anatomic R0 resection.[6] All pancreatic tumors were approached laparoscopically by one surgeon and by open techniques by two other surgeons. For the minimally invasive surgeon, even tumors with preoperative evidence of invasion of the superior mesenteric or portal vein were approached laparoscopically and only converted to open for the vascular reconstruction. Preoperative evidence of invasion of the superior mesenteric artery or metastases were considered contraindications for surgery, and neo-adjuvant chemotherapy was considered.

In high-risk patients with a branch duct variant, enucleation with negative frozen section of the efferent duct was attempted for tumors in the head and neck of the pancreas.[7] Noninvasive IPMNs were stratified into adenoma, borderline neoplasms, and carcinoma in situ (CIS) on histopathology. Invasion was diagnosed when patients were found to have documented histopathological evidence of tumor cells infiltrating the pancreatic connective tissue or metastasis. All patients underwent intraoperative frozen section analysis to confirm presence of negative margins. Total pancreatectomy was performed when negative margins could not be accomplished after re-resection for both invasive and noninvasive tumors, although recent evidence suggests that this may not be necessary for noninvasive tumors.[8]

Complications were defined as major and minor according to the classification system devised by Dindo et al.[9] Any complications that could be managed with medication and fall into category grade IIIa or less were considered minor complications. Any complication that required an intervention, percutaneous or surgical, was considered a major complication; this corresponds to a grade IIIb complication or higher.[9] Five-year actuarial survival was calculated according to Kaplan–Meier, any difference was analyzed with the log rank test to ascertain statistical significance (Excel, Microsoft).

Results

From March 1997 to Febuary 2006 we operated on 36 patients for IPMN's, of which 9 (25%) were operated on laparoscopically and 27 (75%) using open techniques. A total of 14 patients were found to have invasive disease on final pathology. All of these cases were approached via open techniques. Of the remaining patients, 9 (41%) were operated on laparoscopically and 13 (59%) with open techniques (Table 1). The first laparoscopic procedure was performed in 2001. The average age for the laparoscopic group was 58 years compared to 63 in the open group. The

Table 1 Patient Statistics of 22 Patients Undergoing Pancreatic Resection for Noninvasive IPMN, Laparoscopic vs. Open

	Laparoscopic	Open
Number	9	13
Age (years)	58	63
Tumor size (cm)	3.0	3.1
Operative time (min)	274	339
Blood loss (mL)	143	281
LOS (days)	20	24
Average follow-up (months)	20	37

Overall morbidity includes the total number of major and minor complications (see Table 4); none of the differences were statistically significant ($p>0.05$)

mean tumor sizes were also similar at 30 mm and 31 mm for the laparoscopic and open groups, respectively. The mean operative times and estimated blood loss were 274 min and 143 mL, compared to 339 min and 281 mL.

The distribution of procedures is seen in Table 2. Duodenopancreatectomy (DPC) was performed laparoscopically in three patients and in five patients via laparotomy. Distal pancreatectomy with splenic preservation was performed in two and three patients in the laparoscopic and open groups, respectively. Central pancreatectomy was performed in one patient via laparotomy. Total pancreatectomy was performed laparoscopically in two patients. One patient had a previous distal pancreatectomy for a noninvasive CIS IPMN at another institution, and the resultant open DPC was essentially a completion of a total pancreatectomy. Enucleations in the head of the pancreas were performed in the remaining patients, two in the laparoscopic group and two in the open group. An additional two patients underwent open extended enucleations or limited resections in the uncinate process and neck, respectively. In the invasive cohort, eight patients necessitated a DPC, five a distal pancreatectomy, and one a total pancreatectomy. All resection margins were negative, but, as mentioned, a total of four patients required total or completion pancreatectomy. Distribution of subclassifications of noninvasive tumors into adenoma, borderline, and CIS is shown in Table 3. Among the patients with noninvasive disease, an average of 13 lymph nodes (range=10–24) were retrieved after laparoscopic DPC, compared to an average of 16 (range=14–26) in the open group.

One laparoscopic procedure was converted to open (11%) because of difficulty in reconstructing the biliary anastomosis after total pancreatectomy. Five patients (56%) operated on laparoscopically suffered complications (Table 4), two of which required interventions (22%). The first was due to postoperative hemorrhage from a pseudoaneurysm of the gastroduodenal artery (GDA), which was embolized by interventional radiology. The other patient suffered an upper gastrointestinal bleed from the pancreaticogastrostomy, which had to be taken down and redone. Other complications in the minimally invasive group included pancreatic fistula in a total of three patients, requiring drainage in one (11%) patient. One of these cases occurred in the patient with the postoperative bleed from the GDA; fortunately, this complication did not require reoperation.

Among the open cases, 11 patients with noninvasive disease (68%) suffered either major or minor complications (Table 4). A total of five patients suffered major complications, two (15%) of which required reoperation. One patient developed a gastric volvulus postoperatively that was also further complicated by an acute attack of pancreatitis. One patient bled postoperatively from the right hepatic artery and required urgent surgery. This patient subsequently developed a pancreatic fistula that did not require surgery. Three other patients (23%) required drainage of abscesses, two of which were associated with pancreatic fistulas. The remaining minor complications included intra-abdominal

Table 2 Distribution of Procedures Done for Noninvasive Intraductal Papillary Neoplasms, Laparoscopic vs. Open

	Laparoscopic	Open
Total	9	13
DPC	3	5[a]
Splenic-preserving left pancreatectomy	2	3
Total pancreatectomy (conversion)	2 (1)[b]	0
Enucleation (pancreatic wedge resection)	2	2 (2)
Central pancreatectomy	0	1

[a] DPC after left pancreatectomy resulting in completion total pancreatectomy

[b] After the resection, this patient had to be converted to open to perform the bili-enteric anastomosis

Table 3 Final Histopathology of all Noninvasive Intraductal Papillary Neoplasms

	Laparoscopic	Open
Adenoma	3	4
Borderline	4	6
CIS	2	3

Table 4 List of Overall Complications in Patients with Noninvasive Intraductal Papillary Neoplasms

	Laparoscopic	Intervention Required (%)	Open	Intervention Required (%)
Total patients	5 (56)	3 (33)	11 (85)	5 (38)
Pancreatic fistula	3	1 (11)	3	2 (15)
Postoperative hemorrhage	1	1 (11)	1	1 (8)
Intra-abdominal abscess	0	0	3	1 (8)
Necrotizing pancreatitis	0	0	1	0
Upper gastrointestinal bleed	1	1 (11)	0	0
Urinary tract infection	0	0	1	0
Gastric volvulus	0	0	1	1 (8)
Biliary fistula	0	0	1	0
Wound infection	0	0	1	0

Intervention consisted of surgery or percutaneous drainage performed by interventional radiology

fluid collections, biliary fistula, and urinary tract and wound infections.

In the invasive group, 53% of patients suffered complications. One patient presented with necrosis of the right hepatic artery that required a vein graft and was complicated by necrotizing pancreatitis necessitating multiple repeat trips to the operating room. This patient left the hospital after almost 11 months of a prolonged stay in the intensive care unit. Other complications in the invasive group included two partial splenic infarctions that did not require surgery and were treated with antibiotic prophylaxis.

There were no perioperative mortalities. In the noninvasive cohort, the average hospital stay and follow-up was 20 days and 20 months (range=2–43) in the laparoscopic group and 24 days and 37 months (range=1–121) in the open group; none of these differences was statistically significant. As opposed to institutions in North America, patients are usually kept in the hospital until all drains are removed even if they may be ambulating and tolerating a regular diet. In the invasive group, the average length of stay (LOS) was 46 days (range=4–311) and the mean follow-up was 34 months. The overall survival rates were 100% for the laparoscopic and open noninvasive groups and 51% for the group with invasive disease.

Discussion

In an effort to guide the practicing surgeon, a complex system of histopathological classification of IPMNs has been developed and studied. Initial studies differentiated IPMNs that are isolated to the main pancreatic duct from lesions in the smaller ducts, so-called branch duct variant.[10] Combined variants contain components of both types. Although many authors have attempted to ascertain differences in outcomes among these groups, the largest single center experience with IPMNs noted no statistically significant differences in survival, although they did find that the branch–duct variant is more commonly noninvasive.[3] Nonetheless, multiple centers have noted that main duct and combined variants are more often invasive.[11,12] Studies from Japan have found that main duct types and/or the presence of mural nodules are predictive of malignancy and invasion.[12,13]

Although pathologists have further classified noninvasive IPMNs into adenomas, borderline neoplasms, and CIS, the Johns Hopkins group noted no differences in survival. Invasive groups have been further classified into tubular, colloid, mixed, and anaplastic types by some groups.[3] Interestingly, the Hopkins group did find a survival advantage in patients with colloid carcinomas as compared to tubular carcinomas.[3] A new consensus conference in 2005 created an IPMN classification system that separates IPMNs into gastric, intestinal, pancreatobiliary, and oncocytic subtypes.[2] According to Asian studies, branch duct variants are more often gastric-type (98%), and main duct variants are more often intestinal-type (73%); furthermore, 23% of intestinal type IPMNs are found to be invasive vs. 2% for the gastric-type.[14] Because of the current controversy involving classifications of IPMNs, our department of pathology does not subclassify invasive IPMNs.[14]

Prior to the consensus conference of 2006, our operative approach was to resect all noninvasive and invasive IPMNs until an R0 resection could be achieved.[15] This was done by intraoperative frozen section analysis.[16] Unfortunately, this resulted in two patients with noninvasive IPMNs undergoing total pancreatectomy and having to live a life with the difficult task of managing brittle diabetes with all of its associated sequelae, which can even include death.[6] According to the new guidelines, adenomas that are not symptomatic can be observed with yearly screening. Borderline noninvasive cases are still debatable, but it was the consensus that all CIS patients regardless of presence or absence of symptoms should undergo surgery.[15] This argument was extended to include all noninvasive subtypes because of the low risk of tumor recurrence in microscopically positive resection margins.[17] Invasive tumors have a similar natural history to pancreatic adenocarcinomas and R0 resections are the standard of care.[18–20]

At our institution, we attempt preoperative localization in all patients with a suspected IPMN to aid the operative approach, specifically, port placement and patient positioning. The pancreatic duct is imaged via ERCP or MRCP; however, many patients are often diagnosed after helical CT with very thin slices, intravenous contrast, and a pancreatic protocol including a rapid arterial phase.[21] All patients also undergo endoscopic ultrasound to determine whether or not the main pancreatic duct is involved and the proximity to the superior mesenteric vessels and portal veins.[22] In difficult cases we also obtain endoscopic ultrasound fine needle aspirations to assist in our preoperative diagnosis.[23,24] Smaller tumors without evidence of obvious invasion are classified as pancreatic intraepithelial neoplasia and observed.[3,25] Because of the increased risk of malignancy in main duct IPMNs, formal resection is recommended, although recent work suggests that asymptomatic branch duct IPMNs can be observed.[10,25,26] Patients who are good operative candidates, with main duct disease, are offered surgery. High-risk patients with small tumors (<10 mm) can be observed, but all patients regardless of operative risk are offered surgery if they have preoperative evidence of intramural nodules because of increasing evidence that these tumors have a high risk of invasiveness.[27]

Prior to this study, the GDA was clipped laparoscopically with plastic locking clips and reinforced with a 4.0

nonabsorbable suture ligature. Currently, we employ only titanium clips with silk suture ligature or use the endoscopic vascular TA stapler. We now only preserve the spleen when the splenic vein can be preserved without any evidence of tear or stenosis. Ideally, the splenic artery and vein are spared in localized tumors (malignant or benign) of the distal pancreas necessitating resection of the tail; however, if necessary, the splenic artery can be sacrificed proximally if the arterial blood supply via the gastroepiploic is left intact. The splenic vein is always preserved because of reports of delayed segmental portal hypertension after transection of this structure in cases of splenic preservation.[28] If this is not possible, a splenopancreatectomy should be considered.

Limitations of this study are the small number of the cohorts, the fact that only one surgeon performed procedures laparoscopically, and the fact that both cohorts were not completely concomitant. Specifically, the first laparoscopic procedure was done 4 years after the first open IPMN resection. Comparisons with other international institutions are also difficult due to the fact that we have no incentive to discharge patients early, which may partially explain why our LOS may be longer than other results reported in the literature. Nonetheless, the fact that no significant differences exist in LOS when our two groups are compared indicates that this does not seem to be significantly effected. Another problem with our study is the high rates of reoperation and need for percutaneous drainage. This fact, however, is tempered by the fact that we have no perioperative mortalities, which is notably lower than that normally reported in the literature.

Conclusions

The minimally invasive management of IPMNs has been hindered by the fact that many of these tumors present in the head of the pancreas. Surgeons have been reluctant to embrace laparoscopic techniques for lesions in the head of the pancreas because of the perceived difficulty in dissecting the head of the pancreas off of the portal vein, superior mesenteric vein, and superior mesenteric artery and the complexity of the reconstruction. Nonetheless, as more and more surgeons gain experience in both hepato-pancreato-biliary surgery and minimally invasive techniques, the indications for minimally invasive approaches to pancreatic pathology have been increasing.

At our institution, we have now successfully performed eight out of nine laparoscopic procedures for the treatment of noninvasive IPMN. These tumors have identical overall 5-year survival rates to open controls. Overall major and minor complication rates and reoperation rates are similar. Although this series is small, it would appear, in high-volume centers with experience in both pancreatic and laparoscopic surgery, that the minimally invasive approach is appropriate for the management of noninvasive and invasive IPMNs of the entire pancreatic gland; however, larger cohorts are needed to see if any approach has superior outcomes. Because of these favorable results, studies are currently underway to see if the minimally invasive approach is also appropriate for invasive IPMNs.

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Radical Surgical Resection for Carcinoid Tumors of the Ampulla

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Abstract Ampullary carcinoid tumors are extremely rare. The present study describes the clinicopathological features and outcomes for 10 ampullary carcinoid patients who underwent radical resection from 1998 to 2005. During this study period, 294 patients underwent pancreatoduodenectomy for ampullary neoplasms in our institution. The mean patient age was 58.0± 13.4 years, and seven were male. Initial clinical manifestations were jaundice in four patients, nonspecific gastrointestinal symptoms in five, and completely asymptomatic in one. Standard pancreatoduodenectomy was performed in three patients, and pylorus-preserving pancreatoduodenectomy in seven, and there were no major complications. The mean tumor size and volume were 2.1±1.3 cm and 4.1±6.9 ml, respectively. Synaptophysin staining was positive in ten patients and chromogranin staining positive in eight. R0 resection was achieved in all ten patients. Overall and disease-free survival rates were 90 and 80% at 1 year, and 64 and 56% at 3 years, respectively. The liver was the most common site of initial metastasis after curative resection. Univariate analyses revealed that a maximal tumor diameter ≥2 cm and tumor extension beyond the ampulla were risk factors for tumor recurrence. In conclusion, while the majority of ampullary carcinoids are indolent, this tumor is associated with a relatively poor prognosis. We believe that radical resection, with the aim of complete tumor removal and cure, is the treatment of choice.

Keywords Carcinoid tumor · Ampulla of Vater · Neuroendocrine tumor · Pancreatoduodectomy

Introduction

Carcinoid tumors account for only 1–2% of gastrointestinal neoplasms and less than 2% of such tumors occur at the ampulla of Vater.[1,2] To date, only approximately 100 ampullary carcinoids have been described, most in single-case reports.[3]

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Ampullary carcinoid tumors belong to the neuroendocrine tumor family and can cause symptoms usually secondary to their periampullary location. Histopathological assessment using immunohistochemical staining is important for diagnosis. Aggressive surgical resection is the cornerstone of treatment and provides the only possibility for cure. Interestingly, it is reported that the ampullary carcinoid size does not correlate with metastatic potential.[4] While long-term survival has been achieved by local excision of the ampulla, radical resection through pancreatoduodenectomy is accepted as the treatment of choice as it removes all tumor-bearing tissue.[2–8]

The present report describes clinicopathological features and outcomes for 10 ampullary carcinoid tumor patients who underwent pancreatoduodenectomy.

Patients and Methods

From January 1998 to December 2005, 294 patients underwent pancreatoduodenectomy for various neoplastic

diseases of the ampulla (malignant tumors in 277 and benign tumors in 17) in our institution. Of those, ten (3.4%) patients were diagnosed as having ampullary carcinoid tumors. Immunohistochemical analysis was performed for synaptophysin and chromogranin expression. All patients attended routine follow-up every 3 months. Clinical data were retrospectively obtained from the medical records, and the surviving patients were followed up until July 2007.

Pancreatoduodenectomy specimens were analyzed for tumor extent. The maximal tumor diameter was classified as either <1 cm, 1–1.9 cm, or ≥2 cm, and the tumor volume was classified as <1 ml, 1–2.9 ml, or ≥3 ml using the formula for an ellipsoid mass.

Numeric data are expressed as mean±SD. Survival curves were estimated using the Kaplan–Meier method and were compared using the log-rank test. A p value<0.05 was considered to indicate a significant difference.

Results

Clinical Findings

The series consisted of ten cases of ampullary carcinoids undergoing standard or pylorus-preserving pancreatoduodenectomy. The mean patient age was 58.0±13.4 years (range, 33–79), and seven patients were male. The initial clinical manifestations were jaundice (n=4), nonspecific gastrointestinal symptoms including upper abdominal pain and nausea (n=5), and completely asymptomatic (n=1). No patient had specific neuroendocrine symptoms or skin lesions. No patient showed signs of von Recklinghausen's disease or Zollinger-Ellison syndrome.[9,10] Clinical profiles are summarized in Table 1.

Preoperative Workup

All patients routinely underwent multidetector abdomen computed tomography, magnetic resonance cholangiopancreatography/angiography, and duodenofibroscopy or endoscopic retrograde cholangiography. Preoperative endoscopic biopsies were performed in nine patients, resulting in a diagnosis of carcinoid tumor in four patients, and a misdiagnosis of adenocarcinoma in five patients.

Treatment

Three patients underwent standard pancreatoduodenectomy, and seven underwent pylorus-preserving pancreatoduodenectomy. No major complications occurred other than minor transient leaks at the pancreatojejunostomy site. No patient underwent radiological intervention or re-exploration. Adjuvant chemotherapy was administered in three patients.

Table 1 Clinical Features and Outcomes of Patients Undergoing Pancreatoduodenectomy for Ampullary Carcinoid Tumors

Case Number	Sex	Age (years)	Chief Complaint	Tumor Size Category (cm)	Tumor Volume category (ml)	Operation	Adjuvant Chemotherapy	Recurrence	Initial Recurrence Site	Recurrence Treatment	Disease-Free Survival Period (months)	Survival Outcome
1	Male	33	Jaundice	≥2	<1	PPPD	No	Yes	Mesenteric root	Conservative	6	9 months, died of disease
2	Male	62	Jaundice	≥2	≥3	PPPD	Yes	Yes	Liver	Chemotherapy	6	16 months, died of disease
3	Female	56	Jaundice	1–1.9	<1	PPPD	Yes	Yes	Pancreas tail	Chemotherapy	37	42 months, died of disease
4	Male	74	Nausea	≥2	≥3	PPPD	No	No	–	–	31	31 months, died of other cause
5	Female	65	Jaundice	≥2	≥3	PPPD	Yes	Yes	Liver	Chemotherapy, radiotherapy	30	44 months, alive with disease
6	Female	49	Abdominal pain	1–1.9	1–2.9	PPPD	No	No	–	–	38	38 months, alive
7	Male	51	Abdominal pain	1–1.9	<1	PPPD	No	No	–	–	35	35 months, alive
8	Male	49	Incidental	<1	<1	PD	No	No	–	–	29	29 months alive
9	Male	62	Incidental	1–1.9	<1	PD	No	No	–	–	21	21 months, alive
10	Male	79	Abdominal pain	≥2	≥3	PD	No	Yes	Liver	Radiofrequency ablation	13	20 months, alive with disease

PD Pancreatoduodenectomy, *PPPD* pylorus-preserving pancreatoduodenectomy

Pathology and Immunohistochemical Findings

The ampullary carcinoid tumors ranged in size from 0.7 to 5.0 cm in the greatest diameter (mean, 2.1±1.3 cm) and from 0.2 to 22.5 ml in tumor volume (mean, 4.1±6.9 ml). The tumor lesion was confined to the ampulla in five cases (Fig. 1), extended to the duodenum in two, and penetrated into the pancreas in three cases. The depth of tumor invasion was submucosal in three cases, proper muscle in five, and serosal in two cases. Pathology profiles are summarized in Table 1. Lymph node metastasis was detected in two patients. R0 resection was achieved in all ten patients. All ten cases were synaptophysin-positive, and eight were chromogranin-positive (Fig. 2). Pathology findings and immunohistochemistry results are summarized in Table 2.

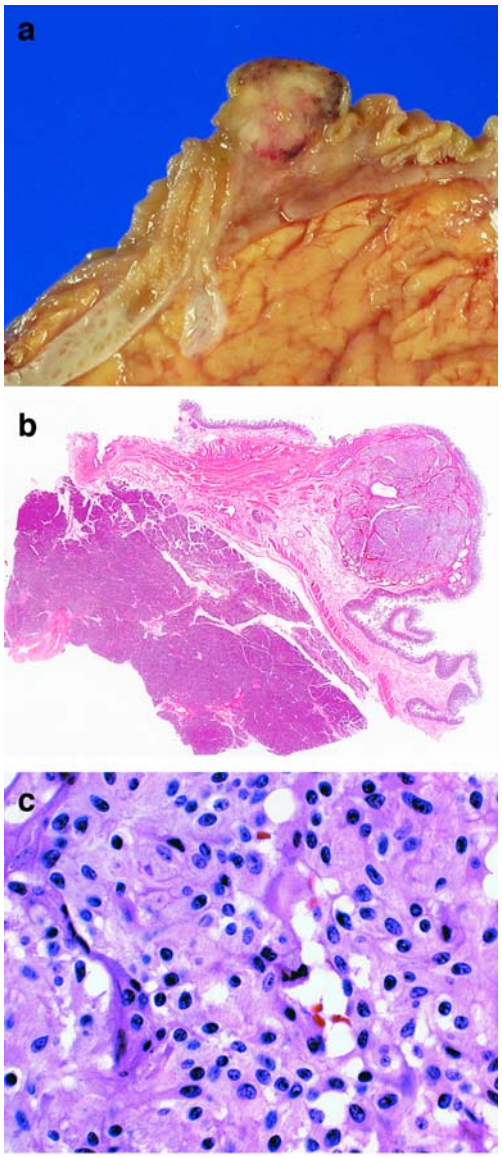

Figure 1 Gross and microscopic photographs of the pancreatoduodenectomy specimen for case 6. **a** The largest tumor diameter was 1.6 cm at the cross-sectioned specimen. **b** Proliferation of neoplastic neuroendocrine cells in the lamina propria and submucosa. Tumor cell invasion of the duodenal papillary muscle (H&E, 1:1 scan). **c** Uniform polygonal tumor cells with finely granular chromatin and eosinophilic cytoplasms (H&E, ×400).

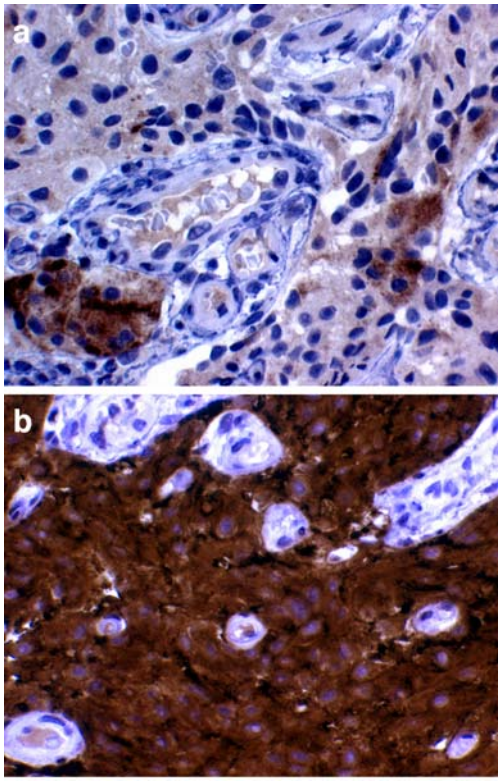

Figure 2 Immunohistochemical study of the ampullary carcinoid tumor for case 6. **a** Weakly positive chromogranin staining (×400). **b** Strongly positive synaptophysin staining. Immunohistostaining showed negative results for α-smooth muscle actin, CD 34, CD 117, and Ki67.

Patient Survival

The duration of follow-up ranged from 9 to 44 months (mean, 28.5±11.7). Six patients were alive at the last follow-up, and four had died. Patient survival data are summarized in Table 1. Four patients died of tumor recurrence, and one of other causes. The overall 1-, 2-, 3-, and 4-year patient survival rates were 90, 80, 64,and 32%, respectively (Fig. 3).

Tumor Recurrence and Risk Factor Analysis

Recurrence of the ampullary carcinoid occurred in five patients. Disease-free 1-, 2-, 3-, and 4-year patient survival rates were 80, 70, 56,and 28%, respectively (Fig. 4). The liver was the most common site of initial metastasis. The mean survival period after tumor recurrence was 8 months (range, 3–14) despite aggressive recurrence treatments.

Table 2 Histopathological and Immunohistochemical Profiles of the Ten Ampullary Carcinoid Tumors

Case Number	Maximal Tumor Diameter (cm)	Tumor Volume (ml)	Adjacent Organ Invasion	Depth of Invasion	Lymph Node Metastasis	Chromogranin	Synaptophysin
1	2	0.6	Duodenum	Serosa	Absent	Positive	Positive
2	2.3	3.6	Pancreas	Proper muscle	Absent	Positive	Positive
3	1	0.3	None	Submucosa	Absent	Positive	Positive
4	3.5	8.3	Pancreas	Proper muscle	Absent	Positive	Positive
5	5	22.5	Pancreas	Serosa	Present	Positive	Positive
6	1.6	1.5	None	Proper muscle	Absent	Positive	Positive
7	1	0.4	None	Submucosa	Absent	Positive	Positive
8	0.7	0.2	None	Submucosa	Absent	Negative	Positive
9	1.5	0.5	None	Proper muscle	Present	Negative	Positive
10	2.7	3.3	Duodenum	Proper muscle	Absent	Positive	Positive

Univariate analyses of the pathological factors revealed that a maximum tumor diameter ≥2 cm and tumor extension beyond the ampulla were risk factors for tumor recurrence (Table 3).

Discussion

While carcinoid tumors are the most common tumors of the small bowel, they very rarely occur at the ampulla of Vater. Due to the ampullary location, the common clinical manifestation is jaundice as per other ampullary neoplasms. In the present series, half of the patients complained of nonspecific gastrointestinal symptoms. In fact, the ampullary mass was not suspected before endoscopic or imaging studies in six of the ten patients. In Korea, Recklinghausen's disease, a neurofibromatosis of autosomal dominant inheritance, is extremely rare, indicating it was unlikely to be associated with any of the current cases.

The diagnostic modalities for ampullary carcinoids are the same as those for more common ampullary adenocarcinomas. Magnetic resonance cholangiopancreatography with angiography appears to be a very valuable evaluation tool for suspected ampullary pathologies, as it can show the enhancing discrete submucosal mass and the biliary/vascular anatomy simultaneously.[7,11] Indeed, ampullary masses are usually suspected of being adenocarcinomas before specific immunohistochemical studies. In the present series, five of the nine patients were initially misdiagnosed before resection as having ampullary adenocarcinomas. Unlike ampullary carcinoids, duodenal carcinoids have different clinicopathological features.[5]

In the present series, diagnostic confusion between an ampullary carcinoid vs an adenocarcinoma did not alter the surgical plan, as the treatments for these two ampullary neoplasms are identical (pancreatoduodenectomy) in our institution. Although endoscopic ampullectomy or local excision for ampullary carcinoids has been reported,[7,8]

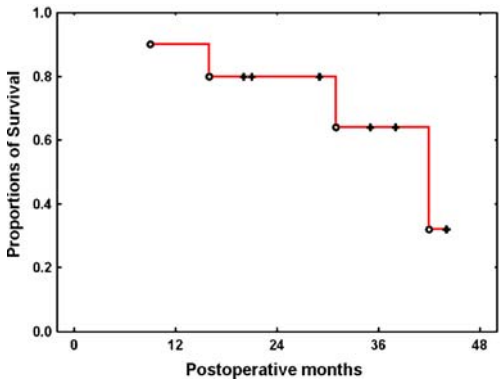

Figure 3 Overall survival curve for the ten patients undergoing pancreatoduodenectomy for ampullary carcinoid tumors.

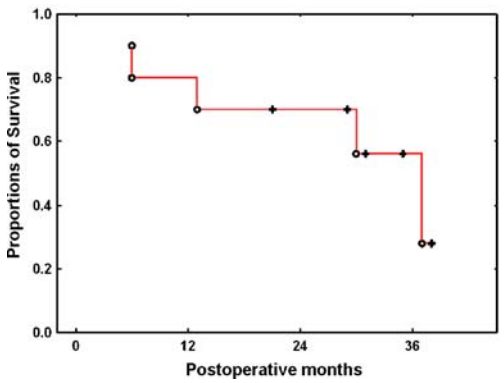

Figure 4 Disease-free survival curve for the ten patients undergoing pancreatoduodenectomy for ampullary carcinoid tumors.

Table 3 Univariate Analysis of the Risk Factors for Tumor Recurrence in Ten Patients Undergoing Pancreatoduodenectomy for Ampullary Carcinoid Tumors

Parameter	Cases	3-Year Recurrence Rate (%)	*p* Value
Maximal tumor diameter			*P*=0.046
<1 cm	*n*=1	0	
1–1.9 cm	*n*=4	0	
≥2 cm	*n*=5	80	
Tumor volume			*p*=0.358
<1 ml	*n*=5	20	
1–2.9 ml	*n*=2	0	
≥3 ml	*n*=4	75	
Adjacent organ invasion			*p*=0.031
Within the ampulla	*n*=5	0	
Invasion to the duodenum or pancreas	*n*=5	80	
Depth of invasion			*p*=0.119
Submucosa or proper muscle	*n*=8	25	
Serosa	*n*=2	100	
Lymph node metastasis			*p*=0.817
Absent	*n*=8	37.5	
Present	*n*=2	100	

aggressive resection through pancreatoduodenectomy is accepted as the treatment of choice.[4] The postoperative courses of the ten patients in the present series were uneventful, and this reflects that the surgical risks associated with pancreatoduodenectomy have decreased in high-volume centers.[12]

It has been reported that ampullary carcinoid tumor size does not correlate with metastatic potential and tumor recurrence. One case review reported that metastasis was present in 46% of ampullary carcinoids >2 cm, in 50% between 1 and 2 cm, and in 66% <1 cm.[4] Another study reported metastases in two tumors measuring less than 2 cm, yet there is no evidence of metastatic disease in a 5-cm-sized tumor.[5] These results indicate that ampullary carcinoids metastasize in approximately half of cases regardless of tumor size. Consistent with those findings, the present study found that lymph node metastasis was not correlated with tumor size. However, maximal tumor diameter ≥2 cm and tumor extension beyond the ampulla were found to be risk factors for tumor recurrence after curative resection, which is compatible with the classical observation for other gastrointestinal carcinoids that metastasis is more commonly associated with larger tumors. As the survival outcomes in terms of tumor size remain unclear, it is not yet reasonable to suggest that resection extent can be determined according to the ampullary carcinoid size. Considering the acceptably low surgical risk in large-volume centers, we believe that pancreatoduodenectomy is the treatment of choice for ampullary carcinoids regardless of size, presuming the patient condition is appropriate.[3,7]

In principle, we have administered adjuvant chemotherapy for large tumors or lymph node metastases in patients undergoing pancreatoduodenectomy for ampullary malignancies. However, in practice, there is no consensus regarding chemotherapy for ampullary carcinoids or ampullary adenocarcinomas. While tumor-targeted radioactive therapy based on somatostatin analogs is a newly emerging treatment option,[13] the expression of somatostatin in ampullary carcinoids is not yet known.[5,14]

In conclusion, although the majority of ampullary carcinoid tumors are indolent in nature, this tumor is associated with a relatively poor prognosis. Therefore, we believe that radical resection, with the aim of complete tumor tissue removal and cure, is the treatment of choice.

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Prognostic Impact of Sarcomatous Change of Hepatocellular Carcinoma in Patients Undergoing Liver Resection and Liver Transplantation

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Abstract Sarcomatous change has been rarely observed in hepatocellular carcinoma (HCC), but it is usually associated with very aggressive tumor behavior and widespread metastasis. To assess the impact of sarcomatous changes, we analyzed the outcomes of 15 patients with sarcomatous HCC after resection (n=11) or liver transplantation (LT) (n=4). No imaging findings characteristic of sarcomatous changes were observed. According to modified pathological tumor-node metastasis staging, the HCC lesions were classified as stage II in five patients, stage III in six, stage IVa2 in two, and stage IVb in one. The Milan criteria were met in 7 of 15 patients, including 3 of 4 in the LT group. R0 resection was achieved in 9 of 11 resected patients, and their 3-year overall and disease-free survival rates were both 18.2%. In the LT group, 3-year overall and disease-free survival rates were 37.5 and 25%, respectively. In patients within the Milan criteria, 2-year overall survival rate was 25% after resection and 33% after LT, showing no prognostic difference. Extrahepatic metastasis as initial recurrence was detected in 80% after resection and 66.7% after LT. In conclusion, we found that the prognosis of patients with sarcomatous HCC was very unfavorable after either resection or LT and that, except for liver biopsy, no diagnostic method could distinguish between sarcomatous and ordinary HCC. Vigorous postoperative systemic surveillance may be helpful for timely detection and treatment of localized metastases.

Keywords Hepatocellular carcinoma · Sarcoma · Hepatectomy · Liver transplantation

Abbreviations

CT	computed tomography
HCC	hepatocellular carcinoma
LT	liver transplantation
TACE	transarterial chemoembolization

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Introduction

The basic histological pattern of hepatocellular carcinoma (HCC) is trabecular, although variant histological features are occasionally observed in resected liver specimens. About 1.8% of resected HCCs have a sarcomatous appearance, a feature associated with very poor prognosis caused by rapid growth, low resectability, and frequent recurrence after curative resection.[1–3] Although the pathogenesis of sarcomatous transformation has not been clarified, sarcomatous components are thought to be derived from a dedifferentiation or anaplasia in HCC rather than a combination of HCC and sarcoma. Spindle cell components usually occupy more than 10% of the viable tumor volume, but they can occupy the entire tumor mass.[4]

To date, only a limited number of sarcomatous HCC cases have been described in literature. Moreover, little is known about the prognosis of sarcomatous HCCs after liver transplantation (LT). To assess the prognostic impact of

sarcomatous changes, we analyzed the outcomes of 15 patients with sarcomatous HCC after resection or LT.

Patients and Methods

Patient Selection

From January 1997 to May 2005, 1,005 adult patients underwent liver resection for HCC in our institution. Among them, 11 patients (1.1%) were diagnosed as having sarcomatous change after microscopic and immunohistochemical examinations of the resected specimens. During the same study period, 1,052 adult patients underwent LT. Among them, 317 recipients were diagnosed as having HCC in the explant liver specimens, with sarcomatous changes detected in 4 (1.3%). The medical records of these 15 patients were retrospectively reviewed and followed up until April 2007 or death.

HCC Workup Before Liver Resection and LT

Preoperative HCC workup included multidetector dynamic liver computed tomography (CT), magnetic resonance imaging, chest CT, positron emission tomography scan, and radioisotope bone scan. Transarterial chemoembolization (TACE) was often performed before surgery, and percutaneous liver core biopsy specimens were occasionally obtained for differential diagnosis. The general guidelines and management for safe liver resection are described in detail elsewhere.[5]

Pathologic Assessment and Immunohistochemistry

All HCC tumors were classified according to the modified pathological tumor-node metastasis (pTNM) system and the Milan criteria.[6,7] HCCs with sarcomatous appearance were assessed immunohistochemically using antibodies directed against vimentin, cytokeratin, cytokeratin 7, hepatocyte antigen, c-Kit, a-smooth muscle actin, and CD34 to differentiate sarcomatous from ordinary HCCs.[8–10]

Postoperative Surveillance

Because patients with sarcomatous HCC were known to have very poor prognosis, these patients were vigorously followed up, especially for extrahepatic metastases. None was treated with adjuvant chemotherapy for preventive purpose.

Statistics

All numeric data are reported as mean and standard deviation or as median and range. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. A p value<0.05 was considered statistically significant.

Results

Clinicopathological Features

The clinicopathological profiles of these 15 patients are summarized in Table 1. Their mean age was 55.5±7.8 years, 14 (93.3%) were men, and all patients were associated with hepatitis B virus infection. Seven patients (46.7%) underwent preoperative TACE (one to six times).

Preoperative percutaneous liver core biopsy specimens were obtained from three patients (20%), 9 days, 11 days, and 14 months before surgery. Sarcomatous changes were observed in the first two patients, whereas ordinary HCC was observed in the third, and TACE was performed four times during the 14 months before surgery.

Median serum a-fetoprotein concentration was 11.5 ng/ml (range, 1.8–675 ng/ml), with only six patients (40%) exceeding the normal reference value of 20 ng/ml. Preoperative imaging, including liver CT, hepatic arteriogram, and magnetic resonance imaging, failed to show any diagnostic clues implicating sarcomatous HCC.[11] All 11 resected patients belonged to Child–Pugh class A, with a mean indocyanine green retention rate at 15 min of 11.5±5.1% (range, 4.4–21.1%).

Four of the five left-sided tumors were removed by left lobectomy, with the fifth removed by medial segmentectomy, whereas all six right-sided tumors were removed by S5 or S6 segmentectomy, although two patients had undergone preoperative right portal vein embolization for right hepatectomy. One patient underwent concurrent distal pancreatectomy for an intraductal papillary mucinous neoplasm. R0 resection was achieved in 9 of 11 patients, whereas the other two were regarded as R2 resections because one had ruptured HCC with omental invasion and the other had unresectable portocaval node metastasis.

Of the four patients in the LT group, three received living-donor right-liver grafts, and one received a deceased-donor whole-liver graft. HCC was diagnosed before LT in all four patients.

According to modified pTNM staging, the HCC lesions were classified as stage II in five patients, stage III in six, stage IVa2 in two, and stage IVb in one. The Milan criteria were met in 7 of 15 patients, including 3 of 4 in the LT group (Table 1).

The pathologic features and the results of immunohistochemical analyses are summarized in Table 2. The results of hepatocyte antigen, c-Kit, a-smooth muscle actin, and CD34 for sarcomatous components were all negative.

Table 1 Clinicopathological Characteristics of 15 Patients with Sarcomatous Hepatocellular Carcinoma Undergoing Resection or Liver Transplantation

Patient No.	Sex	Age (years)	Chief Complaint	Preoperative Treatment	Operation	Resection Type	Tumor Location	Maximal Tumor Size (cm)	Tumor Number	Milan Criteria	pTNM	pTNM Stage	Recurrence	Disease-Free Survival (months)	Initial Recurrence Site	Recurrence Treatment	Survival Status	Survival Period (months)
1	M	56	Incidental	None	LL	R0	S2–4	8	1	Beyond	T4bN0	IVa2	Yes	2	Lung	None	Dead	5
2	M	73	Incidental	None	LL	R0	S2–4	10	1	Beyond	T3N0	III	Yes	55	Liver	TACE	Dead	71
3	M	63	Epigastric discomfort	None	S6 seg	R0	S6	3.5	1	Within	T2N0	III	Yes	11	Lymph node	CTX	Dead	24
4	M	53	Weight loss	TACE	S5 seg	R0	S5	4.2	1	Within	T2N0	II	Yes	5	Liver	TACE	Dead	16
5	M	50	Flank pain	None	S5 seg	R0	S6	7.5	1	Beyond	T3N0	III	Yes	10	Kidney	Nephrectomy	Dead	15
6	M	57	Back pain	None	LL	R0	S2–4	20	1	Beyond	T4bN0	IVa2	Yes	1	Peritoneum	None	Dead	3
7	M	62	Abdomen pain	TACE	S4 seg	R2	S4	11	1	Beyond	T4bN0	IVa2	Yes	2	Peritoneum	Bowel resection	Dead	6
8	M	62	Epigastric discomfort	None	S5 seg	R2	S5	3.3	2	Beyond	T3N1	IVb	Yes	2	Lymph node	CTX & RTX	Dead	4
9	M	46	Palpable mass	TACE	LL	R0	S2–4	15	1	Beyond	T3N0	III	Yes	3	Peritoneum	CTX	Dead	7
10	M	52	Incidental	None	S5 seg	R0	S5	4.8	1	Within	T2N0	II	No	33	-	-	Alive	33
11	M	43	Fatigue	TACE	S6 seg	R0	S6	3.7	1	Within	T3N0	III	Yes	2	Liver & peritoneum	TACE	Dead	7
12	M	54	Liver cirrhosis	TACE	LDLT	R0	S4, 8	3	2	Within	T2N0	II	Yes	2	Peritoneum	None	Dead	3
13	M	59	Liver cirrhosis	TACE	LDLT	R0	S2, 4, 7	2	3	Within	T2N0	II	No	58	-	-	Alive	58
14	F	46	Liver cirrhosis	TACE	LDLT	R0	S8	4	1	Within	T2N0	II	Yes	21	Liver	TACE	Dead	27
15	M	56	Liver cirrhosis	None	DDLT	R0	S3, 6, 8	4.5	3	Beyond	T3N0	III	Yes	12	Liver	TACE	Alive	22

LL Left lobectomy, *seg* segmentectomy, *TACE* transarterial chemoembolization, *CTX* chemotherapy, *RTX* radiotherapy, *LDLT* living donor liver transplantation, *DDLT* deceased donor liver transplantation, *pTNM* modified tumor-node metastasis

Table 2 Histologic and Immunohistochemical Results in 15 Patients with Sarcomatous Hepatocellular Carcinoma Undergoing Resection or Liver Transplantation

Patient No.	Edmondson–Steiner Grade	Tumor Necrosis (%)	Proportion of Sarcomatous Component (%)	Vimentin	Cytokeratin	Cytokeratin 7
1	3/2	50	60	X	N	X
2	3/2	10	10	P	N	X
3	4/4	10	90	P	N	N
4	3/3	80	95	X	X	X
5	3/3	30	10	X	X	N
6	3/2	15	>95	P	N	X
7	4/4	10	>95	X	X	X
8	3/3	20	60	P	P	N
9	3/3	30	90	P	P	N
10	4/4	10	25	X	X	X
11	4/4	70	95	X	P	N
12	4/4	20	90	X	P	X
13	4/3	NA	20	X	P	X
14	3/3	70	80	P	X	N
15	2/2	60	40	X	X	X

Edmondson–Steiner grade is expressed as worst/most grades. Immunohistochemical results obtained from only the sarcomatous components of hepatocellular carcinoma are shown.
NA Not available, *X* not done, *P* positive, *N* negative

Recurrence and Patient Survival

There was no surgery-related mortality. During a follow-up of more than 2 years, tumor recurrence was observed in 10 of 11 patients in the resection group, with all 10 dying of recurrent HCC. Of the four patients in the LT group, three showed tumor recurrence and two died. Overall and disease-free survival curves are depicted in Figs. 1 and 2.

When we assessed patients who met the Milan criteria, we found that the 2-year overall survival rate was 25% after resection and 33% after LT, showing no prognostic difference (Figs. 3 and 4).

Recurrence Patterns and Management

Of the ten resected patients showing tumor recurrence, only two showed intrahepatic metastasis as the initial recurrence, whereas seven showed extrahepatic and one combined metastases. Three of these ten patients met the Milan criteria, with each showing intrahepatic, extrahepatic, and combined metastases, respectively, as initial recurrence. Mean and median survival periods after recurrence were 6.4±5.1 and 4.5 months (range, 1–16 months), respectively, despite vigorous treatments.

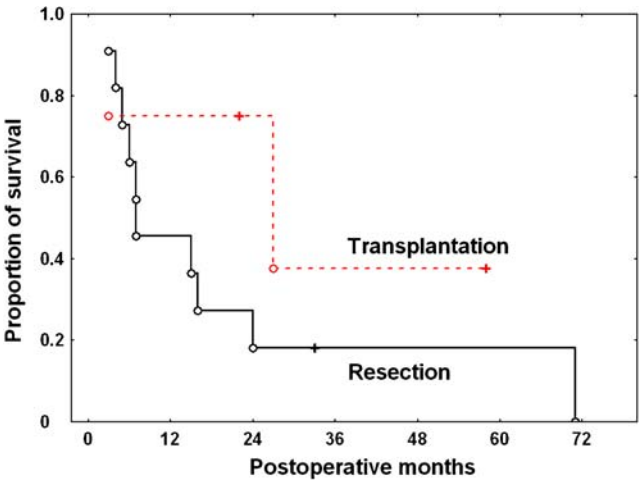

Figure 1 Comparison of overall patient survival curves between patients undergoing resection or liver transplantation for sarcomatous HCC. The 3-year overall survival rates were 18.2% after resection and 37.5% after liver transplantation (p=0.256).

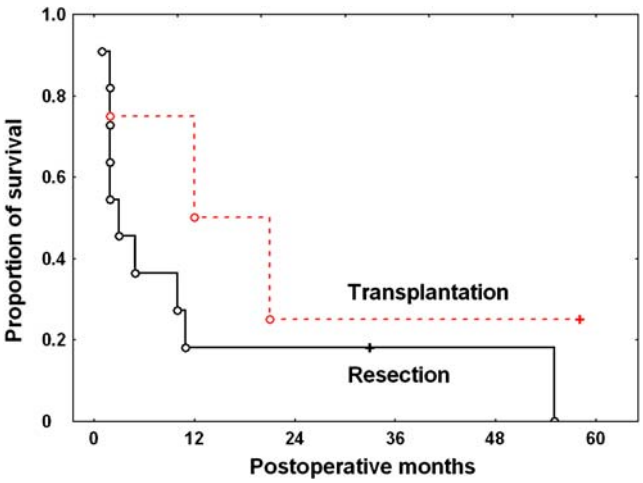

Figure 2 Comparison of recurrence-free patient survival curves between patients undergoing resection or liver transplantation for sarcomatous HCC. The 3-year recurrence-free survival rates were 18.2% after resection and 25% after liver transplantation (p=0.174).

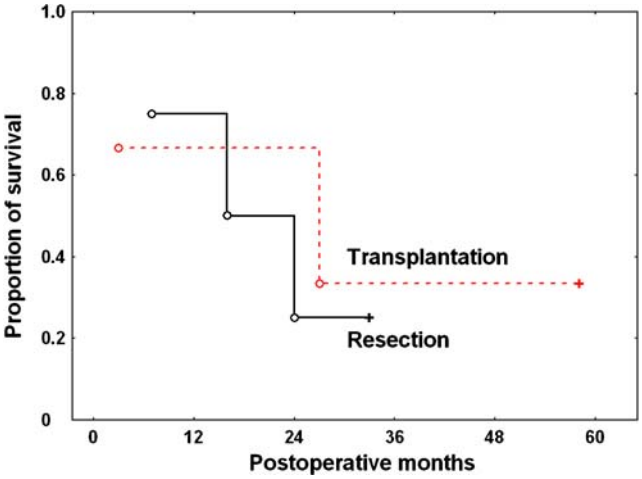

Figure 3 Comparison of overall patient survival curves between patients meeting the Milan criteria who underwent resection or liver transplantation. The 2-year overall survival rates were 25% after resection and 66.7% after liver transplantation (p=0.756).

Of the three LT recipients showing tumor recurrence, two showed intrahepatic and one showed extrahepatic metastases as initial recurrence.

All intrahepatic recurrences were treated with TACE, and resection was attempted for localized extrahepatic metastases. One patient each underwent a right nephrectomy for kidney metastasis, a small-bowel segmental resection for mesenteric metastasis and a lung wedge resection for lung metastasis. Adriamycin-based systemic chemotherapy was performed for only the patients whose general condition permitted such treatment (Table 1).

Discussion

We have shown in this study that patients with sarcomatous HCC have unfavorable outcomes after both LT and resection, with recurrence in 8 of 11 patients and deaths in 6 of 11 patients within the first year after resection. These findings are in good agreement with the results showing that 8 of 13 patients undergoing resection of sarcomatous HCC died of the disease within 1 year and that the survival rate of these patients was significantly worse than that of patients with advanced but ordinary HCC.[3] Even when we excluded the patients with advanced tumors (pTNM stage IV), four of seven recurrences occurred within 1 year after resection. Moreover, of the patients showing tumor recurrence, 80% showed extrahepatic metastases as initial manifestations of recurrence. Mean survival period after recurrence was only 6 months. These results strongly suggest that the sarcomatous variant of HCC behaves very aggressively, with early recurrence and frequent extrahepatic metastases even after curative resection. Because of these features, aggressive surgery with extensive liver resection does not always improve patient survival.

To our knowledge, the post-LT prognosis of patients with sarcomatous HCC has not been reported to date. In this series of 4 LT cases, the outcome was also unfavorable like after resection. When confined to patients within the Milan criteria, the 2-year overall and disease-free survival rates were both only 33.3%. In contrast, we have reported that, in patients meeting the Milan criteria, the 5-year overall survival rate after adult living donor LT was 74.8%.[12] The number of LTs described in this study is too small to draw any conclusions, but it is likely that sarcomatous transformation of HCC carries a very high risk of recurrence, regardless of tumor extent after LT or resection. Multivariate analysis of 513 resected HCC cases showed that the relative risk of patient mortality from sarcomatous changes was nearly fourfold.[13] In fact, such rare but aggressive pathology is considered a main cause of HCC recurrence in LT recipients who met the Milan criteria.

Anti-HCC treatments such as TACE, radiofrequency ablation, and percutaneous ethanol injection therapy have been reported to induce sarcomatous transformation through degeneration, necrosis, and regeneration of tumor cells.[1,14–16] Sarcomatous change was detected in one of our patients, who underwent four sessions of TACE after the initial liver biopsy showed the presence of an ordinary HCC. This change may also be associated with interferon therapy for viral hepatitis C.[17] In contrast, 7 of our 15 patients did not undergo any preoperative anti-HCC treatment.[18]

Sarcomatous changes have also been observed in HCC with normal liver background.[19,20] Interestingly, the worst

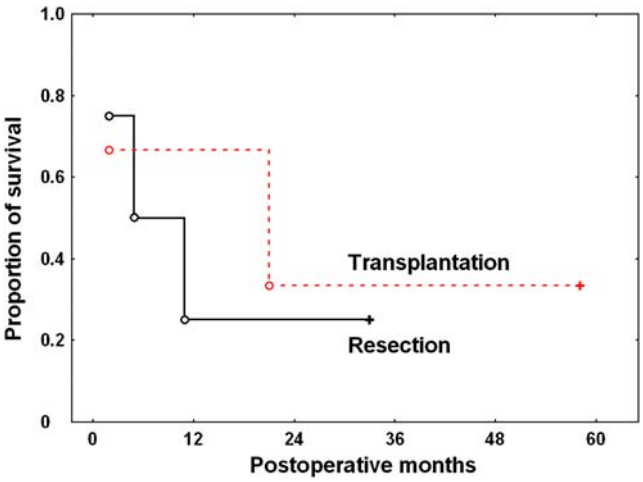

Figure 4 Comparison of recurrence-free patient survival curves between patients meeting the Milan criteria who underwent resection and liver transplantation. The 2-year recurrence-free survival rates were 25% after resection and 33.3% after liver transplantation (p=0.678).

tumor differentiation of the ordinary, non-sarcomatous components in 14 of 15 patients was Edmondson–Steiner grades 3 or 4 (Table 2), suggesting that such dedifferentiation may be associated with sarcomatous transformation.

Sarcomatous changes were identified in two HCC patients who underwent percutaneous liver biopsies 9 and 11 days before surgery, suggesting that preoperative liver biopsies can be used to diagnose these changes. However, it is not yet possible to detect sarcomatous changes by preoperative imaging or serological tumor markers. It had been reported that the sarcomatous HCC appears irregularly demarcated intrahepatic mass with delayed or prolonged peripheral enhancement on CT, but this radiological features was not evidently demonstrated in this series.[11]

Because there was no need for routine preoperative liver biopsy, the significance of percutaneous liver biopsy may be much lower in practice than theoretically because of the rare incidence of sarcomatous HCC. In a study with 178 HCC patients undergoing resection or LT, there was a poor correlation of tumor grading between the preoperative liver core biopsy and surgical pathology.[21] HCC cells with sarcomatous changes have also been observed in ascites, leading to successful cytologic diagnosis.[22]

Sarcomatous tumor cells in HCC have shown infiltrative growth into the liver, and the frequency of widespread metastasis was significantly higher with sarcomatous than with ordinary HCC.[1,23] An autopsy study has shown that, compared with patients with ordinary HCC, those with sarcomatous HCC have a higher frequency of lymph node metastasis.[24] Because sarcomatous transformation has a tendency to early recurrence, especially peritoneal seeding or lymph node metastasis, systemic surveillance such as positron emission tomography scan may be beneficial, especially during the first year after resection or LT.

The survival results after recurrence in the resection group suggest that the treatment of recurrence could not be effective because non-localized recurrence, such as lymph node metastasis or peritoneal seeding, was very common. The effect of chemotherapy for sarcomatous HCC is uncertain to date. No recurrence over 12 months was reported after the combination of etoposide, epirubicin, and cisplatin was used to treat a patient who had undergone resection of a huge sarcomatous HCC.[25] We observed an intrahepatic recurrence in one LT recipient after 12 months; this patient underwent TACE and subsequent lung wedge resection for lung metastasis. Currently, 11 months after resection, he remains alive without further metastasis. These findings provide further evidence that it may be beneficial to treat localized recurrence vigorously, even after LT.

Recurrence characteristics and responses to recurrence treatment after resection of sarcomatous HCC are very similar to those of ordinary HCCs>10 cm in diameter.[26] Thus, the follow-up protocol for patients who undergo resection or LT for sarcomatous HCC should be similar to that of patients who undergo resection of huge HCC having very high risk of recurrence.

Conclusion

We have shown that the prognosis of patients with sarcomatous HCC after both resection and LT is very unfavorable. Percutaneous liver biopsy seems to correctly diagnose sarcomatous HCC, but, because of its rarity, the clinical significance of biopsy appears too low for routine application. Vigorous postoperative systemic surveillance may enable to detect and treat the localized metastases in time.

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Surgical Treatment of Primary Neuroendocrine Tumors of the Liver

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Abstract Primary neuroendocrine tumor (NET) of the liver is a very rare neoplasm, requiring strict exclusion of possible extrahepatic primary sites for its diagnosis. We have analyzed our clinical experience of eight patients with hepatic primary NET. From January 1997 to December 2006, eight patients with a mean age of 50.4±9.5 years underwent liver resection for primary hepatic NET. Seven patients underwent preoperative liver biopsies, which correctly diagnosed NET in four. Of the eight patients, six underwent R0 and two underwent R1 resection. Diagnosis of hepatic primary NET was confirmed immunohistochemically and by the absence of extrahepatic primary sites. All tumors were single lesions, of mean size 8.6± 5.7 cm, and all showed positive staining for synaptophysin and chromogranin. During a mean follow-up of 34.0± 39.7 months, three patients died of multiple liver metastases after tumor recurrence, whereas the other five remain alive to date, making the 5-year recurrence rate 40% and the 5-year survival rate 56.3%. Univariate analysis showed that Ki67 proliferative index was a risk factor for tumor recurrence. In conclusion, although primary hepatic NET is very rare, it should be distinguished from other liver neoplasms. The mainstay of treatment is curative liver resection.

Keywords Neuroendocrine tumor · Carcinoid tumor · Liver · Hepatectomy

Introduction

Neuroendocrine tumors (NET), also known as carcinoid tumors, are rare neoplasms that mainly occur in the gastrointestinal system. The liver is the most common site of NET metastases, but primary NET, although much more rare, can occur in the liver.[1,2] Diagnosis of primary hepatic NET is based on two prerequisites: The liver mass must be immunohistochemically compatible with NET, and the liver should be shown to be the primary tumor site by strict exclusion of metastases from other sites. The diagnostic process of active exclusion of metastases should occur preoperatively, intraoperatively, and even during postoperative follow-up. In this study, we analyzed the clinicopathological features and outcomes of eight patients who underwent surgical resection for primary NET of the liver.

Materials and Methods

During the 10 years from January 1997 to December 2006, 2,736 patients underwent liver resection for various diseases in our institution. Of these, 16 patients were pathologically diagnosed with NET. After excluding eight of these patients (six with metastatic NET, one with tumor features mixed with hepatocellular carcinoma, and one later diagnosed with rectal NET during follow-up), we assessed the clinicopathological characteristics and outcomes in the eight patients with primary hepatic NET. All the patients were routinely followed up every 2–3 months. Their clinical data were retrospectively obtained from their medical records, and the surviving patients were followed up until July 2007.

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During preoperative workup, all patients underwent multidetector abdomen computed tomography (CT), endoscopic screening (duodenofibroscopy and colonofibroscopy), chest CT, somatostatin receptor scintigraphy, and positron emission tomography (PET) scans. Some patients underwent preoperative liver biopsy for differential diagnosis. Final pathologic diagnosis was obtained by histopathological assessment and immunohistochemistry.

Numeric data were expressed as mean ± standard deviation. Continuous numeric parameters were compared with Mann–Whitney *U* test. Fisher's exact test was used for comparison of incidences. Survival curves were estimated by the Kaplan-Meier method. A p value <0.05 was considered statistically significant.

Results

Clinical Findings

The clinical findings of eight patients (four men, four women) with primary hepatic NET who underwent liver resection were analyzed. The mean patient age was 50.4± 9.5 years (range: 37–64 years). The most common clinical manifestation was vague upper abdominal pain. The patients were transferred to our institution after detection of liver mass on imaging studies. The clinical profiles of these patients are summarized in Table 1.

There were no noticeable abnormalities in biochemical liver function profiles, and serum total bilirubin was increased, to 2.9 mg/ml, in only one patient. Serological tumor markers, including α-fetoprotein, CEA (carcinoembryonic antigen), and CA 19-9, were within normal limits, except that one patient had a serum α-fetoprotein concentration of 95.3 ng/ml. Hepatitis B virus infection was identified in one patient, but the other seven showed no evidence of viral hepatitis.

Preoperative Imaging

Dynamic liver CT was first performed for detection of liver mass (Figs. 1 and 2). Various diagnostic screening methods were performed to identify the primary origin of each liver mass, including chest CT, colonofibroscopy, and octreotide, bone and PET scans, and a small bowel series was also performed in one patient. These tests revealed no other sites of origin of NET. Two patients underwent somatostatin receptor scintigraphy, which showed no abnormal finding in one patient (case 3), whereas the other had a filling defect of the liver (case 7, Fig. 3). Seven patients underwent preoperative percutaneous liver biopsies, which correctly diagnosed NET in four patients; the other three patients were misdiagnosed as having hepatocellular carcinoma, adenocarcinoma, and benign hyperplasia, respectively. Two patients underwent transarterial chemoembolization before liver resection.

Surgical Treatment

Systematic liver resection was performed on each patient when that patient's general condition and functional hepatic reserves permitted. Three patients underwent right hepatectomy, two underwent left hepatectomy, and one each underwent central bisectionectomy, left trisectionectomy,

Table 1 Clinical Characteristics of Eight Patients with Primary Neuroendocrine Tumor of the Liver Undergoing Surgical Resection

Patient no.	Sex/age	Chief complaint	Preoperative treatment	Operation	Resection type	Timing of recurrence (months)	Initial recurrence site	Recurrence treatment	Survival period and status
1	M/48	Nonspecific abdominal pain	None	RH	R0	–			121 months, alive
2	F/45	Nonspecific abdominal pain	TACE	LMS	R0	–			61 months, alive
3	F/37	Nonspecific abdominal pain	None	LH+BDR+PVT	R1	13	Liver	CTX	26 months, dead
4	M/55	Incidental	None	RH	R0	–			28 months, alive
5	F/42	Incidental	None	LMS+S1+BDR	R0	–			19 months, alive
6	F/64	Nonspecific abdominal pain	None	RH	R0	–			9 months, alive
7	M/62	Nonspecific abdominal pain	TACE	CBS	R0	1	Liver	TACE	5 months, dead
8	M/50	Nonspecific abdominal pain	None	LTS	R1	2	Liver	None	3 months, dead

RH, right hepatectomy; *TACE*, transarterial chemoembolization; *LH*, left hepatectomy; *BDR*, bile duct resection; *PVT*, portal vein thrombectomy; *CTX*, chemotherapy; *CBS*, central bisectionectomy; *LTS*, left trisectionectomy; *LMS*, left medial sectionectomy; *S1*, caudate lobe resection

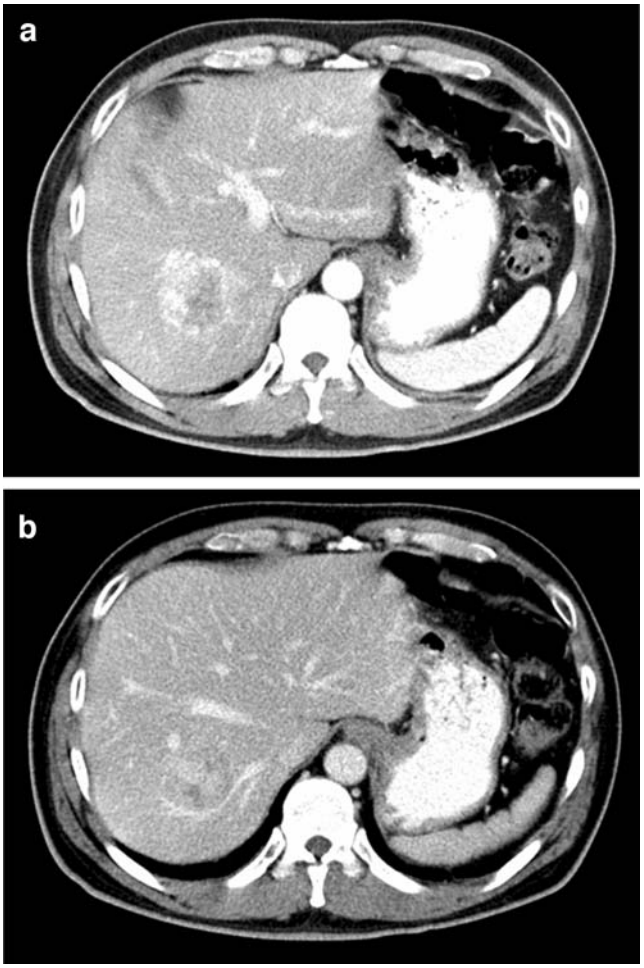

Figure 1 Computed tomographic findings of a primary neuroendocrine tumor of the liver (case 4). **a** At the arterial phase, a 5 cm-sized hypervascular mass was identified with a background of chronic liver disease. **b** Tumor hypervascularity was attenuated at the portal phase. These findings are compatible to those of usual hepatocellular carcinoma.

left medial sectionectomy, and left medial sectionectomy with caudate lobe resection. Bile duct resection and reconstruction were performed in two patients suspected of having bile duct invasion. One patient (case 3) underwent left hepatectomy, bile duct resection and portal vein thrombectomy; in this patient, the portal vein thrombus was also pathologically diagnosed as NET.

There was no perioperative mortality. R0 resection was achieved in six patients, whereas the other two patients were classified as having undergone R1 resection because tumor cells were microscopically identified at the resection margins.

Pathologic and Immunohistochemical Findings

In each patient, the hepatic NET mass consisted of a single lesion, ranging in size from 3.2 to 18 cm in greatest diameter (mean: 8.6±5.7 cm). NET shows unique microscopic findings of insular, trabecular or mixed patterns of cell growth (Fig. 4). Immunohistochemical analysis showed positive stainings of these tumors for synaptophysin, chromogranin, and CD56 (Fig. 5). These pathologic and immunohistochemical findings are summarized in Tables 2 and 3.

Patient Survival and Risk Factor Analysis

The duration of follow-up period ranged from 3 to 121 months (mean: 34.0±39.7 months). Tumor recurrence was observed in three patients, all in the remnant livers. One patient (case 3) showed recurrence after 13 months, underwent palliative chemotherapy, and died 1 year later. The other two patients showed recurrence at the liver resection margin soon after hepatectomy and died after 3 months (case 8) and 5 months (case 7). The remaining

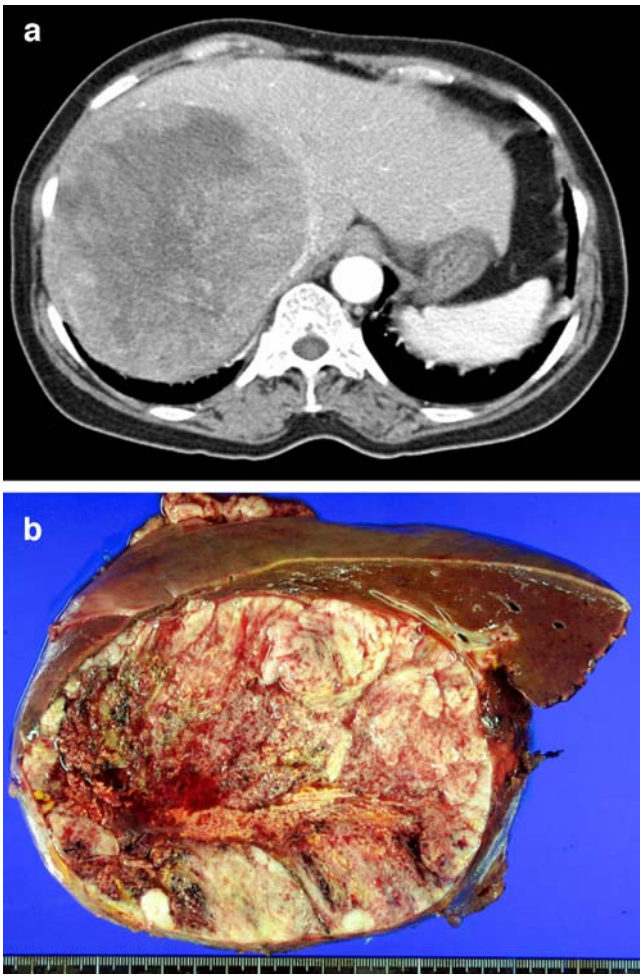

Figure 2 Images of a huge primary neuroendocrine tumor of the liver (case 6). **a** The arterial-phase computed tomographic image showed a huge well-demarcated mass with probable central necrosis in the right liver, suggesting hepatocellular carcinoma or mesenchymal sarcoma. **b** The resected specimen revealed a well-demarcated ovoid expanding mass of nodular type. This mass was confined to the liver parenchyma. The resection margin was tumor-free and there was no lymphovascular or perineural invasion.

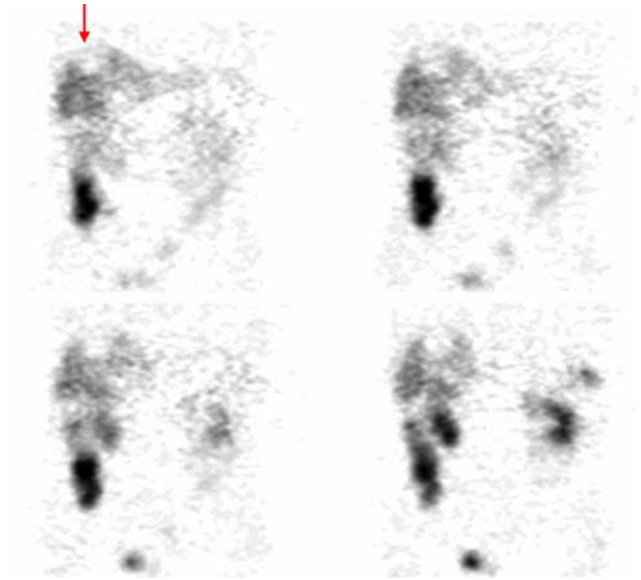

Figure 3 An In^{111} Octreoscan image of a patient (case 7) revealing a cold defect in the right liver (*arrow*), which is compatible to the location of known liver mass.

five patients are alive to date without evidence of tumor recurrence.

The 1-, 3-, and 5-year recurrence rates were 25, 40, and 40%, respectively, and the overall 1-, 3-, and 5-year survival rates were 75, 56.3, and 56.3%, respectively (Fig. 6). Only one out of six patients who had undergone curative resection (case 7) showed tumor recurrence during follow-up. Univariate analysis showed that Ki67 proliferative index was a significant risk factor for tumor recurrence (Table 4).

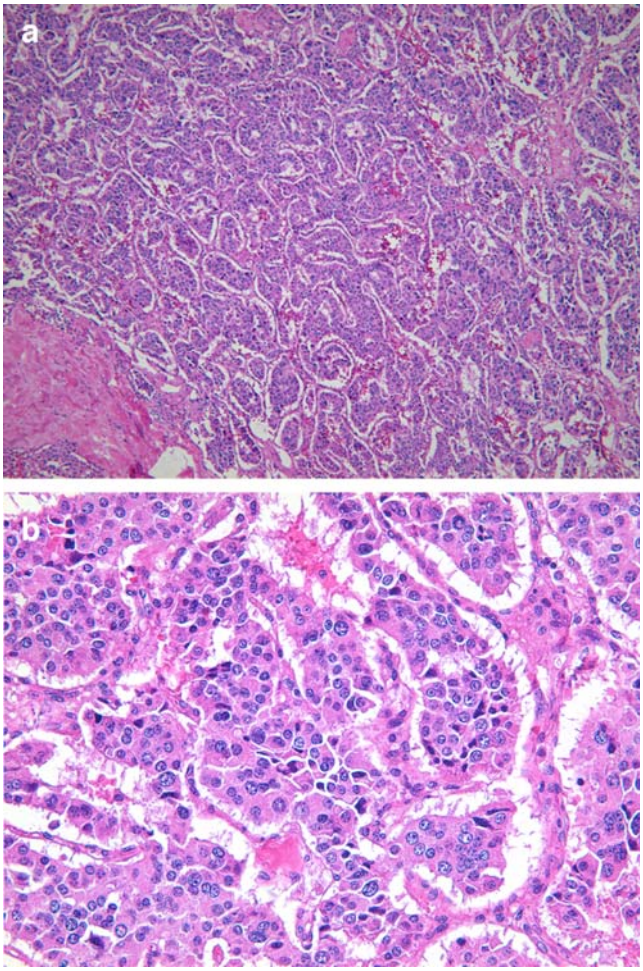

Figure 4 Microscopic examination of a primary neuroendocrine tumor of the liver (case 5). **a** Neoplastic cells are arranged in combined patterns as trabecular arrangement structures and solid nests (H&E ×100). **b** Tumor cells have abundant cytoplasm with a central nucleus and inconspicuous nucleoli (H&E ×200).

Discussion

Only 1–2% of all gastrointestinal neoplasms are NETs, and primary NET of the liver is extremely rare.[1–3] Although the pathogenesis of primary hepatic NET has not been determined, three hypotheses have been proposed. In the first, tumor cells are thought to originate from the neuroendocrine cells in the epithelium of the intrahepatic bile duct. In the second, tumor cells are thought to originate from the ectopic tissue of the pancreas or adrenal tissue within the liver. According to the third, tumor cells originate from the pluripotent stem cells of liver origin after neuroendocrine differentiation.[4–6]

Primary hepatic NET usually does not present any specific clinical manifestations. Of the eight patients in this series, none showed carcinoid syndrome, including facial flushing and diarrhea and, more rarely, wheezing and right heart failure, manifestations due to tumor excretion of serotonin, histamine, bradykinin, prostaglandin, and other signaling molecules.[3,7] This syndrome is often observed in

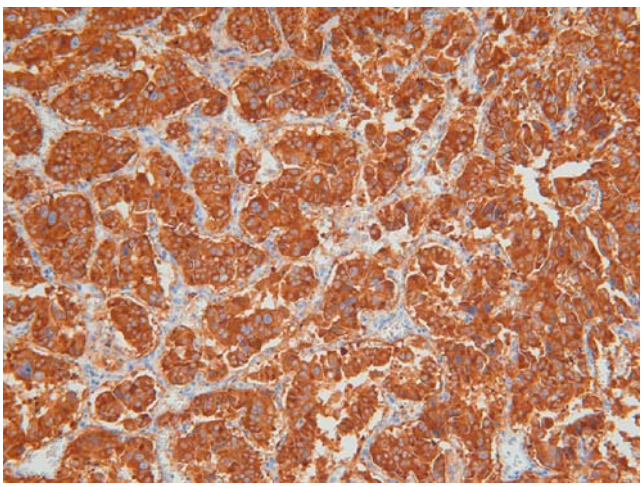

Figure 5 Immunohistochemical staining with antibody to synaptophysin (case 5), a marker of neuroendocrine differentiation (×200).

Table 2 Histolopathologic Findings

Patient no.	Tumor size (cm)	Tumor number	Cellular atypism	Resection margin	Lymphovascular invasion	Tumor necrosis	Mitosis (10HPF)	Ki67 (%)
1	12	1	Monotonous	Negative	Absent	Absent	0	0
2	4.3	1	Pleomorphic	Negative	Present	Absent	1–2	0.2
3	4	1	Monotonous	Positive	Present	Absent	4–5	32.5
4	4.2	1	Monotonous	Negative	Absent	Absent	0–1	4.8
5	3.2	1	Pleomorphic	Negative	Present	Absent	0–1	1.7
6	15	1	Monotonous	Negative	Absent	Present	10	27.8
7	8	1	Monotonous	Negative	Absent	Present	5–7	29.0
8	18	1	Pleomorphic	Positive	Present	Present	15–18	45.1

patients with liver metastases of NET because the excreted neuroendocrine materials enter the systemic circulation without passing through the portal system. Primary hepatic NET usually does not induce carcinoid syndrome, for reasons as yet unclear.

Diagnosis of primary hepatic NET by imaging methods is not simple because these tumors do not appear different from hepatocellular carcinoma, intrahepatic cholangiocarcinoma and metastatic liver cancers on liver ultrasonography, CT, and magnetic resonance imaging.[8,9]

In this study, preoperative liver biopsy was performed in seven of eight patients, and NET was correctly diagnosed in four. This preoperative pathologic diagnosis of hepatic NET can lead to performing further study on the possibility of metastasis from other sites. Among the 15 patients who were pathologically diagnosed with hepatic NET in this series, 8 had NET of primary liver origin, whereas metastatic origin was identified in 7. Thus, while preoperative liver biopsy is useful for differential diagnosis, it does not seem to be essential to perform liver biopsy routinely in patients suspected of NET, considering that its diagnostic accuracy is not high enough, it can add some oncologic risk of tumor spread, and resection is the procedure of choice with relatively favorable outcome.

Somatostatin receptor scintigraphy may be useful in the diagnosis of NET, since majority of these tumors express somatostatin, as well as in the detection of extrahepatic NET.[10] In this study, somatostatin receptor scintigraphy was performed in two patients but was useful in diagnosis of only one. Six patients also underwent FDG-PET scans, which showed hot uptake only by the liver.

NET can be diagnosed by histopathologic assessment using hematoxylin–eosin staining, combined with immunohistochemical analysis using antibodies directed against synaptophysin, chromogranin, CD56, and other markers. We suspected that cellular pleomorphism may be associated with poorer outcome, but pleomorphism was not associated with Ki67 staining or with postoperative prognosis.

Ki67 is known as a marker of tumor proliferation and has been found to be a prognostic factor for various tumors, including breast, soft tissue and lung cancer and meningioma.[11] In addition, patients with malignant NET of the pancreas that have a Ki67 index of <2% have been reported to show better prognosis than do patients with a Ki67 index of ≥2%.[12] In this study, Ki67 was a statistically significant prognostic factor for tumor recurrence, with a median value in the nonrecurrent group of 1.7%.

Table 3 Immunohistochemical Findings

Patient no.	Synaptophysin	Chromogranin	CD56	Hepatocyte
1	+	+	ND	ND
2	+	+	+	ND
3	+	+	ND	−
4	+	+	+	−
5	+	+	ND	−
6	+	ND	ND	−
7	+	+	ND	ND
8	+	+	+	−

+, positive; −, negative; *ND*, not done

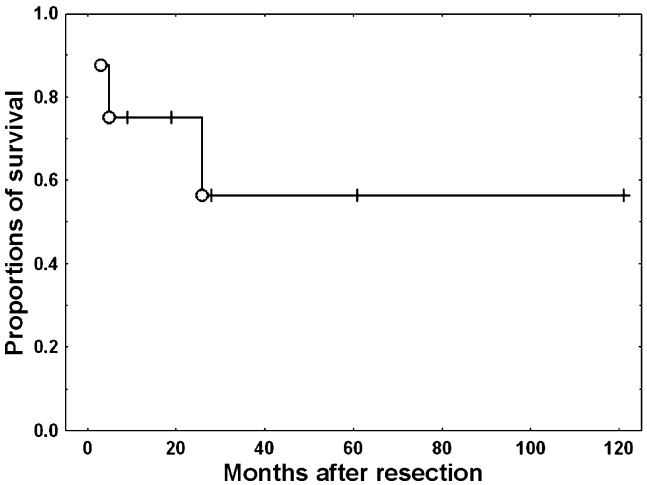

Figure 6 Overall patient survival curve after resection of primary neuroendocrine tumors of the liver.

Table 4 Univariate Analysis of Risk Factors for Tumor Recurrence

Variables	Non-recurrence group (n=5)	Recurrence group (n=3)	P value
Tumor diameter (cm, median)	4.3	8.0	0.655
Ki67 (%, median)	1.7	32.5	0.025
Cellular pleomorphism (n, %)	2 (40%)	1 (33.3%)	0.714
Tumor-positive resection margin (n, %)	0 (0%)	2 (66.7%)	0.107
Lymphovascular invasion (n, %)	2 (40%)	2 (66.7%)	0.500

Histopathological assessment alone cannot distinguish between the primary and metastatic NET. Although a single NET lesion located in the liver is likely a primary hepatic NET, a definitive diagnosis requires additional assessments, before, during, and after surgery, to exclude the possibility of metastasis from other sites.

The main treatment modality for primary hepatic NET is surgical resection of the tumor. In a study of 48 patients with primary NET, the 10-year survival rate after resection was 68%.[13] Liver transplantation can be a treatment for metastatic NET,[14,15] as well as for patients with primary hepatic NET.[16]

The role of chemotherapy in the treatment of primary hepatic NET is not yet known. Systemic administration of 5-fluorouracil to one patient with an inoperable tumor resulted in tumor downstaging, which permitted successful resection.[4] In two other patients, however, the tumor progressed despite systemic and intraabdominal chemotherapy.[4] Transarterial chemoembolization can be used to treat a hypervascular mass, but it is not routinely applied to NET, although it achieved significant tumor size reduction in one patient.[17] Administration of long-acting somatostatin can be used to treat metastatic NET and other tumors showing carcinoid syndrome, but its effect on asymptomatic primary hepatic NET is not yet known.[18]

In conclusion, primary hepatic NET, while very rare, can be distinguished from other liver neoplasms. Its diagnosis is not simple, but preoperative liver biopsy does not seem to be essential for differential diagnosis. Surgical resection is the treatment of choice, with favorable outcomes expected after curative resection.

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Defining the Role of Surgery for Primary Gastrointestinal Tract Melanoma

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Abstract
Objective The objective of the study was to determine the outcomes for primary gastrointestinal melanomas (PGIM).
Material and methods The Surveillance, Epidemiology, and End Results database (1973–2004) was queried.
Results Overall, 659 cases of PGIM were identified. The annual incidence of PGIM was approximately 0.47 cases per million in 2000. Overall median survival time was 17 months. Tumors were identified in the oral–nasopharynx (32.8%), anal canal (31.4%), rectum (22.2%), esophagus (5.9%), stomach (2.7%), small bowel (2.3%), gallbladder (1.4%), and large bowel (0.9%). Univariate analysis demonstrated age, tumor location, stage, surgery, and lymph node status were significant predictors of improved survival. MST has not been reached for tumors located in the large bowel, while tumors located in the stomach demonstrated the shortest median survival (5 months). Improvement in MST was observed for those patients undergoing surgical resection. The presence of lymph node involvement conferred a poorer prognosis. Multivariate analysis of the cohort identified that location, advanced tumor stage, failure to undertake surgical resection, positive lymph node status, and age were all independent predictors of poorer outcome.
Conclusion PGIM occurs most often in the oral–nasopharynx and anal canal. Surgical extirpation is the only identifiable treatment modality that significantly improves survival.

Keywords Gastrointestinal melanoma · SEER · Metastatic melanoma · Outcomes

Introduction

Outcomes for cutaneous melanomas have been extensively examined.[1,2] In addition to their cutaneous location, histologic and immunohistochemical studies have identified normal melanocytes in the mucosa of the gastrointestinal tract.[3–6] Gastrointestinal tract melanoma, however, is an uncommon entity, most often seen as metastatic disease from cutaneous lesions.[7,8] It has been reported that up to 4% of patients with cutaneous melanoma will develop clinical gastrointestinal tract involvement antemortem and up to 60% at autopsy.[9]

It has been argued that the absence of a primary skin lesion in a patient with a gastrointestinal tract melanoma may represent either an undiagnosed or spontaneously regressed cutaneous malignancy. Many case reports document melanoma in the gastrointestinal tract as a solitary lesion without evidence of a cutaneous primary.[10–19] These reports suggest that malignant transformation can occur in the gut independent of cutaneous lesions and primary gastrointestinal melanomas (PGIM) are indeed a true entity.

PGIM are exceedingly rare. Because PGIM account for such a small percentage of the total number of melanomas,

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information on PGIM is not abundant, and the data available to date has generally been from case reports.[10–19] There is no recognized staging system for PGIM, nor are there established treatment protocols for these lesions. Furthermore, there are no reports of large, population-based analyses of PGIM in the current literature. We, therefore, analyzed data from a national cancer registry to guide therapy and better identify prognostic factors associated with survival.

Material and Methods

The Surveillance, Epidemiology, and End Results (SEER) April 2005 release was used to identify all incident cases of PGIM diagnosed from 1973 to 2004 using the ICD-O-3 morphology code.[20] A total of 659 PGIM cases, including patient demographics and clinical characteristics, were extracted from the database. Only the percentages based on available data for each individual variable are given. Patients with missing data were excluded from each respective univariate and multivariate analysis.

The SEER*Stat software (version 6.1.4, National Cancer Institute [NCI], Bethesda, MD) was used to analyze incidence rates and trends from 1973 to 2004. All incidence data was age adjusted and normalized to the 2000 US standard population. Annual percentage change (APC) was calculated using the weighted least-squares method. A p value of less than 0.05 was considered significant.

Statistical analysis was performed with SPSS Statistical Package version 15.0 (SPSS, Chicago, IL). Correlations between categorical variables were made using the Chi-square test. Median, 5- and 10-year overall and disease-specific survivals were calculated by the Kaplan–Meier method. Survival was calculated from the time of the initial diagnosis to the date of last contact (or the date of death, if the patient was deceased). The effects of demographic, clinical, pathologic, and treatment variables on survival were tested by utilizing the log-rank test for categorical values. A multivariate analysis using the Cox proportional hazards model was used to further test prognostic factors found to be significant in the univariate analysis. Specifically, age, tumor location, stage, surgical resection, and lymph node status were included in the multivariate analysis.

Results

Patient Demographics and Clinical Data

From 1973 to 2004, a total of 659 cases of melanoma of the gastrointestinal tract without an antecedent history of cutaneous melanoma were listed in the SEER database. Demographic, tumor, and treatment characteristics of the study population are summarized in Table 1. Men comprised 43.6% (n=287) of the group. Approximately half (n=333, 50.5%) of the group was more than 70 years of age, while the remaining patients were between the ages of 15 to 49 (n=89, 13.5%) and 50 to 69 (n=237, 36%). Only one patient identified was younger than 20 years of age. The patient population was predominately Caucasian (n=566, 94.8%). Over half of the tumors were located in either the anal canal (n=207, 31.4%) or the oral–nasal pharynx (n=216, 32.8%; includes mouth, tongue, tonsils, and nasopharynx; Fig. 1). A majority of the patients (n=233, 41.2%) had localized disease at the time of diagnosis. Among the cases for which data on tumor grade was available (n=81), over half was identified as poorly differentiated (n=55, 67.9%). In the majority of cases,

Table 1 Demographic and Clinical Characteristics

	Number	Percent of Total
Gender	659	100
Male	287	43.6
Female	372	56.4
Age	659	
0–49	89	14
50–69	237	36
70+	333	51
Race	597	100
Caucasian	566	94.8
Non-Caucasian	31	5.2
Site	659	100
Oral–nasophaynx	216	32.8
Esophagus	39	5.9
Stomach	18	2.7
Gallbladder	9	1.4
Small bowel	15	2.3
Large bowel	6	0.9
Rectum	146	22.2
Anal canal	207	31.4
Other	3	0.5
Stage	566	100
Localized	233	41.2
Regional	191	33.7
Distant	142	25.1
Grade	81	100
Well differentiated	2	2.5
Poorly differentiated	55	67.9
Undifferentiated	24	29.6
Surgery	652	100
Yes	535	82.1
No	117	17.9
Radiation	647	100
Yes	124	19.2
No	523	80.8

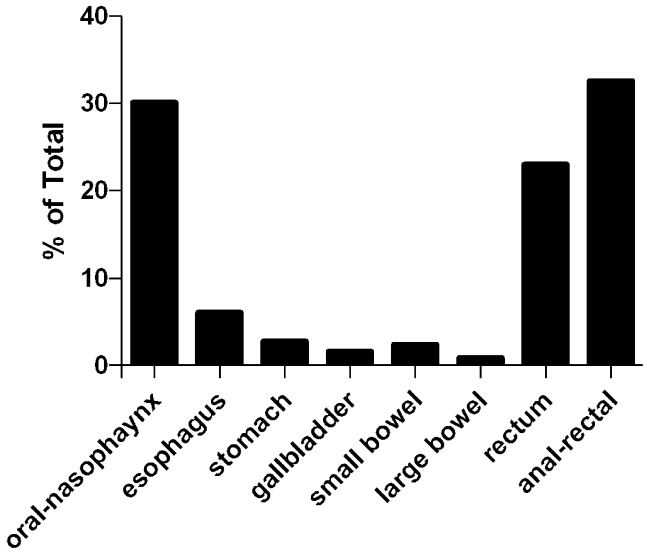

Figure 1 Tumor location given as percentage of total primary gastrointestinal tract melanoma included in study.

surgical extirpation was undertaken (n=535, 82.1%), and radiation was not given (n=523, 80.8%).

Incidence of PGIM

The overall incidence of PGIM was approximately 0.47 cases per million in 2000. A significant trend toward increasing incidence was observed throughout the study period (APC=1.73%, p<0.05; Fig. 2a). Furthermore, an increase in the incidence of PGIM was observed as patient age increased per decade in the study population (Fig. 2b). Adjusted incidence rates to the 2000 US standard population demonstrate that men and women have the same incidence (0.60 per million). African Americans have the lowest incidence (0.47 per million), while the highest incidence rate was observed in Native Americans and Asian/Pacific Islanders (0.75 per million). Incidence rates for Caucasians (0.61 per million) were in between these two groups.

Survival and Clinicopathological Variables

Median, 5-, and 10-year survival are summarized in Table 2. Median overall survival was 17 months with no significant differences between gender (p=0.977) or race (p=0.372). Improved median survival were observed in patients between the ages of 50 to 69 years (18 months, p=0.001) and in those less than 50 years old (18 months, p=0.003) when compared to patients greater than 70 years old (15 months). Among tumor sites, lesions located in the stomach showed the worst prognosis with median survival of 5 months, while tumors located in the gallbladder demonstrated better median survival (41 months). Median survival time for tumors located in the large bowel has not been reached. Local disease showed superior survival when compared to patients with distant disease (30 vs 8 months, p<0.001), while tumor grade did not significantly affect patient outcomes (p=0.898). Kaplan–Meier survival curves illustrating these results are shown in Fig. 3.

Treatment and Survival

The median overall survival of patients who underwent surgical intervention was 19 months, as compared to 8 months for nonoperative cases (p<0.001; Table 3). Surgery also improved survival in patients with local (13 vs 33 months, p<0.001) and distant (11 vs 3 months, p<0.001) disease as well as in patients with poorly differentiated tumors (17 vs 5 months, p=0.005) and undifferentiated tumors (22 vs 9 months, p=0.029). No significant improvement in survival was observed for surgical extirpation of tumors located in the esophagus and small bowel. All patients with tumors located in the

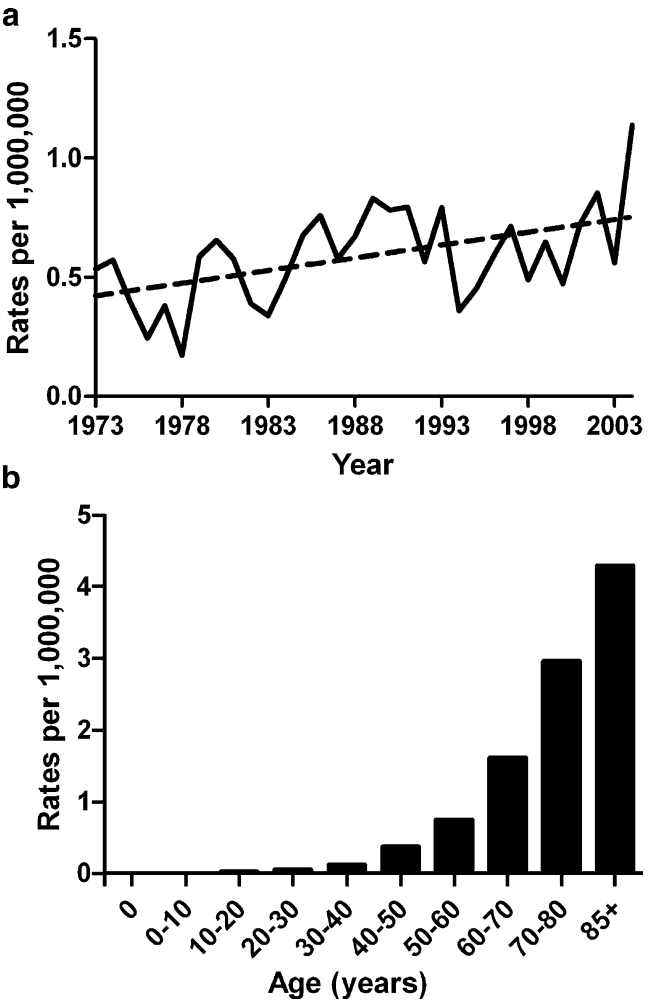

Figure 2 **a** Overall incidence of primary gastrointestinal tract melanoma from years 1973 to 2004. *Solid line* represents rate per 1,000,00 per year. *Broken line* represents best fit straight line. **b** Age adjusted incidence rate to 2000 US standard population.

Table 2 Median, 5-, and 10-year Survival

	Number	Percent	Median Survival	5 year	10 year	*p* value
Overall	659	100.0	17	22	12	
Gender						
Male	287	43.6	17	23	13	0.977
Female	372	56.4	17	22	12	
Age						
0–49	89	13.5	18	29	20	<0.0001
50–69	237	36.0	18	26	16	
70+	333	50.5	15	18	7	
Race						
Caucasian	566	94.8	16	22	12	0.372
Non-Caucasian	31	5.2	16	20	4	
Site						
Oral-nasophaynx	216	32.9	27	30	16	0.001
Esophagus	39	5.9	12	14	0	
Stomach	18	2.7	5	0	0	
Gallbladder	9	1.4	41	29	29	
Small bowel	15	2.3	16	10	10	
Large bowel	6	0.9	ND	56	56	
Rectum	146	22.3	14	17	11	
Anal canal	207	31.6	16	21	11	
Stage						
Localized	233	41.2	30	32	15	<0.001
Regional	191	33.7	17	22	12	
Distant	142	25.1	8	7	2	
Grade						
Well differentiated	2	2.5	11	0	0	0.898
Poorly differentiated	55	67.9	13	16	16	
Undifferentiated	24	29.6	19	23	0	
Surgery						
Yes	535	82.1	19	25	14	<0.001
No	117	17.9	8	10	7	
Lymph nodes						
Negative	65	12.8	33	43	24	0.001
Positive	444	87.2	16	22	11	
Radiation						
Yes	124	19.2	18	23	12	0.906
No	523	80.8	16	22	13	

ND Not determined

gallbladder underwent surgical resection. Survival data in large bowel disease could not be determined as median survival has not been reached. In the cohort that underwent surgical treatment, survival was significantly improved for those not having lymph node involvement (33 vs 16 months, $p=0.001$; Fig. 3c). Although information regarding the goal of radiotherapy treatments (i.e., neo-adjuvant vs adjuvant vs palliative) was not available from the SEER database, radiation therapy did not affect overall survival ($p=0.906$).

Independent Risk Factors

Using variables identified as significant in univariate analysis, a stepwise multivariate analysis was undertaken using the Cox regression model. Among preoperative variables, increasing age and stage were identified as independent predictors of lower overall survival (Table 4). Tumor location also was a significant predictor of outcome. Whereas surgical resection improves survival, the presence of lymph nodes confers a significantly worse outcome.

Discussion

We have presented a population-based study of prospectively collected data to provide a description of prognostic factors important in PGIM. The current literature on outcomes for PGIM consists predominately of case reports or data on cutaneous melanomas metastatic to the gastro-

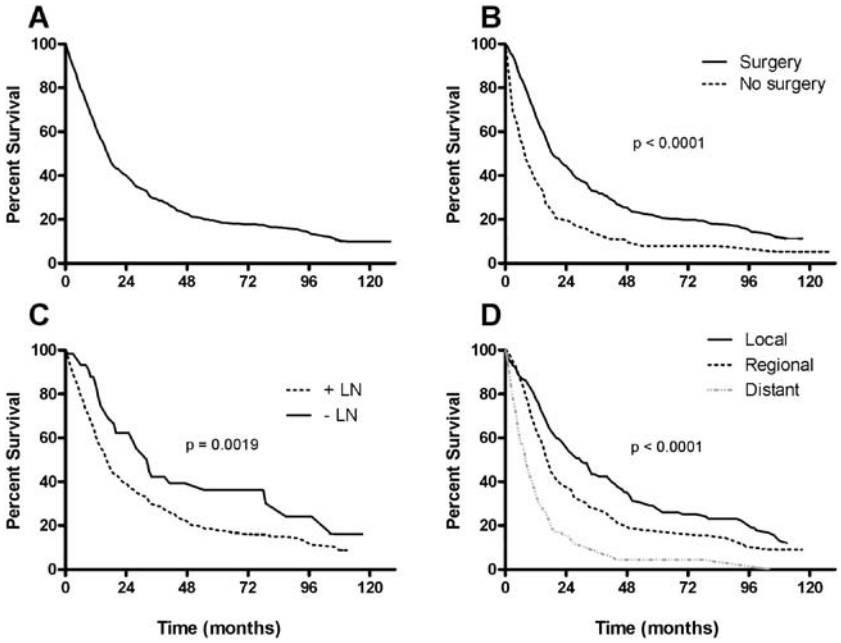

Figure 3 Kaplan–Meier curve for **a** overall survival of entire cohort, **b** overall survival of cohorts having surgery vs not having surgery, **c** overall survival of cohorts having positive lymph nodes at surgery vs those not having positive lymph nodes, and **d** overall survival by stage. *p* value shown for log-rank test between variables. *LN* Lymph nodes.

intestinal tract. To our knowledge, this series is the largest patient cohort of PGIM studied to date.

The SEER Program of the NCI is the largest registry source of information on cancer incidence and survival in the USA.[21] SEER currently collects and publishes cancer incidence and survival data from 17 population-based cancer registries encompassing approximately 26% of the US population. With just more than 6,100,000 incident cancer cases, SEER represents the largest cancer database in the country. The SEER program is the only comprehensive source of population-based information in the USA that includes stage of cancer at the time of diagnosis and patient survival data. The data collected provide insight into tumor behavior and allow us to examine outcomes from current treatment strategies.[22–28]

PGIM may be located anywhere along the gastrointestinal tract, most common locations being the anal canal and the oral–nasopharynx. Malignant melanoma of the gastrointestinal tract is almost always related to metastatic disease from a cutaneous primary. In a review from Memorial Sloan Kettering Cancer Center, metastatic disease to the gastrointestinal tract occurred with the following incidences: small bowel (including duodenum) 70%, liver 68%, colon 22%, stomach 20%, rectum 5%, esophagus 4%, and anus 1%.[29] Because of its rich blood supply, the small intestine is the most frequent site of metastatic disease in melanoma.[30] However, in this series, small bowel only accounted for roughly 2% of the total cases of PGIM.

Other than skin and eye, the anus has been reported to be the third leading location of primary malignant melanoma.[3] In this paper, we observed it to be the second most common location after oral–nasal pharynx, which includes the mouth, tongue, gums, salivary glands, tonsils, and nasopharynx. For anal canal lesions, it is important to note the location of these tumors relative to the dentate line. Lesions located above this delineation should be considered PGIM, while lesions located below should be considered cutaneous in origin and treated accordingly. Cases included in the anal canal group were strictly noncutaneous in origin, as the

Table 3 Effect of Surgical Treatment on Overall Survival

	Median Survival (months)		*p* value
	Surgery	No surgery	
Overall	19	8	<0.001
Stage			
Localized	33	13	<0.001
Regional	17	11	0.196
Distant	11	3	<0.001
Grade			
Well differentiated	32	11	0.317
Poorly differentiated	17	5	0.005
Undifferentiated	22	9	0.029
Site			
Oral–nasophaynx	32	11	<0.001
Esophagus	12	7	0.195
Stomach	12	2	<0.001
Gallbladder	41	41	ND
Small bowel	12	17	0.781
Large bowel	ND	ND	ND
Rectum	16	5	0.001
Anal canal	17	4	<0.001

ND Not determined

Table 4 Cox Proportional Hazard Model for Primary Gastrointestinal Melanoma

	Hazard Ratio	95% CI	*p* value
Age			
0–49	Reference group	Reference group	Reference group
50–69	1.148	0.795 to 1.659	0.461
>70	1.446	1.013 to 2.064	0.042
Site			
Oral–nasophaynx	Reference group	Reference group	Reference group
Esophagus	2.537	1.486 to 4.332	0.001
Stomach	4.584	2.143 to 9.802	<0.001
Gallbladder	1.873	0.664 to 5.283	0.236
Small bowel	1.708	0.821 to 3.550	0.152
Large bowel	2.191	0.292 to 16.415	0.445
Rectum	2.100	1.505 to 2.929	<0.001
Anal canal	2.041	1.509 to 2.760	<0.001
Stage			
Localized	Reference group	Reference group	Reference group
Regional	1.689	1.284 to 2.222	<0.001
Distant	3.406	2.503 to 4.636	<0.001
Surgery			
Yes	Reference group	Reference group	Reference group
No	2.725	1.975 to 3.762	<0.001
Lymph nodes			
No	Reference group	Reference group	Reference group
Yes	1.536	1.037 to 2.275	0.032

SEER database has different categories for cutaneous lesions. Indeed, a fine line does not exist demarcating exactly where the columnar cells of the gastrointestinal tract become cutaneous squamous cells. Tumors have been described in this transition zone, and some speculated whether or not the epithelium here is related to the uroepithlium.[31] None of these cases were included in this study.

Given that more than half of the patients with cutaneous melanoma will develop metastatic disease to the gastrointestinal tract at autopsy, a thorough search for an occult primary cutaneous melanoma is warranted when diagnosed with gastrointestinal melanoma. Similarly, gastrointestinal complaints in a patient with an established diagnosis of cutaneous melanoma should trigger an exhaustive search for evidence of metastatic disease. These may include but not limited to routine laboratory work, computed tomography (CT) scans, upper endoscopy, colonoscopy, and video endoscopy for the small bowel. In an otherwise healthy patient, the presenting symptom of PGIM is similar to a number of other gastrointestinal disorders. Symptoms may include pain, dysphagia, weight loss, anemia, bleeding, and bowel obstruction.[10,12–14]

The incidence data presented in this series suggests that PGIM is on the rise. Indeed, this increase in the number of PGIM diagnosed per year may reflect a true increase in the incidence of this rare entity. Another possible explanation may be that we are becoming more sophisticated with diagnostic testing such as CT scans and endoscopy. Perhaps we are now identifying those lesions that have gone unnoticed and previously undetected.

Nonsurgical outcome data is not available for tumors located in the gallbladder because all the patients in this cohort underwent surgery. The median survival time for this cohort was significantly longer (41 months) when compared to other tumor locations, excluding the large bowel. It is not known why these patients have better overall survival. Indeed, cholecystectomies are associated with less morbidity than resection of any other major organ of the gastrointestinal tract. Median survival time for lesions located in the large bowel could not be determined because it has not been reached. Perhaps early identification and better surveillance in an era where colonoscopy is performed routinely could explain this observation.

The SEER database, although an excellent resource for comparative outcomes analysis, has its limitations. The database provides passive follow-up for its registered cases. Thus, incomplete data reporting remains a problem. In some instances, demographic or disease data, such as race and tumor grade, were not specified. This may reflect a reporting omission or the absence of the data in the patient's medical record. The status of surgical resection margin is not included in the database and could not be included in the analysis. Although data on radiotherapy was

examined, data on chemotherapy was lacking. Information on whether the patient received palliative radiation vs adjuvant or neoadjuvant treatment, including the specific regimen and dosage, were also not available.

Currently, there is no well-defined staging system for PGIM as there is for cutaneous melanomas.[1,32] There are no widely accepted treatment protocols for these tumors as there is for many other gastrointestinal tract malignancies. Surgical resection was the only identifiable treatment modality for which independent predictive prognostic value could be demonstrated. The data presented here is consistent with the available case reports in the literature suggesting surgical extirpation as treatment for PGIM. One major limitation of this retrospective analysis, however, is that there may have been selection bias in the subset of patients treated with surgery. Nonetheless, it is unlikely that better data (i.e., prospective randomized trials) will ever be accomplished to provide additional insight.

Studies suggest nodal status having an impact on survival.[13,33] Lymph node status is a prognostic indicator in cutaneous melanoma.[34] On multivariate analysis, we have also observed this phenomenon for PGIM. In all patients undergoing surgical resection, the cohort that did not have nodal involvement had a much better prognosis of nearly twice the median survival time of node-negative disease. In this large, population-based, nationwide cancer registry study, age, stage, tumor location, and the presence of lymph nodes were independently predictive of prognosis in PGIM. In this series, radiation did not confer a significant survival benefit. Further studies are needed to determine whether or not chemotherapy has a role in prolonging survival.

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Enteral versus Parenteral Nutrition after Gastrointestinal Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials in the English Literature

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Abstract
Background Although previous studies recommend the use of enteral nutrition (EN), the benefit of EN after elective gastrointestinal surgery has not been comprehensively demonstrated as through a meta-analysis. Our aim is to determine whether enteral nutrition is more beneficial than parenteral nutrition.
Methods A search was conducted on Medline, Web of Science, the Cochrane Library electronic databases, and bibliographic reviews. The trials were based on randomization, gastrointestinal surgery, and the reporting of at least one of the following end points: any complication, any infectious complication, mortality, wound infection and dehiscence, anastomotic leak, intraabdominal abscess, pneumonia, respiratory failure, urinary tract infection, renal failure, any adverse effect, and duration of hospital stay.
Results Twenty-nine trials, which included 2,552 patients, met the criteria. EN was beneficial in the reduction of any complication (relative risk (RR), 0.85; 95% confidence interval (CI), 0.74–0.99; P=0.04), any infectious complication (RR, 0.69; 95% CI, 0.56–0.86; P=0.001), anastomotic leak (RR, 0.67; 95% CI, 0.47–0.95; P=0.03), intraabdominal abscess (RR, 0.63; 95% CI, 0.41–0.95; P=0.03), and duration of hospital stay (weighted mean difference, −0.81; 95% CI, −1.25–0.38; P=0.02). There were no clear benefits in any of the other complications.
Conclusion The present findings would lead us to recommend the use of EN rather than PN when possible and indicated.

Keywords Enteral nutrition · Parenteral nutrition · Gastrointestinal surgery · Postoperative complications · Meta-analysis

Abbreviations

EN	enteral nutrition
PN	parenteral nutrition
GI	gastrointestinal
TPN	total parenteral nutrition
PPN	peripheral parenteral nutrition
RR	relative risk
CI	confidence interval
χ^2	chi-squared
RCT	randomized controlled trial
WMD	weighted mean difference
GALT	gut-associated lymphoid tissue

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Introduction

Patients with malnutrition to a degree that is associated with changes and impairments in body composition, tissue wasting, muscle strength, wound healing, and immunity make up 27 to 46% of the surgical and medical patients admitted to the hospital.[1–3] Generally, patients undergoing gastrointestinal (GI) surgery are at risk of malnutrition from

anorexia, dietary restriction, malabsorption, increased intestinal losses, or altered nutrient requirement perioperatively. Preoperative malnutrition is recognized as a major determinant of development of postoperative complications, infections, and mortality, prolongation of duration of hospital stay, and higher costs.[4–9] Health care professionals, therefore, should aim to provide adequate nutrition to malnourished patients. Artificial nutrition is needed when oral intake is likely to be absent for a period of 5–7 days. In all postoperative patients with a functioning GI tract who are unable to tolerate oral intake, enteral nutrition (EN) is recommended within 1–2 days after surgery in severely malnourished patients, 3–5 days in moderately malnourished patients, and 7 days in normally or over-nourished patients.[2] If patients cannot receive adequate EN as a result of GI insufficiency (e.g., short bowel syndrome, bowel obstruction, GI bleeding, bowel ischemia or infarction, severe abdominal distention, severe diarrhea, large volume fistula output, and malabsorption), administration of parenteral nutrition (PN) is life-saving.[10]

EN is considered to be better than conventional PN because it is less expensive, safer, more physiologic, and maintains the nutritional, metabolic, immunological, and barrier function of the intestines in critically ill and surgical patients.[11] From this point of view, many recent clinical studies,[12–14] reviews,[15,16] meta-analyses,[17–23] and guidelines[24–26] strongly recommended the use of EN compared with PN in the critically ill and surgical patients because of a lower infection rate or shorter duration of hospital stay with accompanying cost savings. Some randomized controlled trials (RCTs),[27–44] on the other hand, failed to demonstrate that there was statistical benefit to EN. The mechanisms explaining this benefit of EN over PN remain unknown.[11]

To our knowledge, four meta-analyses[18,20–22] have already statistically aggregated the results of these RCTs in patients before or after surgery. However, there were methodological limitations in the previous reviews, especially with inclusion and exclusion criteria. They combined patients who received preoperative nutritional support with patients who received postoperative nutritional support. The time of administration of EN or PN varied and was given both preoperatively or postoperatively. They had heterogeneity in primary disease and patient population, that is, they included various kinds of surgical patients such as GI, trauma, head surgery, and critically ill patients in the study. Moreover, as far as GI surgery is concerned, a comprehensive literature search has not been performed because some relevant studies on this topic have been missed.

No helpful guidelines exist for practitioners to optimize the benefits and minimize the risk of nutritional support in GI surgery. The object of this meta-analysis is to systematically review and critically appraise RCTs, to statistically aggregate all RCTs that evaluate the hypothesis that administrating EN to patients after GI surgery is beneficial rather than PN, to allow a more precise estimated effect, and to facilitate more effective and consistent delivery of nutritional support that can lead to improved patient outcome.

Materials and Methods

Search Strategy

Using MEDLINE, Web of Science, and the Cochrane Library, we conducted an English literature search for RCTs published from January 1974 to August 2006 that evaluated the clinical benefits of EN and PN in patients after GI surgery. We also manually searched bibliographic reviews. We used the following keywords: “enteral nutrition”, and/or “parenteral nutrition”, and/or “randomized controlled trial” combined with “GI surgery” and/or “abdominal surgery” and/or “postoperative”. No formal inquiry was made to pharmaceutical companies.

Eligibility Criteria for Trials

All published RCTs, which compared one type of nutritional support (EN or PN) with another, were considered. Populations were human adult subjects who underwent elective GI surgery. Intervention was any form of EN or PN. EN was the postoperative delivery of any nutrient in solid or liquid form (including usual food intake) that passed through any part of the digestive tract, regardless of whether the patients received conventional oral diets with intravenous fluids (standard care) or tube feeds (e.g., nasojejunostomy, gastrostomy, or jejunostomy). If three types of intervention (e.g., immunonutrition vs standard nutrition vs PN) were compared in a study, we adapted the comparison between immunonutrition and PN. PN was defined as the administration of nutritional liquids containing a minimum of glucose and amino acids that were postoperatively administered through the central or peripheral venous system. If more than one version of the same study was retrieved, only the most recent study was used. Each study was required to contain information on the methodology of EN and PN. We excluded: (1) trials in which EN was administrated preoperatively or perioperatively; (2) trials that investigated clinical benefit of an oral nutritional supplement (sip feed); (3) trials that compared one type of EN with another type of EN (immunonutrition vs standard nutrition); (4) trials from developing countries (because of potential differences in the operation and postoperative care); (5) trials that evaluated the impact of EN or PN only on nutritional or physiologic outcomes (e.g., nitrogen

balance or amino acid profile); (6) trials that treated patients receiving home parenteral nutrition; (7) trials that included cardiopulmonary, head injury, pediatric, gynecologic, urological, traumatic, emergency, transplantation surgery, chemotherapy, radiotherapy, or critically ill patients; (8) meeting abstracts (because of insufficient data); (9) trials that used administrative data to identify outcomes (because of recent evidence that administrative data were poor for evaluating postoperative complications).

Data Extraction

Data were extracted on study design, setting, patient population, pathology of diseases, site of surgery, the exact regimens, methods of EN and PN, and the outcome variables listed above. The primary end points were the number of patients with any complication, any infectious complication, and mortality. The secondary end points were the number of patients with wound infections or dehiscence, anastomotic leaks, intraabdominal abscesses, pneumonia, respiratory failure, urinary tract infections, renal failure, adverse effects, and the duration of hospital stay. The definitions of the variables given by the authors were used. Data were extracted as the total number of patients affected by complications rather than the total number of incidences of complications. Original investigators were contacted and requested to provide further information of published data on trial populations and interventions, or to report if at least one of the outcome data was incomplete, missing, or not reported on a per-patient basis. Data were extracted independently by two physicians (TM and KE). Disagreements about values or analysis were resolved by discussion.

Assessment of Methodological Quality

Trial quality was assessed by component approach.[46–48] Three methodological key domains of internal validity that have been shown to be associated empirically with biased estimates of treatment effect were assessed: allocation concealment, double blinding of outcome assessment, and handling of withdrawals. We considered allocation sequence to be adequately classified if random-numbered tables, computer-generated random numbers, or minimization was mentioned in the RCT. Sealed, opaque, sequentially numbered assignment envelops, central randomization, and an on-site computerized randomization system were classified as adequate methods of allocation concealment. We considered blinding to be adequately classified if patients, therapists, and outcome assessors all remained unaware of the intervention assignments throughout the trial. Analysis by intention-to-treat was assumed if the reported number of participants randomized and the number analyzed were identical.

Statistical Analysis

Pooled relative risk (RR) estimates of comparative binary outcomes were calculated using the general inverse-variance (I-V) fixed effect model.[49,50] If the results were heterogeneous, the random effect estimates were reported using the DerSimoian and Laird (D+L) method, with the estimates of heterogeneity being taken from the I-V fixed effect model.[49–51] The weighted mean difference (WMD) method was used for combining mean differences of continuous outcomes on the same parameter.[49,50] Pooled estimates were presented with 95% confidence intervals (CI). Heterogeneity was tested using the Cochrane Q test[49,50] and I^2 inconsistency[52,53] that express the percentage of total variance across the studies because of heterogeneity rather than chance across the primary and secondary end points. If heterogeneity was suggested by the Cochrane Q test with $P<0.10$ indicating heterogeneity or by I^2 values of 25%, 50%, and 75% indicating evidence of low, moderate, and high heterogeneity, respectively, we explored a potential cause of heterogeneity using random effect meta-regression models with restricted maximum likelihood estimation across the primary and secondary end points.[49,50,54] In sensitivity analysis for the primary end points, we examined whether effects varied between pathology of disease (malignant or nonmalignant disease), nutritional status (malnourished or malnourished plus well nourished), type of administration route of EN (tube feeding or oral feeding), site of surgery (upper or lower GI lesion), type of EN (immunonutrient or standard nutrient), type of PN (TPN or PPN), administration of parenteral lipid, and geographic location (Europe, or North America). We also excluded one trial whose results had been influential. Methodological key domains (allocation concealment, double blindness, and intention to treat analysis) relating to effects sizes were also considered by using univariate meta-regression analysis. We assessed publication bias visually using a funnel plot and statistically using a regression asymmetry test (Egger's test) and a rank correlation test (Begg's test). $P<0.10$ was considered significant.[55,56] All analyses were performed using the software package Stata Version 8.2 (Stata Corporation, College Station, TX, USA).

Results

Identification of Eligible Trials

The process of identifying eligible clinical trials and the search strategy initially generated 1076 trials. We excluded 801 trials that were not based on patients with GI surgery, 63 trials that were not reported in English, 59 trials that were reviews, comments, or discussions, 24 trials that

tested preoperatively or perioperatively, six trials that were meta-analyses, and one trial that was a meeting abstract. One hundred twenty-two trials met inclusion criteria. Eighty-one trials were excluded because 33 trials tested for critically ill patients, 19 trials for nonsurgical liver diseases, 11 trials for trauma patients, 10 trials for pediatric patients, three trials for obese patients, two trials for patients with pancreatitis, two trials for patients with ileus, and two trials for inflammatory bowel disease. Forty-one eligible trials were identified. Twelve trials were excluded because of four trials[57–60] with incomplete data, four same trials.[61–64]. Two trials[65,66] included oral dietary supplement, and two trials[67,68] included cardiac procedures and vascular diseases. Finally, we identified 29 RCTs concerning post-operative EN vs PN for patients after elective GI surgery (Table 1).

Characteristics of Trials

The included trials were published between 1979 and 2006. Additional unpublished data were obtained from nine trials A total of 2552 participants were included in this meta-analysis, 1276 of which received both EN and PN. EN in all trials was started within 6–24 hours after the operation. All 29 trials included trials that measured at least one end point of interest. Twelve of the 29 trials were comprised of patients with esophageal, gastric, or pancreatic surgery, nine trials had a wide variety of upper- and lower-GI surgery, four trials focused on colorectal surgery, three trials involved small- and large-bowel surgery, and one trial included hepatic surgery (Table 1). Twenty trials stated the underlying pathology of the trial participants, 13 trials of which were comprised of malignant conditions and the remaining seven trials included both malignant and benign conditions (Table 1). No trial included only benign diseases. In twenty-two trials, patients in the EN group were fed through either a naso-jejunal or catheter jejunostomy, and in the remaining seven trials diet was fed orally (Table 1). Control group patients received TPN (total parenteral nutrition) in 13 trials of the 25 trials and PPN (peripheral parenteral nutrition) in 15 trials (Table 1).

Primary Outcomes

The analysis for any complication was based on 13 trials (Fig. 1a). There was evidence of an association of the treatment effect of EN with reduction in any complication (RR, 0.85; 95% CI, 0.74–0.99; P=0.04) and no evidence of heterogeneity between trials (χ^2, 15.30; P=0.23; I^2=22%). Next, 13 trials reported on the analysis of any infectious complications (Fig. 1b). There was evidence of association of the treatment effect of EN with reduction of any infectious complication (RR, 0.69; 95% CI, 0.56–0.86; P=0.001) and no evidence of heterogeneity between trials (χ^2, 13.35; P=0.34; I^2=10%). Finally, data on mortality were available from 15 trials (Fig. 1c). There was no reduction in mortality (RR, 0.79; 95% CI, 0.48–1.30; P=0.35) and no heterogeneity was recognized (χ^2, 10.08; P=0.76; I^2=0%).

Secondary Outcomes

The analysis for anastomotic leaks was based on 17 trials and for intraabdominal abscesses on 16 trials. There was evidence of an association of the treatment effect of EN in both anastomotic leaks (RR, 0.67; 95% CI, 0.47–0.95; P=0.03) and intraabdominal abscesses (RR, 0.63; 95% CI, 0.41–0.95; P=0.03) (Fig. 2). No heterogeneity was recognized in the trial addressing either anastomotic leaks or intraabdominal abscesses. Next, 20 trials reported on analysis for wound infections, six trials for wound dehiscence, 19 trials for pneumonia, four trials for respiratory failure, 11 trials for urinary tract infections, and four trials for renal failure. There was no risk reduction in wound infection (RR, 0.83; 95% CI, 0.59–1.18; P=0.30), wound dehiscence (RR, 0.56; 95% CI, 0.24–1.30; P=0.18), pneumonia (RR, 0.79; 95% CI, 0.55–1.13; P=0.20), respiratory failure (RR, 0.83; 95% CI, 0.42–1.64; P=0.59), urinary tract infection (RR, 0.68; 95% CI, 0.36–1.26; P=0.22), or renal failure (RR, 0.37; 95% CI, 0.08–1.66; P=0.19) (Fig. 2). No heterogeneity was recognized. We next evaluated the adverse effects of both EN and PN. The rates of abdominal distension, diarrhea, nausea, and vomiting were reported in 6, 5, 4, and seven trials, respectively. There were no differences comparing EN with PN in diarrhea (RR, 1.07; 95% CI, 0.74–1.56; P=0.71), abdominal distension (RR, 1.38; 95% CI, 0.84–2.27; P=0.20), and nausea (RR, 1.28; 95% CI, 0.97–1.68; P=0.08), although vomiting was more frequent in EN than in PN (RR, 1.61; 95% CI, 1.25–2.09; P<0.001) (Fig. 2). No heterogeneity was recognized in diarrhea (χ^2, 6.19; P=0.19; I^2=35%), nausea (χ^2, 0.42; P=0.94; I^2=0%), or vomiting (χ^2, 2.05; P=0.92; I^2=0%), except for abdominal distension (χ^2, 9.29; P=0.098; I^2=46%). In a meta-regression analysis, there was evidence of an association of abdominal distension with both the published year of each article (P=0.04) and type of PN (P=0.02), which explained the large proportion of inter-trial heterogeneity. The estimate of between-study variance (τ^2) was reduced from 0.157 to less than 0.001 when covariates were included in the model. Finally, we compared EN with PN for the length of postoperative hospital stay, as reported in 14 trials. Hospital stay was reduced in patients receiving EN as compared to PN (WMD, −1.19; 95% CI, −2.18–0.21; P=0.02) (Fig. 2), and heterogeneity (χ^2, 38.0; P<0.001) was present.

Table 1 Characteristics of Randomized Controlled Trials Evaluating EN and PN after Gastrointestinal Surgery[a]

Study, year	Location	Setting	Patients population (No. of EN/PN)	Malnourished patient (Proportion of EN/PN, %)	Type of feed		Administering route in EN	Pathology of disease		Patients with cancer (%)	Site of surgery (no. of EN/PN)			
					EN	PN		Malignant	Benign		Upper GI[f]	Lower GI	HPB[g]	Other
Sagar et al.[75] 1979	UK	NR	Gastrointestinal surgery (15/15)	NR	EN	PN	NJ[d]	NR	NR	NR	4/4	11/11	–	–
Smith et al.[43] 1985	Australia	NR	Gastrointestinal surgery (25/25)	NR	EN	PN	JII	25/25	–	100	14/8	1/3	4/8	6/6
Heylen et al.[69] 1987	Belgium	University hospital	Gastric surgery (10/10)	NR	EN	TPN[c]	J	10/10	–	100	10/10	–	–	–
Hamaoui et al.[76] 1990	USA	NR	Gastrointestinal surgery (11/8)	NR	EN	TPN[c]	J, NJ, or G[e]	10/5	1/3	78.9	7/0	1/3	2/4	1/1
Schroeder et al.[39] 1991	New Zealand	University hospital	Small- and large-bowel surgery (16/16)	NR	EN	PN	NJ	NR	NR	NR	–	16/16	–	–
Binderow et al.[72] 1994	USA	NR	Small- and large-bowel surgery (32/32)	NR	Regular diet	Traditional manner	Oral	NR	NR	NR	–	32/32	–	–
Reissman et al.[37] 1995	USA	NR	Small- and large-bowel surgery (80/81)	NR	Regular diet	Traditional manner	Oral	NR	NR	NR	–	80/81	–	–
Baigrie et al.[70] 1996	UK	NR	Esophageal and gastric surgery (50/47)	34.0/36.2	EN	TPN	J	NR	NR	NR	50/47	–	–	–
Beier-Holgersen et al.[12] 1996	Denmark	NR	Gastrointestinal surgery (30/30)	13.3/16.7	EN	Placebo	Oral	NR	NR	NR	4/4	26/26	–	–
Braga et al.[27] 1996	Italy	University hospital	Gastric and pancreatic surgery (20/20)	60.0/55.5	EN[b]	TPN[c]	NJ or J	20/20	–	100	11/12	–	9/8	–
Carr et al.[29] 1996	UK	NR	Gastrointestinal surgery (14/14)	NR	EN	PN	NJ	NR	NR	NR	NR	NR	NR	NR

Table 1 (continued)

Study, year	Location	Setting	Patients population (No. of EN/PN)	Malnourished patient (Proportion of EN/PN, %)	Type of feed		Administering route in EN	Pathology of disease		Patients with cancer (%)	Site of surgery (no. of EN/PN)			
					EN	PN		Malignant	Benign		Upper GI[f]	Lower GI	HPB[g]	Other
Ortiz et al.[73] 1996	Spain	NR	Colorectal surgery (95/95)	NR	Regular diet	Traditional manner	Oral	82/83	13/12	86.8	–	95/95	–	–
Schilling et al.[41] 1996	Switzerland	University hospital	Gastrointestinal surgery (14/13)	NR	EN[b]	PN[c]	NJ	14/13	–	100	7/7	7/9	–	–
Gianiotti et al.[14] 1997	Italy	University hospital	Gastric and pancreatic surgery (87/86)	NR	EN[b]	TPN	J or NJ	87/86	–	100	40/39	–	47/47	–
Hartsell et al.[31] 1997	USA	NR	Colorectal surgery (29/29)	NR	Regular diet	Traditional manner	Oral	17/20	9/7	63.8	–	29/29	–	–
Heslin et al.[32] 1997	USA	NR	Esophageal, gastric, pancreatic, and bile duct surgery (97/98)	NR	EN[b]	PN	J	92/93	5/5	94.9	43/56	–	54/42	–
Reynolds et al.[38] 1997	UK	University hospital	Esophageal, gastric, and pancreatic surgery (33/34)	81.8/79.4	EN	TPN[c]	J	33/34	–	100	30/26	–	3/8	–
Sand et al.[40] 1997	Finland	University hospital	Gastric surgery (13/16)	NR	EN	TPN[c]	NJ	13/16	–	100	13/16	–	–	–
Shirabe et al.[42] 1997	Japan	University hospital	Hepatic surgery (13/13)	NR	EN	TPN	NJ	13/13	–	100	–	–	13/13	–
Watters et al.[44] 1997	Canada	NR	Esophageal and pancreatic surgery (13/15)	NR	EN	PN	J	NR	NR	NR	13/15	–	–	–
Stewart et al.[74] 1998	Australia	NR	Colorectal surgery (40/40)	NR	Regular diet	Traditional manner	Oral	NR	NR	NR	–	40/40	–	–
Aiko et al.[71] 2001	Japan	University hospital	Esophageal surgery (13/11)	NR	EN	TPN[c]	J	13/11	–	100	13/11	–	–	–

Bozzetti et al. [13] 2001	Italy	Multi-center hospital	Gastrointestinal surgery (159/158)	100/100	EN	TPN[c]	J or NJ	159/158	–	100	83/76	36/43	38/37	2/2
Braga et al.[28] 2001	Italy	University hospital	Esophageal, gastric, and pancreatic surgery (126/131)	34.1/36.6	EN[b]	TPN[c]	J 126/131	–	100	126/131	–	–	–	
Pacelli et al.[35] 2001	Italy	District hospital	Gastrointestinal surgery (119/122)	100/100	EN	TPN	J or NJ	110/111	9/11	92.9	73/61	20/28	18/17	8/16
Page et al.[34] 2002	UK	District hospital	Esophageal surgery (20/20)	NR	EN	PN	NJ	20/20	–	100	20/20	–	–	–
Rayes et al.[36] 2002	Germany	NR	Gastrointestinal surgery (30/30)	13.3/13.3	EN	TPN[c]	NJ	50/24	10/6	73.3	16/6	12/1	32/23	–
Feo et al.[30] 2004	Italy	University hospital	Colorectal surgery (50/50)	NR	Regular diet	Traditional manner	Oral	50/50	–	100	–	50/50	–	–
Mack et al.[33] 2004	Canada	University hospital	Pancreatic surgery (20/16)	55.0/50.0	EN[b]	Traditional manner	GJ	17/16	3/0	91.7	–	–	20/16	–

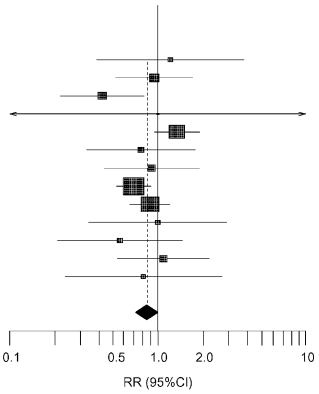
[a] NR indicates data not reported.
[b] Formula of EN includes immunonutrient
[c] PN includes intravenous lipid
[d] NJ, naso-jejunal feeding; IIJ, jejunal feeding
[e] G, gastrostomy feeding
[f] GI, gastrointestinal
[g] HPB, hepatopancreaticobiliary

a

Study	No. of events/total (%) EN	PN	Weight , %	RR (95%CI)
Reissmen et al,[37] 1995	6/80 (7.5)	5/81 (6.2)	1.7	1.21 (0.39-3.82)
Ortiz et al,[73] 1996	17/93 (18.3)	18/93 (19.4)	6.1	0.95 (0.52-1.71)
Beier-Holgersen et al,[12] 1996	8/30 (26.7)	19/30 (63.3)	5.1	0.42 (0.22-0.81)
Hartsell et al,[31] 1997	1/29 (3.4)	1/29 (3.4)	0.3	1.00 (0.06-15.2)
Heslin et al,[32] 1997	44/97 (45.4)	33/98 (33.7)	17.4	1.35 (0.95-1.92)
Sand et al,[40] 1997	5/13 (38.5)	8/16 (50.0)	3.1	0.77 (0.33-1.79)
Stewart et al,[74] 1998	10/40 (25.0)	11/40 (27.5)	4.0	0.91 (0.44-1.90)
Bozzetti et al,[13] 2001	54/159 (34.0)	78/158 (49.4)	30.3	0.69 (0.53-0.90)
Braga et al,[28] 2001	45/126 (35.7)	53/131 (40.5)	22.1	0.88 (0.65-1.21)
Page et al,[34] 2002	5/20 (25.0)	5/20 (25.0)	1.9	1.00 (0.34-2.93)
Rayes et al,[35] 2002	5/30 (16.7)	9/25 (30.0)	2.3	0.56 (0.21-1.46)
Feo et al,[30] 2004	12/50 (24.0)	11/50 (22.0)	4.2	1.09 (0.53-2.24)
Mack et al,[33] 2004	4/20 (20.0)	4/16 (25.0)	1.5	0.80 (0.24-2.71)
Total	216/787 (27.4)	255/792 (32.2)		0.85 (0.74-0.99); *P*=0.04

Test for heterogeneity: Q=15.3, df=12, *P*=0.225

I^2 (95%UI) =22% (0-59)

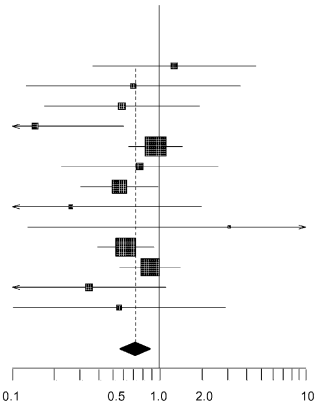


b

Study	No. of events/total (%) EN	PN	Weight, %	RR (95%CI)
Reissmen et al,[37] 1995	5/80 (6.3)	4/81 (4.9)	2.8	1.27 (0.35-4.54)
Braga et al,[27] 1996	2/20 (10.0)	3/20 (15.0)	1.6	0.67 (0.12-3.57)
Schilling et al,[41] 1996	3/14 (21.4)	5/13 (38.5)	3.1	0.56 (0.17-1.88)
Beier-Holgersen et al,[12]1996	2/30 (6.7)	14/30 (46.7)	2.3	0.14 (0.04-0.57)
Heslin et al,[32] 1997	29/97 (29.9)	31/98 (31.6)	25.4	0.95 (0.62-1.44)
Sand et al,[40] 1997	3/13 (23.1)	5/16 (31.3)	3.0	0.74 (0.22-2.53)
Gianotti et al,[14] 1997	13/87 (14.9)	24/86 (27.9)	12.3	0.25 (0.03-1.95)
Shirabe et al,[42] 1997	1/13 (7.7)	4/13 (30.8)	1.1	3.00 (0.13-70.7)
Hartsell et al,[31] 1997	1/29 (3.4)	0/29	0.5	0.59 (0.38-0.92)
Bozzetti et al,[13] 2001	25/159 (15.7)	42/158 (26.6)	23.0	0.87 (0.54-1.39)
Braga et al,[28] 2001	25/126 (19.8)	30/131 (22.9)	20.3	0.56 (0.21-1.46)
Rayes et al,[35] 2002	3/30 (10.0)	9/30 (30.0)	3.1	0.33 (0.10-1.11)
Mack et al,[33] 2004	2/20 (10.0)	3/16 (18.8)	1.6	0.53 (0.10-2.81)
Total	114/718 (15.9)	174/721 (24.1)		0.69 (0.56-0.86); *P*=0.001

Test for heterogeneity: Q=13.35, df=12, *P*=0.344

I^2 (95%UI) =10% (0-49)



c

Study	No. of events/total (%) EN	PN	Weight , %	RR (95%CI)
Smith et al,[43] 1985	4/25 (16.0)	1/25 (4.0)	5.6	4.00 (0.48-33.3)
Hamaoui et al,[76] 1990	1/11 (9.1)	0/8	2.6	2.25 (0.10-49.0)
Reissmen et al,[37] 1995	0/80	4/81 (4.9)	3.0	0.11 (0.01-2.03)
Carr et al,[29] 1996	0/14	1/14 (7.1)	2.6	0.33 (0.01-7.55)
Baigrie et al,[70] 1996	4/50 (8.0)	6/47 (12.8)	17.3	0.64 (0.19-2.12)
Beier-Holgersen et al,[12] 1996	2/30 (6.7)	4/30 (13.3)	9.5	0.50 (0.10-2.53)
Gianiotti et al,[14] 1997	1/87 (1.1)	2/86 (2.3)	4.4	0.50 (0.05-5.41)
Hartsell et al,[31] 1997	0/29	1/29 (3.4)	2.5	0.33 (0.01-7.86)
Heslin et al,[32] 1997	2/97 (2.1)	3/98 (3.1)	8.0	0.67 (0.12-3.94)
Reynolds et al,[38] 1997	2/33 (6.1)	1/34 (2.9)	4.5	2.06 (0.20-21.7)
Sand et al,[40] 1997	0/13	1/16 (6.3)	2.6	0.40 (0.02-9.18)
Stewart et al,[74] 1998	0/40	1/40 (2.5)	2.5	0.33 (0.01-7.95)
Bozzetti et al,[13] 2001	2/159 (1.2)	5/158 (3.2)	9.5	0.40 (0.08-2.02)
Braga et al,[28] 2001	3/126 (2.4)	4/131 (3.1)	11.4	0.78 (0.18-3.41)
Pacelli et al,[35] 2001	7/119 (5.9)	3/122 (2.5)	14.1	2.39 (0.63-9.03)
Total	28/913 (3.0)	37/919 (4.0)		0.79 (0.48-1.30); *P*=0.35

Test for heterogeneity: Q=10.08, df=14, *P*=0.756

I^2 (95%UI) =0% (0-54)

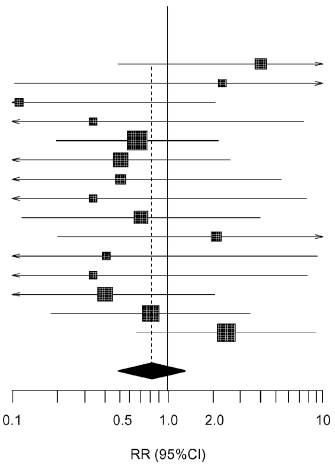


Figure 1 Forest plots of the primary outcomes. Forest plots showing combined estimates of any complication (**a**), any infectious complication (**b**), and mortality (**c**) in patients after GI surgery compared with EN with PN. The black square and horizontal line correspond to the relative risk and 95% confidence intervals, respectively. The area of black squares reflects the weight that each trial contributes to the meta-analysis. The black diamond at the bottom of each graph represents the combined relative risk and 95% confidence intervals, indicating a 15% risk reduction in any complication (**a**), a 31% risk reduction in any infectious complication (**b**), and no risk reduction in mortality (**c**).

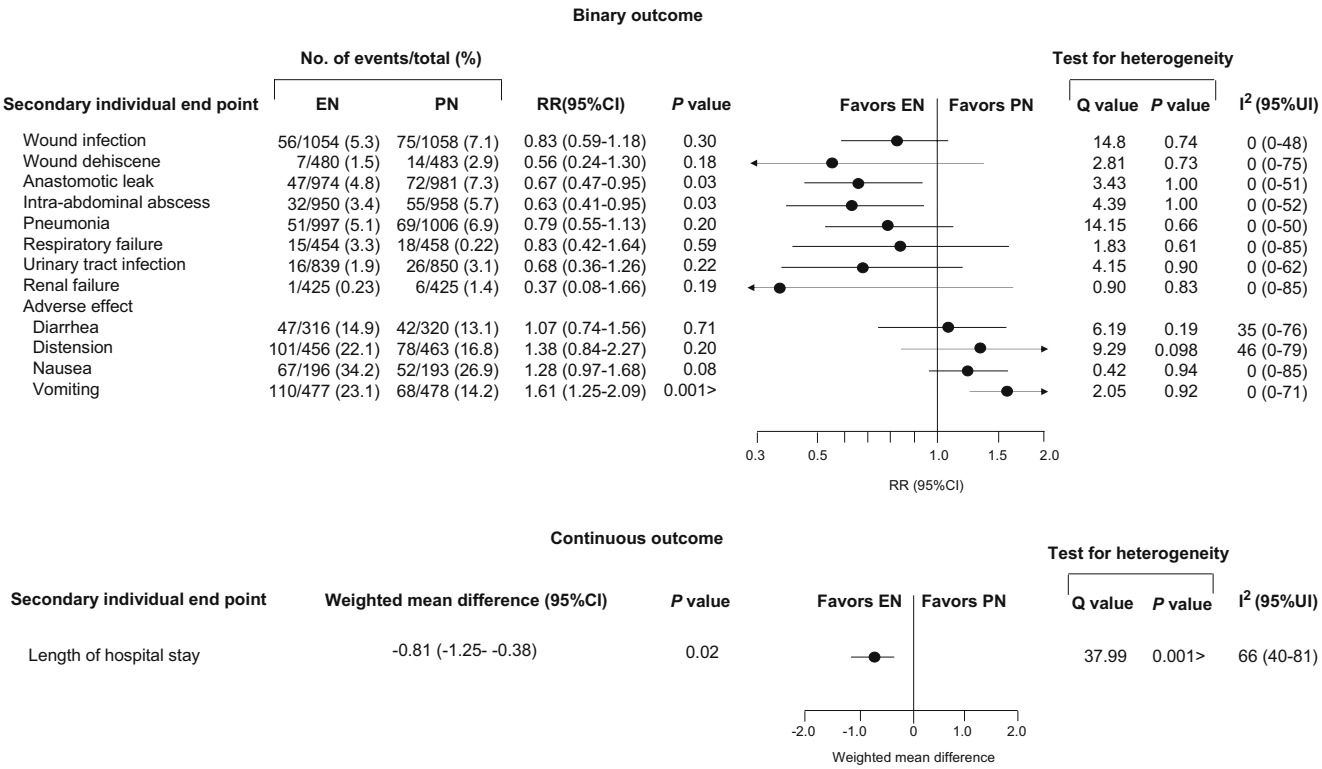


Figure 2 Results of secondary outcomes. The black circle and horizontal lines show combined relative risk and 95% confidence intervals of wound infection, wound dehiscence, anastomotic leak, intraabdominal abscess, pneumonia, respiratory failure, urinary tract infection, renal failure, and adverse effects.

Sensitivity Analysis

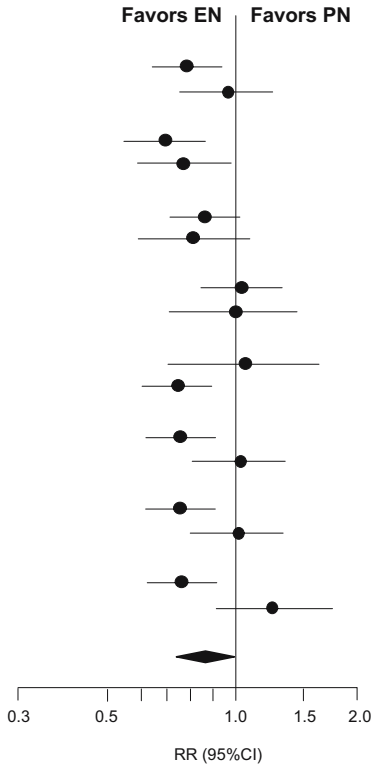
In sensitivity analysis, we stratified trials to examine whether estimates varied between subgroups. EN was beneficial in the reduction of any complications when compared with PN, among trials that included malignant diseases (RR, 0.79; 95% CI, 0.65–0.95; P=0.01), malnourished patients (RR, 0.69; 95% CI, 0.55–0.88; P=0.002), standard nutrient (RR, 0.74; 95% CI, 0.61–0.89; P=0.002), TPN (RR, 0.76; 95% CI, 0.62–0.92; P=0.004), PN with parenteral lipid (RR, 0.76; 95% CI, 0.62–0.92; P=0.01), and a European country (RR, 0.77; 95% CI, 0.65–0.90; P=0.002) (Fig. 3a). No significant differences in the rate of any complication existed in both types of administration of EN and the surgery site. Secondly, EN was beneficial in the reduction of any infectious complication compared with PN among trials that included malignant diseases (RR, 0.69; 95% CI, 0.53–0.89; P=0.01), malnourished patients (RR, 058; 95% CI, 0.39–0.87; P=0.01), tube feeding (RR, 0.71; 95% CI, 0.57–0.89; P=0.002), both immunonutrient (RR, 0.72; 95% CI, 0.54–0.96; P=0.03) and standard nutrient (RR, 0.64; 95% CI, 0.45–0.92; P=0.02), TPN (RR, 0.66; 95% CI, 0.49–0.88; P=0.001), PN with parenteral lipid (RR, 0.67; 95% CI, 0.50–0.89; P=0.01), and a European country (RR, 0.68; 95% CI, 0.52–0.87; P=0.003), but not for the surgery site (Fig. 3b). There was also no significant difference between any variable in mortality (Fig. 3c). Finally, pooled estimates were not materially changed for any complication (RR, 0.78; 95% CI, 0.66–0.91; P=0.002), any infectious complication (RR, 0.62; 95% CI, 0.49–0.80; P<0.001), and mortality (RR, 0.66; 95% CI, 0.38–1.13; P=0.13) after the trials that had influenced the formulation of the study hypotheses were excluded.

Key Domains of Trial Quality Assessment and Effect Sizes

Measures of allocation concealment were described for seven trials (41%). A double-blind trial was performed in only one study. Fifteen of 29 trials (52%) were analyzed using intention-to-treat without missing data (Table 2). The association between methodological key domains and the treatment effect size of EN compared with PN for postoperative complications was explored. In meta-regression analysis, there was no significant association (P>0.10) with allocation concealment and intention-to-treat analysis for the primary outcomes (Table 3). However, double-blinded outcome assessment influenced treatment effect sizes of any complications (P=0.048) and any infectious complication (P=0.03) (Table 3). The association between effect size of any infectious complication and double-blinded outcome assessment still remained when all methodological key domains were included in a multivariate analysis (P=0.046).

a

Sensitivity analysis	No. of study	RR (95%CI)	*P* value
Pathology of diseases			
Malignant	5	0.79 (0.65-0.95)	0.01
Malignant and benign	8	0.97 (0.76-1.23)	0.78
Nutritional status			
Malnourished	2	0.69 (0.55-0.88)	0.002
Combined	4	0.75 (0.58-0.98)	0.03
Administration route of EN			
Tube feeding	7	0.87 (0.73-1.02)	0.09
Oral feeding	6	0.81 (0.59-1.12)	0.20
Site of surgery			
Upper GI	4	1.04 (0.83-1.29)	0.75
Lower GI	5	1.00 (0.69-1.44)	0.99
Type of EN			
Immunonutrient	2	1.08 (0.71-1.64)	0.70
Standard	11	0.74 (0.61-0.89)	0.002
Type of PN			
TPN	5	0.76 (0.62-0.92)	0.004
PPN	8	1.02 (0.81-1.28)	0.88
PN with intravenous lipid			
With lipid	4	0.76 (0.62-0.92)	0.01
Without lipid	9	1.01 (0.80-1.27)	0.93
Geographic location			
European country	9	0.77 (0.65-0.90)	0.002
North America	4	1.28 (0.93-1.77)	0.13
Overall	13	0.85 (0.74-0.99)	0.04



b

Sensitivity analysis	No. of study	RR (95%CI)	*P* value
Pathology of diseases			
Malignant	9	0.69 (0.53-0.89)	0.01
Malignant and benign	4	0.84 (0.57-1.23)	0.37
Nutritional status			
Malnourished	2	0.58 (0.39-0.87)	0.008
Combined	3	0.82 (0.58-1.27)	0.383
Administration route of EN			
Tube feeding	11	0.71 (0.57-0.89)	0.002
Oral feeding	2	1.34 (0.26-6.94)	0.72
Site of surgery			
Upper GI	8	0.79 (0.61-1.02)	0.07
Lower GI	4	0.92 (0.42-2.00)	0.83
Type of EN			
Immunonutrient	6	0.72 (0.54-0.96)	0.03
Standard	8	0.64 (0.45-0.92)	0.02
Type of PN			
TPN	7	0.66 (0.49-0.88)	0.001
PPN	6	0.83 (0.63-1.14)	0.32
PN with intravenous lipid			
With lipid	6	0.67 (0.50-0.89)	0.01
Without lipid	2	0.76 (0.54-1.07)	0.12
Geographic location			
European country	9	0.68 (0.52-0.87)	0.003
North America	4	0.96 (0.65-1.41)	0.83
Overall	13	0.69 (0.56-0.86)	0.001

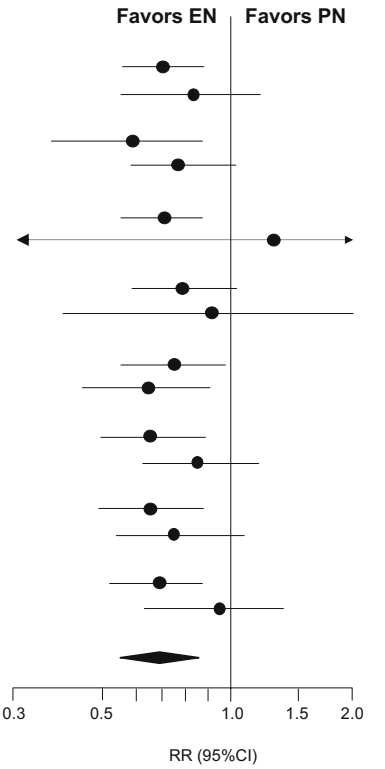


Figure 3 Subgroup analysis stratified by pathology, nutritional status, administration route, site of surgery, type of EN, type of PN, intravenous lipids, and geographic location in any complication (**a**), any infectious complication (**b**), and mortality (**c**). The black circle and horizontal line correspond to the relative risk and 95% confidence intervals, respectively.

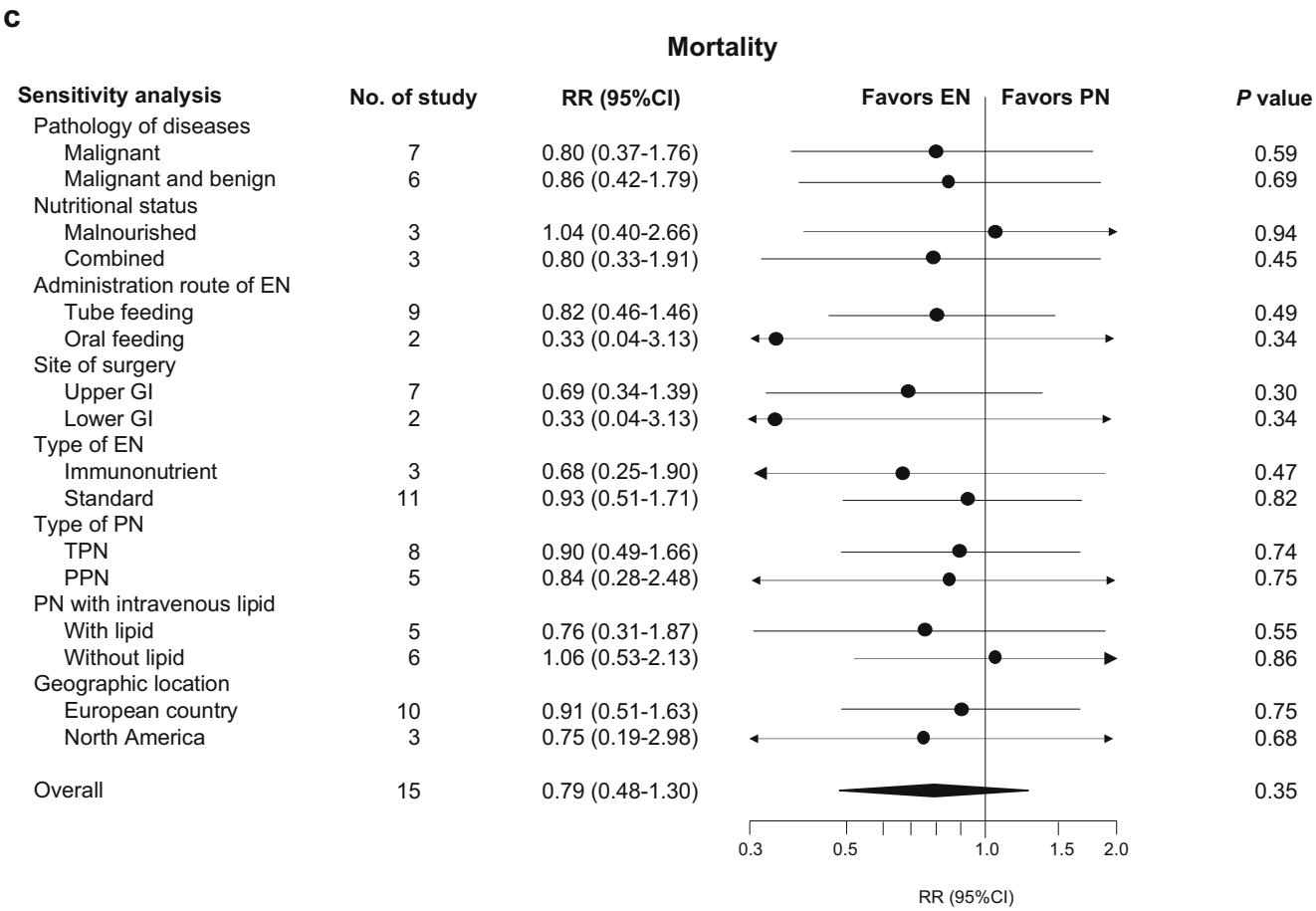


Figure 3 (continued)

Publication Bias

Publication bias was assessed for all pooled RRs with CI using Eggar's and Begg's tests.[55,56] No evidence of publication bias was found, except for wound infection. The probability of publication bias of wound infection was $P=0.08$ for Eggar's test.

Discussion

Our study showed that EN after GI surgery was associated with a significant reduction in the number of any complication, any infectious complication, anastomotic leaks, intraabdominal abscesses, and duration of hospital stay, with no significant effect on mortality and other complications. The present results are consistent with those of reviews[15,16] and meta-analyses[17–23] that combined surgical patients with critically ill patients, in which EN has significantly fewer infectious complications except for any complications, anastomotic leaks, and intraabdominal abscesses, but not mortality. However, these results should not be generalized to elective surgical patients. A study,[79] a review,[79] and three meta-analyses[77,80,81] in which the benefit of immunonutrition was evaluated, suggested that the effects of immunonutrition, composed of immune modulating nutrients and enhanced inflammatory and immunologic responses could be different depending on the patient population, for example, critically ill patients, elective surgical patients, or patients with cancer. Recent studies demonstrated that novel therapies (e.g., human recombinant activated protein C and low-dose hydrocortisone therapy) that had been shown to be effective in critically ill patients decreased the inflammatory responses in critical illness, rather than stimulated it.[82–84] Therefore, we believe that EN for surgical patients should be analyzed separately from critically ill patients because they are generally at much lower risk than critically ill patients and the underlying pathophysiology accompanying critical illness is complex, variable, not well-defined, and different from that of surgical stress.[77]

In subgroup analysis, significant reductions in any complications and any infectious complications were recognized in cases of patients with administration of TPN or parenteral lipids. The question remains whether the effects seen in our study are the results of a salutary

Table 2 Methodological Quality Included in this Meta-Analysisa

Study	Method of allocation concealment	Double blinding	Participants included in analysis, % of EN/PN[b]
Sagar et al.[75]	NR	NR	Intention-to-treat
Smith et al.[43]	Randomization using sealed envelopes	NR	62.5/62.5
Heylen et al.[69]	NR	NR	NR
Hamaoui et al.[76]	Random number table	NR	NR
Schroeder et al.[39]	NR	NR	Intention-to-treat
Binderow et al.[72]	NR	NR	NR
Reissman et al.[37]	NR	NR	NR
Baigrie et al.[70]	NR	NR	NR
Beier-Holgersen et al.[12]	NR	Yes	Intention-to-treat
Braga et al.[27]	NR	NR	23.1[c]
Carr et al.[29]	NR	NR	93.3/93.3
Ortiz et al.[73]	NR	NR	97.9/97.9
Schilling et al.[41]	NR	NR	93.3/86.7
Gianiotti et al.[14]	NR	NR	Intention-to-treat
Hartsell et al.[31]	NR	NR	Intention-to-treat
Heslin et al.[32]	Randomization using sealed envelopes	NR	Intention-to-treat
Reynolds et al.[38]	NR	NR	Intention-to-treat
Sand et al.[40]	NR	NR	Intention-to-treat
Shirabe et al.[42]	NR	NR	Intention-to-treat
Watters et al.[44]	Randomization using block design	NR	86.7/93.7
Stewart et al.[74]	Computer-generated random numbers	NR	90.9[c]
Aiko et al.[71]	NR	NR	Intention-to-treat
Bozzetti et al.[13]	Computer-generated random numbers, sealed envelopes	NR	Intention-to-treat
Braga et al.[28]	Computer-generated random numbers, sealed envelopes	NR	Intention-to-treat
Pacelli et al.[35]	Computer-generated random numbers	NR	Intention-to-treat
Page et al.[34]	Randomization using sealed envelopes	No	87.0[c]
Rayes et al.[35]	Randomization using sealed envelopes	No	85.7[c]
Feo et al.[30]	Computer-generated random numbers, sealed envelopes	NR	Intention-to-treat
Mack et al.[33]	Randomization using sealed envelopes	No	Intention-to-treat

[a] NR indicates not reported.
[b] Percentage of those evaluated for the outcome compared with the number randomized by EN/PN
[c] Includes both participants of EN and PN.

effect of EN or a detrimental effect of PN. First, a previous recommendation[86] demonstrated that TPN increased the overall risk of postoperative complications by approximately 10% when TPN was administrated to nourished patients. Second, it has been demonstrated that hyperglycemia associated with TPN can contribute to subsequent infectious complications.[85,87] This has been supported by Van den Berghe et al.[88] who report that tight glucose control improves outcomes from PN in critical illness. Zaloga,[10] however, stated that the trial of Van den Berghe et al. could not directly address the issue because the trial did not randomize the patients with EN versus PN to tight glucose control versus conventional control. Gramlich et al.[19] stated that there was no difference in the treatment effect between

Table 3 Results from Univariate Meta-Regression Analysis Relating Methodological Key Domains to Effect Size (Primary End Points) in Trials Comparing EN with PN for Complication and Mortality after Gastrointestinal Surgery[a]

Methodological key domain	Any complication			Any infectious complication			Mortality		
	No. of trials	Ratio of RR (95% CI)	*P*	No. of trials	Ratio of RR (95% CI)	*P*	No. of trials	Ratio of RR (95% CI)	*P*
Concealment of randomization									
Yes	8	1.00 (Referent)	0.39	5	1.00 (Referent)	0.19	7	1.00 (Referent)	0.23
Unclear	5	0.81 (0.49–1.32)		8	0.72 (0.45–1.17)		8	0.51 (0.17–1.54)	
Blinding of outcome assessment									
Yes	1	1.00 (Referent)	0.048	1	1.00 (Referent)	0.03	1	1.00 (Referent)	0.57
No	12	2.16 (1.01–4.62)		12	5.04 (1.22–20.80)		14	1.65 (0.30–9.05)	
Handling of dropouts and withdrawals									
Intention-to-treat analysis performed	8	1.00 (Referent)	0.80	9	1.00 (Referent)	0.74	9	1.00 (Referent)	0.86
Intention-to-treat analysis not performed	6	0.90 (0.39–2.08)		4	0.89 (0.43–1.83)		7	0.91 (0.31–2.61)	

A ratio of relative risk of less than 1 indicates that methodologically inferior trials exaggerate the benefits of EN compared with PN. A ratio of relative risk above 1 indicates the opposite.

[a] CI = confidence interval

trials in which PN groups received more calories or had a higher incidence of hyperglycemia in the meta-analysis. Thus, definitive data that support the idea that tight glucose control should be beneficial for reduction in infectious complications or mortality are not yet available. Third, long-chain triglycerides, of which dietary lipids are primarily composed, have detrimental effects that increase the production of arachidonic acid and may suppress mononuclear phagocytic function.[89–91] From this evidence, our findings imply that fewer complications are associated with EN compared with TPN or parenteral lipids, not because of the beneficial effects of EN, but because of the detrimental effects of TPN or parenteral lipids.

The authors believe that this meta-analysis has a number of advances over most previous meta-analyses, including a stronger methodological strict and explicit inclusion and exclusion criteria, subgroup analysis, the use of component approach for methodological quality assessment, and the comprehensive literature search. Previous meta-analyses had broad populations of patients with different illness severity. Peter et al.[22] aggregated eight trials, Braunschweig et al.[17] six trials, Heyland et al.[77] three trials, Simpson et al.[23] three trials, and Lewis et al.[20] 11 trials that postoperatively administrated EN vs PN. These meta-analyses, however, had a fewer number of trials than were included in our study. Moreover, there was no heterogeneity between trials for the primary and secondary end points in our study, except for duration of hospital stay and abdominal distention. Even after influential trials were excluded, the pooled estimates for the primary and secondary end points were not changed. Although the results of our study may be novel, they are robust.

Although it is widely recommended that methodological quality assessment should be undertaken, the number and variety of quality assessment scales make it unclear how to achieve the best assessment. We used a component approach to assess the effect of methodological quality on the results because it has been indicated that the use of quality summary scores to identify a high-quality study is problematic. Deficiency in reporting the quality of RCTs is intertwined with deficiency in design, conduct, and analysis of RCTs.[46, 47] In univariate analysis relating methodological key domains, we found that blinding of outcome assessment was the only factor significantly associated with effect size. However, we found no tendency for the smaller studies to show larger treatment effects (Table 3). This is because only one trial out of 13 commented on whether outcome assessments were carried out in a clearly unbiased manner, indicating that it is unlikely that the estimate shows a true-pooled estimate. There is, in addition, another issue that must be considered. Double blinding appears important in preventing bias, but is not as important as allocation concealment.[48] Although double blinding exaggerates estimates by approximately 19%, allocation concealment has been shown to yield 41% lager estimates.[48] We found no significant association of allocation concealment with effect estimates (Table 3). When restricting eight trials with allocation concealment for any complications and seven trials for mortality, no significant differences between EN and PN were evident, indicating that the two interventions may be equally effective for any complications (RR, 0.88; 95% CI, 0.75–1.04; $P=0.12$) and mortality (RR, 1.09; 95% CI, 0.55–2.16; $P=0.80$). As for any infectious complications, a difference between EN and PN was evident (RR, 0.75; 95% CI, 0.59–0.96; $P=0.03$).

There are several limitations to our study. First, a study by Pacelli et al.[35] that constituted a major part of the weighting for this analysis, and did not show a benefit of

EN in the reduction of complications, was excluded from this study because the authors did not explicitly define any complication or any infectious complication, and the complication was separately reported and identified as a major or minor complication, instead of the total number of patients with complications. The difference in any complications between EN and PN is still of borderline significance. Second, only a minority of all trials included (4%) commented on whether outcome assessments were carried out in a clearly unbiased manner.[12] No sham jejunostomy or gastrostomy tubes were placed in any studies, and oral intake was not systematically recorded, either of which might have introduced biases to their outcomes. Moreover, a double-blinded RCT is unlikely to be conducted in the future because it is difficult to manage the volume of input or output of EN or to give a placebo through the sham tube, taking intravenous infusion volume and the adverse effects of EN into consideration. Third, it is important to consider the nutritional status of patients because preoperative nutritional condition frequently influences patient outcomes. However, only nine trials in all (31%) included information about the nutritional status of patients, identifying them as malnourished or nourished patients. Only two trials (7%) reported that the participants were all malnourished. Finally, there are unavoidable limitations in this study because of variability in treatment. For example, there are differences in each clinical setting in terms of the method of operation, skill of the surgeons, type and duration of antibiotics use, severity of the disease, and difference in race.

It is frequently stated that TPN results in mucosal atrophy and increased intestinal permeability that results in damage to the intestinal barrier. This consequently predisposes the intestine to bacterial translocation and may be an explanation for the increased infectious morbidity in TPN as compared to EN.[92,93] However, other human studies[94,95] have not shown any mucosal atrophy with complete bowel rest and TPN. It was also reported that bacterial translocation occurred in humans at a rate of about 15% in elective surgical patients, but this incidence was not different among patients receiving PN versus EN.[96] A recent study demonstrated no correlation between failure of gut barrier function and septic complication after GI surgery.[97] On the other hand, atrophy and dysfunction of gut-associated lymphoid tissue (GALT), which is a critical component of the mucosal defense barrier, have recently been demonstrated to reduce the immunologic barrier of the GI tract and the respiratory tract, resulting in severe infectious complications and multiple organ failure.[98,99] Thus, mechanisms of the beneficial effects of EN over PN still remain unclear in humans.

Our results demonstrated that the risk of vomiting was significantly increased among patients with EN. This supports a comment in a previous review[11] that EN cannot be said to be safer than PN. Moreover, some patients in the EN groups changed from EN to PN because of the adverse effects of EN (20% of EN group patients in the study of Reissman et al.,[37] 20% in that by Ortiz et al.,[73] 9.1% in that by Reynolds et al.,[38] 10% in that by Stewart et al.,[74] 8.8% in that by Bozzetti et al.,[13] 6.3% in that by Braga et al.,[28] and 11.7% in that by Pacelli et al.[35]). The switch-over rate might have introduced bias toward the benefit of EN.

In conclusion, our study demonstrates that EN, compared with PN, was associated with fewer complications, infectious complications, anastomotic leaks, intraabdominal abscesses, and decreased duration of hospital stay. EN was especially beneficial for patients with malnutrition or malignant diseases. The present findings would lead us to recommend the use of EN in patients after GI surgery rather than PN if EN could be initiated within 24 hours. However, there is still no direct evidence to suggest that bacterial translocation in the gut is reduced by EN and increased in patients with PN, and that GI tract function and morphology are promoted by EN in humans. Therefore, no definite conclusions remain about the debate as to whether EN or PN is more beneficial for patients receiving inadequate and inappropriate nutritional support. Optimal nutritional demand should be met according to the nutritional or individual status of patients. PN should be employed concomitantly with EN.

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Intraabdominal Schwannomas: A Single Institution Experience

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Abstract
Introduction Intraabdominal schwannomas are rare, benign tumors. This study presents a single institution experience with 12 such tumors.
Methods Between 1991 to 2006, 12 patients with a pathologically proven intraabdominal schwannoma were identified from a series of 216 mesenchymal tumors and were reviewed retrospectively.
Results There were nine females and three male patients with a median age of 58 years (range 35–88 years). Eleven patients were symptomatic, and the tumors were located in the stomach (n=8), jejunum, colon, rectum, and lesser sac. Multiple preoperative investigations including endoscopies with biopsies and computed tomography (CT) scans were performed, but none yielded a correct definitive preoperative diagnosis. The median tumor size was 52 mm (range 18–95 mm). Pathological examination demonstrated the 11 gastrointestinal tract (GIT) schwannomas to be solid homogenous tumors, which were highly cellular and were composed of spindle cells with positive staining for S100 protein. The pathological appearance of the lesser sac schwannoma was distinct as it demonstrated cystic degeneration with hemorrhage and Antoni A and B areas on microscopy typical of soft tissue schwannomas. All 12 patients were disease-free at a median follow-up of 22 months (range 1–120 months).
Conclusion Intraabdominal schwannomas are rare tumors, which are most frequently located within the GIT. GIT schwannomas are difficult if not impossible to diagnose preoperatively as endoscopic and radiologic findings are nonspecific. The treatment of choice is complete surgical excision because of diagnostic uncertainty, and the long-term outcome is excellent as these lesions are uniformly benign.

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Introduction

Nerve sheath tumors are a subclass of soft-tissue neoplasms that include benign and malignant schwannomas and neurofibromas.[1] Schwannomas are common tumors, which are most frequently detected in cranial and peripheral nerves. The occurrence of intraabdominal[2] and retroperitoneal schwannomas[3] are, however, extremely rare. Intraabdominal schwannomas occur most frequently in the alimentary tract, and the most common site is the stomach.[4–6] Other intraabdominal sites are even rarer and these have been reported in the greater omentum,[7] lesser

sac,[8] and the biliary tree.[9] Gastrointestinal tract (GIT) schwannomas have been shown to demonstrate distinct histological features from conventional soft tissue schwannomas.[10,11] These tumors belong to the family of GI mesenchymal tumors of which the most common are gastrointestinal stromal tumors (GIST) followed by smooth muscle tumors. Schwannomas have been reported to represent only 3% of all GI mesenchymal tumors.[5]

GIT schwannomas were first reported by Daimaru et al. in 1988,[12] and since then, only a few series' have been reported in the pathological literature, which were often multiinstitution reviews.[5,6,11–13] Reports of this condition outside the pathology literature have been limited to case reports[2,4] and a single multiinstitution experience (from the Armed Forces Institute of Pathology files) of eight patients.[10] This report details the experience with intraabdominal schwannomas at a large tertiary referral center. To the best of our knowledge, this is the largest single institution review of these unusual tumors.

Methods

The records of 216 patients who underwent surgical resection of an intraabdominal mesenchymal tumor (not including retroperitoneal tumors) between 1991 to 2006 at the Department of General Surgery and Colorectal Surgery, Singapore General Hospital were retrospectively reviewed. All pathology slides and paraffin blocks of the patients were retrieved and reexamined by one of the above two pathologists (SMK, WMY). In addition, immunohistochemical staining was performed for cases that were not immunostained previously. Of these 216 patients, 12 (5.6%) had a pathologically proven schwannoma, and their case notes and radiological reports were reviewed retrospectively. One of these patients (patient 9) has been reported previously.[14]

Results

The patients' clinicopathological, surgical data and outcome are summarized in Tables 1 and 2. There were nine females and three males with a median age of 58 years (range 35–88 years). Eleven patients were symptomatic and the most common symptoms were epigastric discomfort (n=4) and upper GI bleed (n=2). None of the patients had von Recklinghausen's disease. The tumors were located in the stomach (n=8), jejunum, colon, rectum, and lesser sac.

Most of the patients underwent multiple preoperative investigations, but none had a correct definitive preoperative diagnosis. The tumors were most frequently thought to be GISTs (n=9). All eight of the patients with gastric tumors underwent upper GI endoscopy, which demonstrated a submucosal lesion, three of which had central ulceration. Six patients had an endoscopic biopsy of the lesion, which was nondiagnostic in five (too superficial) and suggestive of a stromal tumor in one (small number of spindle cells). Patient 5 had an endoscopic ultrasound with fine-needle aspirate, which was also nondiagnostic (inadequate cells). Computed tomography (CT) scan was performed in seven patients and ultrasonography (US) in two patients. The six gastric tumors appeared on CT as a solid homogenous exophytic or intraluminal lesion arising from the stomach. The lesser sac schwannoma was thought to be a septated pancreatic cyst on both CT and US.[14]

Eleven patients underwent laparotomy and resection of tumor. One patient underwent transanal resection of rectal schwannoma. The median tumor size was 52 mm (range 18–95 mm). Pathological examination demonstrated the 11 GI schwannomas to be solid homogeneous tumors, which were highly cellular and were composed of spindle cells. These stained uniformly for the S100 protein. The pathological appearance of the lesser sac schwannoma was, however, distinct as it demonstrated cystic degeneration with hemorrhage with Antoni A and B areas on microscopy. None of the schwannomas demonstrated dysplastic or malignant cells. All 12 specimens demonstrated positive immunostaining for S100. The remaining immunohistochemical staining results were as follows: CD117 was negative in 11 of 11 cases, CD34 was negative in 11 of 11 cases, smooth muscle actin was positive in 1 of 11 cases, and desmin was negative in 10 of 10 patients. All 12 patients were disease-free at a median follow-up of 22 months (range 1–120 months).

Discussion

Intraabdominal schwannomas are rare tumors. In our experience, these comprised of 5.6% of mesenchymal tumors, which mirrored the incidence of 2.9% to 6% reported by others.[5,11,13] These tumors are most frequently located in the GIT of which the vast majority (73%) are found in the stomach.[5,11,13] Extremely rare cases of extragastrointestinal intraabdominal schwannomas have been reported in the lesser sac,[8] biliary tree,[9] liver,[15] and greater omentum.[7] Because of the rarity of extragastrointestinal intraabdominal schwannomas, the following discussion will focus mainly on the clinicopathological features of GIT schwannomas.

GIT schwannomas have been reported to occur in patients over a wide range of age groups with a median age of 50 to 60 years.[5, 11] Most series' report a female preponderance.[6,11,12,16] These tumors range in size from 0.5 to 11 cm, which is markedly smaller than GISTs and which, not infrequently, grow to more than 20 cm in size.[11,17]

Table 1 Patients' Demographics, Presentation and Preoperative Investigations

Case	Age/ Sex	Presentation	Preoperative investigations	Preoperative diagnosis
1	58/F	Incidental, follow-up of lung cancer	CT—solid homogenous mass from greater curve of stomach OGD–submucosal lesion Biopsy—not representative (too superficial)	GIST
2	88/F	Small bowel obstruction from intussusception,	x-ray—intestinal obstruction	Small bowel obstruction
3	59/M	Epigastric discomfort	CT—solid homogeneous lesion from greater curve OGD—submucosal lesion Biopsy—gastritis (too superficial)	GIST
4	60/F	Upper GI bleed	OGD—submucosal lesion	GIST
5	35/F	Epigastric discomfort, bloatedness	CT—small homogenous solid nodular lesion from greater curve OGD—submucosal lesion Biopsy—too superficial EUS-FNA—insufficient material	GIST
6	37/F	Epigastric discomfort, bloatedness	US—solid hypoechoic mass arising from stomach OGD—submucosal lesion with central ulceration Biopsy—too superficial	GIST
7	58/M	Incidental	US and CT—septated cyst of pancreas OGD—extrinsic compression	Pancreatic cystic neoplasm
8	36/F	Epigastric mass, 2y	CT—large extraluminal homogenous solid gastric mass with necrosis OGD—malignant-looking submucosal lesion with central ulceration Biopsy—chronic inflammation with necrotic tissue	Malignant GIST
9	58/F	Upper GI bleed	CT—large gastric intraluminal homogenous soft tissue mass OGD—submucosal lesion with ulceration Biopsy—spindle cells suggestive of stromal tumor	GIST
10	70/M	Epigastric discomfort	OGD— extrinsic compression of lesser curve CT, MRI—well-defined enhancing mass indenting posterior wall of stomach	GIST
11	54/F	Abdominal pain	Colonoscopy—malignant neoplasm of colon	Carcinoma
12	41/F	Per-rectal bleed	Colonoscopy and transrectal ultrasonography—submucosal tumor	GIST

M=male, F=female, GI=gastrointestinal, CT=computed tomography, OGD=esophagogastroduodenoscopy, GIST=gastrointestinal stromal tumor

Table 2 Size, Operative Data, and Follow-up of the 12 Patients with Schwannomas

Case	Size, mm	Site	Operation	Outcome (months)
1	53	Stomach, greater curve	Gastric wedge resection	DF, died of lung cancer, 18 m
2	35	Jejunum	Small bowel resection	DF, 12 m
3	80	Stomach, greater curve	Gastric wedge resection	DF, 96 m
4	75	Stomach, lesser curve	Gastric wedge resection	DF, 12 m
5	18	Stomach, greater curve	Gastric wedge resection	DF, 1 m
6	50	Stomach, antrum	Distal gastrectomy	DF, 18 m
7	70	Lesser sac	Excision of tumor	DF, 28 m
8	95	Stomach, antrum	Subtotal gastrectomy	DF, 30 m
9	60	Stomach, greater curve	Gastric wedge resection	DF, 36 m
10	33	Stomach, posterior wall	Gastric wedge resection	DF, 24 m
11	30	Ascending colon	Right hemicolectomy	DF, 120 m
12	29	Rectum	Transanal excision	DF, 20 m

mm=millimeter, DF=disease-free, m=months

Pathologically, GIT schwannomas are regarded as distinct tumors from conventional schwannomas, which arise from the central nervous system and soft tissues.[10,11] These tumors are assumed to arise from the nerve plexus of the gut wall.[10–12] Macroscopically, these are round or fusiform and are often described as homogenous, firm, or rubbery.[5,11] Degenerative changes such as necrosis, hemorrhage, and cystic change, which are frequently found in soft tissue schwannomas such as those in the retroperitoneum,[3] are seldom present.[5,11] Microscopically, unlike conventional schwannomas, GIT schwannomas are not encapsulated, although most are well circumscribed. These are frequently surrounded by a cuff of lymphoid aggregates,[5,6,12,13,18] are highly cellular, and are composed mainly of bipolar spindle cells. Verocay bodies, vascular hyalinization, Antoni A and B areas, and a typical palisading structure are typically absent unlike conventional schwannomas. The pathologic findings of the GIT schwannomas in the present analysis were consistent with these previously described findings.

On the other hand, the lesser sac schwannoma in this study[14] demonstrated the typical pathologic features of peripheral and soft tissue schwannomas[3] including cystic degeneration with hemorrhage and typical Antoni and B areas. This observation suggests that the lesser sac schwannoma did not arise from extensive extramural growth of a gastric schwannoma resulting in loss of contact with the external muscle coat of the gut as has been suggested for some extragastrointestinal GISTs.[19] Instead, it probably originated from one of the branches of the vagus nerve at the lesser curvature of the stomach.[14] Based on cases reported in the literature, the pathologic appearance of extragastrointestinal intraabdominal schwannomas are variable with some cases in the omentum[7] or lesser sac[8] having the typical appearance of conventional schwannomas, whereas those in the liver[15] and biliary tree[9] were reported to have features similar to GIT schwannomas.

On immunohistochemistry, the cells of GIT schwannomas diffusely and strongly express vimentin and S100 proteins.[11] The S100 immunostaining pattern is both in a nuclear and cytoplasmic distribution.[5] GIT schwannomas may rarely express CD34 cells, but CD117, SMA, and desmin are uniformly negative.[20] Hence, immunohistochemistry is extremely useful in distinguishing GIT schwannomas from the other GI mesenchymal tumors such as GISTs, which express CD117 (almost always) and CD34 (frequently) and true smooth muscle tumors, which express smooth muscle actin (SMA) and desmin.[17]

GIT schwannomas are usually detected preoperatively via cross-sectional imaging or endoscopy. However, preoperative diagnosis is difficult as none of these modalities have shown any pathognomonic features unique to this tumor. Presently, because of its rarity, there are limited data reporting the CT features of GIT schwannomas in the literature with only a single-case series of eight patients to date.[10] On CT scan, these tumors have a homogeneous pattern of attenuation on both unenhanced and contrast-enhanced scans with tumor enhancement occurring in the equilibrium phase. The main differential diagnoses of GIT schwannomas are GISTs, which are the most common mesenchymal tumors of the GI tract.[10] Although these tumors most frequently have a heterogeneous appearance on CT because of hemorrhage, necrosis or cystic change, 8–13% of GISTs may appear as homogeneous tumors, making them indistinguishable from GI schwannomas.[21,22] Other neoplasms such as lymphomas and GI adenocarcinomas may also have overlapping features with GIT schwannomas.[10] In this study, all six gastric schwannomas appeared as solid homogenous tumors on CT. Presently, experience with the US features of GIT schwannomas is extremely limited.[23] Gastric schwannomas have been reported to appear as a solid homogeneous hypoechoic mass,[23] which was similar to the US appearance of patient 6.

Similar to cross-sectional imaging, the endoscopic features of GI schwannomas are nonpathognomonic.[23,24] The endoscopic findings are almost always nonspecific as these tumors appear grossly as submucosal lesions, which are indistinguishable from other mesenchymal tumors. Futhermore, endoscopic biopsies are usually not representative of the deeper submucosal tissue. Even when the endoscopist succeeds in obtaining samples from the deeper tissues, these usually demonstrate nonspecific spindle cells, and there is usually insufficient tissue for the pathologist to obtain a definite diagnosis. These problems were well-illustrated in the present analysis whereby none of eight patients who underwent gastroscopy had a definitive diagnosis.

Thus far, all series[5,10–13,18] in the literature addressing GIT schwannomas regard these tumors as uniformly benign. However, isolated case reports of "malignant schwannomas" also termed malignant peripheral nerve sheath tumors have been reported.[25] Whichever, these malignant tumors arise from benign schwannomas remains controversial.[24] Presently, most pathologists regard these malignant tumors with neural differentiation as distinct tumors from GIT schwannomas, giving them the term gastrointestinal autonomic nerve tumors (GANTs).[6] Nonetheless, although benign, the treatment of choice of GIT schwannomas is complete surgical excision in fit, healthy patients as it is frequently impossible to distinguish these tumors from other GIT mesenchymal tumors such as GIST and smooth muscle tumors, which are malignant or have malignant potential. The outcome after surgical resection is excellent and to date, there is no evidence in the literature to suggest that GIT schwannomas have malignant potential.[5,6, 10–13,18]

In conclusion, intraabdominal schwannomas are rare tumors, which are most frequently located within the GIT.

Very rarely, these may arise from outside the GIT. GIT schwannomas are difficult, if not impossible, to diagnose preoperatively as endoscopic and radiologic findings are nonspecific. The treatment of choice is complete surgical excision because of diagnostic uncertainty, and the long-term outcome is excellent as these lesions are uniformly benign.

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An Obstructing Large Schwannoma in the Esophagus

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Abstract Esophageal schwannoma is very rare neoplasm, which is difficult to diagnose by endoscopy or radiologic evaluations. The diagnosis is not confirmed until immunohistochemical tests are performed after a surgeon has resected the lesion. We present the case of a 65-year-old male patient with an esophageal schwannoma having a palpable neck mass and severe dysphagia. The postoperative pathological findings revealed a strong immunoactivity to S-100 protein but negative activity to smooth muscle actin and C-kit. These results support the characteristics of schwannoma in the tumor.

Keywords Esophagus · Schwannoma · S-100 protein

Introduction

Esophageal schwannoma that have been classified as a subset of gastrointestinal stromal tumor is very rare; the majority of schwannomas have an excellent prognostic course. The differentiation of schwannoma from the other submucosal tumors is very difficult on preoperative examination by esophagoscopy, esophagography, and computed tomography. Diagnosis requires histology and immunohistochemical staining. We are reporting a case of benign schwannoma of the esophagus, an obstructing large esophageal schwannoma palpated on the neck, which has not yet been reported in literature.

Case Report

A 65-year-old man presented with a 2-year history of palpable neck mass and severe dysphagia, worse for solids. Upper gastrointestinal endoscopy was not available because of complete obstruction by a mass lesion. Computerized tomography (CT) and magnetic resonance image (Fig. 1) showed a lobulated retroesophageal mass from upper margin of the C5 spine to the lower margin of the T1 spine. The tumor had high attenuation composed of heterogenous soft tissue and contained cystic or necrotic parts in the lower portion. Ultrasound-guided needle aspiration was used for more definitive identification. The pathology revealed a cellular smear composed of aggregates and individually scattered spindle cells with hyperchromatic nuclei, most consistent with low-grade leiomyosarcoma. Other possibilities include peripheral nerve sheath tumor and solitary fibrous tumor. Surgical mass enucleation was performed to treat the dysphagia and substantiated the diagnosis. On gross inspection, the external surface was surrounded by thin membranous tissue with focal adipose tissue measuring 7×6×4 cm. The cross section revealed a homogeneous yellow (Fig. 2, left). Immunohistochemically, the tumor was diffuse and strongly positive for S-100 protein (Fig. 2, right), whereas it was negative for C-kit and smooth muscle actin. Two years after surgery, the patient is well, without any recurrence.

Discussion

Neurogenic tumors are classified according to Ranson's histopathologic classification published in 1940.[1] This

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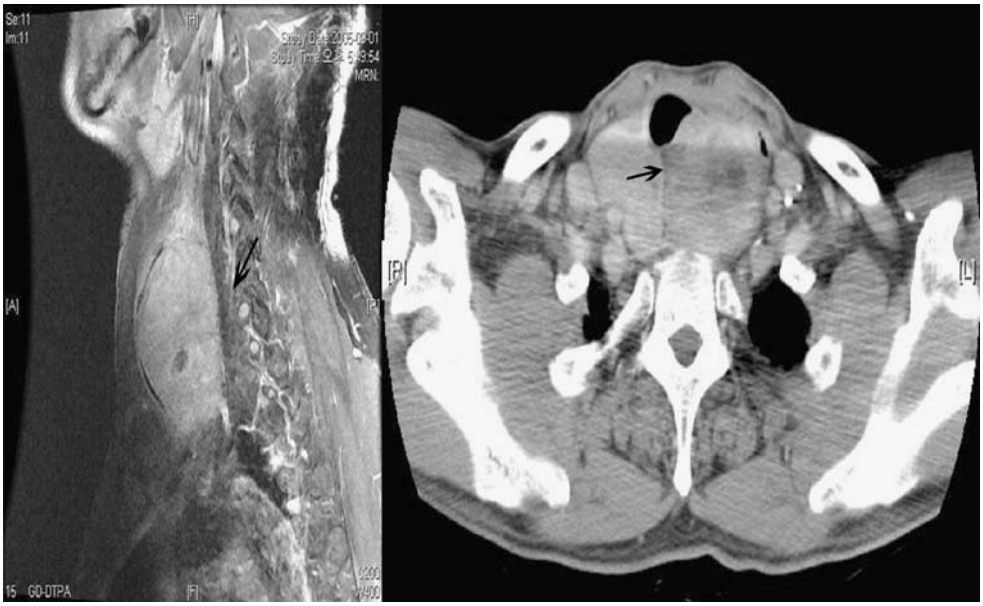

Figure 1 Magnetic resonance imaging showing a large round, obstructing mass between the C5 and T1 levels with necrotic portion in the lower portion (*left*, *black arrow*), and preoperative CT shows a large mass displacing the esophagus, which was seen in 1 o'clock direction (*right*, *black arrow*).

classification system divides neurogenic tumor into nerve sheath tumors and neuroblastic tumors of the sympathetic system. Schwannoma is the most common peripheral nerve sheath tumor. It usually occurs solitary and very rarely in the gastrointestinal tract.

Schwannoma of the gastrointestinal tract are submucosal tumors, commonly covered by normal mucosa and principally involving the submucosa and muscularis propria.[2] In Asia, esophageal schwannoma is extremely rare. As of 2006, there have only been 27 cases reported,[3] and because of its rarity, the typical preoperative diagnosis is an esophageal submucosal tumor, leiomyoma, leiomyosarcoma, or another type of mediastinal tumor. For this reason, it is not possible to establish a definitive and correct preoperative diagnosis by imaging study because of the similarity to other stromal esophageal tumors.

However, CT may be helpful for differentiating esophageal schwannomas from other submucosal tumors in some cases. Esophageal schwannomas show homogenous characteristics on post-enhanced CT, whereas other stromal tumors usually appear heterogenous.[4] Endoscopic ultrasonography is also good for differentiating benign from other submucosal lesions, especially if supplemented by guided fine needle aspiration, and may provide valuable information for treatment planning.[5]

Diagnosis depends on the pathological findings, especially on immunohistochemical test. For example, Daimaru et al. reported that 24 of 306 diagnosed gastrointestinal spindle cell tumor cases were determined to be schwannoma by immunohistochemical methods. When these 24 cases were rechecked with hematoxylin and eosin, only 9 cases were diagnosed as schwannoma. This supports the high likelihood for misdiagnosing schwannoma as spindle cell tumor before the emergence of immunohistochemical staining.[6] Pathologically, schwannomas have bundled S-100 protein positive spindle cells in a fibrous, S-100 protein

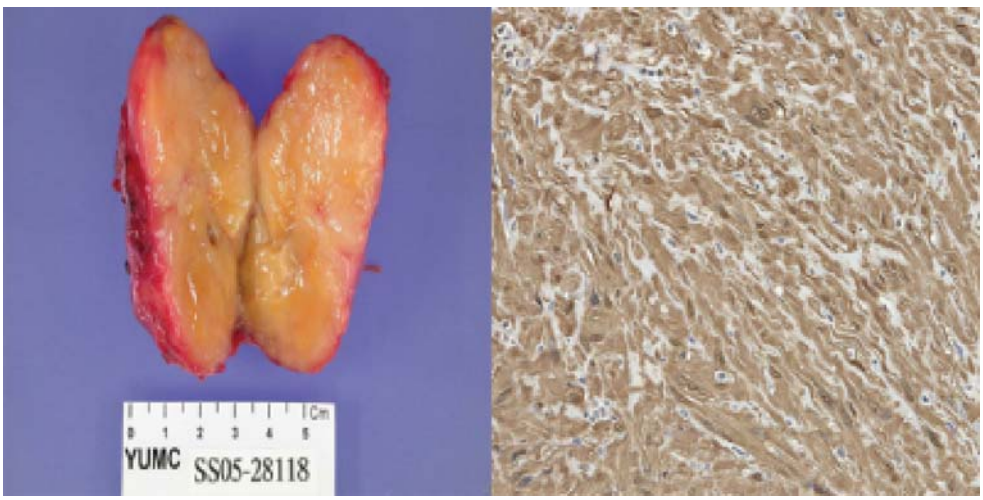

Figure 2 Grossly, the mass (7×6×4 cm) revealed a homogenous yellow cross section (*left*). Immunohistochemical test using S-100 protein shows positive staining of bundles of spindle cells (*right*) (×200).

negative background and are negative for smooth muscle markers such as actin, desmin, CD117, and CD34. Hematoxylin and eosin staining reveals fascicular arrangement of spindle cells and palisading cell nuclei.[7]

Indications for surgery are large lesions producing symptoms or any evidence of ingrowing mass. In most reported literature, management was by surgery, either thoracotomy with tumor enucleation.[8] If a submucosal tumor of the esophagus has a diameter of 2 cm or less, removal can be accomplished endoscopically.[9] If it is noted as high grade on biopsy or more than 10 cm in size, the appropriate therapy is en bloc esophagectomy with tumor-free resection margin.[10]

The prognosis with benign schwannomas of the gastrointestinal tact is usually excellent.

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Laparoscopic Heller Myotomy and Dor Fundoplication for Esophageal Achalasia. How I do It

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Abstract The advent and the success of minimally invasive surgery have changed the treatment algorithm for esophageal achalasia. Today, a laparoscopic Heller myotomy and partial fundoplication is considered the treatment of choice for this disease. This article describes the technique of laparoscopic Heller myotomy and Dor fundoplication.

Keywords Esophageal achalasia · Pneumatic dilatation · Laparoscopic Heller myotomy · Esophagectomy

During the 1970s and 1980s, although it was recognized that a myotomy was more effective than pneumatic dilatation, it was generally accepted by the medical community that pneumatic dilatation was the primary form of treatment for esophageal achalasia. As a consequence, even in tertiary care centers, the experience was limited to few myotomies per year, mostly for patients who still had dysphagia after multiple dilatations, or for those who suffered a perforation at the time of a dilatation.

The application of minimally invasive surgery to the treatment of esophageal achalasia has determined an unexpected change in the treatment algorithm of this disease. Today, a laparoscopic Heller myotomy is considered by most gastroenterologists and surgeons as the primary treatment for achalasia, reserving pneumatic dilatation to the few failures of this operation.[1,2] This shift in practice is due to the recognition that minimally invasive surgery is better than other treatment modalities. The operation, in fact, relieves dysphagia in about 90% of patients, and it allows a short hospital stay, minimal postoperative discomfort, and a fast recovery time.[1–10]

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The following describes a step-by-step approach of a laparoscopic Heller myotomy and Dor fundoplication for the treatment of esophageal achalasia.

Positioning of the Patient on the Operating Room Table

After induction of general anesthesia with a single lumen endotracheal tube, the patient is positioned supine on the operating table over a beanbag. The beanbag is used to create a saddle under the patient's perineum to avoid sliding during the operation when a steep reverse Trendelenburg position is used. The legs are extended on stirrups, with the knees flexed only 20 to 30°. The surgeon stands in between the patient's legs.

Position of the Trocars

Five trocars are used for the operation (Fig. 1). The first trocar is placed in the midline, 14 cm distal to the xiphoid process, and it is used for the 30° scope camera. A second trocar is placed in the left mid clavicular line at the same level with the camera, and it is used for inserting a Babcock clamp and instruments to divide the short gastric vessels. A third trocar is placed in the right midclavicular line at the same level of the previous two trocars, and it is used for the insertion of a retractor to lift the left lateral segment of the liver. The fourth and a fifth trocars are placed under the right and left costal margins, so that their axes form an angle of about 120° with the camera. They are used for the dissecting and suturing instruments.

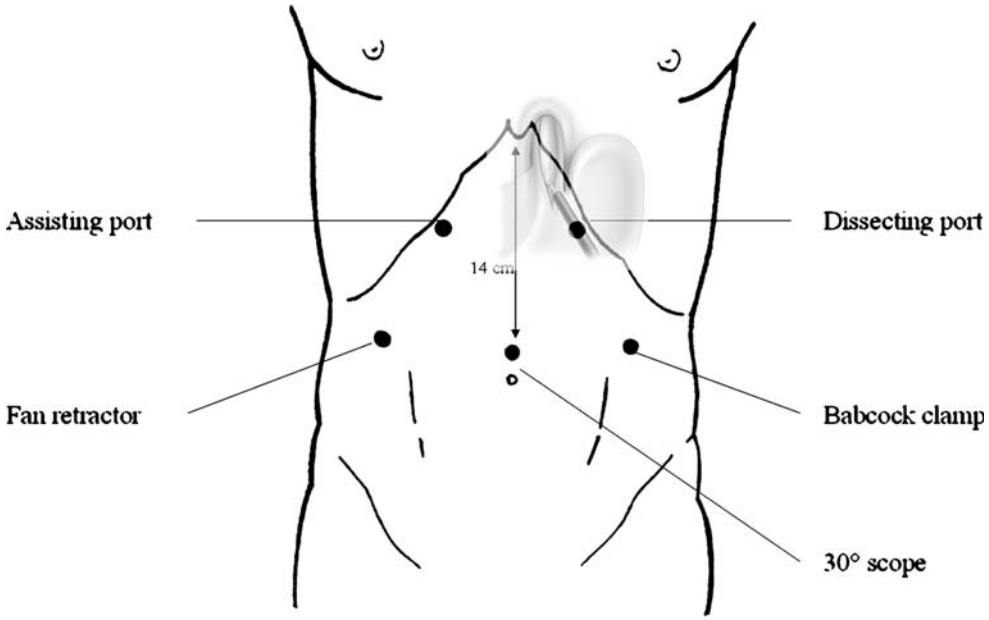

Figure 1 Trocar placement.

Dissection

The operation is usually started by dividing the gastro-hepatic ligament. The right crus of the diaphragm is identified and separated from the esophagus by blunt dissection. After the peritoneum and phreno-esophageal membrane overlying the esophagus are transected, the left pillar of the crus is separated by blunt dissection from the esophagus. The dissection is continued in the posterior mediastinum, lateral and anterior to the esophagus, to expose 6 to 7 cm of the esophagus. No posterior dissection is necessary if Dor fundoplication is planned. During this part of the dissection, it is important to identify and preserve the posterior and anterior vagus nerves. The short gastric vessels are then divided. When a large hiatal hernia is present, it is safer to divide the short gastric vessels first and reach the left pillar of the crus after such division.

When dealing with a sigmoid esophagus, it is important to extend the dissection more proximally in the posterior mediastinum and to also dissect posterior to the esophagus. This dissection allows straightening of the esophageal axis, avoiding stasis of food after the myotomy.[2]

Esophageal Myotomy

The fat pad is removed to expose the gastroesophageal junction. Traction is applied by a Babcock clamp to expose the right side of the esophageal wall. The myotomy is performed using the hook cautery in the 11 o'clock position. After reaching the sub-mucosal plane in one point, about 3 cm above the gastroesophageal junction, the myotomy is then extended for about 6 cm upward and onto the gastric wall for about 2.0–2.5 cm (Fig. 2). During the last few years, the length of the myotomy onto the gastric wall has been increased, as there is evidence that a longer myotomy provides better relief of dysphagia.[3] It is important to be cautious in patients previously treated with intrasphincteric injection of botulinum toxin, as fibrosis can be present at the level of the gastroesophageal junction, with consequent loss of the normal anatomic planes. In these circumstances, the myotomy can be very difficult, and there is an increased risk of mucosal perforation.[7,8,11] If a perforation is suspected, the esophagus should be submerged with water, and air insufflated through the oro-gastric tube. Methylene blue injection via the oro-gastric tube can also be used. Once the hole is identified, it is closed with fine (5-0) absorbable sutures. After the myotomy is completed, the muscle edges are gently

Figure 2 Completed myotomy.

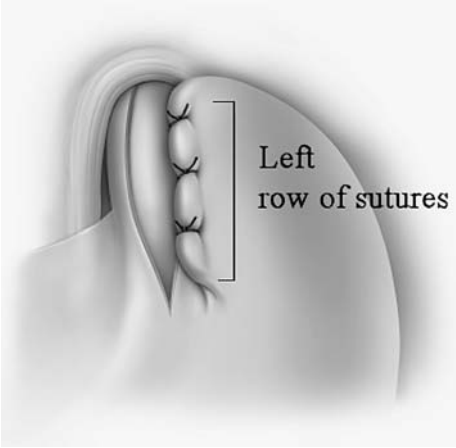

Figure 3 Dor fundoplication: left row of sutures.

separated to expose the mucosa for about 40% of the circumference.

Dor Fundoplication

It is generally accepted that if a myotomy alone is performed, reflux occurs in about 50% of patients.[4,12] A 360° fundoplication is generally avoided, as it is felt that with time, it is accompanied by a progressive increase in esophageal retention with poor emptying and recurrence of symptoms.[13] A partial fundoplication is the procedure of choice, as it takes into account the lack of peristalsis. There are no data comparing the results of a posterior and an anterior fundoplication. We do favor the Dor fundoplication (anterior 180° fundoplication) as it does not require posterior dissection and because it covers the exposed mucosa.

The Dor fundoplication is constructed by using two rows of sutures. The first row of sutures is on the left, and comprises three stitches. The uppermost stitch is triangular and incorporates the gastric fundus, the left side of the esophageal wall and the left pillar of the crus. The second and the third stitches incorporate the esophageal and the gastric wall only (Fig. 3). The stomach is then folded over the exposed mucosa so that the greater curvature lies next to the right pillar of the crus. The right row of sutures also has three stitches. The uppermost stitch includes the gastric fundus, the right side of the esophageal wall and the right pillar of the crus. The second and the third stitches are placed between the greater curvature of the stomach and the right side of the esophageal wall. Finally, two or three stitches are placed between the gastric fundus and the rim of the esophageal hiatus (without incorporating the esophageal wall) to decrease the tension of the right row of sutures (Fig. 4).

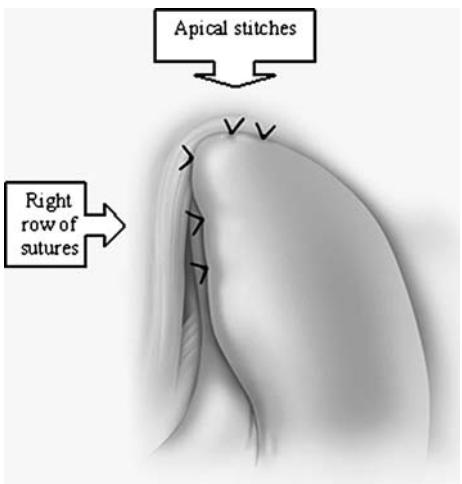

Figure 4 Completed Dor fundoplication.

Postoperative Course

Patients are fed the morning of the first postoperative day and are instructed to avoid meat or bread for 2 weeks. About 70% of patients are discharged within 23 h, and 90% of patients are discharged within 48 h. Most patients resume their regular activity within 2 weeks.

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Management of Appendiceal Mass: Controversial Issues Revisited

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Abstract
Purpose Although appendix mass occurs in 10% of patients with acute appendicitis, its surgical management is surrounded with controversy. This article reviews some of the controversial issues in the management of appendix mass.
Methods A search of the English literature was conducted for "appendiceal mass," "interval appendicectomy," and "laparoscopic appendicectomy" and manual cross-referencing.
Results and Conclusion The majority of the studies were small and retrospective. Emergency appendicectomy for appendix mass is emerging as an alternative to conventional conservative treatment. It is feasible, safe, and cost-effective, allowing early diagnosis and treatment of unexpected pathology. However, the appropriate timing for emergency surgery is not clear. After successful conservative management, interval appendicectomy is not necessary and can safely be omitted, except in patients with recurrent symptoms. In patients over 40 years of age, other pathological causes of right iliac mass must be excluded by further investigations (colonoscopy and computerized tomography scan), and a close follow-up is needed. Laparoscopic appendicectomy whether in emergency or interval settings is feasible and safe and should replace the conventional open method. Large prospective, randomized controlled trials are lacking, and therefore, such trials are needed to scientifically compare emergency surgery vs conservative management without interval appendicectomy.

Keywords Appendiceal mass · Interval appendicectomy · Laparoscopy

Introduction

Acute appendicitis is the most common surgical emergency. It may be complicated by the development of an appendiceal mass in 2–10% of cases.[1,2] This mass results from a walled-off appendiceal perforation and represents a wide pathological spectrum ranging from an inflammatory mass that consists of the inflamed appendix, some adjacent viscera, and the greater omentum (a phlegmon) to periappendiceal abscess.[3] Fever and leucocytosis are common, but the mass may be missed clinically in the obese and in those with marked tenderness and rigidity at presentation. Hence, it may first be detected when the patient is already under anesthesia for emergency appendicectomy, posing a dilemma for trainee surgeons. Ultrasonography has been advocated as the diagnostic modality of choice, revealing the diagnosis in 72% of cases, but computerized tomography (CT) scan is superior[2]. Some management issues has been surrounded with controversy with no general agreement among surgeons; a recent questionnaire study of 67 consultant and specialist registrar surgeons in the Mid-Trent region of England showed no agreed consensus on the management of appendiceal mass.[4] Another more recent questionnaire survey of 90 consultant general surgeons in England revealed that 53% of surgeons perform interval appendicectomy routinely at 6 weeks to 3 months, mainly because of concerns about recurrence.[5]

This article discusses some of those controversial management issues and draws management recommendations based on a review of the available English literature.

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Methods

A Medline search of the English literature was conducted using the Medical Search Headings and keywords: "appendiceal mass," "interval appendicectomy," and "laparoscopic appendicectomy." Further articles were obtained from manual cross-referencing of the literature reviewed. Case reports and articles with less than five patients were excluded.

Conservative Vs Emergency Treatment of Appendix Mass

The surgical management of acute appendicitis presenting with appendiceal mass remains controversial. The standard treatment that was introduced by Ochsner[6] in 1901, advocating conservative regimen, has proved popular over the years and has been shown to be safe and effective.[1,7–13] It allows the acute inflammatory process to subside in more than 80% of the cases before interval appendicectomy is performed some 8–12 weeks later.[7–13] Failure to respond may, however, be encountered in 10–20% of the patients with development of appendiceal abscess that can be drained percutaneously or if multiloculated via an extraperitoneal approach. Furthermore, while waiting for interval appendicectomy after discharge, up to 46% of the patients may develop recurrent symptoms of appendicitis that require readmission.[1–3] Also, before the planned interval appendicectomy, delayed emergency surgery becomes necessary in 15% of the cases.[1,14] The most serious criticism is the fear of missing an unexpected pathology such as Crohn's disease, ileo-cecal tuberculosis, and most importantly, cecal malignancy in 8–15% of the cases.[10,15] Early emergency surgery is feasible and as safe as the non-operative approach and is associated with shorter hospital stay,[16–22] with the advantage that unexpected cecal pathology will be treated. The only disadvantage of emergency surgery is that, in some cases, the inflammatory condition may be mistaken for malignancy necessitating ileo-cecal resection or right hemicolectomy with its attendant morbidity and mortality.[23] The extent of resection will depend on whether the pathology is inflammatory or malignant, which may be difficult to decide during surgery, even with intraoperative frozen section. Ileo-cecal resection was found to be associated with a significantly shorter mean operative time (144 vs 201 min; $p<0.001$), lower morbidity rate (3 vs 22%; $p= 0.043$), and shorter mean postoperative hospital stay (6.8 vs 11.2 days; $p=0.011$) than right hemicolectomy.[23] The arguments for and against conservative and emergency operative managements are summarized in Table 1.

Emergency Surgery for Appendix Mass

In the 1970s, early surgery for appendix mass was shown to be safe, associated with shorter hospital stay and without major morbidities.[16,17] However, acceptance by the surgical community remained cautious.

In nine articles (Table 2) on emergency surgery for appendix mass with a total of 340 patients [123 (36%) children], there was general agreement that emergency surgery for appendix mass is feasible, safe, cost-effective,

Table 1 The Argument For and Against Conservative and Emergency Surgery Approaches

	Advantages	Disadvantages
Conservative approach	Safe	Failure rate and recurrent symptoms in 5–46%
	Allows acute episode to settle	Delayed emergency surgery in non-responders is hazardous
	Good response in >91%	Costly (long HS, intravenous antibiotics, analgesia, etc.)
		IA may be needed; this requires second admission
		Has complication rate of 12–23%
Emergency Surgery	Safe, feasible and cost-effective	May be difficult especially if delayed
	Acceptable operative time	Differentiation between inflammatory and malignant masses may be difficult (FS may be necessary)
	No need for another admission	Unnecessary ileo-cecal resection may be performed.
	No need for IA	May have higher complication rate than IA
	Deals with pathology and other unexpected pathology rapidly	
	No need for close follow-up and investigations	

IA Interval appendicectomy, *FS* frozen section, *HS* hospital stay

Table 2 List of Articles on Emergency Surgery for Appendiceal Mass ($n=9$)

Author	Year	Number of patients	LA vs OA	Comments
Vakili [16]	1976	34	OA	Early surgery is safe, feasible, has short HS, and has no major morbidity
Foran et al.[17]	1978	13	OA	Early surgery has shorter HS than the conservative approach
Marya et al.[18]	1993	30	OA	Early surgery is safe, feasible, and cost-effective. It has comparable infection rate, operating time, and hospital stay to conservative approach
Samuel et al.[19] (children)	2002	82	OA	Early surgery is beneficial, but IA is needed for those treated conservatively
De and Ghosh[20]	2002	87	OA	Early surgery is associated with low cost, low morbidity, and short HS
Tingstedt et al.[14]	2002	43	OA	Early surgery is associated with complications. Conservative approach is advocated
Senpati et al.[21]	2002	10	LA	Early LA is feasible and safe. It has equal operative time and HS to that of non-mass appendicitis
Erdogan et al.[13] (children)	2004	19	OA	Early surgery has a high complication rate (26.3%)
Goh et al.[22] (children)	2005	22	LA	Early LA has no morbidity or mortality. It has longer operative time (103 vs 87 min) than LA for non-mass cases
Total, 9 articles	1976–2005	$n=340$	2 LA	2 studies[14,13] out of 9 were against emergency surgery

LA Laparoscopic appendicectomy, *OA* open appendicectomy, *HS* hospital stay

associated with reduced hospital stay, with minimal morbidity but no mortality and with more or less comparable infection and operating time to that performed after conservative treatment.[16–23] Two studies[13,14], however, found early surgery to be associated with high complication rate of 26%, and therefore, conservative approach was advocated instead.

In a prospective nonrandomized study, Samuel et al.[19] showed early surgical intervention to be more beneficial over the conservative approach in a cohort of 82 children, especially in terms of hospital stay (4.8 vs 13.2 days; $p<0.05$).[19] At a mean of 4.3 weeks, recurrent symptoms were seen in 19 (39.6%) patients of the conservative group.[19] Furthermore, periappendiceal abscesses and adhesions were found at interval appendicectomy in 38 (79%) and 39 (81.3%), respectively, compared to 100% in those who underwent emergency surgery.[16,19,21] In another controlled clinical trial, 30 patients with appendix mass treated by early surgery were compared with 26 patients who were treated conservatively.[18] The two groups had similar infection rate (17 vs 18%), mean operating time (38.7 vs 35.2 min), and mean hospital stay (15 vs 19 days). Furthermore, 15% of patients in the conservative group developed episodes of recurrent acute symptoms while waiting for interval appendicectomy, and their return to work was delayed.[18] In a retrospective study of 87 patients presenting with appendix mass who underwent emergency appendicectomy within 24 h of admission, the mean operative time was 65 min, and only 29% developed minor wound infections and majority of patients (81.6%) were discharged within 7 days. It was concluded that emergency surgery is feasible and associated with low morbidity.[20]

The timing of emergency surgery is very important, as delayed emergency surgery is expected to be difficult and hazardous. In a recent prospective randomized controlled trial, appendicectomy performed after the appendix mass had resolved was shown to be associated with longer operative time, higher incidence of adhesions, higher incidence of incision extension, and more postoperative complications than interval appendicectomy.[24]

On the other hand, others argue that emergency surgery is difficult and associated with high complication rate that approaches 26%.[13,14] In a comparison of the outcome of 50 patients treated conservatively and 43 who were operated on for appendiceal abscess, complications were found to be common among patients who were operated on, but 4 (8%) of the patients treated conservatively had another pathology detected during follow-up.[14] In an evaluation[13] of 19 children who were operated on immediately and 21 children who were managed by interval appendectomy, the mean hospital stay was similar (8.7 vs 8.9 days), but the complication rate was higher in the emergency group (26%). Appendectomy could not be done in one patient who required another laparotomy 8 weeks later. In the conservative group, however, two patients (8.6%) failed to respond and another two returned with perforated appendicitis.[13] Furthermore, those who were treated conservatively in both

studies needed close follow-up and investigations to exclude other ileo-cecal pathology, which may be encountered in the conserved cases. However, both studies were retrospective and contained a small number of patients.

In conclusion, most reported literature on emergency surgery advocated this approach as safe, feasible, and cost-effective.

Interval Appendicectomy: Is It Necessary?

Another controversial issue is the need for interval appendicectomy (IA) after successful conservative treatment. A survey of 663 surgeons in North America revealed that IA is routinely performed by 86% of the surveyed surgeons.[25] The most cited reason is the risk of recurrent appendicitis, which is reported to occur in 21–37% of the cases.[10,19,25,26] Another recent questionnaire survey of 90 consultant general surgeons in England (response rate of 78%) revealed that 53% of surgeons perform IA routinely at 6–12 weeks mainly because of concerns about recurrence.[5] This argument of recurrent appendicitis has been questioned, as the risk that is greatest during the first 2 years occurs in less than 20% of cases, and the risk becomes minimal after the first 2 years of the initial episode.[1,3,10,17] Hence, more than 80% of patients can be spared the morbidity of a surgical intervention. Also, the study from the Mid-Trent region, UK, showed that less than 25% manage asymptomatic appendix mass without IA.[4] It is of interest to find in this survey that specialist registrars are less likely to offer patients IA after successful conservative management ($p<0.05$).[4]

A prospective non-randomized study of 48 IA specimens showed 37 (77%) appendices to have a patent lumen, whereas only 11 (23%) showed fibrosis and obliteration of appendicular lumen.[19] This fact has led some authors to advocate IA for patients who have undergone successful conservative treatment. However, this means subjecting 23% of patients to unnecessary IA that necessitate a second admission and is not entirely free of complications; the reported complication rate is 12–23%.[2,7,8,12,27] In another large retrospective study of 233 patients (108 males, 125 females), the histological examination of the IA specimen showed a normal appendix without signs of previous inflammation in 30% of cases,[2] which argues against routine IA. Moreover, a recent large retrospective population-based cohort study of 1,012 patients treated initially conservatively showed that only 39 patients (5%) developed recurrent symptoms after a median follow-up of 4 years with males sex having slight influence on recurrence, but neither age nor type of appendicitis had such an influence.[25] It is, therefore, concluded that IA after initial successful conservative treatment is not justified and should be abandoned.[25] Lower recurrence rate of 2% has been reported by others[2] with the risk becoming minimal after 2 years of the initial episode.[3] Also, a recent prospective randomized controlled trial showed that patient treated conservatively without IA had the shortest hospital stay and duration of work days lost.[24] Furthermore, only 10% of the patients developed recurrent appendicitis during a median follow-up period of more than 33 months. This overwhelming evidence argues strongly against IA after successful conservative treatment of appendix mass.

Moreover, in 30 patients presenting with appendix mass, 3 required emergency appendicectomy within 48 h of admission, and another 2 underwent an interval appendicectomy for recurrent symptoms after 2 and 3 months. The remaining 25 (83%) patients did not require any intervention over a mean follow-up of 15.5 months.[28] Therefore, it was concluded that IA should not be the rule in every patient presenting with appendiceal mass.[28] Karaca et al. treated 17 children with appendiceal mass out of 866 patients with acute appendicitis (1.96%) conservatively with triple antibiotics for a week.[29] The mean hospital stay was 9.7 days, and mass regression was confirmed on repeat ultrasonography. They were followed up by clinical examination and ultrasound for 1–60 months; 11 patients underwent barium enema also. Ultrasonography demonstrated complete disappearance of the mass, and barium enema revealed normal appendix in 10 out of 11 patients. No recurrent appendicitis was detected during follow-up of 1–7 years. It was concluded that conservative treatment is feasible with no need for IA.[29]

In another experience of ten pediatric patients who were treated conservatively with intravenous triple antibiotic therapy for a week, one returned after 2 months with perforated appendicitis that required emergency appendicectomy. The other nine remained well and asymptomatic at 6 months to 13 years. Based on this small experience, the authors argued against IA.[30] However, a week of intravenous triple antibiotics in hospital[29,30] and repeated ultrasonography[29] is certainly not cost-effective and necessitated the stay of children and one of their parents in the hospital.[29,30] A recent retrospective review of 106 patients (89 males, 76 females) with a mean age of 53.6 (range, 7–89) years also found that recurrent symptoms after conservative treatment occurred in 25.5% of the cases with most of the recurrences (83%) occurring within the first 6 months. Moreover, very few will benefit from prevention of recurrent symptoms if IA is performed after 6 to 12 weeks. An interesting finding also was that complication rates for appendicectomy performed before or after recurrence of symptoms were equal at 10%. However, 17 patients (10.3%) had their diagnosis changed after follow-up or surgery with 5 patients (3%) found to have colon cancer. It was, therefore, concluded that performance of colonoscopy or barium enema is essential in patients who are treated conservatively and that IA can only benefit less than 20% of

patients, another argument against routine IA.[31] In terms of costs, IA is also not a cost-effective approach, as it increases the cost per patient by 38% compared with follow-up and appendectomy only if recurrence occurs.[32]

If no IA is to be performed after successful conservative treatment, the fear of missing hidden pathologies such as Crohn's disease, tuberculosis, or cancer that masquerade as an appendiceal mass remains an important issue. This can be excluded by barium enema or colonoscopy, which should be performed especially in patients aged 40 years or more after the acute episode has subsided.[10,29] However, there is no general consensus as to the right time to perform such an investigation. Timing is important as incompletely resolved appendix mass may mimic cecal carcinoma on barium enema, giving false positive results. Colonoscopy augmented by CT scan is far superior in excluding cecal pathology. Such investigations can be performed safely after 6–8 weeks.[33–35]

Table 3 summarizes the published articles on conservative approach and advocating IA, whereas Table 4 lists the articles that argue against IA after conservative treatment.

First Encounter Under Anesthesia

A common scenario is when a surgical trainee first discovers the appendix mass when the patient is relaxed under general anesthesia for an emergency appendicectomy. Such scenario may be encountered in 55% of cases.[1] Although reversal of anesthesia has been advocated to give conservative treatment a chance, it runs the risk of 'failure' with the subsequent need for delayed emergency operation, which is often difficult, hazardous, and associated with high morbidity.[24] Failure rate of conservative treatment in the reported literature is variable, ranging from 8.5–15.5%.[7–14,17,34] Much higher rate of 46% has also been reported.[1,2] In the author's unit, such scenario may be encountered in less than 20% of cases, and in more than 95% of appendix masses discovered upon palpation of the abdomen under general anesthesia, the appendix was easily removed by immediate open appendicectomy with minimal morbidity (unpublished data). Hence, under such circumstances, it is justifiable to proceed with the planned operation, but the presence of a senior colleague is mandatory.

Appendix Mass in the Laparoscopic Era

Horwitz has discouraged performance of laparoscopic appendicectomy (LA) in children with complicated appendicitis caused by the increased risk of intraabdominal abscesses.[36] This fear was, however, later dismissed by other workers who advocated LA as a good alternative to open method.[37] LA in management of patients with appendiceal mass was first reported by Vargas et al. who performed laparoscopic IA at 6–12 weeks after successful conservative treatment in 12 patients. The procedure was conducted successfully and safely in 11 out of 12 cases with a median hospital stay of 1 day and no perioperative morbidity.[38] Since then, an increase in percentage of IAs performed by the laparoscopic method from 30 to 85% has been noted,[39] and the total operating time of the laparoscopic IA did not differ from that of the interval open method (95 vs 103 min), but the hospital stay was much shorter in the interval laparoscopic group (0.55 vs 3.07 days, $p<0.001$).[39]

Table 3 Articles Advocating Interval Appendicectomy ($n=9$)

Author	Year	Total no.	Cons	Remarks
Skoubo-Kristensen and Hvid[8]	1982	193	169	Conservative followed by IA is advocated IA has 3.4% complication rate
Shipsy and O'Donnell[1]	1985	77	69	Conservative followed by IA is advocated
Vargas et al.[36]	1994	12	12	Conservative treatment is safe and effective Laparoscopic IA is safe
Ericksson and Styrud[26]	1998	38	38	HS is 3 days Postoperative complications, 13% One had appendiceal base cancer
Friedell and Perez-Isqierdo[11]	2000	5	5	IA is advocated after conservative treatment
Gillick et al.[12]	2001	427	411	Complication of IA 2.3% Conservative followed by IA is advocated
Erdogan et al.[13]	2004	40	21	Conservative is safe IA is recommended
Owen et al.[39]	2006	36	36	Laparoscopic IA can be safely performed in children Laparoscopic IA is associated with a short HS Laparoscopic IA has minimal morbidity and scarring

Cons Conservative, *IA* interval appendicectomy, *HS* hospital stay

Table 4 Articles Against Interval Appendicectomy (*n=11*)

Reference	Year	Total no.	Cons	I.A	Remarks
Thomas[27]	1973	37	33	31	IA is associated with complications
Foran et al.[17]	1978	43	30	0	Conservative approach has longer hospital stay than emergency surgery. It may miss other pathology (10%) and run the risk of symptom recurrence. Patients need to be closely examined to exclude other hidden pathology
Hoffmann et al.[10]	1984	44	44	0	Conservative without IA is advocated This eliminates morbidity and the expense of appendicectomy in 80% of cases
Bagi and Duetolm[9]	1984	40	37	0	2 patients had delayed diagnosis of other pathology (cecal cancer and Crohn's disease) Conservative group needs closer FU
Ein and Shandling[30]	1996	10	10	0	No need for IA
Adala[28]	1996	30	27	0	No need for IA
Gahukamble et al.[32]	2000	59	59	32	No need for IA if appendiceal lumen is obliterated
Karaca[29]	2001	17	17	0	IA is unnecessary, but follow-up with ultrasonography or barium enema is needed
Tingstedet et al.[14]	2002	83	50	0	4 (8%) had tumor. Conservative is advocated. However, FU is necessary to exclude other pathology. No need for IA
Willemsen[2]	2002	233	233	233	In IA, 30% normal appendix. Complication 18%. Once all other pathology is excluded no need for IA
Lai et al.[31]	2006	165	165	70	Minimal benefit from routine IA FU colonoscopy or barium enema is essential. Colon cancer diagnosed in 10.3%

Cons Conservative, *IA* interval appendicectomy, *FU* follow-up

Nguyen et al. compared 38 adult patients with appendiceal mass who underwent interval LA with 15 patients who underwent open IA. It was found that there was no difference in the operative time between the two groups, and moreover, the hospital stay was shorter in the laparoscopic group.[37] Senapati et al. also reported their experience with emergency LA in ten patients with appendiceal mass and compared them to patients who had LA for non-mass-forming appendicitis. There was no difference between the two groups in terms of operative time (median, 45 vs 40 min, $p=0.085$) and postoperative hospital stay (median, 2 vs 2 days). It was concluded that early emergency LA for appendiceal mass is feasible and safe, obviates the need for a second hospital admission, and also avoids misdiagnoses.[21] In another study comparing a group of 17 patients (aged 16–60 years) with appendiceal mass who were treated conservatively followed by interval LA at an average of 4.9 months later and a second matched group of 15 patients who underwent immediate appendicectomy, there was no difference between the two groups in the operative time and complication rate.[40]

In a recent retrospective study of 35 children who underwent interval LA after a median interval of 93 days (range, 34–156 days), the median operative time was 55 min (range, 25–120 min), and the median length of stay for interval LA was 1 day (range, 1–3 days) and without any complications.[41]

In summary, in the era of laparoscopy, there is an increase in percentage of interval appendicectomies performed laparoscopically. LA can be conducted safely and successfully in early emergency surgery for appendiceal mass and in the interval setting after successful conservative treatment with a short hospital stay and minimal morbidity, analgesia, and scarring. The operative time and hospital stay are comparable to those of LA performed for non-mass-forming appendicitis. Table 5 summarizes the articles published on LA for appenidceal mass.

Management Recommendation

Based on the available evidence, which comprises mainly of small retrospective rather than prospective non-randomized studies and only one small prospective randomized controlled trial, what should now be recommended for the management of an appendix mass in the era of laparoscopy? With the advent of LA, early emergency appendicectomy has emerged as an attractive management option,[21,40] as it is feasible, safe, and associated with significantly much lower wound-related complications.[21,42] If this approach is to become a standard, the fear of missing or delaying the diagnosis of other pathologies will be eliminated, and the overall hospital stay will certainly be reduced. However, one should accept the odd occasion when an ileo-cecal

Table 5 Articles on Laparoscopic Appendicectomy for Appendiceal Mass ($n=6$)

Reference	Year	No. of patients	ELA	ILA	Comments
Vargas et al.[38]	1994	12 adults	0	12	ILA is safe with no morbidities
Nguyen et al.[39]	1999	53 adults	0	38 (vs 15 OIA)	No difference in ORT HS is shorter after ILA
Senapati[21]	2002	10 adults	10	0	Comparable ORT and HS to LA in non-mass
Gibeily et al.[40]	2003	32 adults	15	17	No difference in ORT and HS
Goh et al.[22]	2005	22 children	22	0	Longer ORT and HS than non mass appendicitis
Owen et al.[39]	2006	35 children	0	35	LA can be safely performed with minimal morbidity and scarring
Total, 6		164 (107 adults; 57 children)	37	90	

ELA Emergency laparoscopic appendicectomy, *ILA* interval laparoscopic appendicectomy, *HS* hospital stay, *ORT* operative time, *OIA* open interval appendicectomy

resection is performed in difficult cases and for masses mistaken for malignancy. Also, once this approach is widely accepted, the debate on whether or not to perform IA will eventually vanish. Nevertheless, larger prospective randomized multi-center clinical trials are needed to establish the safety of emergency appendicectomy for appendix mass and also the safety of omitting IA in those treated conservatively. Such studies should look into the possible differences—if any—in the management of appendiceal masses in various age groups (pediatric vs adults) and different sexes (males vs females). Although Andersson et al.[43] reported no adverse effects on fertility in 9,840 Swedish women aged under 15 years when they underwent appendicectomy for perforated appendix, the possibility of increased infertility in females with appendiceal masses treated conservatively should also be studied to see if emergency surgery is more beneficial in affected females to make stronger argument for emergency management, at least, in females.

From the reviewed literature, for surgeons adopting conservative management, IA can be safely omitted, and other pathologies are excluded by colonoscopy, which may be augmented by CT scanning. This helps to avoid a second hospital admission and a surgical procedure, which is

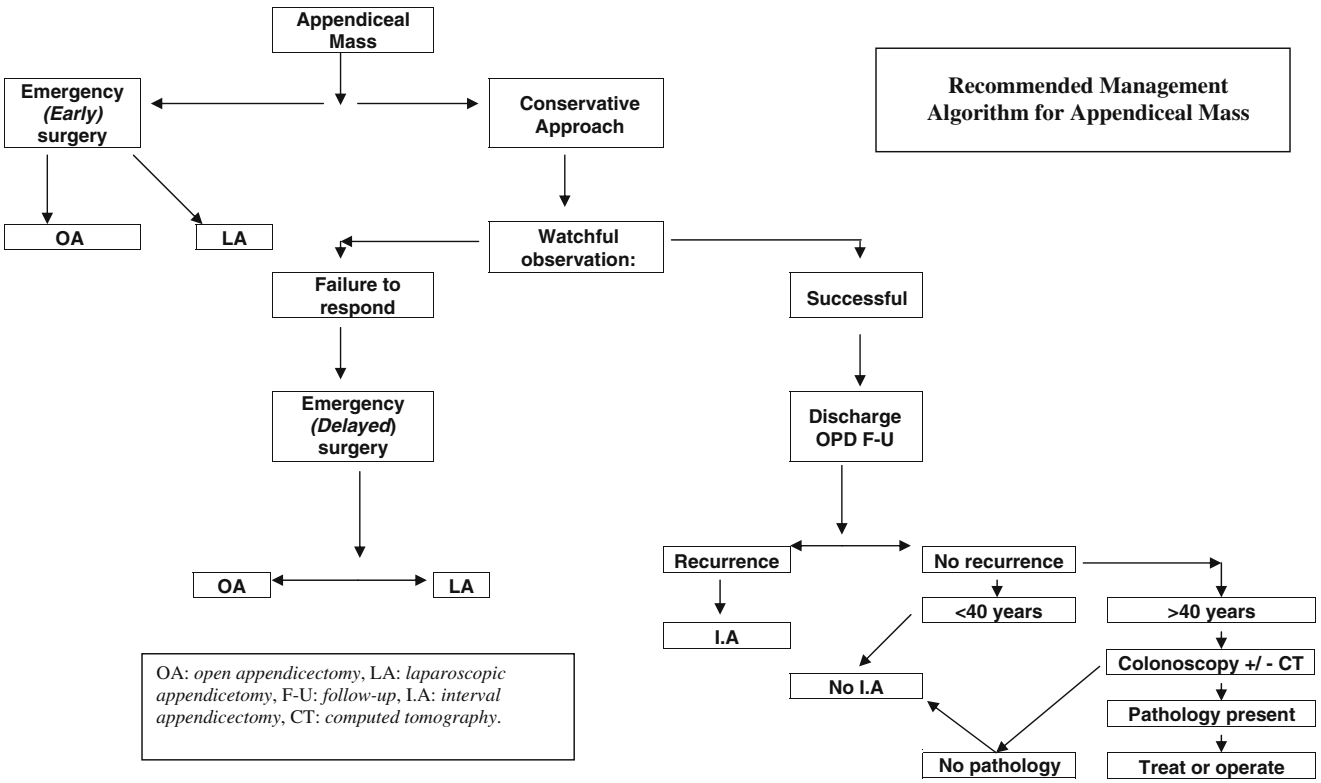

Figure 1 Recommended management algorithm for appendiceal mass.

associated with some complications. However, IA is still reserved for patients with recurrent symptoms and can be performed safely by laparoscopic means. A suggested algorithm of appendiceal mass management is shown in Fig. 1.

Conclusion

For the time-being—based on the available evidence—the management of appendiceal mass can either be nonoperative (conservative) or operative (emergency appendicectomy). Emergency appendicectomy (laparoscopic or open) for management of appendiceal mass is gaining popularity and is advocated, as it is safe, feasible, and cost-effective. For surgeons adopting conservative approach to appendiceal mass, IA can safely be omitted provided there is no recurrence of symptoms, and all other pathological causes of right iliac fossa mass has been thoroughly excluded by close follow-up and investigations such as colonoscopy and CT scan, especially in patients aged 40 years and over. For patients with recurrent symptoms after successful conservative treatment, laparoscopic IA is recommended. Although emergency surgery for appendiceal mass is increasing, it is unlikely to completely abolish the conservative approach in the near future as emergency surgery is not yet commonly practiced. However, IA can safely be omitted in the conserved patients except in patients with recurrent symptoms.

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Duodenocaval Fistula After Irradiation and Resection of a Retroperitoneal Sarcoma

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Keywords Duodenocaval fistula · Graft complications · Aortoenteric · Duodenalcaval fistula · DCF · Aortoduodenal fistula · Complications of retroperitoneal sarcoma resection

Duodenocaval fistulae (DCF) are rare with only 38 previously reported cases in English literature[1]. This often lethal condition typically arises as a complication from trauma, peptic ulcer disease, or transmural migration of ingested foreign bodies. Twelve patients have developed duodenocaval fistulae after resection of retroperitoneal tumors, and ten of these patients also have had post-operative external beam irradiation[1]. We present a case of DCF occurring 1 month after completion of pre-operative external beam irradiation and resection of a retroperitoneal myxofibrosarcoma.

Report of a Case

A 69-year-old man completed a course of external beam irradiation of 45 cGy delivered in 25 fractions over 35 days and 2 weeks subsequently underwent resection of a retroperitoneal myxofibrosarcoma. The patient's recovery was complicated by a superficial wound infection, which was treated with open wound packing and intravenous cefazolin for 7 days. Seventeen days after hospital discharge, his recovery was interrupted further by fever of 39°C and rigors. Upon readmission, he appeared ill and anorexic. He denied nausea, vomiting, hematemesis, melena, dysuria, and hematuria. He was normotensive with a heart rate of 64 and a temperature of 37.8°C. His abdominal examination was unremarkable except for a focal area of suppuration along the inferior aspect of his incision, which was treated by incision and drainage. Broad-spectrum antibiotic coverage was started. Laboratory findings revealed hemoglobin of 10.1 g/dl, white blood cell count of 3.56×10^9/l, and INR of 1.1. Computed tomography (CT) of his chest, abdomen, and pelvis with enteric and intravenous contrast revealed a small sterile peri-aortic fluid collection confirmed by aspirate cultures.

During his first evening of hospitalization, a recurrent episode of septicemia (tachycardia, hypotension, rigors, chills, and fever of 40°C) occurred. His antimicrobial therapy was broadened with fluconazole and metronidazole. Blood cultures obtained during this episode revealed a methicillin resistant *Staphylococcus aureus* and *Enterobacter cloacae* bacteremia, and *Candida glabrata* fungemia. His septicemia recurred nightly despite modifications of his broad-spectrum antibiotic and antifungal therapy. Transesophageal echocardiography and an indium-labeled white blood cell scan failed to localize a source for his septicemia. On his seventh hospital day, a repeat abdominal CT scan with enteric and intravenous contrast suggested a duodenocaval fistula (Fig. 1).

To confirm the suspected diagnosis before attempting resection of the involved duodenum and IVC in an irradiated field, an upper gastrointestinal endoscopy was performed cautiously. Despite confirmation of the diagnosis by the presence of fresh clot in the third portion of the duodenum, intraluminal hemorrhage and hemodynamic instability prompted termination of the endoscopy without attempts at temporary endoscopic control before definitive operation. Even with immediate cardiopulmonary resuscitation, the patient died. Postmortem examination confirmed the cause

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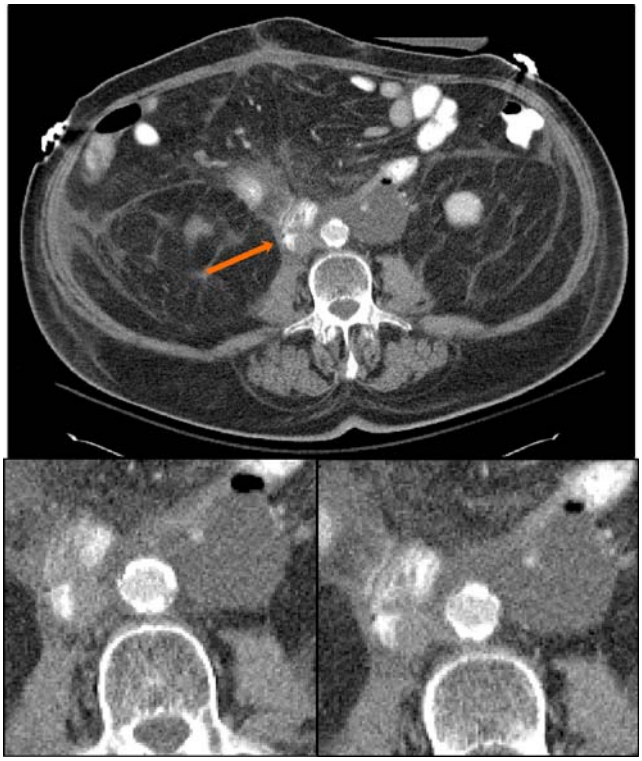

Figure 1 Enhanced CT chest abdomen and pelvis reveals mildly enlarged mediastinal lymph nodes, which have increased in size since previous exam. In the abdomen and pelvis, there is little change since 8-24-05 exam. Small amount of free fluid around the liver and in the right lower quadrant has developed. Otherwise the exam is unchanged. Left para-aortic fluid collection is stable.

of death as exsanguination from a duodenocaval fistula (Fig. 2).

Discussion

Duodenocaval fistulae are an uncommon but highly lethal entity. The high mortality rate has been attributed to the difficulty of diagnosis before attempts at definitive therapy[1]. DCF are most commonly seen in men with an average age of 50 years. The mortality rate of DCF approaches 40%.[2] From a literature review of 35 patients who developed DCF, the most common etiology of DCF was trauma followed by resection of a retroperitoneal tumor combined with adjuvant postoperative irradiation. Two patients in this review had tumor resection without postoperative irradiation. Four cases of DCF were due to retroperitoneal sarcoma, one of whom survived; this patient did not have a history of postoperative radiation therapy. The frequent association of a duodenal ulcer with these fistulae suggests that the fistula is related to fibrosis and post-irradiation mucosal damage.[2]

Patients with DCF classically present with septicemia and gastrointestinal tract bleeding.[3] Nearly 70% of patients with DCF have noted at least one of these symptoms but only 45% present both septicemia and digestive tract hemorrhage.[2] Other presentations include non-specific complaints as abdominal pain, weight loss, fever of unknown origin, diarrhea, small bowel obstruction, hemorrhagic shock, respiratory distress, and stroke secondary to cerebral air embolism after gastroduodenoscopy[1]. Regardless of clinical symptoms or signs, the diagnosis of DCF is particularly difficult. CT correctly can identify DCF in approximately 50% of patients. Upper gastrointestinal endoscopy can identify the site of visible bleeding in 30% of patients but often underestimates the depth of penetration.[1] Contrast enterography and inferior vena caval venography are alternative diagnostic studies but the yield is low.[1] Most frequently because DCF remain clinically occult, the diagnosis is made most successfully by laparotomy.[1]

Previous reports have noted the development of DCF years after retroperitoneal tumor resection and high-dose irradiation. We did not find any report of DCF in which irradiation preceded tumor resection as encountered herein. Although pre-operative irradiation potentially allows removal of the duodenum at risk for fistula, resection is usually averted unless the duodenum is grossly invaded by malignancy because such resection may entail pancreatoduodenectomy. Regardless of the timing of irradiation, however, the etiological role of irradiation in conjunction with operation should be similar. Previous reviews have

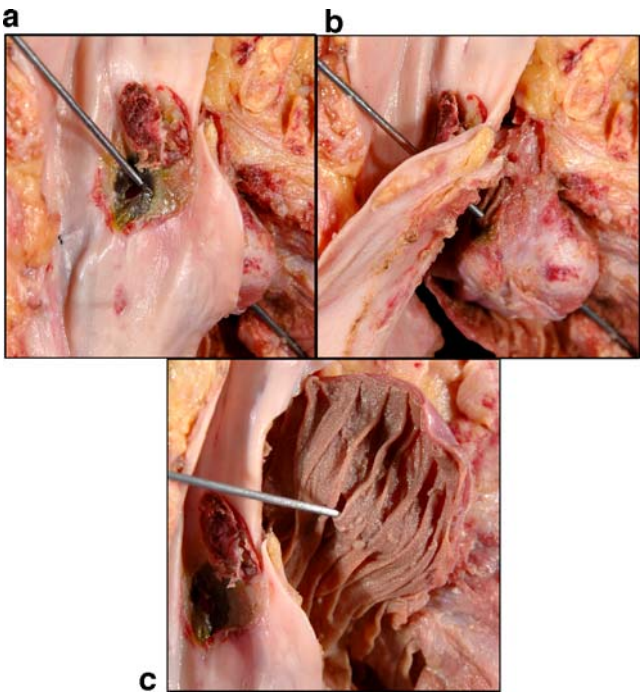

Figure 2 Postmortem examination. The opened vena cava is shown here (**a**) with a probe within the fistula tracking to the duodenum (**b**). **c** Opened duodenum with the probe within the fistulous tract.

suggested that ulcers precede the development of fistulae after irradiation[1]. Ionizing irradiation of 45 Gy, as our patient received, can cause chronic clinical enteritis in nearly 5% of patients.[1] Other recognized consequences of irradiation have included vasculitis, stricture, hemorrhage, enteroenteric fistula, and visceral perforation.[4] The contribution of the preceding operation in DCF has been generally ignored. Unrecognized damage to the duodenal wall or IVC, repaired duodenotomies or venotomies, and removal of interposed tissue during resection of the retroperitoneal tumor has likely contributed to some DCF. Subsequent adherence of the duodenum and IVC in an irradiated field predisposes even shallow ulceration to transmural penetration and fistula formation.

Recurrent septicemia after resection of a retroperitoneal tumor without imaging evidence of intraabdominal abscess, regardless of the presence of gastrointestinal bleeding, should strongly suggest an enterovascular fistula and prompt urgent abdominal exploration. Although our patient died before an attempt repair of the fistula, we believe that the operative approach should be similar to that recommended for aortoduodenal fistula. The IVC should be exposed by a right-sided medial visceral rotation (Extended Kocher Maneuver). If further exposure is needed, a Cattell–Braasch maneuver can be performed by detaching the posterior attachments of the small bowel mesentery toward the duodenojejunal ligament. Care should be taken to minimized traction on the duodenum to avoid tearing of the fistulous tract. Once the fistulous tract is identified, control of the IVC should be obtained through compression above and below the injury. The fistulous tract should be divided and the duodenum and IVC both repaired primarily. Muscle or omental flaps may be considered for larger openings that would require repair under tension. A gastrostomy tube for venting, a jejunal feeding tube, and a percutaneous transhepatic cholecystostomy tube should be placed to allow for duodenal exclusion while this injury mends.

Conclusion

Duodenocaval fistulae are often illusive entities diagnosed only at autopsy. Physicians managing the care of patients undergoing retroperitoneal tumor resection with radiotherapy pre- or post-operatively, must maintain a high index of clinical suspicion, as patients may present with little more than sepsis and fever of unknown origin as in the presented case. The effects of pre-operative radiation and duodenocaval fistulae have not been well studied; future research into this area will likely reveal beneficial, life-saving clinical information. Further advances in diagnostic imaging will aide physicians with the diagnosis of this uncommon but often morbid complication. For the present, CT scanning along with sound clinical judgment is the best way to diagnose duodenal caval fistulae.

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Isolated Periportal Tuberculosis: Characteristic Findings of Clinical Imaging

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Abstract Isolated periportal tuberculous lymphadenopathy is a rare clinical entity. This report describes a 56-year-old woman with the disease, who showed characteristic findings on clinical imaging studies. Computed tomography showed a low-density mass with peripheral enhancement and calcification, adjacent to the pancreatic head and caudate lobe of the liver. 2-[Fluorine 18]fluoro-2-deoxy-D-glucose positron emission tomography imaging co-registered with computed tomography showed slightly increased uptake along the periphery of the lesion. The diagnosis was confirmed at laparotomy. The manifestation of the disease is nonspecific, and preoperative differential diagnosis from neoplastic disease is often difficult. Its clinical and radiological features are briefly reviewed.

Keywords Abdominal tuberculosis · FDG-PET · Computed tomography

Introduction

Tuberculosis remains a global epidemic, with an estimated incidence of 8–9 million new cases every year. It is believed that the number of patients is slowly increasing worldwide, mainly because of the spread of human immunodeficiency virus (HIV) infection and the advent of multidrug-resistant strains.[1]

Extrapulmonary involvement of the disease has become more common following the increase in comorbid HIV infection,[2] and abdominal tuberculosis is one of the most prevalent forms.[3] However, because the clinical manifestations of the disease vary, preoperative diagnosis is often difficult, and in many cases the diagnosis is confirmed during exploratory laparotomy.[3,4] Isolated abdominal tuberculous lymphadenopathy is extremely rare, which makes the diagnosis even more challenging. In this report, we describe a case of isolated periportal tuberculous lymphadenopathy, and discuss the radiological features of the disease.

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Case Report

A 56-year-old woman was referred to our hospital with epigastric and back pain after eating. She had been diagnosed with gallstones by her primary care doctor. Chest and abdominal radiographs and blood examination findings were normal and HIV antibody was negative. Ultrasonography showed a periportal hypoechoic lesion dotted with peripheral calcification, in addition to gallstones. Contrast-enhanced computed tomography (CT) demonstrated gallstones and a low-density mass, 2 cm in diameter, with peripheral enhancement and calcification, located adjacent to the pancreatic head and caudate lobe of the liver (Fig. 1). On magnetic resonance imaging (MRI), the mass was hypointense on T1-weighed images, mildly hyperintense on T2-weighted images, and hyperintense on diffusion-weighted images. 2-[Fluorine 18]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) imaging co-registered with CT revealed slightly increased uptake along the periphery of the lesion, with peak standardized uptake value of 2.8 (Fig. 2). Findings of upper gastrointestinal endoscopy, colonoscopy, and endoscopic retrograde cholangiopancreatography were normal.

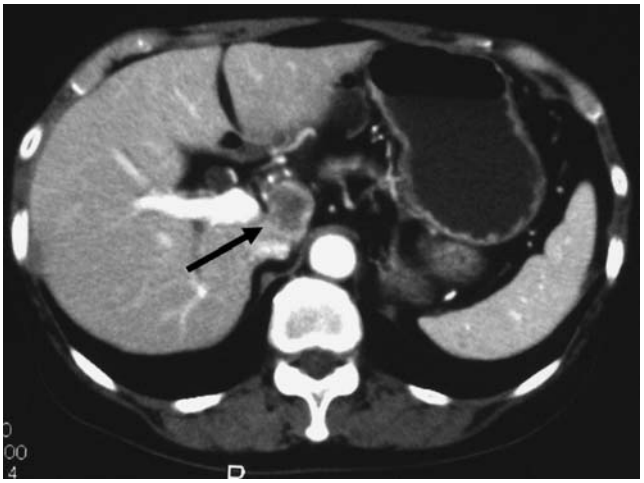

Figure 1 Preoperative computed tomography shows a low-density mass with peripheral enhancement and calcification adjacent to the pancreatic head and caudate lobe of the liver (*arrow*).

Although the nodule was suspected to be related to inflammatory changes according to the results of FDG-PET, we could not rule out a hepatic or pancreatic malignant tumor, and laparotomy was performed. We found a mass between the pancreatic head and caudate lobe, which was severely adherent to the common hepatic artery. The lesion was resected, and cholecystectomy was performed. Pathologic examination of frozen sections of the mass revealed epithelioid cell granuloma with caseous necrosis, and abdominal tuberculous lymphadenopathy was diagnosed intraoperatively.

The postoperative course was uneventful. Culture of the resected specimens was negative, whereas polymerase chain reaction (PCR) test was positive for *Mycobacterium tuberculosis*. Chest CT was normal, and culture and PCR of sputum were negative. She received antituberculous therapy postoperatively.

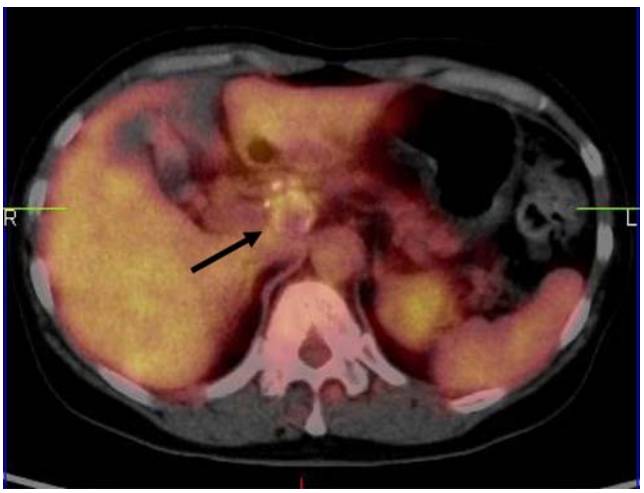

Figure 2 FDG-PET imaging co-registered with CT shows slightly increased uptake of FDG along the periphery of the lesion (*arrow*).

Discussion

Lymphadenopathy is a common manifestation of tuberculosis within the abdomen, with a reported prevalence of 16.8 to 56% of patients with abdominal tuberculosis.[3–5] The mesenteric, periportal, and upper paraaortic regions are mainly involved, which is generally presumed to reflect the lymphatic drainage of the bacteria from the bowel after ingestion of infected materials. Hematogenous dissemination of the pathogen from a distant site of infection or direct spread from neighboring infected organs could also lead to lymphatic involvement in the abdomen.[4–6]

Most cases of abdominal tuberculous lymphadenopathy are associated with multiple lymphatic involvement or infection of other organs.[5,6] Isolated periportal lymphadenitis is uncommon, and is difficult to differentiate from malignant disease. The clinical symptoms are usually vague and nonspecific, and include abdominal pain, weight loss, and fever, although obstructive jaundice may occur in some exceptional cases.[7] Imaging modalities can provide useful diagnostic information. On ultrasonography, the affected lymph nodes are hypoechoic in most cases, with an echogenic periphery or calcification within the nodule in some patients.[5] Yang et al.[6] reported that on enhanced CT, lymph nodes in tuberculous lymphadenopathy were circular or ovoid, measuring less than 4 cm in diameter, and were mostly demonstrated as low-attenuation areas with peripheral enhancement, which might represent caseation at the center of the lesion and viable inflammatory tissue in the margins. They suggested the usefulness of the enhancement pattern on CT in distinguishing tuberculous lymphadenopathy from lymphoma, because lymph nodes in the latter showed homogenous enhancement. MRI is also useful, especially in analyzing the relationships between affected lymph nodes and the adjacent bile duct or vessels. It demonstrates the lesion as T1 iso- or hypointense and T2 hyperintense, and peripheral rim enhancement can be seen in most cases.[8]

Recently, FDG-PET has been proven useful in distinguishing between malignant and benign lesions. However, an active inflammatory process, reflecting the high glucose metabolism at the site, also leads to increased uptake of FDG, and makes differentiation difficult. Although there have been few reports on FDG-PET imaging of abdominal tuberculous lymphadenopathy, it has been demonstrated that pulmonary tuberculosis causes an increase in FDG uptake, and caution should be exercised in interpreting the images.[9,10] In our patient, PET showed a slightly elevated level of FDG uptake around the rim of the lesion, indicating central necrosis and active inflammation along the margins of the lymph node. This imaging pattern, more clearly observed when co-registered with CT, correctly reflects the pathological features of tuberculous lymphadenopathy.

FDG-PET could be useful in making a differential diagnosis from neoplastic disease.

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