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Bariatric Surgery Training: Getting Your Ticket Punched

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Abstract Laparoscopic bariatric surgery has gained popularity but has been proven to be a technically challenging set of operations that requires a long learning curve. Trainees must acquire advanced laparoscopic skills and knowledge of the perioperative care of the bariatric patient. The challenge is to ensure that those surgeons performing gastric bypass, gastric banding, and duodenal switch procedure are trained appropriately. In the past, very different opportunities have been available for the general surgeon seeking to practice bariatric surgery. Early on, many surgeons began performing bariatric surgery without any formal training. Later, weekend courses, mini-fellowships, and formal minimally invasive surgery/bariatric fellowships were established. Today, best practice requires an intensive training experience and ongoing commitment to the field.

Keywords Bariatric surgery · Training · Credentialing · Guidelines · Laparoscopy

Introduction

Recent studies have documented an unprecedented growth in bariatric surgical procedures.[1] Pope et al.[2] showed that the incidence of bariatric surgery in the US more than doubled between 1990 and 1997, without substantial changes in perioperative morbidity and mortality. Since 1997, there was exponential growth in bariatric surgery volumes until about 2004; after which, volumes have tended to plateau by best estimates. Insurance companies have alleged that there has been a significant increase in morbidity and mortality with this exponential increase in bariatric surgery, but the data to confirm this are not published or confirmed. It is clear that this era has been associated with the conversion of surgical approach from celiotomy to laparoscopy for the increasing numbers of bariatric operations. Laparoscopic Roux-en-y gastric bypass, adjustable gastric banding, and duodenal switch can be technically challenging operations, and surgeons must master the techniques, perioperative care, and long-term follow-up. As the demand for bariatric surgery rises, it is crucial for surgeons to identify training safeguards.

Bariatric surgery is the only durable treatment for the disease process of morbid obesity.[3,4] Nonoperative therapy is associated with little success. In a case–control study, Christou and colleagues[5] showed that patients undergoing bariatric surgery had a lower 5-year mortality (0.68%) compared to the controls (6.17%). A metaanalysis by Buchwald and colleagues[6] clearly showed that bariatric surgery is effective in improving the medical comorbidities associated with severe obesity. Several studies assessing the

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cost effectiveness of various weight loss strategies have demonstrated the advantage of a surgical approach.[7,8]

Bariatric surgery is held to a different standard than other major surgical procedures. Large-volume centers performing bariatric surgery in the University Health Consortium (academic teaching centers) have shown a decrease in the mortality rate after gastric bypass to 0.3%, a rate lower than many published single-institution series in the past.[9] However, despite these improvements in bariatric surgery, it was an article by Flum et al.[10] that showed the mortality for Medicare patients as being 2% which garnered the most national attention in a negative way by the lay press during 2005. However, when one compares this 2% mortality figure for Medicare patients undergoing bariatric surgery to figures of 4, 3.9, 5, 9.2, and 4.6% for mortality after coronary artery bypass, elective aortic aneurysm repair, lung resection for cancer, esophagectomy, and pancreatic resection in Medicare patients,[11] bariatric surgery compares quite favorably. With an increasing growth in bariatric surgery has come an increasing scrutiny regarding its appropriate use, associated outcomes, and training.

Learning Curve

To acquire the skills needed to perform laparoscopic bariatric surgery, a surgeon must understand a breath of knowledge and acquire advanced laparoscopic and open technical skills. Most new laparoscopic procedures have a well-studied learning curve, such as cholecystectomy, inguinal hernia, Nissen fundoplication, splenectomy, and colectomy.[12–14] Bariatric surgery is no exception, and once the surgeon is beyond the learning curve, the mortality rates on average drop to less than 1%, conversion rates to 3%, major morbidity rates to less than 5%, major leak rates to less than 2%, and operative times to less than 2 h.[15,16]

The learning curve is probably 75 to 100 cases. Schauer et al.[17] showed that during their initial experience with laparoscopic Roux-en-y gastric bypass, overall operating time and complications were significantly lower after an experience of 100 cases. Oliak et al.[18] demonstrated a low mortality rate and conversion rate early on in the learning curve; only after 75 cases did complication rates plateau. Operative times decreased substantially during the first 75 cases and then more gradually. Provost and colleagues[19] also reported fewer major complications after their first 70 cases. Wittgrove and Clark[20] demonstrated a decrease in leak rate (3 to 1%) and operative time (4 h to 90 min) with experience.

Specialty societies, insurance companies, and state regulatory agencies have developed guidelines in bariatric surgery.[21–25] In 2003, the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) issued guidelines[24] and recommended: (1) completion of a formal residency training in general surgery, (2) formal training in open bariatric surgery, and (3) formal training in laparoscopic surgery documented by the applicant's program director. If the surgeon has not had formal residency or fellowship training in laparoscopic and/or bariatric surgery, a structured curriculum is required. All applicants must document practical experience. However, these recommendations do not require a specific case number.

In the same year, the American Society for Bariatric Surgery (ASBS) recommended for laparoscopic bariatric surgery that the surgeon should: (1) have privileges to perform "open" bariatric surgery; (2) have privileges to perform advanced laparoscopic surgery; (3) document three proctored cases in which the assistant is a fully trained bariatric surgeon; and (4) document the outcomes of 15 laparoscopic bariatric surgical cases performed as the primary surgeon, which demonstrated an acceptable perioperative complication rate.[23]

The Department of Public Health in the Commonwealth of Massachusetts charged the Betsy Lehman Center for Patient Safety and Medical Error Reduction to convene an expert panel on weight-loss surgery. Full privileges for laparoscopic and open bariatric surgery required a review of the first 15 independently performed cases by a committee that included the chief of surgery at the surgeon's institution and an experienced (>100 cases) weight-loss surgeon. Results should demonstrate no substantial deviation in risk-adjusted outcomes for accepted norms and benchmarks.[25]

In 2005, the ASBS updated its credentialing requirements (http://www.asbs.org/html/about/grantingpriviledges.html). The ASBS emphasized that the surgeon should work within an integrated program that provides dietary instruction, counseling, support group, exercise training, psychological assistance, and access to follow-up. "Open" privileges require 15 open bariatric cases during general surgery residency or postresidency. Surgeons who primarily perform laparoscopic surgery may obtain open bariatric surgery privileges after documentation of 50 laparoscopic cases and 10 open cases supervised by an experienced bariatric surgeon. For operations which do not divide the stomach, such as laparoscopic adjustable gastric band, the surgeon needs only to document 10 cases with satisfactory outcomes. All surgeons should work in an accredited facility and document continuing medical education related to the specialty of bariatric surgery.

Training Opportunities

Surgeons who embark on laparoscopic bariatric surgery with no formal training usually are already skilled at advanced laparoscopy and experienced in bariatric surgery. Ideally, they will work closely with partners who complement their abilities. Many of the pioneers in the field began after

practicing in animals and cadavers. Conceivably, some residents today are finishing residency with sufficient laparoscopic bariatric experience to forego any additional formal training. However, the question arises: how much training is enough to be competent?

Both surgeon and institutional volume have been shown to affect outcomes in several large-population-based studies besides Medicare.[26] In the state of Washington, those surgeons who had performed less than 20 bariatric operations had a 4.7 times higher incidence of patient mortality than experienced surgeons.[26] Courcoulas et al.[27] observed a major difference in mortality for bariatric surgeons in Pennsylvania who performed less than 10 procedures per year vs those who performed high volumes of surgery (5 vs 0.3%). This study failed to show a statistical significance for hospital volume as it did for surgeon volume, but surgeons at low-volume hospitals had higher complication rates.[27] Other studies though have shown that hospital volume is important. Nguyen et al.[9] showed a difference in mortality after gastric bypass in low-volume (<50 cases/year) vs high-volume (>100 cases/year) hospitals of 1.2 vs 0.3%. Hospital volume may be an indicator of better process within an institution.

The argument that volume alone is not an appropriate predictor of good outcomes was presented recently by Livingston and Engle (submitted). In this study, the authors used Monte Carlo modeling to demonstrate that the observed distribution of mortality as a function of hospital volume was very similar to the expected frequency attributable to random sampling alone. A relatively small number of excess deaths in very low-volume facilities caused statistically significant results for volume outcome studies. The authors pointed out that, based on National Inpatient Survey data, although 74% of all bariatric surgeries are performed in high-volume centers, 73% of all hospitals currently offering these services are now classified as low volume. Low-volume rural hospitals have 12% of their patients insured with Medicare and 45% are poor. High-volume urban hospitals have 7% of their patients insured by Medicare and 15% are poor. Thus, statistical studies which suggest that high volume is necessary for best outcomes have resulted in a disproportionate denial of access for services to the poor and those insured by Medicare.

The ideal method for confirming best outcomes at institutions would be to have a system in place for all hospitals that would provide accurate risk-adjusted outcome data. The current National Surgical Quality Improvement Program administered by the American College of Surgeons has made progress in that field for all general surgery but has not yet been adapted to bariatric surgery.

Despite the increased scrutiny associated with bariatric procedures, our current inability to risk stratify patients does not allow for the accurate comparison of outcomes between centers or surgeons. In part, this has been the motivation behind the support for the Center for Medicare Services' recent national coverage decision to base reimbursement for bariatric surgery not on outcomes (which might favor operating on lowest risk individuals only) but on participation in an accreditation program that assures that the proper structure and process measures are in place to deliver optimal care. The use of strict volume-based cutoffs for these accreditation programs has been the source of much debate. Given the absence of risk-adjustment strategies, even this surrogate metric of quality can be problematic. Future evaluations that evaluate the processes of care that occur at higher volume institutions are critical to better understand the volume-to-outcome relationship in bariatric surgery and improve care based on it.

Weekend Course

Some surgeons with substantial laparoscopic and bariatric experience have attended a 2-day course held at a national meeting, hospital, or industry facility before performing their first laparoscopic bariatric surgery procedure. While this approach has worked well for many surgeons entering the field, for a few surgeons and their patients, this fast track has had disastrous outcomes. It should be emphasized that, for the most part, practicing surgeons have entered the field only after significant preparation and with caution so as to avoid high initial complication rates. SAGES describes a formal course in their guidelines for granting privileges as "a limited period of instruction that should offer Category I Continuing Medical Education (CME) credits that meet American Medical Association standards.[24] The course should be taught by instructors with appropriate clinical experience and have a curriculum that includes didactic instruction as well as hands-on experience utilizing inanimate and/or animate models." Most importantly, SAGES maintains that a formal course alone is not a sufficient training to begin performing bariatric surgery independently.[24]

Typically, these courses are sponsored by academic institutions committed to providing continuing medical education. In 2001, Scott et al.[28] surveyed surgeons who attend weekend courses. Most participants reported that the course was insufficient to prepare a surgeon to perform laparoscopic Roux-en-y gastric bypass.

Mini-Fellowships

Few general surgery residency programs offer significant experience in advanced laparoscopy including antireflux surgery, colon surgery, and bariatric surgery. In fact, in

many training programs, surgical residents may complete their training with fewer than 10 advanced cases—an experience woefully inadequate to gain competency.[29] A recent ruling by the American Board of Surgery stating that residents must finish with a minimum of 25 advanced laparoscopic cases is the first sign that this deficiency is being appreciated and corrected. Furthermore, the majority of practicing general surgeons who were trained before the laparoscopic era never received formal hands-on training in advanced laparoscopic techniques.

Mini-fellowships range from 4-day programs without an operative component to a 3- to 6-month experience as an integrated surgical fellow experience. Weeklong mini-fellowships usually include attendance at preoperative and postoperative clinics and animate and inanimate skills lab. Participants often observe several laparoscopic bariatric operations. As a prerequisite, most mini-fellowships encourage prior attendance at an introductory 2-day, university-sponsored CME- or ASBS-approved bariatric surgery course. The 1-week intensive courses recommend the entire bariatric team, including the primary general surgeon, operating-room first assistant, bariatric program coordinator, and other staff, to participate. Extended mini-fellowships will often include a proctored experience in the operating room as well. While the "hands-on" experience is better, rarely can the surgeon already in practice commit to being away from his/her practice for several months.

Schauer's group[30] previously reported the experience at the University of Pittsburgh with the mini-fellowship concept with a focus on laparoscopic bariatric surgery. Of the 10 surgeons who completed the training, none of the trainees had prior experience in laparoscopic bariatric surgery. Program operative experience averaged 42 cases (range 29–66). Trainees were integrated into all preoperative and postoperative hospital and outpatient care on the service, including workshops and seminars. Seven graduates reported of adopting a laparoscopic bariatric surgery practice, and three reported of implementing new bariatric programs. The active surgeons reported of performing an average of 101 laparoscopic bariatric procedures (range 18–264) over a mean practice period of 10 months (range 4–16). Thus, a 6-week focused mini-fellowship with hands-on operative and clinical participation may enable well-selected practicing surgeons to acquire the skill and experience necessary to successfully implement a laparoscopic bariatric surgical practice.

A 1-year fellowship with an emphasis on laparoscopic bariatric surgery supervised by an expert in the field is the ideal training modality available presently that provides training to achieve not only baseline competency but also proficiency. Fellowships which focus almost exclusively on bariatric surgery are relatively few in number compared to fellowships which include some bariatric surgery experience with other minimally invasive surgery (MIS) experience (see below). Currently, these yearlong fellowship opportunities are insufficient to meet the present demand.

Minimally Invasive Surgery/Bariatric Fellowship

Specialized fellowships in MIS with emphasis in bariatric surgery have increased in number over the past decade. Currently, over 90 such fellowships exist, with the experience in bariatric surgery being variable. There are currently less than 20 fellowships that focus almost exclusively on bariatric surgery. However, many of the current MIS fellowships do have a substantial component of bariatric surgery as part of the training.

The Fellowship Council administers the fellowship candidate match and the accreditation process for these fellowships.[31] The Fellowship Council has established guidelines based on the six core competencies advocated by the Accreditation Council for Graduate Medical Education for all residency and fellowship training programs. Fellows should know about established and evolving issues in biomedical and clinical sciences, have a substantial experience in preoperative, operative, and postoperative surgical care and decision making, demonstrate the capacity for practice-based learning and improvement, have the ability to have appropriate communication skills and professionalism, and have the ability to understand and function in a systems-based health-care environment. Adequate case volume, adequate academic exposure, appropriate supervision, appropriate clinical duties and responsibilities, and an environment conducive to achieving these goals are all important elements of the fellowship, which are scrutinized by the Fellowship Council during the accreditation process.

Oliak et al.[32] assessed the impact of fellowship training on a surgeon's early experience with laparoscopic Roux-en-y gastric bypass. Of the two surgeons compared, one completed a 1-year laparoscopic surgery fellowship in which he participated in 130 laparoscopic Roux-en-y gastric bypass operations. The second surgeon was experienced in advanced laparoscopy and had completed 20 open gastric bypasses and a 2-day course in which he performed 10 procedures on pigs. While conversion rates were comparable, the second surgeon had longer operative times, more frequent major complications, and more severe complications. While this comparison by itself is inconclusive, their data support the idea that fellowship training improves perioperative outcomes during a bariatric surgeon's early experience. In another comparison, they found that the learning curve was shorter for surgeons who initiated their

experience at an institution with an established laparoscopic bariatric program.[33]

Currently, most MIS fellows participate in the preoperative, intraoperative, and follow-up care of the bariatric patient. However, a tremendous variation exists among programs in terms of caseload. As MIS–bariatric fellows hone their laparoscopic skills, they gradually begin to perform certain portions of the operations (i.e., small-bowel portion and gastric portion). However, with the public scorecard posted on government Web sites, it has become progressively more difficult to have fellows function autonomously at the risk of potentially having a higher incidence of complications. The true experience of operating independently may therefore not be experienced by the fellow until after he or she is away from the relatively protected learning environment of the fellowship institution.

Guidelines for Bariatric Privileges

In 2006, The Bariatric Training Committee of the ASBS published the guidelines for granting privileges in bariatric surgery.[34] Surgeons should work at an accredited facility within a multidisciplinary team. The program must demonstrate commitment to long-term follow-up and have a system in place to prevent, monitor, and manage complications. To be credentialed, surgeons need to document 50 cases with satisfactory outcomes from residency and/or fellowship under the supervision of an experienced bariatric surgeon.

While variation still exists across fellowship programs, the guidelines for an ideal fellowship training in bariatric surgery have also been proposed. Such a fellowship would offer opportunities for didactic interactions, journal club, peer-review conferences, and resident teaching rounds. Topics covered may include epidemiology, history, physiology, preoperative evaluation, psychological assessment, postoperative management, restrictive and malabsorptive procedures, revisional surgery, managing postoperative complications, nutritional deficiencies, and outcomes. Additionally, fellows participate in M&M conference, including review of all complications. During a 1-year fellowship, trainees contribute to the advancement of knowledge within the specialty of bariatric surgery with publication of abstracts, manuscripts, and oral presentations. Moreover, the clinical fellow participates in at least 100 weight-loss operations. Ultimately, the fellow logs the surgical cases and complications for review by the program director and the Fellowship Council during a program accreditation.

Despite the fact that bariatric surgery restores health and can be done safely, the payors, the press, and even to some extent the public remain highly critical and skeptical of bariatric surgery, maintaining zero tolerance for bad outcomes. The mortality rate for bariatric surgery varies by patient population, operation performed, and the expertise of the surgeon and experience of the institutional team performing the operation. Surgeons must take the high road and follow practices that ensure the safest conduct of bariatric surgery to the largest number of patients. Training the next generation of surgeons is critical to safely imparting lessons learned in bariatric surgery.

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A Prospective Evaluation of an Algorithm Incorporating Routine Preoperative Endoscopic Ultrasound-Guided Fine Needle Aspiration in Suspected Pancreatic Cancer

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Abstract
Background Whether tissue diagnosis is required in the preoperative evaluation of patients with suspected pancreatic cancer remains controversial. We prospectively evaluated the accuracy, safety, and potential impact on surgical intervention of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in the preoperative evaluation of suspected pancreatic cancer.
Methods All patients who underwent EUS-FNA at our institution (n=547) over a 4.5-year period were enrolled. Patients underwent surgical exploration and resection based on their comorbidity status, evidence of resectability based on spiral computed tomography (CT) and EUS imaging reviewed in a multidisciplinary approach.
Results Of 547 patients enrolled (median age 64 years, 60% male), 49% presented with obstructive jaundice. The operating characteristics of EUS-FNA of solid pancreatic masses were: sensitivity 95% (95% CI: 93.2–95.4), specificity 92% (95% CI: 86.6–95.7), positive predictive value 98% (95% CI: 97–99), negative predictive value 80% (95% CI: 74.9–82.7). The overall accuracy of EUS-FNA was 94.1% (95% CI: 92.0–94). Of the 414 true positive patients by EUS-FNA, 138 (33%) were explored. Of patients deemed operable by combined imaging, 42% had surgical resection. Eighty-two percent of true positive patients were ultimately found inoperable and received palliative therapy or chemotherapy. Of the 94 patients with true negative cytology based on extended follow-up, only 7 (7%) underwent surgical resection. Of those with false negative diagnoses (n=24), 5 patients underwent exploration/resection based on detection of mass lesions by EUS. The remaining patients had unresectable disease. Mild self-limiting pancreatitis occurred in (0.91%).
Conclusions EUS-FNA is a safe and highly accurate method for tissue diagnosis in suspected pancreatic cancer. This approach allows for preoperative counseling of patients, minimizing surgeon's operative time in cases of unresectable disease, and avoids surgical biopsies in the majority of patients with inoperable disease. In addition, it allows for conservative management of patients with benign biopsies. We still, however, recommend exploration of patients with clinical scenario suspicious for pancreatic cancer, a mass found on EUS or CT, but inconclusive or negative cytology.

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Keywords Pancreatic cancer · Fine needle aspiration · Cytology · Endoscopic ultrasound

Introduction

Carcinoma of the pancreas is a devastating disease and is the fourth leading cause of cancer death in the United States [1]. In 2005, it is estimated by the American Cancer Society that 32,180 patients will develop pancreatic cancer, and 31,800 will die from the disease. Despite advancement in imaging and surgical techniques, pancreatic cancer is rarely curable and has an overall 5-year survival of less than 4%[1,2]. For patients with localized disease tumor size less than 2 cm with no lymph node metastasis and surgical resection, the actuarial survival rate is 18–24%[3]. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has emerged as a safe and accurate technique for tissue diagnosis in patients with suspected pancreatic cancer[4–6]. We have previously reported that EUS-guided FNA is an accurate and cost-effective modality for the initial and secondary diagnosis for patients with suspected pancreatic cancer[4,7] Moreover, EUS-FNA has replaced endoscopic retrograde cholangiopancreatography (ERCP) and brush cytology as the endoscopic test of choice for tissue acquisition because of higher success rates and lower risk of post-procedural complications, mostly pancreatitis, offered by EUS-FNA, especially in patients without obstructive jaundice[8]. Whether tissue diagnosis is required in the preoperative evaluation of patients with suspected pancreatic cancer remains controversial. We prospectively evaluated the accuracy, safety, and potential impact on surgical intervention of EUS-FNA in the preoperative evaluation in patients suspected to have pancreatic cancer.

Materials and Methods

We maintain an Institutional Review Board (IRB)-approved prospective data base at the University of Alabama at Birmingham Endoscopic Ultrasound Program (UAB) strictly for research purposes. The Institutional Review Board of UAB approved this research protocol for EUS-FNA of solid pancreatic masses. All patients referred for evaluation of suspected pancreatic cancer were enrolled in this study (July 2000 until December 2005). All patients provided written informed consent to undergo the procedure. Patients were placed in the left lateral decubitus position and were sedated with intravenous meperidine, midazolam, and/or droperidol according to the judgment of the endoscopist as previously described[4]. Once a solid focal pancreatic lesion was identified, EUS-FNA was performed with a curvilinear echoendoscope (Olympus UC-30P, or UCT 140, Melville, NY) as previously described[4] (Figs. 1, 2 and 3). In addition, features of chronic pancreatitis were recorded as previously defined. Patients whose pancreas exhibited four or more features were considered to have evidence for chronic pancreatitis[9]. Color Doppler sonography was performed to exclude intervening vascular structures and

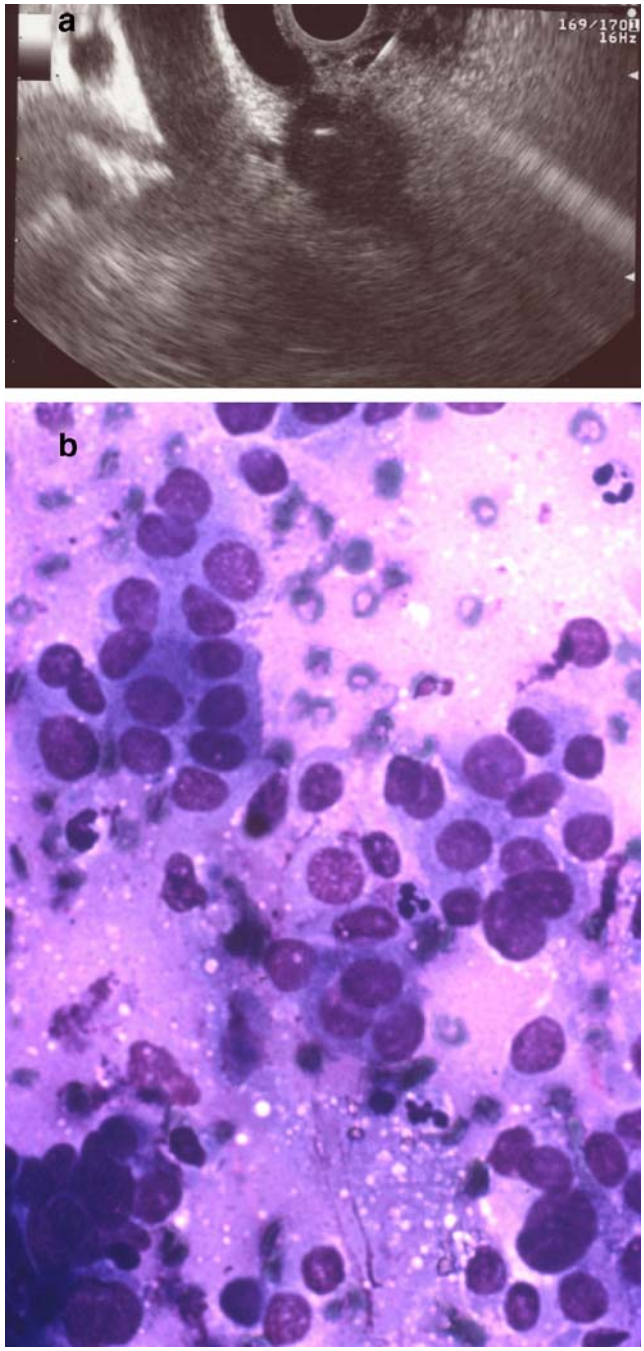

Figure 1 **a** A 59-year-old patient presents with obstructive jaundice. ERCP shows distal CBD stricture. Brushing cytology was negative. Pancreatic protocol CT scan showed no mass. EUS-FNA identified a 19×18 mm hypoechoic mass in the head of the pancreas leading to CBD obstruction. EUS-FNA cytology confirms the presence of carcinoma. **b** Cytologic features consistent with malignancy (Papanicoulou stain 40×). The patient underwent R0 Whipple's resection.

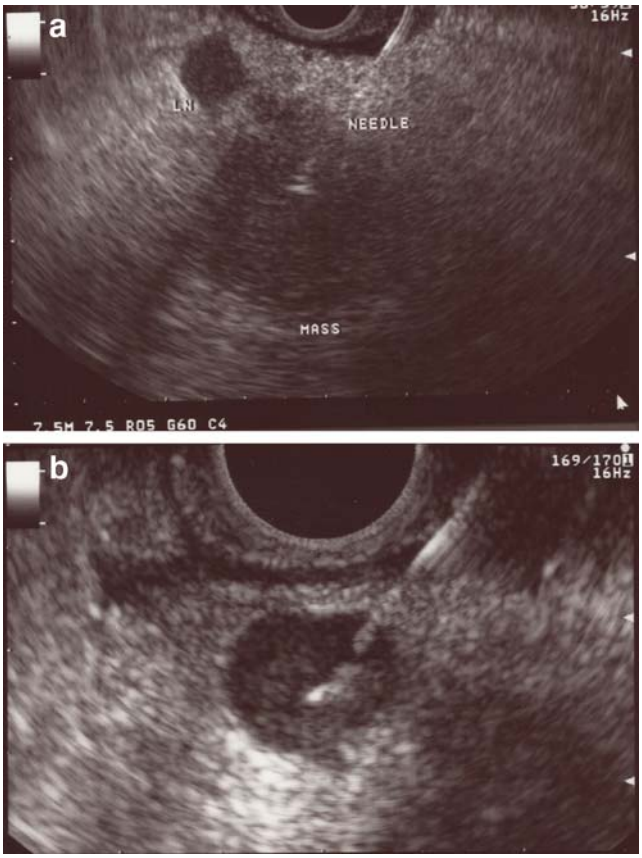

Figure 2 **a** This patient presents with obstructive jaundice. EUS-FNA identified pancreatic adenocarcinoma with N1 disease. **b** EUS-FNA of peri-pancreatic lymph nodes showing carcinoma. The patient underwent preoperative neoadjuvant therapy (Olympus UC-30 P, scanning at 5 Mhz).

to choose a vessel-free needle track. All EUS-FNAs were performed utilizing a 22-gauge needle (Echotip, Wilson-Cook, Winston Salem, NC, or the Olympus EZ shot 22-gauge needle, Melville, NY) inserted through the working channel of the echoendoscope as previously described[4]. No suction was applied during biopsy unless the initial attempt yielded no cellular material (<5% of the cases). The aspirates were then placed onto glass slides and were prepared as previously described[4]. The smears were reviewed immediately by a cytopathologist on site to ensure specimen adequacy. At least five passes were obtained from each target lesion unless cytology evaluation performed on site confirmed the presence of malignant cells. We utilized the final cytology reports in our analysis. The cytologic diagnoses were classified into either malignant or benign (including chronic pancreatitis). The cytologic diagnoses were then categorized into the following groups: positive for malignancy, suspicious for malignancy, atypical cells-indeterminate for malignancy, benign/reactive process, or non-diagnostic. Final diagnosis of pancreatic cancer was defined by the following criteria: (1) histologic evidence of pancreatic cancer, (2) initial malignant cytology with a clinical and/or imaging follow-up that was consistent with the diagnosis of pancreatic cancer, such as death from disease or clinical progression. Lesions were considered benign if there was a lack of tumor progression for at least 6 months in conjunction with continued patient well-being. Reference standard for classification of disease included: surgical resection, death from pancreatic cancer, and repeat radiologic and/or clinical follow-up.

Complications were defined as any deviation from the clinical course after EUS that was associated with the procedure as observed by the endosonographer, the recovery room nurses, or reported by the patients[10,11]. Excessive bleeding at the FNA site, perforation, hypotension, and the need for reversal medication was carefully documented. Any symptoms reported by the patient during recovery time were carefully assessed and documented by the endoscopist. Patients with abdominal pain were asked to be evaluated by their referring physicians or by the endoscopist depending on convenience to the patients. For these patients, serum amylase and lipase were initially performed; abdominal computed tomography (CT) scan was performed if symptoms persisted. Acute pancreatitis was defined as upper abdominal pain associated with nausea or vomiting and accompanied by at least threefold elevation of serum amylase or lipase. Immediate (intra-procedural and in the recovery area) complications were evaluated in all patients. Serious adverse events were defined as over sedation requiring the administration of a reversal agent and those that resulted in a physician or emergency department visits hospitalization or death as we previously described[4].

Patients clinical history, imaging findings (CT, EUS) were reviewed in a multidisciplinary approach in a weekly conference. The decision to explore or operate on the patient was left to the referring surgeon based on evidence of resectability or lack of the need for biliary bypass and comorbidity.

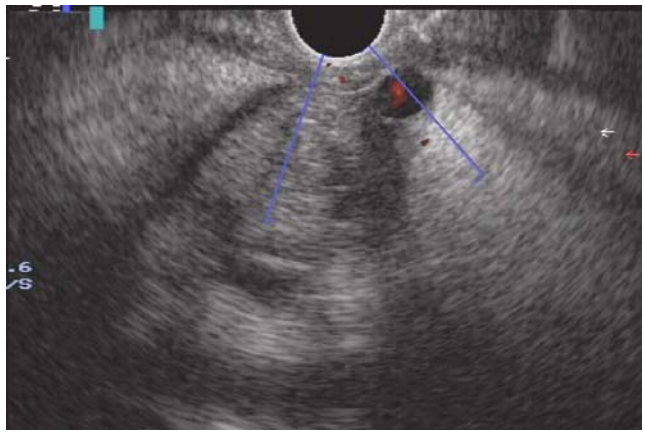

Figure 3 Curvilinear echoendoscope showed splenic artery invasion-EUS-FNA confirms carcinoma. The patient underwent preoperative neoadjuvant therapy (Olympus UC-30 P, scanning at 5 Mhz).

Table 1 Clinical Presentation and Investigations Before EUS-FNA

Characteristic	Number of Patients and Percentage (%); *N*=547
Pain in abdomen	
Yes	365 (66.7)
No	182 (33.3)
Pancreatitis attack	
Yes	45 (8.2)
No	502 (91.8)
Weight loss	
Yes	435 (79.5)
No	112 (20.5)
Jaundice	
Yes	268 (49.0)
No	279 (51.0)
Satiety	
Yes	68 (12.4)
No	479 (87.6)
Prior CT done	
Yes	454 (83.0)
No	93 (17.0)
Prior tissue diagnosis attempt	
Yes	217 (39.97)
No	328 (59.96)
Unknown	2 (0.37)

Statistical Analysis

Continuous variables were reported as means (with medians) and standard deviation, while categorical variables were reported as proportions. Dichotomized variables were compared using Fisher's exact two-tailed test and continuous variables using Mann–Whitney–Wilcoxon (MWW) test. Statistical significance was set at 0.05. The analysis was conducted with SAS statistical software (version 9.0 Cary, NC, USA).

Results

Of 547 procedures performed during the study period (median age=64 years, males=60%, whites=76%), 49% presented with obstructive jaundice. The clinical presentation and investigations before EUS-FNA of the cohort of patients are shown in Table 1. Abdominal pain, acute pancreatitis, weight loss, were present in 67, 8, and 79%, respectively. Notably, 39% of the patients had prior attempt at tissue diagnosis, mostly by ERCP brushing (85%) or other image-guided biopsy before EUS-FNA (15%). The mass characteristics as imaged by EUS are found in Table 2. Sixty-one percent of the masses were found in the head or uncinate of the pancreas, while 39 percent were present in the body or the tail of the gland. The mean diameter of the mass was 36 mm. The median number of EUS-FNA passes was 3. Coexisting EUS features of pancreatitis were present in 17% of the cases. The mean follow up for the cohort and for those with benign disease were 330 days (SD 311 days) and 531 days (SD 368 days), respectively.

The final diagnosis on long term follow-up was: adenocarcinoma of the pancreas (73%), other lesions including neuroendocrine tumors (7.3%), benign or chronic pancreatitis (19%), and indeterminate in 1%. EUS-FNA cytology reading was malignant (69%), atypical/suspicious (9%), benign 20%, and failed/indeterminate 1% (Table 3). The operating characteristics of EUS-FNA of solid pancreatic masses were: sensitivity: 95% (95% CI: 93.2–95.4), specificity 92% (95% CI: 86–6-95.7), positive predictive value 98% (95% CI: 97–99), negative predictive value 80% (95% CI: 74.9–82.7). The overall accuracy of EUS-FNA was 94.1% (95% CI: 92.0–94).

A total of 11 patients (2%) suffered from a major complication: acute pancreatitis (0.9%) of which two patients were hospitalized and one patient recovered with outpatient analgesics. Three patients were admitted for severe pain after the procedure, all of whom were treated with analgesics and were subsequently discharged with no sequela. Two patients developed fever and were admitted for intravenous antibiotics; one patient recovered with IV

Table 2 Characteristics of Mass and Procedure

Characteristic	Number of Patients and Percentage (%); *N*=547
Location	
Head	334 (61.1)
Other	213 (38.9)
Larger axis (mm)	
Mean (SD)	35.86 (42.8)
Median (IQR)	33 (14)
Number of passes	*N*=542[a]
Mean (SD)	3.23 (2.3)
Median (IQR)	3 (4)
FNA reading (initial)	
Benign	111 (20.3)
Atypical	24 (4.4)
Suspicious	25 (4.6)
Malignant	380 (69.5)
Failed/ Indeterminate	7 (1.3)
Final diagnosis	
Benign mass/ Pancreatitis	103 (18.8)
Adenocarcinoma	398 (72.8)
Other	40 (7.3)
Indeterminate	6 (1.1)
EUS finding of CP	
Yes	89 (16.3)
No	458 (83.7)

[a] "Failed" procedures (n=4) and a procedure (n=1) with "missing information" excluded

Table 3 Initial Cytopathology and Final Diagnosis of Solid Pancreatic Mass Lesions

EUS-FNA Cytology	Final Diagnosis			
	Benign	Malignant	Indeterminate/ Unknown	Total
Benign	91	17	3	111
Atypical	8	15	1	24
Suspicious	1	22	2	25
Malignant	2	379	0	381
Failed/inadequate	1	4	1	6
Total	103	437	7	547

antibiotics and the other required surgical debridement for necrosis. One patient required the use of reversal medication.

A total of ten patients had minor complications after the procedure: sore throat ($n=1$), vomiting ($n=1$), abdominal pain ($n=5$), fever ($n=1$), exaggerated bleeding ($n=2$) at the site of the biopsy (that was not clinically apparent) were among the symptoms reported by the patients after the procedure.

Of the 414 patients with true positive biopsies, 82% were deemed inoperable in the final analysis. Of the 414 true positive patients by EUS-FNA, 138 (33%) were explored. Of the explored patients, that were deemed resectable by combined imaging, 43% had surgical resection. Sixty one percent received palliative therapy or chemotherapy. (See algorithm in Fig. 4). Of the 94 patients with true negative cytology based on extended follow up, only 7 (7%) underwent surgical resection. Of those with false negative diagnoses ($n=24$), 5 patients underwent exploration/resection based on detection of mass lesions by EUS. The remaining patients had unresectable disease by combined EUS and CT criteria.

Discussion

Image-guided fine needle aspiration has been traditionally been limited to pancreatic cancer patients with unresectable disease. Arguments against preoperative fine needle aspiration and tissue diagnosis have been advocated due to inaccuracies of these methods, potential complications, high false negative rates and lack of evidence that a preoperative biopsy can alter management. Currently, patients who have the clinical presentation and imaging supportive of the diagnosis of pancreatic cancer are offered

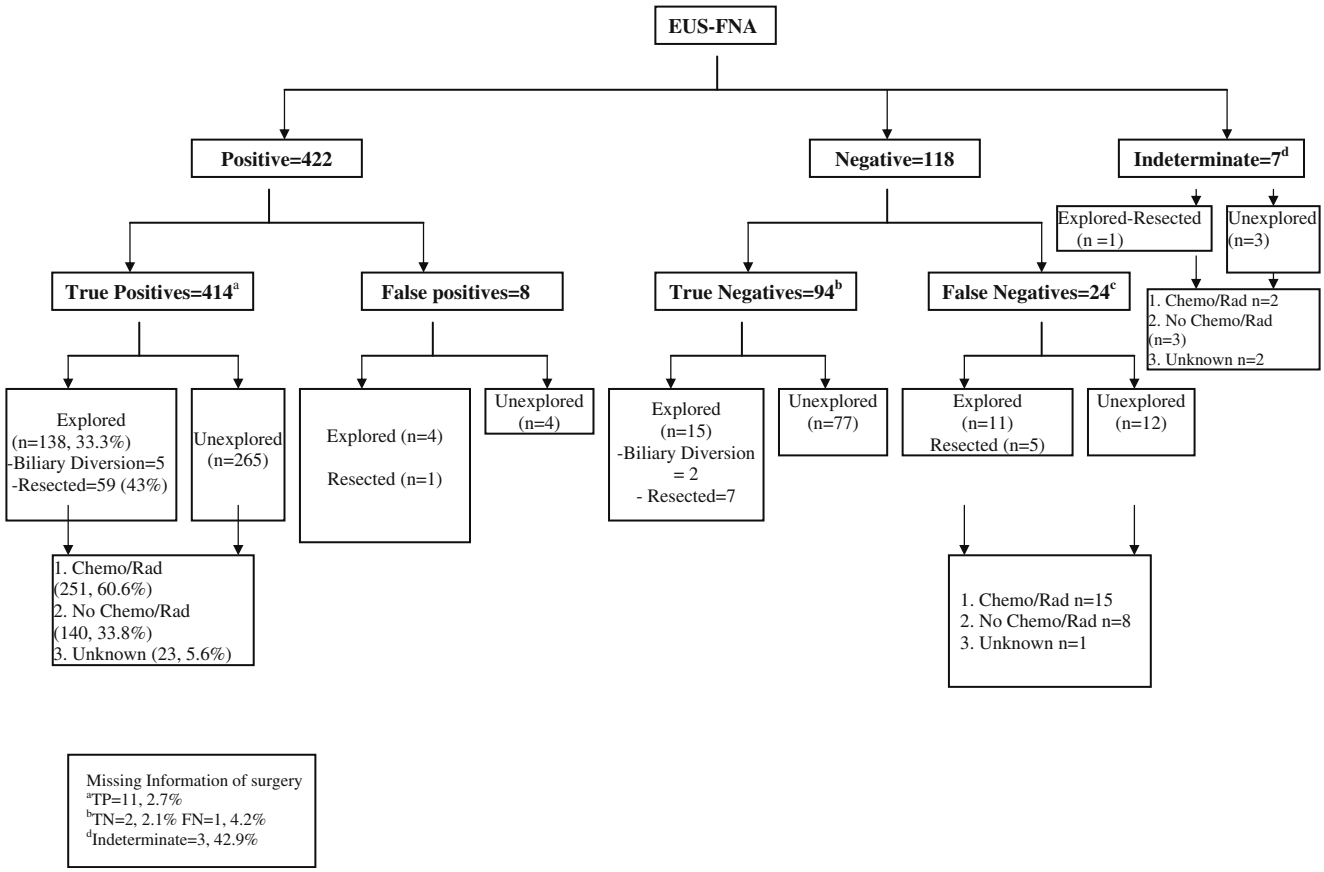

Figure 4 EUS-FNA-based treatment algorithm of patient with pancreatic cancer from this cohort.

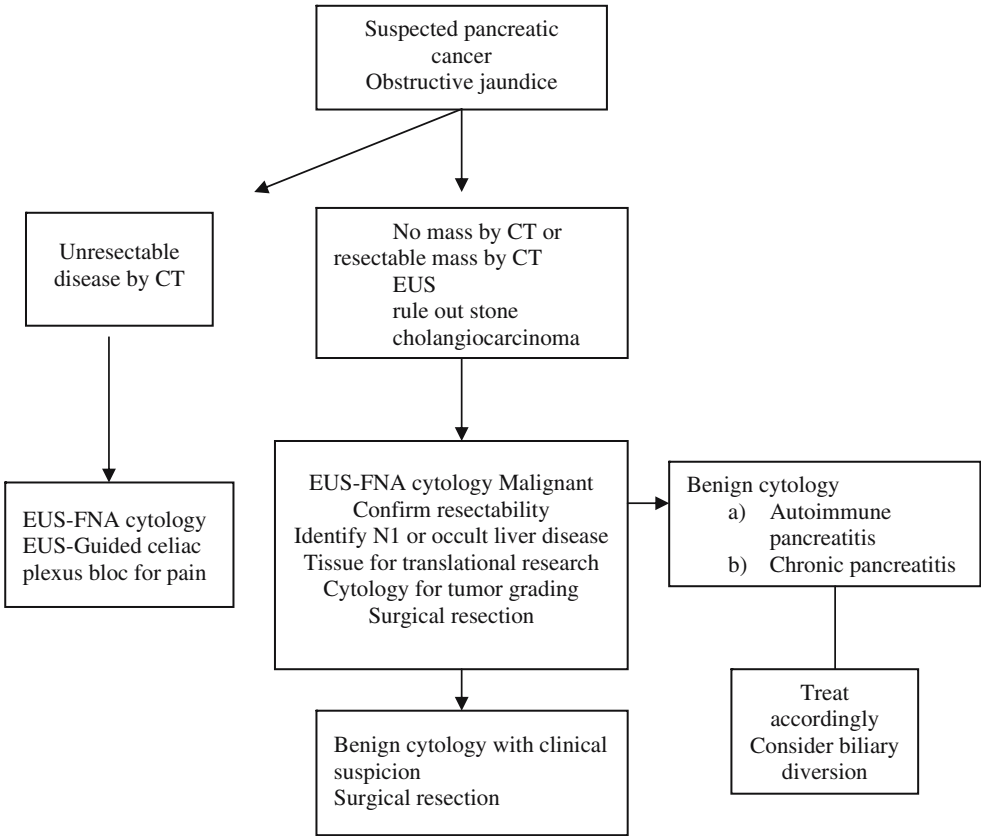

Figure 5 Proposed algorithm for EUS-FNA based approach in patients with suspected pancreatic cancer.

an exploration, and if confirmed resectable in the operating room, they undergo surgical resection.

In this investigation, according to our current set up, we show that EUS-FNA is a safe procedure with a high degree of accuracy. The operating characteristics of EUS-FNA of solid pancreatic masses were: Sensitivity: 95% (95% CI: 93.2–95.4), specificity 92% (95% CI: 86.6–95.7), positive predictive value 98% (95% CI: 97–99), negative predictive value 80% (95% CI: 74.9–82.7). The overall accuracy of EUS-FNA was 94.1% (95% CI: 92.0–94). Moreover, we have extensively documented acute and 30-day complications associated with EUS-FNA.[4,12,13] The technique, in our hands, has an acceptable and a superior safety profile compared to other imaged-guided percutaneous approaches[14,15].

Pancreatitis remained the most feared complication, as it might delay surgery and renders an originally resectable tumor unresectable; however, in this large series, it did not affect any of our patients' ability to undergo surgical resection. Seeding has been reported but is exceedingly rare[16]. Data, however, suggest that EUS-FNA has lower risk of seeding compared to CT-guided biopsy.[17] This can be explained by the close proximity of the echoendoscope to the pancreatic, mass and hence, a shorter distance to the mass lesion.

Advantages of preoperative EUS-FNA include: obtaining tissue diagnosis in patients with unresectable pancreatic cancer, sampling peri-pancreatic lymph nodes and thus offering this group of patients neoadjuvant therapy, proving different types of cytology such as lymphoma, islet cell tumor, small cell carcinoma or metastatic disease that require a different management strategy; proving that the patient has autoimmune pancreatitis or chronic pancreatitis, and thus, altering the therapy or the type of surgery, counseling elderly patients and their families with certainty before surgery. In addition, EUS can be used to palliate pain in the same sitting by performing celiac plexus neurolysis at the time of initial staging if patient is found in operable[18] Moreover, our group has shown that cytologic features and differentiation predicts survival in patients with pancreatic adenocarcinoma[19]. Finally, EUS-FNA provides the opportunity to obtain tissue for translational research. (Fig. 5)Our ability to improve survival in patients with pancreatic cancer hinges on development of new therapies that are more effective in the treatment of this deadly disease. In this largest series to date, 82% of the patients with true positive diagnosis in this cohort were inoperable; thus, this spared intraoperative biopsies in the majority of patients.

Disadvantages of EUS-FNA include: risk of complication, false reassurance to the patient, and missing an opportunity to cure the disease with delay in diagnosis. Another major limitation of EUS is its limited penetration in private practice.

In addition, the technique is operator dependent and has a long learning curve as we have previously demonstrated[20].

We have shown that EUS-FNA has an acceptable safety profile. In addition, our strategy include offering surgery to patients with clinical scenario that is consistent with pancreatic cancer the chance for early resection if a mass is seen by EUS and biopsies as false negative due to either technical limitations or sampling error. We believe that EUS and EUS-FNA play a crucial role in the management of patients with pancreatic cancer when used in a multidisciplinary approach.

In conclusion, EUS-FNA is a safe and highly accurate method for tissue diagnosis in suspected pancreatic cancer. This approach allows for preoperative counseling of patients, minimizing surgeon's operative time in cases of unresectable disease, and avoids surgical biopsies in the majority of patients with inoperable disease. It allows also conservative management of patients with benign biopsies. We still, however, recommend exploration for patients with clinical scenario suspicious for pancreatic cancer, a mass found on EUS or CT but with inconclusive or negative cytology.

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Resected Serous Cystic Neoplasms of the Pancreas: A Review of 158 Patients with Recommendations for Treatment

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Abstract
Background Serous cystic neoplasms of the pancreas are regarded as a benign entity with rare malignant potential. Surgical resection is generally considered curative.
Objective To perform the largest single institution review of patients who underwent surgical resection for serous cystic neoplasms of the pancreas in the hopes of guiding future management.
Methods Between June 1988 and January 2005, 158 patients with serous cystic neoplasms of the pancreas underwent surgical resection. A retrospective analysis was performed. Univariate and multivariate models were used to determine factors influencing perioperative morbidity and mortality. Major complications were defined as pancreatic fistula or anastomotic leak, postoperative bleed, retained operative material, or death. Minor complications were defined as wound infection, postoperative obstruction/ileus requiring total parenteral nutrition (TPN), delayed gastric emptying, arrhythmia, or other infection.
Results The mean age of the patients was 62.1 years, with 75% being female. The majority of patients were symptomatic at presentation (63%), with abdominal pain as the most common symptom. Of the 158 patients, 75 underwent distal pancreatectomy, 65 underwent pancreaticoduodenectomy, nine underwent central pancreatectomy, five underwent local resection or enucleation, and four underwent total pancreatectomy. Mean tumor diameter was 5.1 cm. Mean operative time was 277 min. Mean postoperative length of hospital stay was 11 days. One patient was diagnosed at presentation with serous cystadenocarcinoma. The remaining 157 patients were initially diagnosed with benign serous cystadenoma. One of three patients with locally aggressive benign disease later presented with metastatic disease. Resection margins for all 158 patients were negative for tumor, and only one (0.6%) showed lymph node involvement. There was one intraoperative death. The incidence of major perioperative complications was 18%, whereas the incidence of minor complications was 33%. Men were significantly more likely to experience minor perioperative complications (OR=3.74, P=0.008), whereas patients greater than 65 years showed a trend toward fewer major complications (OR=0.36, P=0.09).
Conclusions Surgically resected serous cystic neoplasms of the pancreas are typically seen in asymptomatic women as 5 cm neoplasms and are predominantly benign. Most are resected via either a left- or right-sided pancreatectomy with low mortality risk, but with notable major or

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minor morbidity. Cystadenocarcinoma is a rare finding on initial resection of serous cystic neoplasms. However, initial pathology specimens exhibiting benign but locally aggressive neoplasia may indicate an increased likelihood of recurrence or metachronous metastasis, although this claim is limited by a small patient subpopulation in this study and warrants further review.

Keywords Serous cystic neoplasm of pancreas · Serous cystadenoma · Pancreas resection

Introduction

Serous cystic neoplasms (SCNs) of the pancreas are almost always benign. They are one of the most common primary pancreatic cystic neoplasms, and are distinguished by their perceived lack of malignant potential from mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs).[1] SCNs constitute 10–15% of all cystic masses of the pancreas and 1–2% of all pancreatic neoplasms.[2,3] However, SCNs are being increasingly diagnosed with more widespread use and improving technology of imaging techniques.[4,5] These neoplasms show a predilection for middle-aged and older women and are often discovered incidentally.[6] Symptoms are frequently nonspecific, with abdominal pain being the most common, occurring in 50–60% of all cases.[7] Computed tomography is thought to be the diagnostic test of choice to properly identify serous neoplasm of the pancreas, with SCNs often exhibiting specific classic features.[8] SCNs are typically unifocal and present as large, well-demarcated, often honeycombed cystic masses, which are often small, but can grow as large as 25 cm. Diffuse or multifocal disease is uncommon. The cysts are loculated, contain mucin-free serous fluid, and are surrounded by cuboidal or flattened epithelium.[9]

Unlike MCNs and IPMNs, SCNs are generally regarded as almost always benign, although their potential for malignant conversion remains a topic of debate.[10] Caused in large part by the uncertainty over malignant potential and the natural history of the disease, currently there is no accepted standard of treatment or follow-up for SCNs. For many, observation and routine surveillance are preferred.[11] Some investigators recommend complete resection of all SCNs because of the perceived malignant potential of the disease, the relative frequency of symptoms and complications, and the challenge of an accurate preoperative diagnosis.[2,12,13] Those that utilize a selective approach advocate for resection in the setting of tumors that are symptomatic, poorly defined, and larger sized.[7,14] Indeed, symptomatology appears to be the predominant and only universally accepted indication for operative intervention. In all cases, resection is considered curative, with no postoperative surveillance recommended.

The goals of our large (158 patients) single institution review were to evaluate clinical parameters, pathologic features, and overall patient outcome after resection of SCNs of the pancreas, in the hope of guiding future management.

Methods

Between June 1988 and January 2005, 158 patients with serous cystic neoplasms of the pancreas underwent surgical resection. A retrospective analysis of a database was performed. The study was approved by the Institutional Review Board for Human Research and complied with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Major complications were defined as pancreatic fistula or anastomotic leak, postoperative bleed, retained operative material, or death. Minor complications were defined as wound infection, postoperative obstruction/ileus requiring TPN, bowel obstruction responsive to conservative non-operative treatment, delayed gastric emptying, arrhythmia, or other infection. Follow-up data were collected from postoperative admissions and/or clinic visits. Univariate and multivariate models were used to determine factors influencing perioperative morbidity and mortality. The chi square test was used for comparison between categorical outcome variables versus categorical independent variables, whereas *t* test was used to compare between continuous outcome variables versus categorical independent variables. Multiple logistic regression was used in final analysis. Statistical significance was defined as $p<0.05$. Statistical analysis was performed using Stata 9. Data are given as mean ± standard deviation, where appropriate.

Results

Demographics

Table 1 outlines the patient population in our series. The mean age of patients was 62.1±13.3 years, with a range of 26 to 89 years of age. Most patients were non-Hispanic Whites (81%). The majority of patients (75%) were female. There was no significant difference in age of presentation between males and females.

Table 1 Patient Characteristics

	n (%)	Mean±SD
Total patients	158	
Sex		
Male	40 (25)	
Female	118 (75)	
Age (years)		62.1±13.2
Symptomatic	101 (64)	
Abdominal pain	75 (47)	
Weight loss	22 (14)	
Nausea/vomiting	10 (6)	
Jaundice	6 (4)	
Gastrointestinal bleed	3 (2)	
Operation		
Distal pancreatectomy, splenectomy	75 (47)	
Whipple	65 (41)	
Central pancreatectomy	9 (6)	
Local resection or enucleation	5 (3)	
Total pancreatectomy	4 (3)	
Tumor size (cm)		5.1±3.7
Operative time (minutes)		277±117
Postoperative hospital stay (days)		11.3±8.9
Death	1 (0.6)	
Major complication	29 (18)[a]	
Hemorrhage	2 (1.2)	
Pancreatic leak	21 (13)	
Bile leak	5 (3)	
Retained operative material	1 (0.6)	
Minor complication	52 (33)[b]	
Wound infection	8 (5)	
Delayed gastric emptying	5 (3)	
Postoperative ileus	4 (2)	
Arrhythmia	8 (5)	
Other infection	21 (12)	
Final pathologic diagnosis		
Serous cystadenoma	156 (98)	
Serous cystadenocarcinoma	2 (2)[c]	

[a] Patients over 65 years showed a trend toward fewer major complications (OR=0.36, P=0.09).
[b] Men had significantly more minor complications than women (OR=3.74, p=0.008).
[c] One patient who was diagnosed with serous cystadenoma on initial resection later recurred and was therefore reclassified with cystadenocarcinoma.

Presentation

Most patients presented with symptoms (64%). The most common symptoms were abdominal pain (74%), weight loss (22%), nausea/vomiting (10%), jaundice (6%), and GI bleed (3%). Men tended to be symptomatic more than women (45% of men versus 34% of women, not significant). Symptoms did not correlate with location or size of tumor. Of 158 patients, 66 (42%) underwent a computed tomography (CT) scan at our institution, whereas the remaining were referred and treated with outside studies. Figure 1 shows two representative CT scans of patients with SCNs.

Operative and Postoperative Course

All patients in this series were treated operatively. Of the 158 patients, 75 (47%) underwent distal pancreatectomy for neoplasm of the body or tail of the pancreas, 65 (41%) underwent pancreaticoduodenectomy for right-sided tumors, nine (6%) underwent central pancreatectomy for neoplasms of the neck or proximal body, five (3%) underwent local resection or enucleation, and four (3%) underwent total pancreatectomy for neoplasms extensively involving the gland. The average operative time was 277 min. The average transfusion requirement was 0.8±3.9 units of packed red blood cells. One operative death was caused by intraoperative hemorrhage from visceral vessels during pancreaticoduodenectomy. Overall, the incidence of major complications was 18%, whereas the incidence of minor complications was 33%. The most common major complication was pancreatic leak or fistula with an incidence of 13%. Men were significantly more likely to have minor complications than women (OR=3.75, p=0.008). Patients >65 years of age also showed a trend toward fewer major complications (OR=0.36, p=0.088). Tables 2 and 3 describe complications by age and gender, respectively. Mean postoperative length of hospital stay was 11.3 days (SD=8.9 days).

Pathology

For 158 resected tumors, the mean tumor size was 5.1±3.7 cm. Tumors were located in the head (42%), body or tail (48%), proximal neck or body (7%), and with diffuse involvement of the entire gland (3%). All resection margins were negative. One patient with a benign SCN exhibited lymph node involvement. Of all 158 patients, one patient at primary resection was noted to have biopsy proven serous cystic neoplasm of the liver and was therefore diagnosed with serous cystadenocarcinoma. The remaining 157 patients were diagnosed at primary resection with serous cystadenoma of the pancreas. Of these 157 patients, three were noted in final pathology report to have "locally aggressive disease" on histologic examination. One of these three patients recurred 13 years later, with disease in the liver and retroperitoneal tissue and was therefore diagnosed with serous cystadenocarcinoma.

Discussion

Classified as a benign neoplasm, serous cystic neoplasm (SCN) of the pancreas is the most common primary cystic

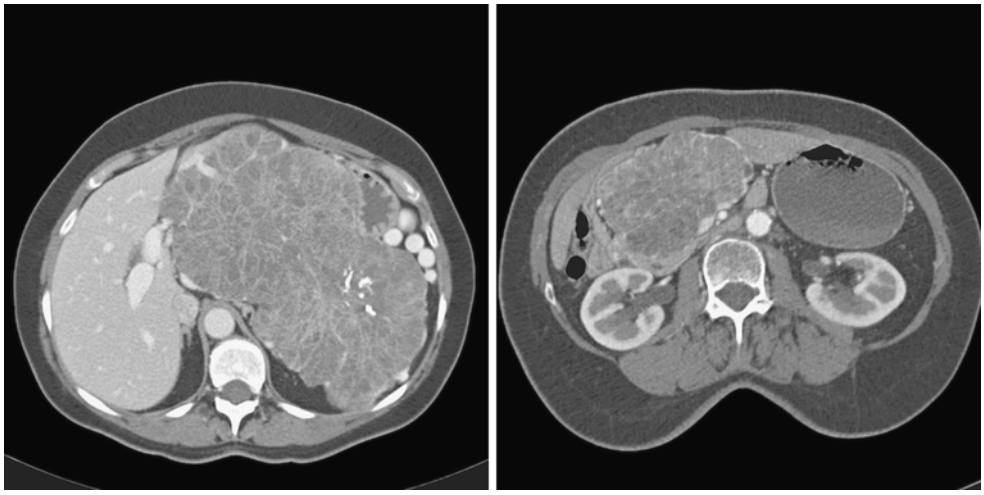


Figure 1 Computed tomography (CT) scans of two patients, each with serous cystadenoma of the pancreas. The image on the right is from a 64-year-old female who presented with abdominal pain. Her 10-cm neoplasm in the head of the pancreas was resected with a Whipple procedure without complication. The image on the left is from a 59-year-old female who presented with pain and "fullness." Her 27-cm mass originating from the tail of the pancreas was resected with a distal pancreatectomy and splenectomy without complication.

neoplasm of the pancreas and accounts for 1–2% of all primary pancreatic neoplasms[1]. SCNs had long been classified with mucinous cystic neoplasms, until Compagno and Oertel[15] as well as Hodgkinson and others[16] defined and separated serous from mucinous cystic neoplasms. They recognized that the mucinous variants such as mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) have a significantly greater malignant potential than SCNs.

George et al.[10] first introduced a malignant variant known as serous cystadenocarcinoma. There have since been multiple case reports of malignant SCN histologically indistinguishable from benign SCN of the pancreas, but marked by malignant behavior, most commonly invasive or metastatic disease.[12,17–23] One study suggested that up to 3% of reported SCNs were in fact malignant or had malignant potential.[8] This malignant variant is defined by the presence of metastases to extrapancreatic organs or tissues.[24] Vascular and perineural invasion, and local invasion into the duodenum or stomach, are not criteria for the diagnosis of malignancy.

There currently exists no consensus for management of SCNs. Many advocate simple surveillance given the almost universally benign nature of the disease and the relative morbidity and mortality associated with resection.[11] However, a schedule of surveillance, which adequately defines when expectant management should yield to intervention, has yet to be agreed upon. Furthermore, because other cystic neoplasms of the pancreas have significant malignant potential, it is imperative that the diagnosis of SCN be certain before committing to expectant management and surveillance. Others support a selective approach to resection based on symptoms, tumor size, or indeterminate preoperative diagnosis, among other factors.[13,14] There continue to be those who support resection of all SCNs. They cite the real, albeit rare, malignant potential, the risk of an incorrect

Table 2 Complications Compared with Age of Patients

	≤65 years	>65 years	*p* value
Number of patients	89	69	
Major complications (total)	19	9	.088
Hemorrhage	1	1	
Pancreatic leak	14	7	
Bile leak	3	2	
Retained operative material	1	0	
Minor Complications (total)	31	19	N.S.
Wound infection	4	4	
Delayed gastric emptying	3	2	
Postoperative ileus	3	1	
Small bowel obstruction*	3	0	
Arrhythmia	5	3	
Deep vein thrombosis	1	0	
Other infection	12	9	

Note that patients greater than 65 years showed a trend toward fewer major complications (OR=0.36, P=0.088).

Table 3 Complications Compared with Patient Gender

	Male	Female	*p* value
Number of patients	40	118	
Major complications (total)	6	23	N.S.
Hemorrhage	0	2	
Pancreatic leak	6	15	
Bile leak	0	5	
Retained operative material	0	1	
Minor complications (total)	17	33	0.008
Wound infection	3	5	
Delayed gastric emptying	1	4	
Postoperative ileus	1	3	
Small bowel obstruction*	1	2	
Arrhythmia	3	5	
Deep vein thrombosis	1	0	
Other infection	7	14	

Note that males had significantly more minor complications than women (OR=3.74, p=0.008).

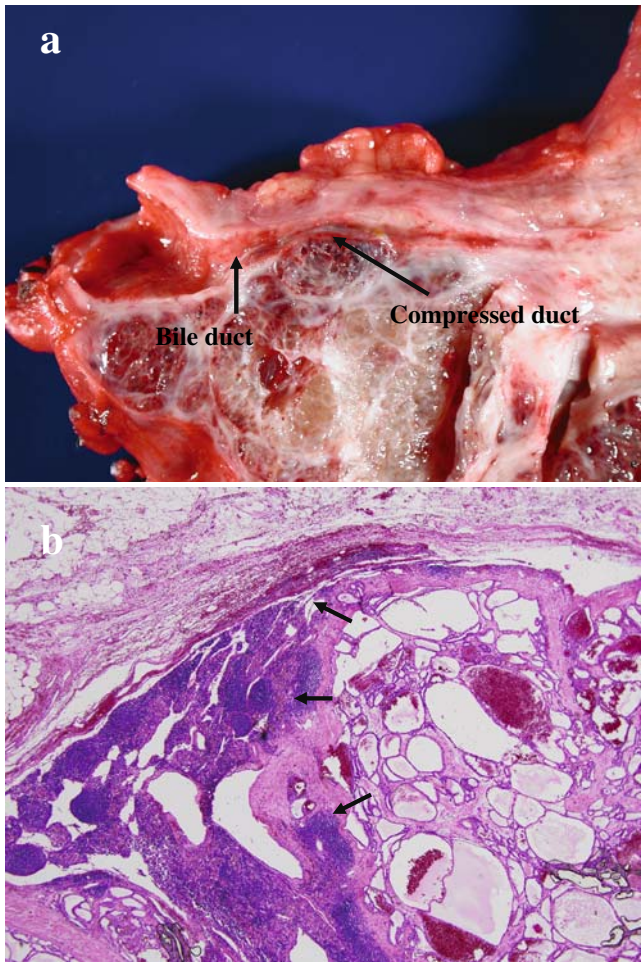
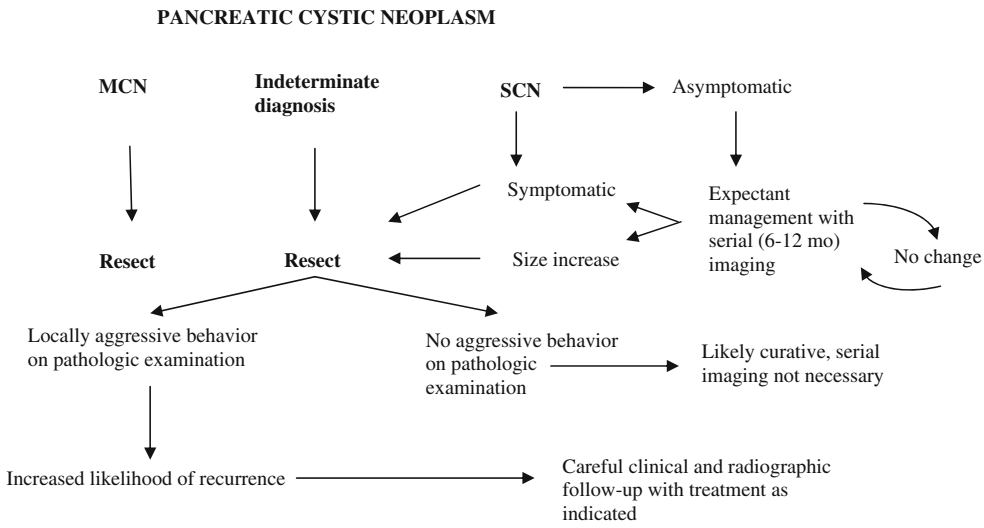


Figure 2 Locally aggressive serous cystic neoplasm (SCN). Although classically benign, SCNs may rarely exhibit locally aggressive behavior. In one patient, tumor compresses the bile duct (a). On microscopic examination, this neoplasm exhibits bland histological appearance, lacking both architectural and cytologic atypia (b). However, this SCN shows uncommon locally aggressive behavior by growing up against and into a neighboring lymph node (arrows).

preoperative diagnosis, and the potential for symptoms and complications. Resection is generally considered curative and no postoperative monitoring is advocated.

Here we report the largest single institution experience with SCNs to date. The mean age of the 158 patients was 62.1 years, with 75% being female (Table 1). This is consistent with previous studies, which have also shown a predilection for the disease in middle-aged to elderly females. Most patients were symptomatic at presentation (64%). The most common symptoms were abdominal pain (47%), weight loss (14%), nausea/vomiting (6%), jaundice (4%), and GI bleed (2%). The proportion of symptomatic patients is similar to or higher than that found in most other reviews.[8,14,15] The higher rate of symptomatic patients may partly be explained by the extensive referral nature of the practice at Johns Hopkins and the fact that all our patients underwent resection. In our series, 42% of the SCNs arose in the head of the pancreas, 48% in the body or tail, 7% in the neck or proximal body, and only 3% of lesions exhibited diffuse involvement of the entire gland. Mean tumor diameter was 5.1 cm, similar to the size found in the contemporary series of Tseng et al.[14]. All resection margins were negative, with only one SCN exhibiting lymph node involvement. There was one intraoperative death, caused by excessive hemorrhage from visceral vessels at the time of attempted pancreaticoduodenectomy. In our experience, surgery for these lesions carried minimum mortality risk (0.6%), but notable major (18%) and minor (33%) morbidity risk. This risk of complications approximates the risk of pancreatic surgery for other conditions (such as adenocarcinoma of the pancreas), but the mortality rate for resection of SCN is less.[25] It is worth noting that males had a significantly greater risk of experiencing minor complications than women. The reasons for this difference are not immediately apparent and warrant further investi-

Figure 3 Proposed approach to the patient with a cystic neoplasm of the pancreas.



gation. No patient died of his or her disease. This fact, in conjunction with the aforementioned risks of surgery, would support a cautious approach to the resection of these neoplasms.

In our series, only 0.6% (1/158) of the patients with an SCN presented initially with metastatic disease. This patient presented with multifocal disease in the pancreas and liver, and was therefore diagnosed with a serous cystadenocarcinoma. Indeed, after resection of her pancreatic tumor, she returned to clinic 1 year later with extensive growth of a biopsy-proven SCN in the liver, which proved nonoperable. Remarkably, both her primary and liver metastases had a histologically bland appearance, lacking both architectural and cytologic atypia. An additional three patients in this study were noted, upon pathologic review, to have "locally aggressive" neoplasms at the time of initial resection. These neoplasms were histologically identical to the more benign behaving tumors, but showed locally aggressive behavior. Locally aggressive behavior describes extension of the neoplasm beyond the pancreas into an adjacent organ such as the duodenum or bile duct, or local invasion into a blood vessel (Fig. 2). Resection margins were negative for these three tumors. One of these three patients returned in follow-up 13 years after resection of the primary tumor, with biopsy-proven recurrence in the liver and retroperitoneal soft tissue. Again, both the primary and the liver metastases had a histologically bland appearance, lacking both architectural and cytologic atypia. As this represented an extrapancreatic recurrence, the diagnosis for this patient was retrospectively adjusted to reflect a serous cystadenocarcinoma. Thus, a total of two of the 158 patients (1.3%) in this series either presented with or ultimately developed metastatic disease.

Currently, resection for SCN is considered curative, with no follow-up beyond postoperative care recommended. Here we report one case of recurrence after resection of the primary tumor. This tumor was one of three that exhibited locally aggressive behavior at the time of initial resection. Only two of the remaining 157 resected specimens exhibited a similar pattern. Locally aggressive growth therefore may offer an important clue as to which neoplasms have the potential to recur as cystadenocarcinoma. It will be interesting to follow the two additional patients whose tumors exhibited locally aggressive growth. At the time of submission, these two patients had not undergone any additional clinical or radiographic follow-up at our institution. Their current lack of metastatic disease or recurrence may be explained by the fact that their primary resections were relatively recent (1999 and 2000) compared to the primary resection for the patient whose disease later recurred (1992). Further follow-up and search for this tumor characteristic is warranted, as the presence of locally aggressive behavior may help identify a subpopulation of patients who do not have metastases at presentation, but for whom additional follow-up surveillance is warranted.

The proper management of patients with a SCN remains elusive. The first step is to distinguish this lesion from the clearly premalignant lesions: IPMNs and MCNs. Beyond that, there are divergent paths. Based on our findings, we propose the following algorithm (Fig. 3). If SCN cannot confidently be distinguished from MCN or IPMN, the patient should undergo resection. When the diagnosis of SCN is confidently determined based on clinical and radiographic evidence, perhaps only symptomatic tumors should be resected. If the decision is made to avoid resection initially, we do recommend serial imaging at a 6- to 12-month interval, with resection for growth (more than 1 cm change in diameter) or the development of symptoms. Postresection, gross and microscopic review of the neoplasm should document not only the presence or absence of metastases, but also any locally aggressive growth as previously defined. For neoplasms exhibiting this rare characteristic, patients should be counseled that although in most cases SCNs are cured with primary resection, a small subpopulation of cases may recur, and may require additional imaging follow-up and treatment, as indicated.

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The Pathogenesis of Barrett's Esophagus: Secondary Bile Acids Upregulate Intestinal Differentiation Factor CDX2 Expression in Esophageal Cells

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Abstract
Introduction Clinical evidence strongly suggests that bile acids are important in the development of Barrett's esophagus, although the mechanism remains unknown. Caudal-related homeobox 2 (CDX2) is a transcription factor recently implicated in early differentiation and maintenance of normal intestinal epithelium and is suggested to play a key role in the pathogenesis of intestinal metaplasia in Barrett's esophagus.
Objective The aim of this study was to investigate the effect of primary and secondary bile acids on CDX2 mRNA expression in human esophageal cells.
Methods Human esophageal cells: (1) squamous, immortalized by SV40 (Het-1A); (2) adenocarcinoma (SEG-1); and (3) squamous cell carcinoma (HKESC-1 & HKESC-2), were exposed in cell culture for 1–24 h to 100–1,000 μM deoxycholic, chenodeoxycholic, and glycocholic acids. Total RNA was extracted before and after bile acid treatment and reverse transcribed to cDNA. CDX2 mRNA expression was determined by both quantitative real-time and reverse transcription PCR (RT-PCR).
Results CDX2 mRNA expression was absent before bile acid exposure in all cell lines. CDX2 expression increased in a dose- and time-dependent fashion with deoxycholic and chenodeoxycholic, but not glycocholic, acid in all four cell lines. The maximal induction of CDX2 expression was seen in SEG-1 adenocarcinoma cells. Expression in Het-1A cells also increased significantly as did expression in HKESC-1,2 cells, although to a lesser extent than in adenocarcinoma.
Conclusions These findings show that secondary bile acid stimulation upregulates *CDX2* gene expression in both normal and cancer cell lines. They further support the role of bile acids in the pathogenesis of Barrett's esophagus and link the clinical evidence of a high prevalence of luminal bile acids in Barrett's to expression of the gene thought to be responsible for the phenotypic expression of intestinal metaplasia.

Keywords Barrett's esophagus · Gastroesophageal reflux disease (GERD) · Caudal-related homeobox 2 (CDX2)

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Introduction

The prevalence of Barrett's esophagus (BE), a premalignant epithelium and esophageal adenocarcinoma, has risen rapidly over the past two decades.[1,2] Barrett's is characterized by the replacement of the normal esophageal squamous epithelium with a metaplastic epithelium resembling a more distal intestinal type. It is known to occur almost exclusively in patients with gastroesophageal reflux disease (GERD). The anatomy, physiology, and reflux characteristics distinguishing patients with and without Barrett's esophagus were extensively investigated over the decades of the 1980s and 1990s. The presence of bile acids in the refluxed material has been consistently observed in patients

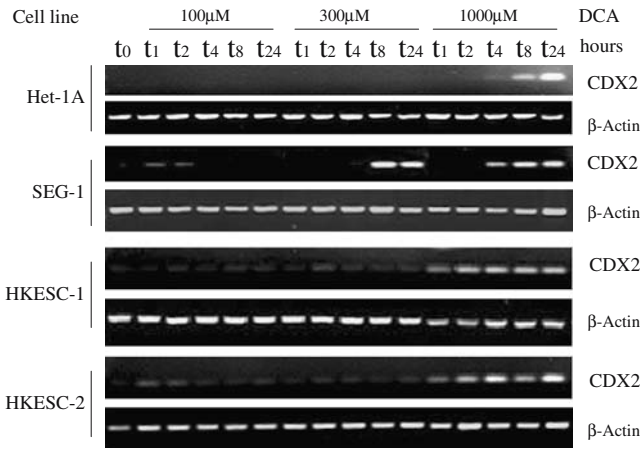


Figure 1 RT-PCR analysis of CDX2 and β-actin mRNA expression in esophageal cells Het-1A, SEG-1, HKESC-1, and HKESC-2 after 100–1,000 μM deoxycholic acid (DCA) exposure for 1–24 h. PCR products were electrophoresed on 2% agarose gel containing ethidium bromide.

with Barrett's esophagus, strongly suggesting that they are important in its pathogenesis. The exact molecular mechanisms underlying this intestinal metaplastic and/or differentiation process remains largely unknown.[2,3]

Caudal-related homeobox 2 (CDX2) is a homeobox transcription factor that plays an important role in the early differentiation and maintenance of intestinal epithelium.[4] Immunohistochemical staining studies have recently confirmed that CDX2 protein is overexpressed in human Barrett's epithelium, indicating that this intestinal transcription factor may be an early feature of intestinal metaplasia during the development of BE.[5,6] Ambulatory esophageal studies using both spectrophotometric and aspiration techniques have shown that there is much higher bile acid exposure in the esophagus of BE patients than in non-Barrett's GERD counterparts.[5] Animal studies have suggested that bile acids may enhance CDX2 expression in rat esophageal keratinocytes in BE.[6] To date, however, there is little evidence of a direct association between bile acids and CDX2 in human esophageal cells. The aim of this study was to investigate whether bile acid exposure can affect CDX2 mRNA expression in a variety of human esophageal cell lines.

Materials and Methods

Cell Lines and Culture

Four human esophageal cell lines (Het-1A, SEG-1, HKESC-1, and HKESC-2) were used in this study. The characterization of these has been described previously.[7–10] Briefly, Het-1A, purchased from the American Type Culture Collection (Manassas, VA), is a human esophageal squamous epithelial cell line immortalized by the SV40 transfection.[7] SEG-1 is a Barrett's esophageal adenocarcinoma cell line (a kind gift from Dr. David Beer, University of Michigan, Ann Arbor, MI).[8] HKESC-1 and HKESC-2 are esophageal squamous cell carcinoma cell lines.[9,10] All four cell lines were cultured in low glucose Dulbecco's Modified Eagle Medium (DMEM; Invitrogen, Carlsbad, CA), supplemented with 10% fetal bovine serum (FBS; Invitrogen) and 100 U/ml penicillin G and 100 μg/ml streptomycin (Invitrogen), at 37°C in a humidified incubator containing 5% CO_2. The cells were detached from the flasks before subculturing by the removal of the medium and the addition of 1 ml of 0.25% trypsin for 3 to 10 min.

Treatment of Cell Lines with Bile Acids

At 70% confluence, cells were placed in serum-free DMEM for 24 h before bile acid exposure. The four esophageal cell lines were exposed to 100, 300, and 1,000 μM deoxycholic acid (DCA), chenodeoxycholic acid (CDC; Sigma, St. Louis, MO), and glycocholic acid (GC; Pfaltz & Bauer, Waterbury, CT) in serum-free medium for 1, 2, 4, 8, or 24 h, respectively. Cells were harvested at the end of each time point with 0.05% trypsin solution (Invitrogen).

RNA Extraction and cDNA Synthesis

Total RNA was extracted using the Invitrogen Micro-to-Midi Total RNA Purification System (Invitrogen Life Technologies, Carlsbad, CA) immediately before bile acid exposure

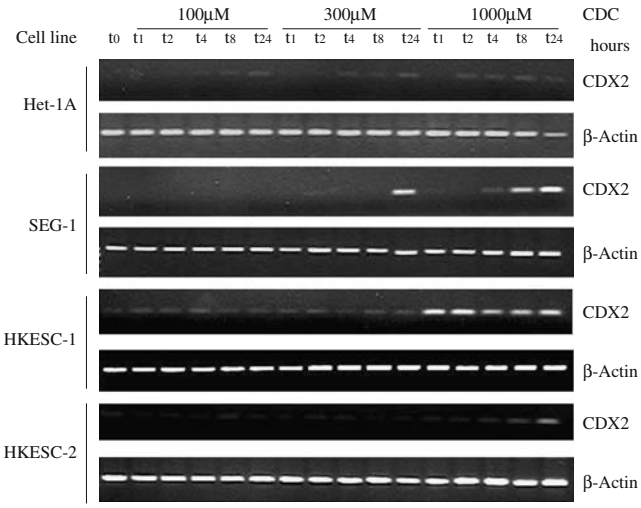


Figure 2 RT-PCR analysis of CDX2 and β-actin mRNA expression in esophageal cells Het-1A, SEG-1, HKESC-1, and HKESC-2 after 100–1,000 μM chenodeoxycholic acid (CDC) exposure for 1–24 h. PCR products were electrophoresed on 2% agarose gel containing ethidium bromide.

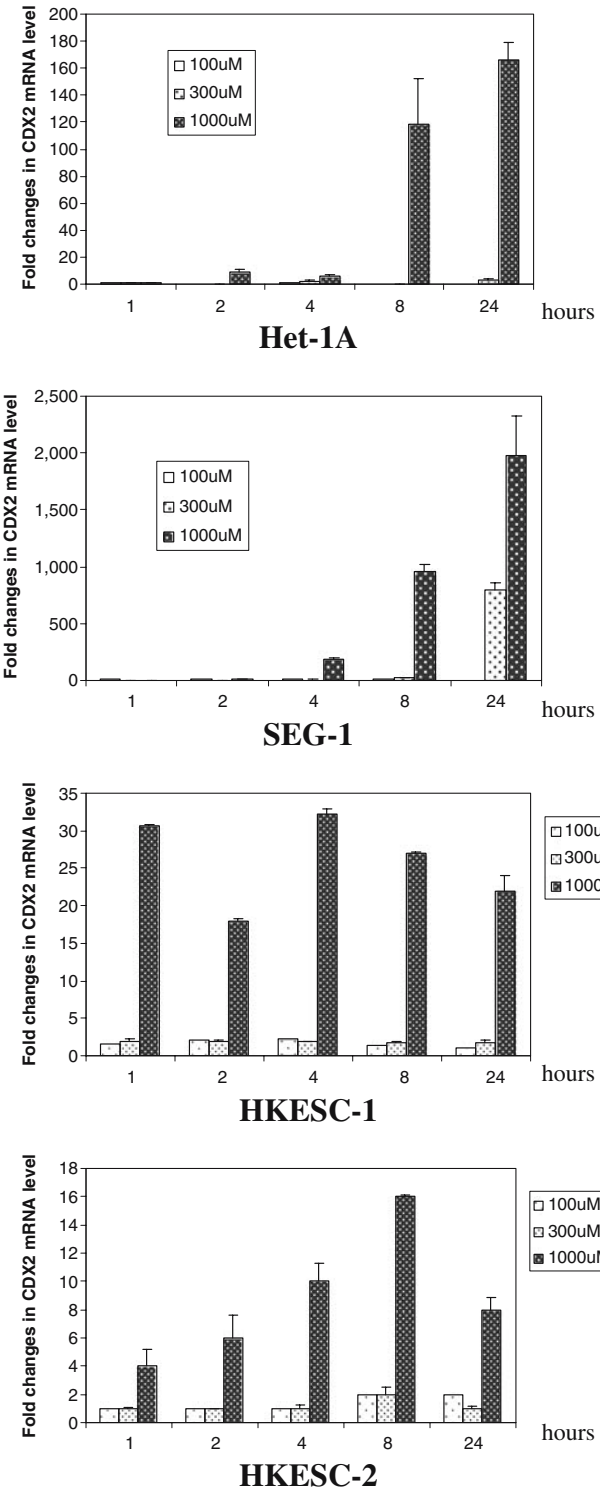


Figure 3 Real-time PCR analysis showing CDX2 mRNA changes in folds in esophageal cells Het-1A, SEG-1, HKESC-1, and HKESC-2 after exposing 100–1,000 μM deoxycholic acid (DCA) for 1–24 h.

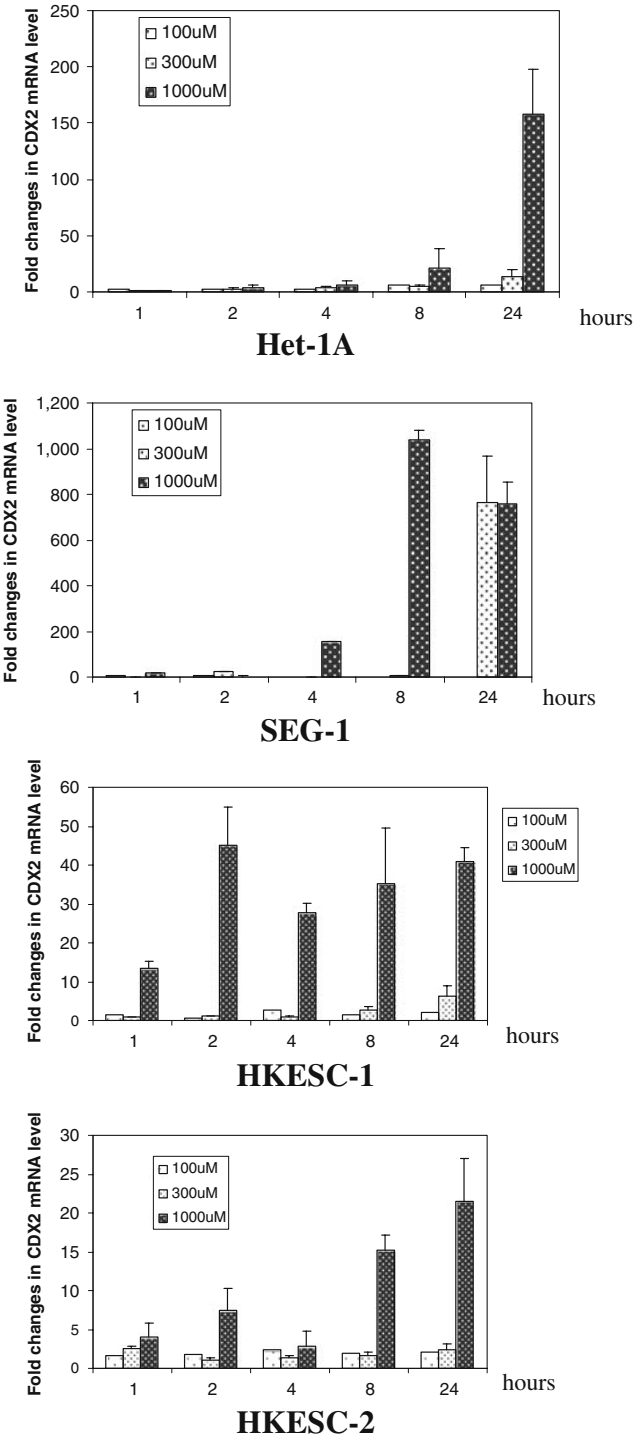


Figure 4 Real-time PCR analysis showing CDX2 mRNA changes in folds in esophageal cells Het-1A, SEG-1, HKESC-1, and HKESC-2 after exposing 100–1,000 μM chenodeoxycholic acid (CDC) for 1–24 h.

(t_0) and at time points 1 (t_1)-, 2(t_2)-, 4(t_4)-, 8(t_8)-, and 24 (t_{24}) h after the end of the bile acid exposure period. Total RNA, 0.25 μg, was reverse-transcribed to cDNA using iScript cDNA Synthesis kit (Bio-Rad Laboratories, Hercules, CA) according to the manufacturer's protocol. The reverse transcribed cDNA was then diluted fivefold in RNAse-free water. Two microliters cDNA thus obtained was used for the PCR.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

Two microliters cDNA were amplified in a 20-μl PCR reaction mixture containing 1×iQ SYBR Green Supermix (Bio-Rad) and 0.5-μM primers. The cDNA was amplified as follows: 95°C for 10 min, followed by 30 cycles of 1 min denaturation at 94°C, 1 min annealing at 55°C (for primers of CDX2) or 58°C (for primers of β-actin), 1 min extension at 72°C. The final step of extension was for 10 min at 72°C. The primers were: CDX2-F, 5′-ACC AGG ACG AAA GAC AAA TAT CGA-3′ and CDX2-R, 5′-TGT AGC GAC TGT AGT GAA ACT CCT TCT-3′; β-actin-F, 5′-CAA ATA TGA GGC ATT GTT ACA GG-3′ and β-actin-R, 5′-TGG TCT CAA GTC AGT GTA CAG GTA A-3′. The primers were synthesized by Integrated DNA Technologies, Inc. (Coralville, IA). The cycle number was optimized for each gene-specific primer pair to ensure that amplification was in the linear range and the results were semiquantitative. Twelve microliters of RT-PCR product were visualized by electrophoresis on a 2% agarose gel stained with ethidium bromide.

Real-Time PCR Quantification of mRNA Expression

Real-time PCR reactions were performed in duplicate with 2 μl cDNA, 1×iQ SYBR Green Supermix(Bio-Rad) and 0.5-μM primers, in a final reaction volume of 20 μl. Real-time PCR was performed using the RotorGene real time DNA amplication system (Corbett Research, Sydney, Australia). The primers for CDX2 were as those used in RT-PCR. The primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were GAPDH-F, 5′-GGC TCT CCA GAA CAT CAT CCC TGC-3′ and GAPDH-R, 5′-GGG TGT CGC TGT TGA AGT CAG AGG-3′. The PCR protocol includes initial denaturing 95°C for 15 min, followed by 45 cycles of 95°C for 1 min, 60°C (for CDX2) or 55°C (for GAPDH) for 1 min, and 72°C for 1 min. Detection of the fluorescent product was carried out at the end of the 72°C extension. PCR products were subjected to a melting curve analysis, and the data were analyzed and quantified with RotorGene analysis software.

Results

CDX2 mRNA Expression After Bile Acid Exposure

Representative RT-PCR results after exposure to deoxycholic acid (DCA) are shown in Fig. 1. CDX2 mRNA expression was minimal to absent before bile acid exposure in all four cell types. In normal esophageal squamous cells (Het-1A), CDX2 expression was highly upregulated by 1,000-μM DCA treatment for 8 h (Fig. 1). In Barrett's esophageal adenocarcinoma cells (SEG-1), CDX2 expression was highly upregulated in a dose- and time-dependent fashion. In esophageal

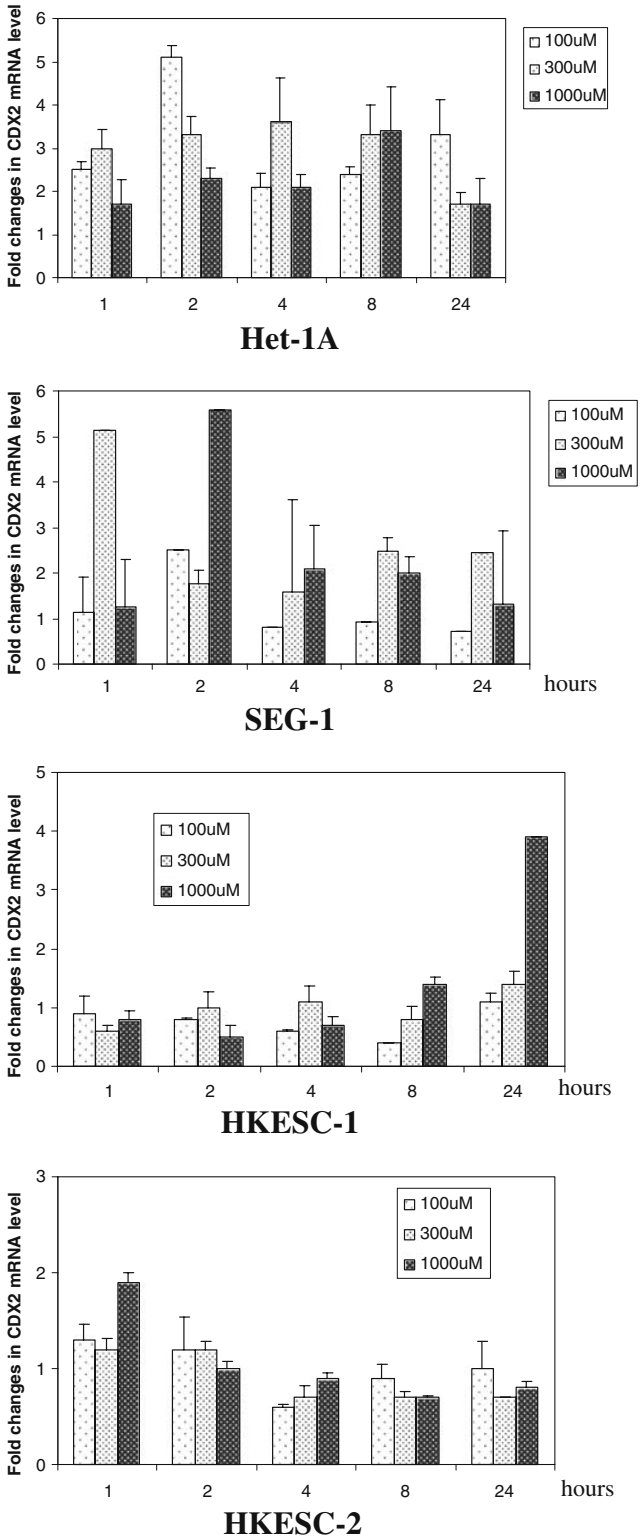


Figure 5 Real-time PCR analysis showing CDX2 mRNA changes in folds in esophageal cells Het-1A, SEG-1, HKESC-1, and HKESC-2 after exposing 100–1,000 μM glycocholic acid (GC) for 1–24 h.

squamous carcinoma cells (HKESC-1 & HKESC-2), CDX2 expression was highly upregulated by 1,000-μM DCA exposure for 1 h, and the upregulation maintained for the 2- to 24-h time points (Fig. 1). Cdx2 upregulation was similar after exposure to chenodeoxycholic acid in each of the four esophageal cell lines, although to a lesser extent (Fig. 2). Glycocholic acid exposure had no measurable effect on CDX2 expression in any of the four cell lines (data not shown).

Quantitation of CDX2 mRNA Expression by Real-Time PCR

To further confirm the RT-PCR results and to quantitate the CDX2 expression, real-time quantitative PCR was used to measure CDX2 mRNA expression. Time- and dose-dependent upregulation of CDX2 mRNA expression after deoxycholic, chenodeoxycholic, and glycocholic acid exposure is shown in Figs. 3, 4, and 5, respectively. As shown in Fig. 3, HET-1 cell CDX2 expression increased 9-, 6-, 119-, and 166-fold after treatment with 1,000 μM DCA for 2, 4, 8 and 24 h, respectively. SEG-1 cell CDX2 upregulation can be detected after 1 h exposure to DCA at concentrations ranging from 100 to 1,000 μM. The maximal induction of CDX2 expression (1973-fold increases) in SEG-1 cells was achieved with 1,000-μM DCA treatment for 24 h (Fig. 3). Similarly, CDX2 mRNA increased two to 31-fold in squamous carcinoma HKESC-1/2 cells after 300 and 1,000-μM DCA treatment for 1 h. The maximal increase of CDX2 expression in HKESC-2 was 16-fold after 1,000-μM DCA treatment for 8 h (Fig. 3).

Upregulation of CDX2 after exposure to chenodeoxycholic and glycocholic acid are shown in Figs. 4 and 5, respectively. CDX2 expression increased in an obvious dose- and time-dependent fashion with CDC treatment in esophageal squamous Het-1A cells with a maximal induction of 158-fold after 1,000-μM CDC treatment for 24 h. Maximal upregulation in SEG-1 cells was 1,037-fold and 21- to 45-fold in HKESC-1/2 cells each after exposure to 1,000 μM CDC.

In contrast, upregulation after exposure to GC was minimal (four- to sixfold) in each of the cell types (Fig. 5). Figure 6 compares the time-dependent CDX2 expression for each of the three bile acids across the four cells lines at 100, 300, and 1,000 μM, respectively.

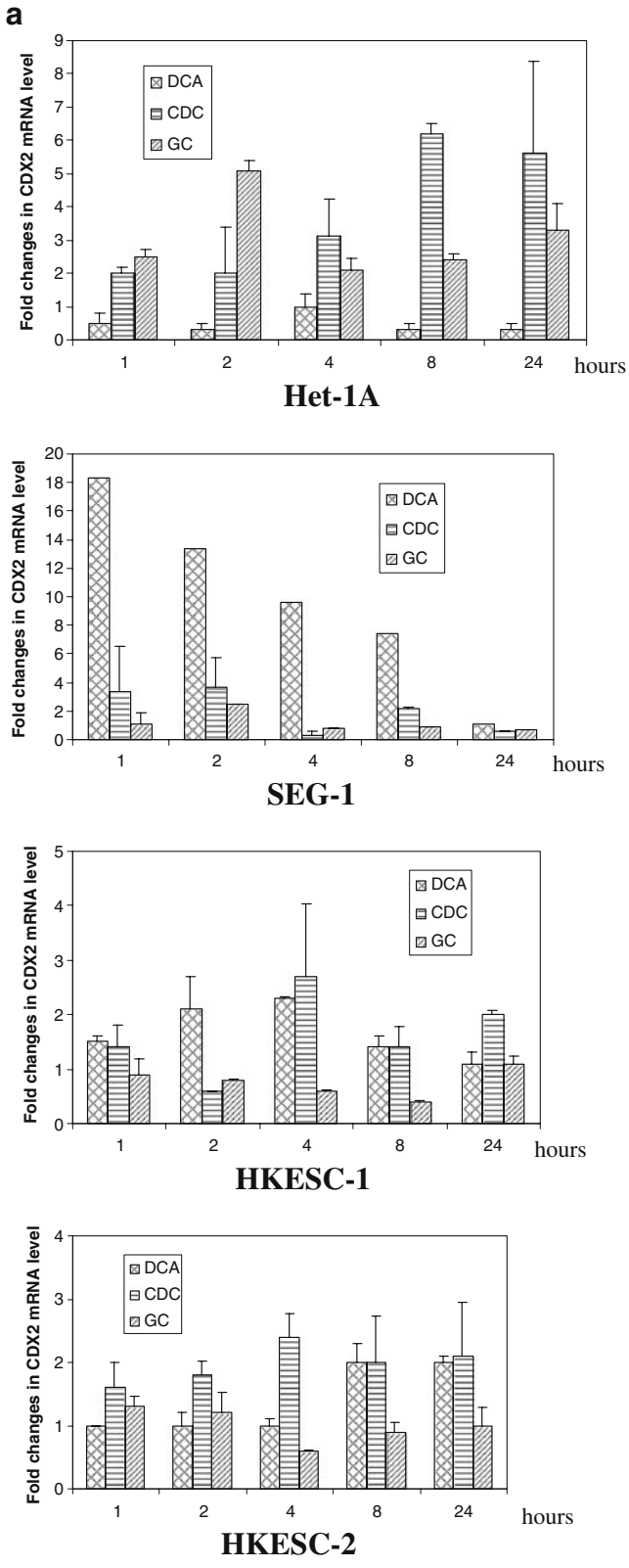
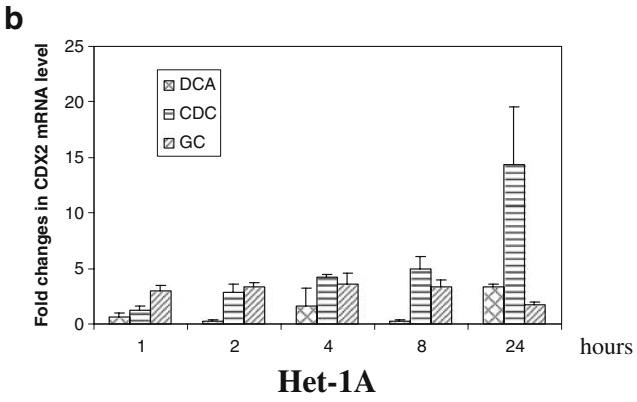
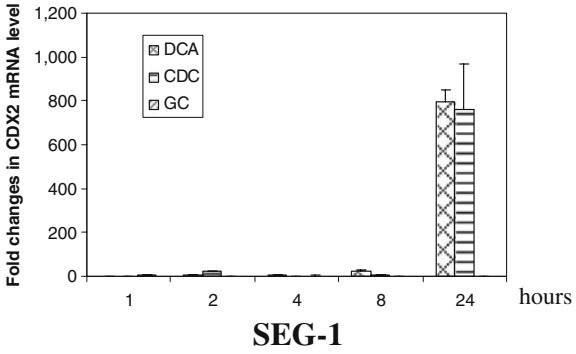
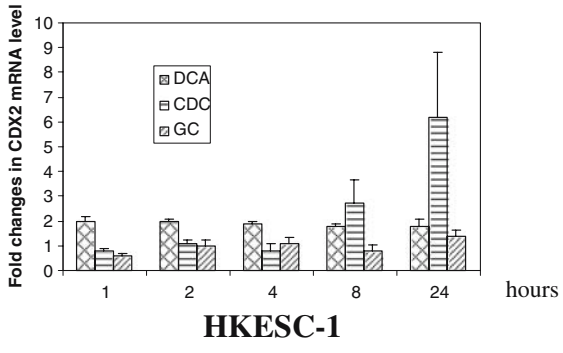
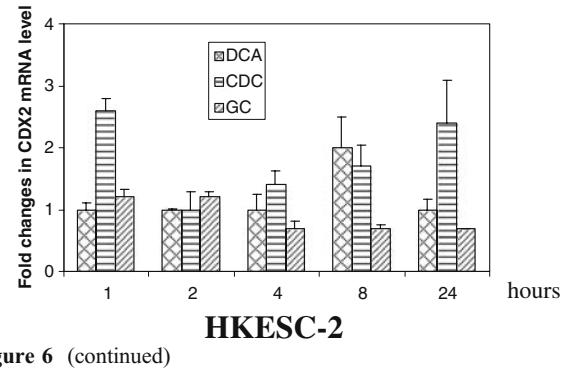


Figure 6 **a** Comparison of CDX2 mRNA changes in folds in esophageal cells Het-1a, SEG-1, HKESC-1, and HKESC-2 after exposure for 1–24 h to 100 μM deoxycholic (DCA), chenodeoxycholic (CDC), and glycocholic (GC) acids. **b** Comparison of CDX2 mRNA changes in folds in esophageal cells Het-1a, SEG-1, HKESC-1, and HKESC-2 after exposure for 1–24 h to 300 μM deoxycholic (DCA), chenodeoxycholic (CDC), and glycocholic (GC) acids. **c** Comparison of CDX2 mRNA changes in folds in esophageal cells Het-1a, SEG-1, HKESC-1, and HKESC-2 after exposure for 1–24 h to 1,000 μM deoxycholic (DCA), chenodeoxycholic (CDC), and glycocholic (GC) acids.









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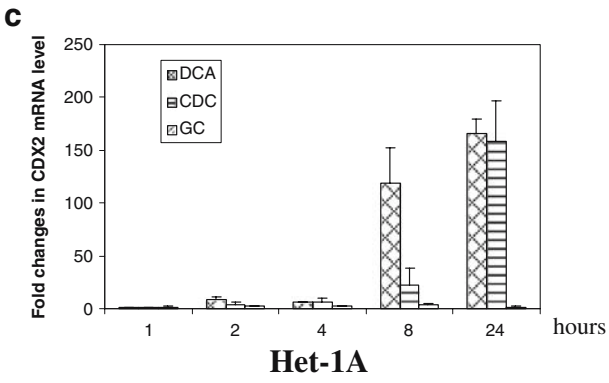

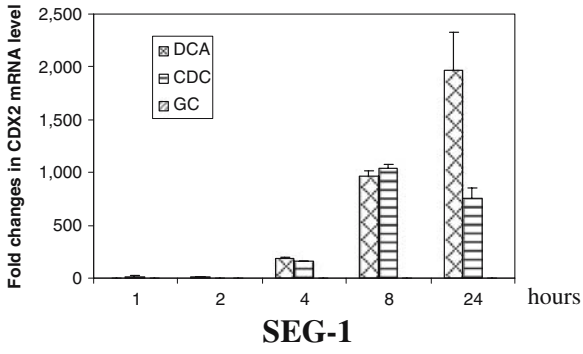

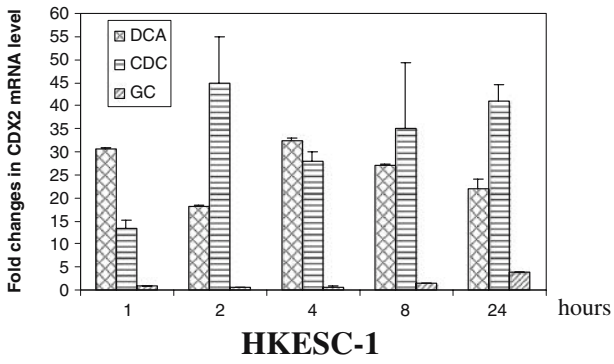

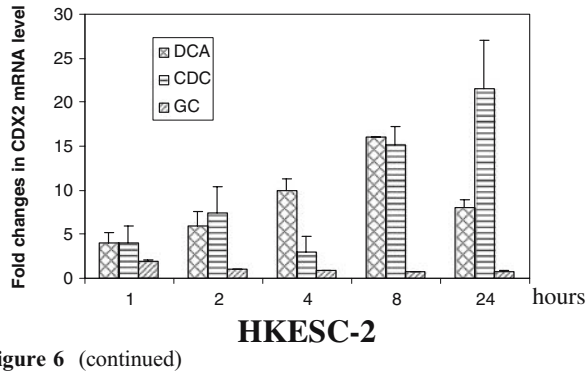

Figure 6 (continued)

Discussion

We have shown that bile acid exposure can induce CDX2 expression in human esophageal normal and cancer cells. CDX2 mRNA expression increased dramatically with unconjugated bile acids DCA and CDC, but not with GC (conjugated) exposure in all four esophageal cell lines. DCA showed the strongest effect on CDX2 transcription among the three bile acids tested. The maximal induction of CDX2 expression (up to 1973-fold increases) was seen in

SEG-1 adenocarcinoma cells after 1,000−μM DCA exposure for 24 h. These findings provide a direct link between bile acid and CDX2 expression in esophageal cells.

Barrett's esophagus (BE) is a complication of chronic gastroesophageal reflux disease (GERD). The exact molecular pathogenesis underlying this process is largely unknown. Because Barrett's is in essence an intestinal differentiation, it is plausible that transcription factors that play an important role in normal intestinal differentiation may also play a role in the development of BE. CDX2 is a promising candidate transcription factor. CDX2 is a caudal homeobox gene and plays a key role in early differentiation and the maintenance of intestinal epithelium.[2] A tightly conserved sequence of approximately 180 DNA basepairs encoding DNA-binding transcription factors was discovered in invertebrates, whose function seemed to be to induce the replacement of one body part or segment with another not normally found at that site. This "box" of genes was referred to as the homeobox set *(homeo,* Greek prefix indicating likeness or resemblance). Mammalian analogues of these genes, including *Cdx2* have been shown to be important in "caudal" embryonic development namely, formation of the gut and skeletal systems. Homozygous mouse knockout embryos die at implantation. Heterozygous animals develop intestinal polyposis and mouse gene transfection results in the phenotypic appearance of intestinal metaplasia in the foregut.

We and others have previously shown that CDX2 expression is increased in biopsies of human Barrett's epithelium when compared with normal squamous mucosa.[3,4,11–14] Similarly, CDX2 overexpression was also observed in intestinal metaplastic epithelium in the human stomach.[15] Transfection studies showed that CDX2 was able to induce undifferentiated rat IEC6 cells into the differentiation of goblet cells and absorptive enterocytes.[2] Transgenic mouse studies further showed that induction of Cdx2 expression in mouse stomach resulted in the development of intestinal metaplasia in the gastric mucosa.[16,17] Thus, the transgenic mouse studies provided the causal connection between Cdx2 expression and the development of intestinal metaplasia.[16,17] Here we provide in vitro evidence of causal link between bile acids and CDX2 expression induction in human esophageal cells, although the exact mechanism by which bile acids induce CDX2 expression is not known. Our observations further support the role of bile acids in the development of Barrett's esophagus and link the clinical evidence of a high prevalence of esophageal luminal bile acids to the intestinal differentiation-specific gene *CDX2* expression.

Our results showed that CDX2 expression can be induced in normal esophageal squamous cell Het-1a and esophageal squamous carcinoma cells HKESC-1 and HKESC-2 (Figs. 1, 2, 3). These in vitro findings are consistent with the observations from clinical specimens by Moons et al.[3] They detected CDX2 mRNA in approximately one-third of the normal appearing squamous epithelial samples of patients with Barrett's esophagus.[3] This indicates that the molecular changes (CDX2 upregulation) have already happened in these normal appearing squamous epithelium before the morphologic emergence of BE.[3] These findings suggest that CDX2 is an early marker during the development of Barrett's esophagus.

In conclusion, we have shown that bile acid exposure induces CDX2 expression in vitro in human esophageal cells, including normal, adenocarcinoma, and squamous carcinoma cell lines. These findings provide evidence of a direct link between bile acid and CDX2 in esophageal cells. They further support the role of bile acids in the pathogenesis of Barrett's esophagus and link the clinical evidence of a high prevalence of intraluminal bile acids in Barrett's esophagus to expression of the gene thought to be responsible for the phenotypic appearance of intestinal metaplasia.

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Cholecystosteatosis: an Explanation for Increased Cholecystectomy Rates

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Abstract
Introduction Over the past decade, obesity has become epidemic, and the number of cholecystectomies as well as the percentage with acalculous cholecystitis have increased. We have recently reported that congenitally obese mice and lean mice fed a high fat diet have increased gallbladder wall lipids and poor gallbladder emptying. Therefore, we tested the hypothesis that compared to patients with a normal gallbladder, patients with both acalculous and calculous cholecystitis would have increased gallbladder wall fat.
Methods Sixteen patients who underwent cholecystectomy for acalculous cholecystitis were identified. Sixteen nondiseased controls who underwent incidental cholecystectomy during surgery for liver or pancreatic disease and 16 diseased controls whose gallbladder was removed for chronic calculous cholecystitis were chosen to match the acalculous patients for gender and Body Mass Index. Pathology specimens were reviewed in a blinded fashion for gallbladder wall fat, thickness, and inflammation.
Results Acalculous cholecystitis patients were younger ($p<0.01$) than nondiseased or diseased controls. Gallbladder wall fat was significantly increased ($p<0.02$) in the acalculous and calculous cholecystitis patients compared to the nondiseased controls. Gallbladder wall thickness ($p<0.02$) and inflammatory score ($p<0.01$) were highest in the calculous cholecystitis patients.
Conclusions These data suggest that compared to nondiseased controls, (1) patients with acalculous cholecystitis are younger and have increased gallbladder fat and (2) patients with calculous cholecystitis have increased gallbladder fat and inflammation. We conclude that increased gallbladder fat may lead to poor gallbladder emptying and biliary symptoms. Thus, cholecystosteatosis may explain, in part, the increased need for cholecystectomy and the higher percentage of these patients with acalculous cholecystitis.

Keywords Biliary dyskinesia · Cholecystitis · Gallstones · Obesity · Steatosis

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Introduction

Gallbladder disease continues to be a major health care problem in the United States. Since the introduction of the laparoscopic technique in the late 1980s, the rate of cholecystectomy has increased significantly.[1–5] More than 750,000 cholecystectomies are performed each year, and the cost of caring for these patients approaches 10 billion dollars annually.[6] During this same time frame, obesity has reached epidemic proportions,[7] and the prevalence of diabetes has increased more than 60%.[8] In addition, the proportion of elective cholecystectomies performed for chronic acalculous cholecystitis has more than doubled.[9,10] How-

ever, a good explanation for these trends has not been established.

Chronic acalculous cholecystitis (biliary dyskinesia) may be defined as classic biliary symptoms with the absence of gallstones or other structural abnormalities that may explain the problem.[11] For several decades, approximately 5% of patients with biliary colic were diagnosed with chronic acalculous cholecystitis.[12] However, in recent years, the percentage of patients coming to cholecystectomy with acalculous cholecystitis has increased to 20–25%.[13] Both calculous and acalculous cholecystitis are more common in females, and the influence of estrogen and progesterone on biliary motility has been suggested to play a role in the pathogenesis of this phenomenon.[14–16] Recent data from our laboratory, however, have shown that congenitally obese mice and lean mice fed a high fat diet have increased gallbladder wall lipids and poor gallbladder contractility.[17] Therefore, we tested the hypothesis that compared to patients with a normal gallbladder, those with both acalculous and calculous cholecystitis would have increased gallbladder wall fat and inflammation (cholecystosteatosis).

Methods and Materials

Patient Population

The medical records of patients undergoing cholecystectomy at the Indiana University Medical Center between April 2004 and April 2006 were reviewed. Sixteen of the author's patients with chronic acalculous cholecystitis were identified. All of these patients had typical biliary symptoms as seen in the ultrasound, which was negative for gallstones and an abnormal cholescintigraphy. The mean and median gallbladder ejection fractions were 15 and 17%, respectively, with a range of 0–35%. None of these biliary dyskinesia patients had acute acalculous cholecystitis, obstruction of the cystic duct or common bile duct, prolonged fasting or were receiving total parental nutrition (TPN).

Both nondiseased and diseased control patients who were matched for gender and body mass index (BMI) were then chosen from the cholecystectomy database. Sixteen nondiseased controls who underwent incidental cholecystectomy during surgery for liver or pancreatic disease and 16 diseased controls whose gallbladder was removed for symptomatic chronic acalculous cholecystitis were chosen for comparison. None of the nondiseased or diseased controls had acute gallbladder inflammation, obstruction of the cystic duct or common bile duct, prolonged fasting or acalculous cholecystitis. None of the nondiseased controls had biliary "sludge", cholesterolosis, microlithiasis, or gallstones. All of the diseased controls had an ultrasound which demonstrated gallstones. Gross pathology confirmed that 14 of the 16 had cholesterol gallstones, and two had black pigment gallstones.

Data on these groups with respect to age, gender, BMI, diabetes mellitus, hypertension, and hyperlipidemia are presented in Table 1. Patients were considered to have diabetes, high blood pressure, or hyperlipidemia if they were receiving medications for these disorders. The patients with acalculous cholecystitis were significantly younger ($p<0.01$) than the nondiseased or diseased controls (41±3 vs 56±4 and 54±4 years, respectively). However, the three groups did not differ with respect to gender, BMI, or metabolic syndrome disorders. To eliminate the influence of this age difference on the results, a subgroup of eight patients from each group who were matched for age and identically matched for gender were chosen (Table 1B). These subgroups also were matched for BMI, diabetes, hypertension, and hyperlipidemia.

Gallbladder Pathology

Surgical pathology specimens were reviewed by a single investigator blinded to the patients' diagnosis and demo-

Table 1 Patient Demographics

Groups	N	Age	Female (%)	BMI	DM (%)	HTN (%)	Hyperlipidemia (%)
Groups Matched for Gender and BMI							
Nondiseased controls	16	56±4	63	27±1	19	50	25
Acalculous Cholecystitis	16	41±3*	88	29±3	25	44	19
Calculous chOolecystitis	16	54±4	63	27±2	31	44	38
Subgroups Matched for Age and Gender							
Nondiseased Controls	8	42±5	75	27±3	0	38	13
Acalculous Cholecystitis	8	42±2	75	24±2	25	38	25
Calculous Cholecystitis	8	43±3	75	27±2	13	13	13

MI Body mass index, *DM* diabetes mellitus, *HTN* hypertension
*$p<0.01$ vs other groups

graphics. The thickness of the fat and the total gallbladder wall thickness (millimeters) were measured microscopically in H&E stained gallbladder sections. The percentage of fat in the gallbladder wall was then calculated. Surgical pathology specimens also were scored for inflammation by the same investigator in a blinded fashion. A grading scale was developed based on the amount of inflammatory cells presents (0 to 2) and mucosal thickening (0 to 2). An inflammatory score (IS) from 0 to 4 was assigned to each gallbladder specimen. Figure 1 shows microscopic sections from typical patients who were (a) nondiseased or had (b) acalculous cholecystitis, or (c) calculous cholecystitis.

Statistical Analysis

Statistical analyses were performed using Sigma Stat Statistical Software (Jandel Corp., San Rafael, California). Patient's age, BMI, gallbladder wall thickness, percent fat in the wall and inflammatory score are expressed as mean± SEM, and were tested for statistical differences by Student's unpaired *t* test. The percent of patients in each group or subgroup who were female or had diabetes, hypertension, or hyperlipidemia were tested for statistical differences by the Fisher Exact test. A *p* value of less than 0.05 was considered statistically significant.

Results

Gallbladder Wall Thickness and Fat

Gallbladder wall thickness and percent of fat in the wall are shown in Fig. 2a. No significant difference was observed in gallbladder wall thickness between nondiseased controls and patients with acalculous cholecystitis. The gallbladder wall was significantly ($p<0.03$) thicker in the calculous cholecystitis group versus the nondiseased controls and the acalculous cholecystitis groups (3.0±0.4 vs 1.8±0.2 and 1.9±0.2 mm, respectively).

The percent of fat in the gallbladder wall was significantly higher in the acalculous cholecystitis group compared to the nondiseased controls (25±7 vs 6±3%, $p<0.02$). The percentage of fat in the gallbladder wall also was significantly higher in the calculous cholecystitis group compared to the nondiseased controls (29±6 vs. 6±3%, $p<0.01$). No significant difference was observed in the percentage of wall fat between the acalculous and calculous cholecystitis groups. The gallbladder wall fat was primarily located in the subserosal layer (Fig. 1b and c).

Gallbladder wall thickness and percent of fat in the wall in the age and gender matched subgroups are shown in Fig. 2b. No significant difference was observed in wall thickness among the three groups who averaged 42 years old and were 75% female (Table 1B). The percent of fat in the gallbladder wall was significantly higher in the acalculous cholecystitis subgroup compared to the nondiseased controls (30±9 vs 3±2%, $p<0.02$). The gallbladder wall fat percentage also was significantly higher in the calculous cholecystitis subgroup compared to the nondiseased controls (22±7 vs 3±2%, $p<0.02$). No significant difference was observed in gallbladder wall fat percentage between the acalculous and calculous cholecystitis subgroups.

Gallbladder Wall Inflammation

Gallbladders of patients from the calculous cholecystitis group had a significantly ($p<0.01$) higher total inflammatory score than acalculous cholecystitis and nondiseased control groups (2.9±0.2 vs 1.8±0.2 and 1.3±0.3, respectively) (Fig. 3a).

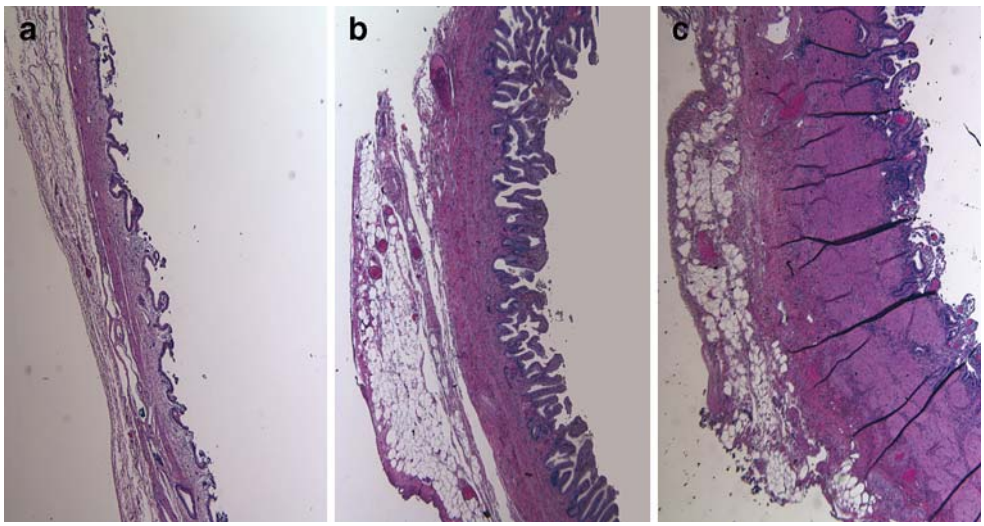

Figure 1 **a** Histologic section from nondiseased control patient's gallbladder with thin wall, no fat, and no inflammation. **b** Histologic section from chronic acalculous cholecystitis patient's gallbladder with thin wall, increased fat, and no inflammation. Fat is primarily in the subserosal layer. **c** Histologic section from chronic calculous cholecystitis patient's gallbladder with thick wall, increased fat, and inflammation. Fat is primarily in the subserosal layer.

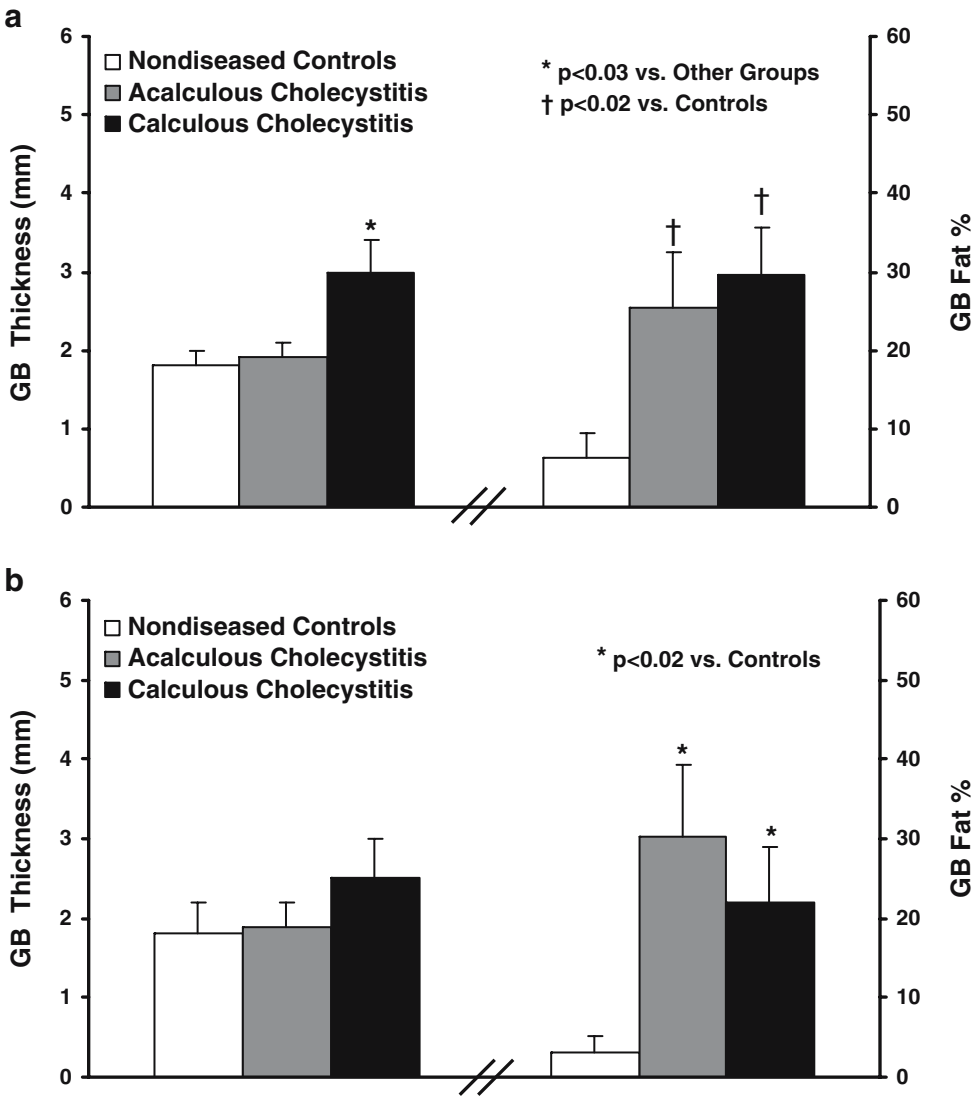

Figure 2 **a** Gallbladder (*GB*) wall thickness and fat percentage in nondiseased controls (n=16), acalculous cholecystitis (n=16), and calculous cholecystitis (n=16) groups. **b** Gallbladder (*GB*) wall thickness and fat percentage in the three subgroups (n=8 each) matched for age and gender.

No significant difference in total inflammatory score was observed between the nondiseased controls and the acalculous cholecystitis group. Both the inflammatory cell amount and the mucosal thickness elements of the inflammatory score showed the same trends and statistical significance as the total score.

In the age- and gender-matched subgroups, gallbladders of patients from the calculous cholecystitis subgroup also had a significantly ($p<0.05$) higher total inflammatory score than the acalculous cholecystitis and nondiseased controls subgroups (2.4±0.3 vs 1.4±0.3 and 1.3±0.3, respectively) (Fig. 3b). No significant difference in total inflammatory score was observed between the nondiseased controls and the acalculous cholecystitis subgroup. In these subgroups the inflammatory cells were significantly increased ($p<0.05$) in the calculous cholecystitis vs the acalculous cholecystitis subgroup, while the mucosal thickness was significantly increased ($p<0.01$) in the calculous cholecystitis vs the nondiseased controls.

Discussion

In this study, 16 patients with chronic acalculous cholecystitis who had typical biliary symptoms and a mean gallbladder ejection fraction of 15% who underwent cholecystectomy were identified. A group of 16 patients undergoing incidental cholecystectomy and another 16 patients with symptomatic chronic calculous cholecystitis whose gallbladders were removed during the same time period served as nondiseased and diseased controls, respectively. The controls were matched for gender, BMI, and elements of the metabolic syndrome. The acalculous cholecystitis patients had increased gallbladder wall fat compared to the nondiseased controls group. In comparison, the calculous cholecystitis patients had both significantly increased gallbladder wall fat and inflammation.

In the present study, patients in the acalculous cholecystitis group were significantly younger and had a high (but not

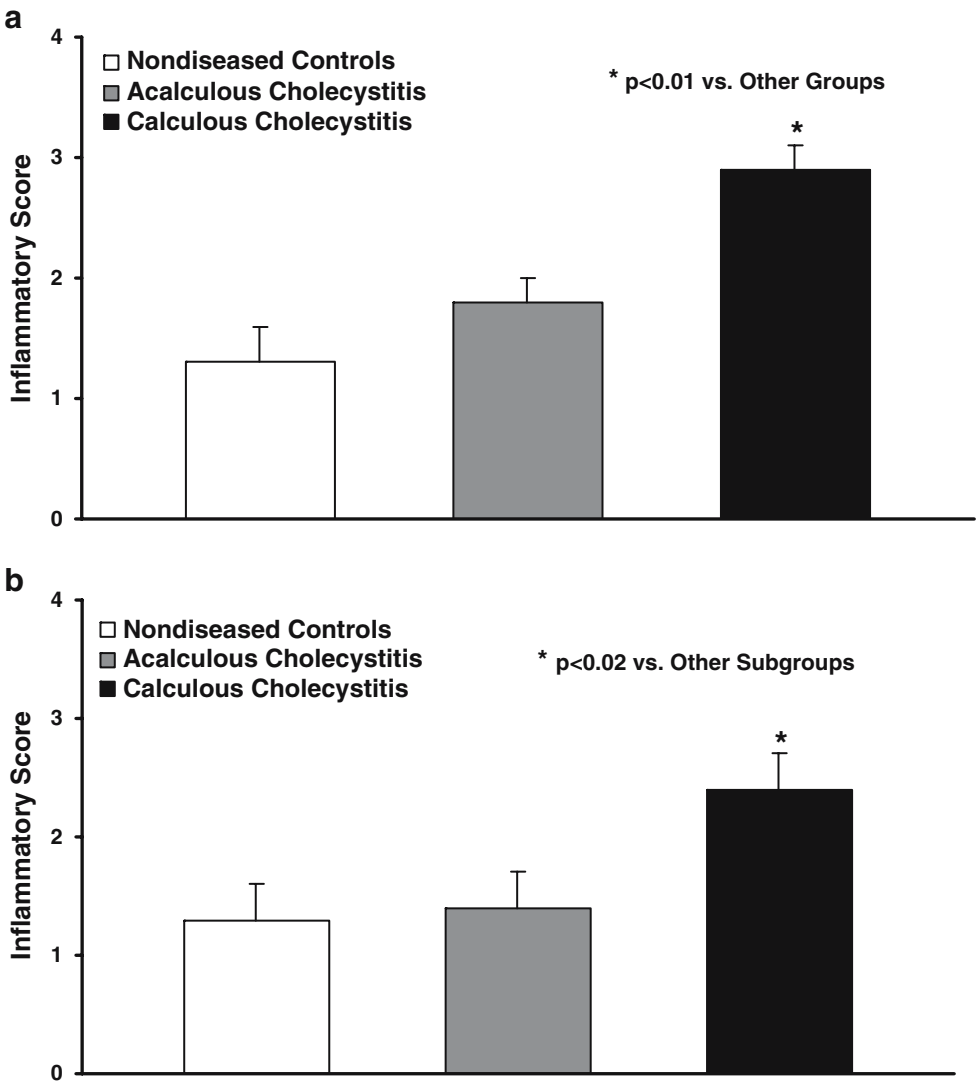

Figure 3 **a** Gallbladder wall total inflammatory score in the nondiseased controls (n=16), acalculous cholecystitis (n=16), and calculous cholecystitis (n=16) groups. **b** Gallbladder wall total inflammatory score in the three subgroups (n=8 each) matched for age and gender.

significant) percentage of females compared to nondiseased controls and patients with calculous cholecystitis. These findings were similar to other studies.[18] Therefore, to better control for age and gender, we identified a subgroup of eight patients from each of the original groups. In this subanalysis, the percent of fat in the gallbladder wall remained significantly higher in the two diseased groups compared to nondiseased controls. However, in both analyses, patients with calculous cholecystitis had mucosal abnormalities and inflammatory cell infiltrates, which were not seen in the control or acalculous cholecystitis gallbladders.

The diagnosis of biliary dyskinesia is used when ultrasonography and microscopic bile examination have excluded the presence of gallstones and other structural abnormalities in the patients with "typical biliary pain".[11] "Typical biliary pain" was defined by the "Rome II" Committee on Functional Gastrointestinal Disorders.[19] Some physicians use an ejection fraction of less than 50% as a cut off for poor gallbladder emptying, and others use 35%.[20–22] The dose of cholecystokinin (CCK) and the rate of infusion vary among studies.[20–22] Still, other investigators employ a fatty meal, and some use ultrasound rather than cholescintigraphy.[23] Population screening studies performed with ultrasonography have shown that the frequency of biliary-type pain without gallstones was 7.6% in men[24] and 20.7% in women.[25] Little is known about the pathophysiology of the disease and the mechanism of pain in these patients. Yap et al.[26] hypothesized that narrowing of the cystic duct may impair gallbladder emptying. Alternatively, Amaral et al.[27] have demonstrated an impairment in gallbladder muscle contraction as an explanation for the abnormal gallbladder emptying. Others hypothesized that the abnormal gallbladder emptying might result from an increase in tone or resistance at either the cystic duct or the sphincter of Oddi.[11]

Recent studies from our laboratory have demonstrated that congenitally obese leptin-deficient and leptin-resistant mice have large gallbladders which respond poorly to neurotransmitters in a muscle bath.[28–30] We have also shown that

gallbladder response correlates inversely with serum glucose, insulin, cholesterol, and triglycerides.[31] In addition, we have demonstrated that administration of leptin to leptin-deficient mice restores gallbladder contractility, decreases gallbladder dry weight,[32] and decreased the gene expression of enzymes responsible for lipid metabolism including fatty acid synthase, HMG Co A reductase, and diacylglycerol acyltransferase (unpublished data). More recently, we have shown that lean mice fed a high fat diet have increased gallbladder wall cholesterol and cholesterol/phospholipid ratio compared to lean mice fed a low fat chow diet.[17]

Increased membrane cholesterol and cholesterol/phospholipid ratio have been shown in a number of different cell types, including smooth muscle cells, to influence membrane fluidity and membrane-bound protein function.[33,34] Yu et al.[35] have reported that prairie dogs fed a high cholesterol diet have increased gallbladder wall cholesterol, decreased phospholipids, and increased cholesterol/phospholipid ratio. Chen et al.,[36] from the same laboratory, also have shown that the smooth muscle cells of human gallbladders with cholesterol stones have increased cholesterol and cholesterol/phospholipid ratios when compared with gallbladders from patients with pigment stones. They also demonstrated that the membrane fluidity was decreased in the cholesterol stone group and negatively correlated with the cholesterol/phospholipid ratio. In addition, as the cholesterol/phospholipid ratio increased, gallbladder muscle-cell contraction decreased. Moreover, the addition of second messengers such as inositol 1,4,5-triphophate, diacylglycerol, or calmodulin normalized contractility suggesting that this phenomenon occurs at the cell membrane level.

The significance of adipose tissue as an endocrine organ first surfaced in 1994 with the ground-breaking discovery of leptin.[37,38] Subsequent studies have demonstrated that white adipose tissue is a major endocrine and secretory organ, which releases a wide range of protein signals and factors termed adipokines.[39–42] A number of adipokines, including leptin, adiponectin, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), are linked to inflammation and the inflammatory response.[41,42] TNF-α is a pro-inflammatory adipokine that plays a primary role in stimulating expression of other inflammatory mediators including leptin and IL-6.[43] TNF-α participates in the pathophysiology of several inflammatory diseases including vasculitis and Crohn's diseases.[44,45] In the gallbladder, TNF-α leads to an inflammatory response, which has been shown to alter gallbladder absorption and secretion.[46] Electron microscopy studies by Gilloteaux et al.[47,48] of gallbladders from patients with cholesterol gallstones also have demonstrated lipid mucosomes in the mucosa. These authors have postulated that mucosal lipids affect absorption and/or secretion. In addition, we have recently demonstrated that leptin-deficient obese mice, fed a high carbohydrate diet, have increased TNF-α and IL-1β in their gallbladder wall (unpublished data).

The present study shows that gallbladders of patients with poor gallbladder emptying have increased gallbladder wall fat compared to age, gender, BMI, and metabolic syndrome matched controls. Early studies from this and other laboratories suggested that decreased gallbladder emptying and abnormal gallbladder absorption were early events in gallstone pathogenesis.[49,50] More recent studies have suggested that increased insulin resistance and hyperlipidemia also are associated with altered gallbladder volume and motility,[23,31] factors that may lead to biliary pain. A recent murine study from this laboratory suggested that diet-induced and congenital obesity are associated with increased gallbladder wall fat and poor gallbladder emptying.[17] However, in this study we cannot rule out that fat accumulates in the dysmotile gallbladder and that fat deposition is a result of dysmotility rather than a cause.

The concept that fat in an organ leads to an inflammatory process which is associated with insulin resistance and leads to organ damage is not unique to the gallbladder. Fat has been implicated in dysfunction of cardiac and skeletal muscle and the kidneys and liver.[51–53] Nonalcoholic fatty liver disease (NAFLD) is thought to be a precursor of nonalcoholic steatohepatitis (NASH).[54,55] Similarly, the accumulation of fat in the gallbladder wall (cholecystosteatosis) may initiate an inflammatory process that alters gallbladder motility, absorption, and secretion and leads to gallbladder inflammation and gallstone formation. However, histological evidence of mucosal inflammation (steatocholecystitis) may be a late event that occurs after gallstones have formed.

A potential weakness of this study is the relatively small number of patients. However, the fact that the increased percentage of fat in the gallbladder wall remained statistically significant in the subgroup analysis with even smaller numbers adds to the credence of this observation.

Conclusion

This study documents that patients with typical biliary symptoms and poor gallbladder emptying have increased gallbladder fat. Thus, another consequence of the obesity epidemic may be an increased incidence of cholecystosteatosis which, in part, may explain the increased number of cholecystectomies with a higher percentage of patients with acalculous cholecystitis.

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DISCUSSION

Dr. Bingener-Casey (San Antonio, TX): Thank you very much for the opportunity to review this interesting paper ahead of time. Against the backdrop of rising obesity and cholecystectomy rates, your group examined whether fatin the gallbladder wall of diseased gallbladders versus normal gallbladders would be increased. In the manuscript you do not describe how you actually measured the fat content in the gallbladder wall, if you used histomorphometry or if you used Sudan red or any biochemical method. It would be interesting to know forothers to confirm your findings. You also showed that only thechronic cholecystitis group had an increase in inflammatory cells. So my question is, is it truly steatocholecystitis that you saw inthe patients with acalculous cholecystitis or biliary dyskinesia? And then, did the symptoms of the patients with biliary dyskinesia resolve? Is there a correlation between the amount of fat content you saw in the ejection fraction which would support your hypothesis? Is the fat content in the gallbladder wall of patients with biliary dyskinesia different than it was before the introduction of laparoscopic cholecystectomy? Do you have any historical control? And how do you plan to correct for confounderssuch as a changed risk-benefit ratio of laparoscopic versus open cholecystectomy if you are trying to explain the increased rates of cholecystectomy for both biliary dyskinesia and acalculous cholecystitis with increased fat in the gallbladder wall?

Dr. Al-Azzawi: With respect to your first question, we measured the thickness of the fat and the full wall thickness in millimeters in H&E stained gallbladder sections. From these two values, we calculated the percentage of gallbladder fat in the wall.

With respect to your second question regarding inflammatory cells, they were only increased in the gallstone patients. However, we believe that cytokines are increased in the chronic acalculous cholecystitis patients. We have data demonstrating increased gallbladder wall fat and cytokines in animals fed a high fat diet. These animals have decreased gallbladder emptying in the absence of gallstones. We are prospectively collecting human gallbladders for fat and cytokine analysis, but this study has not been completed.

With respect to clinical outcomes, the number of patients whose gallbladders were examined histologically was small. In our experience, however, patients who have typical biliary symptoms, a very low ejection fraction and no gallstones generally get a good clinical response from cholecystectomy.

All of our patients with chronic acalculous cholecystitis had very low ejection fractions and most had elevated gallbladder fat. Therefore, no obvious correlation was found.

With respect to your questions of gallbladder fat content with open versus laparoscopic cholecystectomy, we have no data. However, the percentage of patients with chronic acalculous cholecystitis coming to cholecystectomy clearly has increased in recent years.

Dr. H. Kaufman (Los Angeles, CA): Very nicely presented. Your BMI in the symptomatic group with a mean BMI less than 30 doesn't really seem to fit the demographic of someone with chronic cholecystitis. Can you speak to the BMI range? Also, have you looked at

patients with larger BMIs to see if there is an increase in gallbladder wall fat as BMI increases?

Dr. Al-Azzawi: The BMI of the patients ranged from 15 to 56, but the mean in each group was less than 30. Initially, we matched the groups for gender and BMI and found differences in gallbladder fat but not in metabolic syndrome parameters. We thought that controlling for patient BMI was important in demonstrating differences in gallbladder wall fat.

Dr. R. Prinz (Chicago, IL): I just wanted to ask you about your control group. It seems that these were patients undergoing operations for tumors in the liver and pancreas. If that is correct, does that malignancyhave an effect here on the amount of fat you are going to find in the control patients, since many of these will either have lost weight or certainly have had anorexia near the time their gallbladder is removed? So I would like your comments on that.

Dr. Al-Azzawi: Only six of our 16 control patients had adenocarcinomas. Four had non invasive intraductal papillary mucinous neoplasms of the pancreas, two had hepatic adenomas, two had neuroendocrine tumors, and two had benign pancreatobiliary problems. Again, these control patients were matched with the acalculous and calculous cholecystitis patients for BMI.

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Concepts and Preliminary Data Toward the Realization of Image-guided Liver Surgery

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Abstract Image-guided surgery provides navigational assistance to the surgeon by displaying the surgical probe position on a set of preoperative tomograms in real time. In this study, the feasibility of implementing image-guided surgery concepts into liver surgery was examined during eight hepatic resection procedures. Preoperative tomographic image data were acquired and processed. Accompanying intraoperative data on liver shape and position were obtained through optically tracked probes and laser range scanning technology. The preoperative and intraoperative representations of the liver surface were aligned using the iterative closest point surface matching algorithm. Surface registrations resulted in mean residual errors from 2 to 6 mm, with errors of target surface regions being below a stated goal of 1 cm. Issues affecting registration accuracy include liver motion due to respiration, the quality of the intraoperative surface data, and intraoperative organ deformation. Respiratory motion was quantified during the procedures as cyclical, primarily along the cranial–caudal direction. The resulting registrations were more robust and accurate when using laser range scanning to rapidly acquire thousands of points on the liver surface and when capturing unique geometric regions on the liver surface, such as the inferior edge. Finally, finite element models recovered much of the observed intraoperative deformation, further decreasing errors in the registration. Image-guided liver surgery has shown the potential to provide surgeons with important navigation aids that could increase the accuracy of targeting lesions and the number of patients eligible for surgical resection.

Keywords Image-guided surgery · Liver resection · Surface registration · Laser range scanning · Finite element

Of the 147,000 projected new cases of colorectal cancer for 2004,[1] it is estimated that 50% of all colorectal primary tumors will develop a liver metastasis at some point in the disease, and 20% of cases will develop a metastasis solely in the liver.[2] Metastatic liver cancer takes a rapid course. When untreated, the median survival rate is between 5 and 12 months with a 5-year survival rate approaching zero.[3–6] The most common form of treatment is surgical resection. For metastases, studies have reported a 5-year survival rates of 20–50%, with much of the variance attributed to bias in patient selection. For primary liver tumors, the 5-year

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survival rates varied from 24 to 76% due to variables such as age, size of tumor, and presence of cirrhosis.[2,7–10] With 70–90% of all patients ineligible for resection, ablative techniques provide a promising alternative.[11–15]

In the cases of resection and ablation, if the surgeon can direct therapy to the target with an ever higher degree of accuracy, it could lead to smaller resection margins, improved outcomes, and more patients eligible for treatment. To that end, image-guided surgical techniques could provide this improvement in accuracy over conventional techniques. At the heart of image-guided surgery (IGS) is a process known as registration in which a mathematical mapping is determined between the intraoperative anatomical presentation of the organ and the preoperatively acquired tomograms. From this mapping, a real-time update of surgical position can be displayed in reference to preoperative imaging studies. If intraoperative data are properly and accurately acquired for the liver, then a successful registration will provide navigational assistance to resect subsurface targets (tumors and cysts) and to avoid critical structures (vasculature and biliary trees), thus augmenting the anatomical expertise of the surgeon with an additional source of information. Image-guided surgery techniques are also quite flexible, as they can readily incorporate streams of data commonly available in the operating room, such as intraoperative ultrasound or physiological monitoring, and merge them with new modalities, such as the tracking and laser range scanning systems mentioned below.

Before computing a registration between image and physical space, translational motion due to respiration must be quantified and compensated. Many imaging studies of the liver have shown this motion to be periodic, principally in the cranial–caudal direction. A comprehensive review on the issue can be found.[16] Most studies report the magnitude of the motion to be on the order of 10–30 mm in the closed abdomen.[17–20] Herline et al.[21] acquired respiratory motion data during two open liver resection cases at three different locations on the liver surface. The motion also was observed to be periodic, and the mean (±SEM) distance between peak inhalation and peak exhalation was 10.3±2.5 mm. Banovac and Cleary[22] took results from prior studies on liver respiration and used them to develop a respiring liver phantom on which they performed needle placement experiments. In that study, two users were able to successfully puncture liver tumors in 87.5% of the attempts.

Previous registration studies involving image-guided liver surgery can be divided into three categories. The first set consists of registrations based on the geometric features of the liver. Corresponding features between the dataset are identified and aligned by minimizing a distance measure between the two sets of features.[23–26] The second category uses the complex, feature-rich liver vasculature to drive the registration between preoperative images and intraoperative ultrasound data.[27–29] The final type of registration is intensity based, where a correlation measure between two image sets is maximized. This method requires intraoperative ultrasound or tomographic data and is intended for guidance during minimally invasive ablation applications.[30–32] Currently, most image-guided studies in the liver have been restricted to phantoms, animal models, and minimally invasive interventional cases. In this paper, we present the first description of surface registration using a laser range scanner during open abdominal hepatic tumor resections. Issues that could affect the accuracy of the registration, including liver motion due to respiration, were addressed and analyzed.

Materials and Methods

Image Acquisition and Segmentation

Preoperative image volumes were acquired by computed tomography (CT) or magnetic resonance imaging. Both modalities used triphase studies that produce an uncontrasted image volume, a volume with arterial phase contrast, and a third volume where the contrast has washed out of the arteries and provides more emphasis on the venous vasculature. This imaging protocol is standard for patients undergoing liver tumor resection. The pixel spacing for these images ranged from 0.6 to 1.0 mm. The preferred slice thickness was 2.0 mm although, in these studies, the acquired volumes ranged from 0.8 to 5.0 mm. For this study, it is highly desirable that the tomographic slices do not overlap.

From the resulting tomograms, the liver was segmented from the surrounding abdominal viscera. Two methods of segmentation were performed. The first involved the authors manually outlining the contour of the liver, which can take 4 h or longer. To greatly reduce user interaction, our group has developed a semiautomatic method[33,34] that is based on the level-set technique.[35] This method was specifically designed to identify the edges of the liver, which can be difficult to discern near the ribs and heart. After segmentation is completed, there is a brief review and user interaction phase with the surgeon to further refine the segmentation. Corresponding results from an example manual and semiautomatic segmentation of a CT slice are shown in Fig. 1. The segmented contours are used to generate a three-dimensional surface model using the marching cubes methods.[36] Further refinement is performed using surface fitting software (FastRBF Toolkit; FarField Technology, Christchurch, New Zealand) involving radial basis functions as described previously.[37] This method provides a smoother representation with less points as illustrated in Fig. 2.

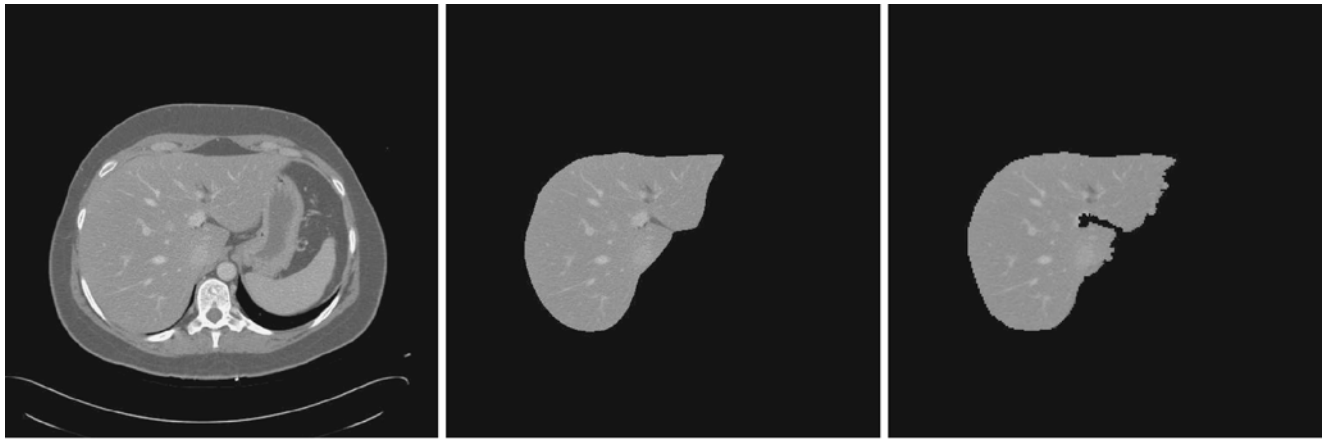


Figure 1 Comparison of manual and level-set segmentations of the liver.

Intraoperative Data

To digitize individual points in three-dimensional space, the OPTOTRAK 3020 (Northern Digital, Waterloo, Ontario, Canada) optical localization system was used. The system consists of an infrared camera, which determines the position and orientation of specialized probes embedded with infrared diodes (IREDs). Points are digitized by placing them in contact with the probe tip. The OPTOTRAK system is capable of acquiring single points with a root-mean-square accuracy of 0.1 mm.[38] Surface data are generated by sweeping the probe across the entire organ, allowing the tracking system to rapidly collect digitized points on the surface. For this study, the update rate for the probe's position was set to 40 Hz. Figure 3 displays the OPTOTRAK system in use, acquiring points on the liver surface.

Dense surface representations were acquired intraoperatively with a commercially available laser range scanner (RealScan 200C; 3D Digital Corp., Sandy Hook, CT, USA). This method serves as a complementary means to acquire surface data. The range scanner uses the principle of optical triangulation to rapidly capture thousands of three-dimensional points in a noncontact fashion. The laser used is very low in power, a class I eye-safe laser, and orders of magnitude below the maximum permissible exposure level for skin as stated in the American National Standard for Safe Use of Lasers (ANSIZ136.1). The range scanner itself is relatively compact (9.6×9.8×3.1 inches), as can be seen in Fig. 3, where it has been positioned in the operating room. Ongoing research is being performed in collaboration with the authors to develop a laparoscopic range scanner that will allow for dense surface acquisition in minimally invasive procedures.[39]

In addition to collecting three-dimensional surface data, the scanner simultaneously acquires a video image of the scene and then texture maps the appropriate color information onto each three-dimensional point. The texture-mapped point data are extremely useful in identifying the exposed liver surface from the resulting range scans and in segmenting it from the rest of the intraoperative scene. Figure 4 shows the video image acquired by the scanner,

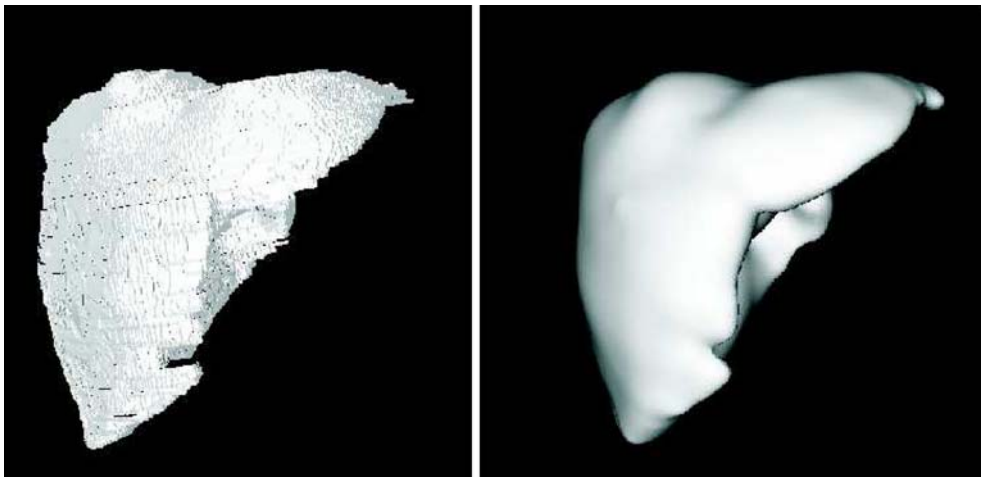


Figure 2 Surface model generation from the segmented contours. The initial surface mesh (*left*) is generated using the marching cubes method. It is refined (*right*) with a surface fitting technique that employs radial basis functions,[37] providing a smoother surface with less vertices, potentially increasing the speed and accuracy of the registration.

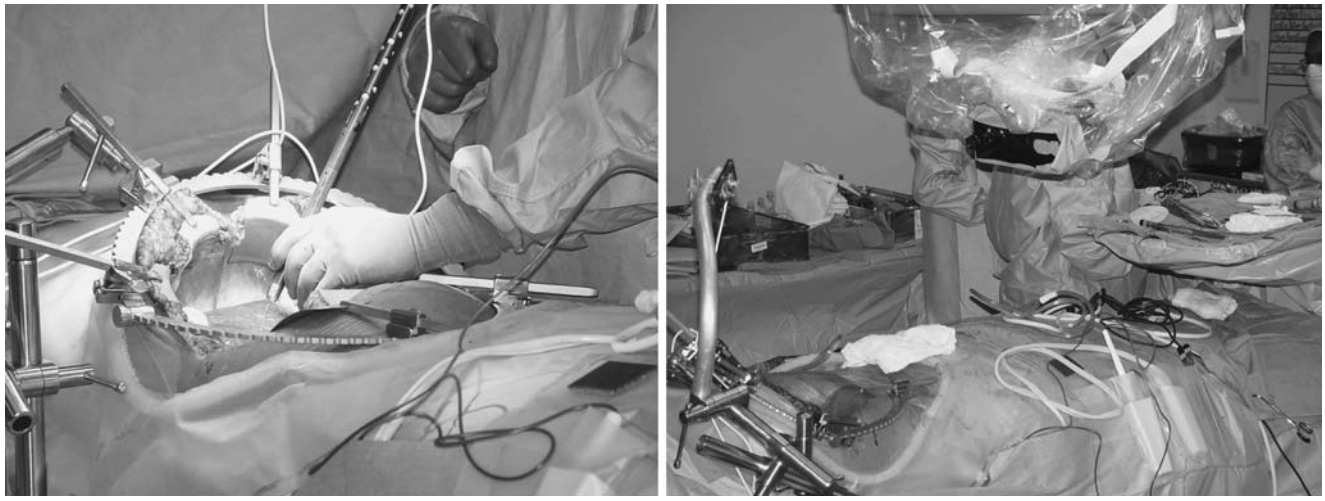


Figure 3 Surface data acquisition in the operating room. In the *left image*, the surgeon is digitizing points on the liver surface with the optically tracked probe. The *right image* shows the range scanner in position to acquire surface data of the liver intraoperatively.

along with the three-dimensional point cloud and how these data sets are combined with texture mapping.

To have relevance in the surgical suite, the output points of the range scanner must be reported in reference to the OPTOTRAK localization system. To that end, individual IREDs that are tracked by the OPTOTRAK camera are rigidly attached to the scanner. A calibration procedure was developed to link the position of the IREDs with the range scanner system, and tracking studies were performed.[26–40] A more robust method of IRED placement on the range scanner was developed, allowing for tracking with sub-millimetric errors.[41]

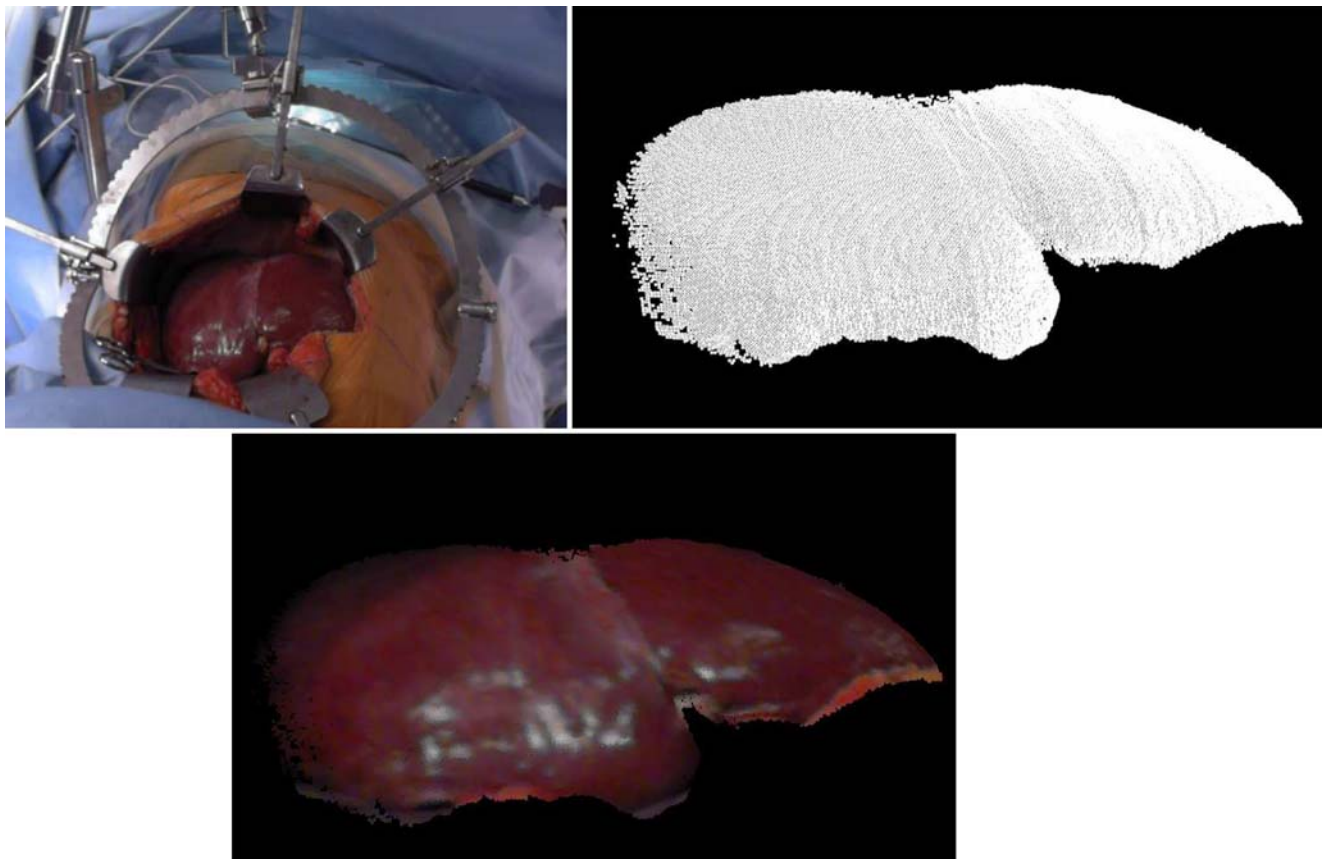


Figure 4 Data acquisition with the range scanner. The video snapshot on the *top left* and the three-dimensional data on the *top right* are combined to form a texture mapped point cloud, which is shown in the *bottom image*.

Rigid Registration

The surface of the liver has been chosen as the feature for registration. Intraoperative surface data are acquired using the range scanner or the tracked probe. These data are then registered with the surface model generated from the preoperative tomographic image volume using the iterative closest point (ICP) method.[42] To make the searching process more efficient, *k–d* trees were used.[43,44]

The ICP registration method can be susceptible to gross misalignment if a suitable initial estimate is not provided. We identify anatomical landmarks on or near the liver and use them to obtain an initial registration. Before the procedure, a set of four or five landmarks is identified in the image volume by the surgeon, and the landmarks' three-dimensional image coordinates are recorded. Typical landmarks include the inferior tip of the liver, the lateral tip of the right lobe, the portal vein bifurcation, and the junction of the inferior vena cava with the liver. In some instances, unique geometric features on the exposed liver surface are used. Then, the corresponding positions of these landmarks are identified intraoperatively by touching them with the tracked probe and recording the probe's position. Once the position of each anatomical landmark has been acquired, a point-based registration is computed that minimizes the root-mean-square distance between corresponding anatomical landmarks.[45–47] Due to the possibility of deformation and the difficulty in localizing landmarks, the resulting transformation is not accurate enough for guidance, but it usually can provide an acceptable guess that is close enough to result in ICP reaching a suitable minimum.

Intraoperative Deformation

The liver consists of soft tissue that undergoes deformation due to a number of surgical loads (resection, immobilization, and repositioning). Deformation could compromise the accuracy of targeting lesions if only a rigid mapping is used to register between the intraoperative data and the preoperative images. Thus, we implemented a biomechanical model of the liver using the finite element method (FEM) to handle deformation. The FEM analysis provides a powerful tool for modeling soft-tissue deformation and has been applied to the brain shift problem in neurosurgical procedures.[48–51] Efforts to implement finite element modeling in liver resections have been limited to virtual reality and surgical simulation, where accuracy of the deformation is sacrificed to achieve realistic deformations at real-time frame rates for the purposes of training and planning.[52–55] To begin the analysis, a volumetric mesh is generated from the patient's preoperative images, and it serves as the model used to solve a system of partial differential equations, which simulates the patient's liver undergoing a deformation. The simulation is driven by boundary conditions that describe the forces interacting with the liver surface. Some regions of the liver are held fixed, whereas others move freely. The third and most important category of boundary condition deforms points on the liver surface to match them with the intraoperative representation. More information on the implementation of the finite element model can be found in Cash et al.[56].

Surgical Navigation Software

The Operating Room Image-Oriented Navigation (ORION) system was created at Vanderbilt University to handle the tasks required for an image-guided surgical procedure. ORION was developed under Windows NT/2000 using Microsoft Visual C++ 6.0 and Win 32 API. Under the current framework, ORION is capable of rendering updates at a rate of 30–40 frames per second. For this study, new components were developed in ORION that involved fast surface registration, communication with the laser range scanner, and three-dimensional rendering of the liver surface. In addition, our group has collaborated with MeVis (Center for Medical Diagnostic Systems and Visualization, Bremen, Germany) to incorporate their vascular segmentation and representation capabilities[57] for surgical planning into ORION so that it can display the probe position with respect to their models of the vasculature, tumors, and resection planes. A screen shot from ORION during one of the procedures is shown in Fig. 5.

Clinical Acquisition

Institutional review board approval was obtained at both Vanderbilt University Medical Center and Washington University School of Medicine for the intraoperative acquisition of liver surface data. Informed consent was obtained from eight patients (five at Vanderbilt and three at Washington University) undergoing standard liver tumor resection procedures. Of these eight cases, only one patient was undergoing resection for a primary tumor; the other seven presented with metastatic liver tumors. Three of the patients were female, whereas five of the patients were male, and their mean age was 59.4±9.2 years. The results presented from case 6 of this group have been previously published by our group.[26,58]

For the purpose of registration, planned periods of apnea were used to decrease respiratory-related liver motion. These apneic periods were part of the approved institutional review board protocol, and each occurred at the same point in the respiratory cycle so that the liver would reside approximately in the same location for every registration. There were two to five brief apneic periods, each lasting no more than 4 min, over the course of the procedure. During

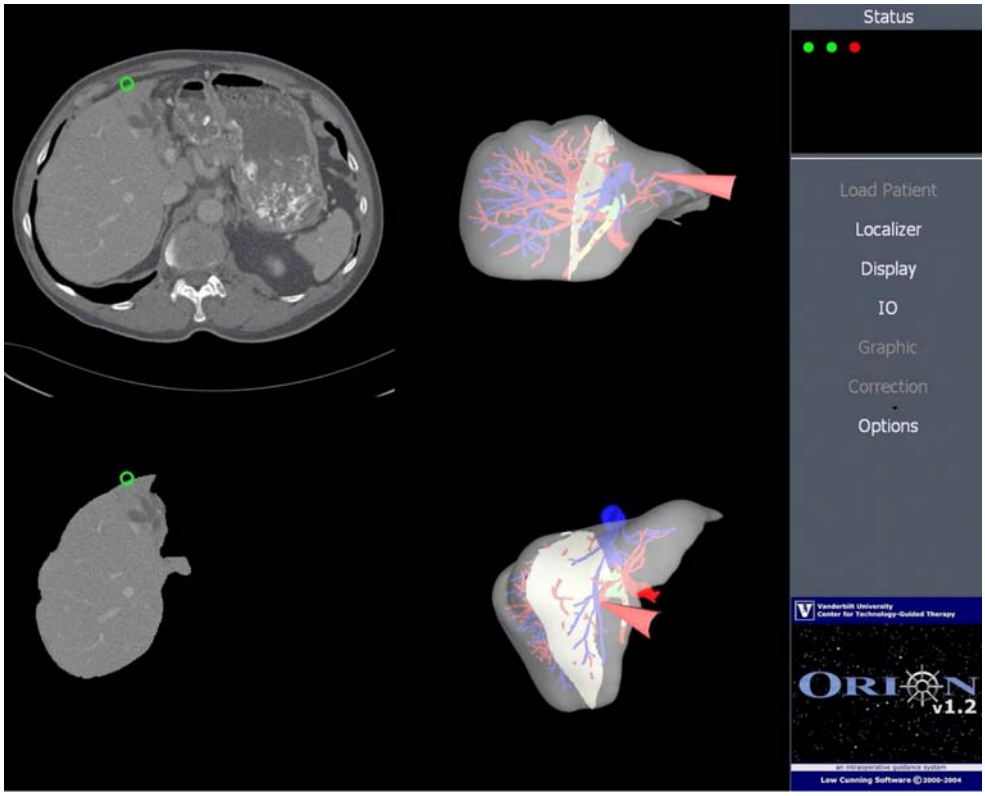


Figure 5 Screen shot of the ORION surgical navigation software. ORION is displaying, from the *top-left panel clockwise*, the native tomogram, two different perspectives of the three-dimensional liver and the vasculature as segmented by MeVis, and a tomographic slice of the segmented liver.

each apneic period, physical space data were acquired for the registration process. First, point-based landmarks were digitized with a sterilized, tracked probe for the purposes of determining an initial estimate of the registration that served as input to the ICP algorithm. After the initial alignment, surface data were captured with either the probe or the range scanner. The probe was placed in contact with the liver and swept across the surface. The range scanner attaches to a surgical arm that stays out of the operating field while not in use. When ready to scan, the surgical arm is swiveled into the intraoperative scene as shown in Fig. 3. After a brief setup for positioning the scanner and determining the correct parameters, the surface is scanned. The scanner has the potential to acquire anywhere from 15,000 to 45,000 points on the liver surface. The number of points acquired is dependent on the organ size and the area of liver surface visible to the scanner. In four of the eight cases, range scan data of the liver surface were available. In all but one case, surface data were acquired using an optically tracked probe.

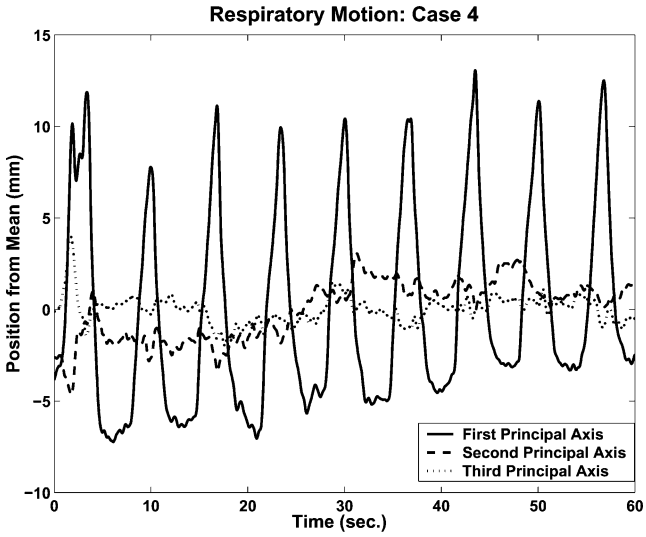
Experimental Studies

In this study, three separate experiments were performed in the operating room to determine the feasibility of this image-guided liver surgery system. The first set of experiments examined the nature and magnitude of motion in the liver due to respiration. In these experiments, a tracked probe was placed on the liver surface, and three-dimensional position information was acquired for 30–60 seconds, corresponding to 4–10 breathing cycles. During this acquisition, the tip of the probe was placed on a point of the liver surface. The surgeon maintained contact with this point and allowed the probe to move with the organ during the respiratory cycle. The probe tip's three-dimensional position was recorded at a rate of 40 Hz, and the time course of this position data represented the motion path for this particular liver surface point during respiration. To analyze the resulting motion data, noise was removed using a moving average filter. Then, the three-dimensional path representing the liver point's motion during these respiratory cycles was examined using principal

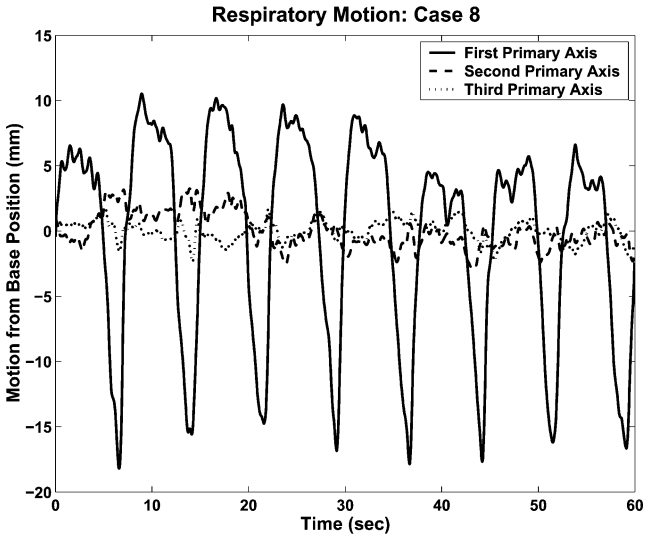
Table 1 Principle Component Analysis of Respiratory Motion Data

Case	Percent of motion attributed to primary axis	Motion along primary axis (mean±SEM) (mm)
1	87	12.5±1.2 (n = 5)
3	97	11.2±3.5 (n = 4)
4	91	17.1±1.4 (n = 21)
5	74	6.8±1.8 (n = 13)
6	80	14.1±1.7 (n = 7)
7	80	11.9±2.0 (n = 6)
8a	96	24.6±1.9 (n = 8)
8b	98	29.7±1.2 (n = 8)

No respiratory data were acquired in case 2, and two separate sets of respiratory data were acquired in case 8.



(a) Case 4



(b) Case 8

Figure 6 Time plot of respiratory data. The data are aligned according to the axes provided by the primary component analysis. The origin is the mean of the original respiration data.

component analysis (PCA). This PCA reorganizes the coordinate system so that it is aligned with the three axes where the variance is the greatest. If PCA indicates that the variance along one of these axes is greater than the other two, this signifies that the point travels primarily along one dimension during respiration.

The second set of experiments focused on the accuracy of the surface registration algorithm. For each subject, two registrations were performed. "Registration A" involved computing the registration between the intraoperative surface data of the patient and the preoperative surface manually segmented from the tomographic data. "Registration B" performed the same registration except that it used the results from the level-set semiautomatic segmentation rather than the manual method. Both registrations used the same intraoperative data and transformed them into the preoperative image coordinate system. The difference between these registrations was defined by taking each point in the intraoperative surface and calculating the distance between its resulting position from registration A and its resulting position from registration B. If the root-mean-square distance taken over all the intraoperative points is small, it indicates that the two registrations produce similar results. Similar registrations indicate that variations between the two segmentations are effectively negligible and the semiauto-

Table 2 Surface Registrations Between Intraoperative Range Scan Data and Preoperative Surfaces

Case	No. of scan points	Registration A (manual) RMS residual (mm)	Registration B (semiautomatic) RMS residual (mm)	RMS difference (A to B) (mm)
1	19,000	6.2 (18.7)	6.4 (19.8)	1.8 (3.2)
2	20,000	5.0 (18.4)	5.0 (16.7)	2.2 (3.3)
6	29,000	2.3 (11.9)	2.3 (11.5)	1.4 (2.7)
7	48,000	5.5 (19.2)	5.2 (18.5)	3.5 (5.7)

Registration A involves manually segmented preoperative surfaces. Registration B uses surfaces from the semiautomatic level-set technique. The second column indicates the number of intraoperative data points (rounded to the nearest 1,000). The third and fourth columns provide the root-mean-square (RMS) (and maximum) surface residual for registrations A and B. The final column holds the RMS difference between registrations A and B.

Table 3 Surface Registrations Between Intraoperative Tracked Probe Data and Preoperative Surfaces

Case	No. of scan points	Registration A (manual) RMS residual (mm)	Registration B (semiautomatic) RMS residual (mm)	RMS difference (A to B) (mm)
2	1,600	6.5 (24.9)	6.7 (23.4)	2.3 (5.2)
3	500	5.7 (20.9)	5.0 (19.4)	19.5 (35.6)
4	1,500	5.0 (14.6)	4.9 (19.8)	5.6 (7.7)
5	700	6.0 (17.1)	5.9 (17.1)	6.5 (10.0)
6	2,400	3.0 (20.0)	3.0 (21.2)	1.2 (1.9)
7	1,900	6.4 (24.8)	6.4 (26.4)	2.9 (5.5)
8	2,200	6.5 (20.5)	6.0 (17.9)	3.7 (5.5)

Registration A involves manually segmented preoperative surfaces. Registration B uses surfaces from the semiautomatic level-set technique. The second column indicates the number of intraoperative data points (rounded to nearest 1,000). The third and fourth columns provide the root-mean-square (RMS) (and maximum) surface residual for registrations A and B. The final column holds the RMS difference between registrations A and B.

matic segmentation will be suitable, thus greatly reducing processing time before surgery. Also, this result likely means that there are unique geometric features that were captured both intraoperatively and preoperatively, which drive the rigid registration to the same end result.

To assess the accuracy of the registration, targeting studies were performed as part of the registration experiments. Targets are geometrical features that can be identified in both the intraoperative and preoperative data but are not involved as part of the registration process. The most reliable targets are point-based landmarks that can be localized in both modalities with a high degree of accuracy. However, there are no point-based rigid landmarks available during this application, so other methods of targeting must be developed. For three of the cases, the inferior edge of the liver could be manually identified in the range scan data, and it was broken into three adjoining regions to serve as targets for initial studies. When one of these regions served as the target region, it was removed from both surfaces. After the registration was performed, a surface target error was calculated. Two metrics were used for surface target error. The first was a root-mean-square closest-point residual error between the two targets, identical to the metric used in the registration algorithm itself. A more rigorous metric uses the distance between each point on the preoperative target region and the intersection where the point's surface normal crosses with the intraoperative target surface.

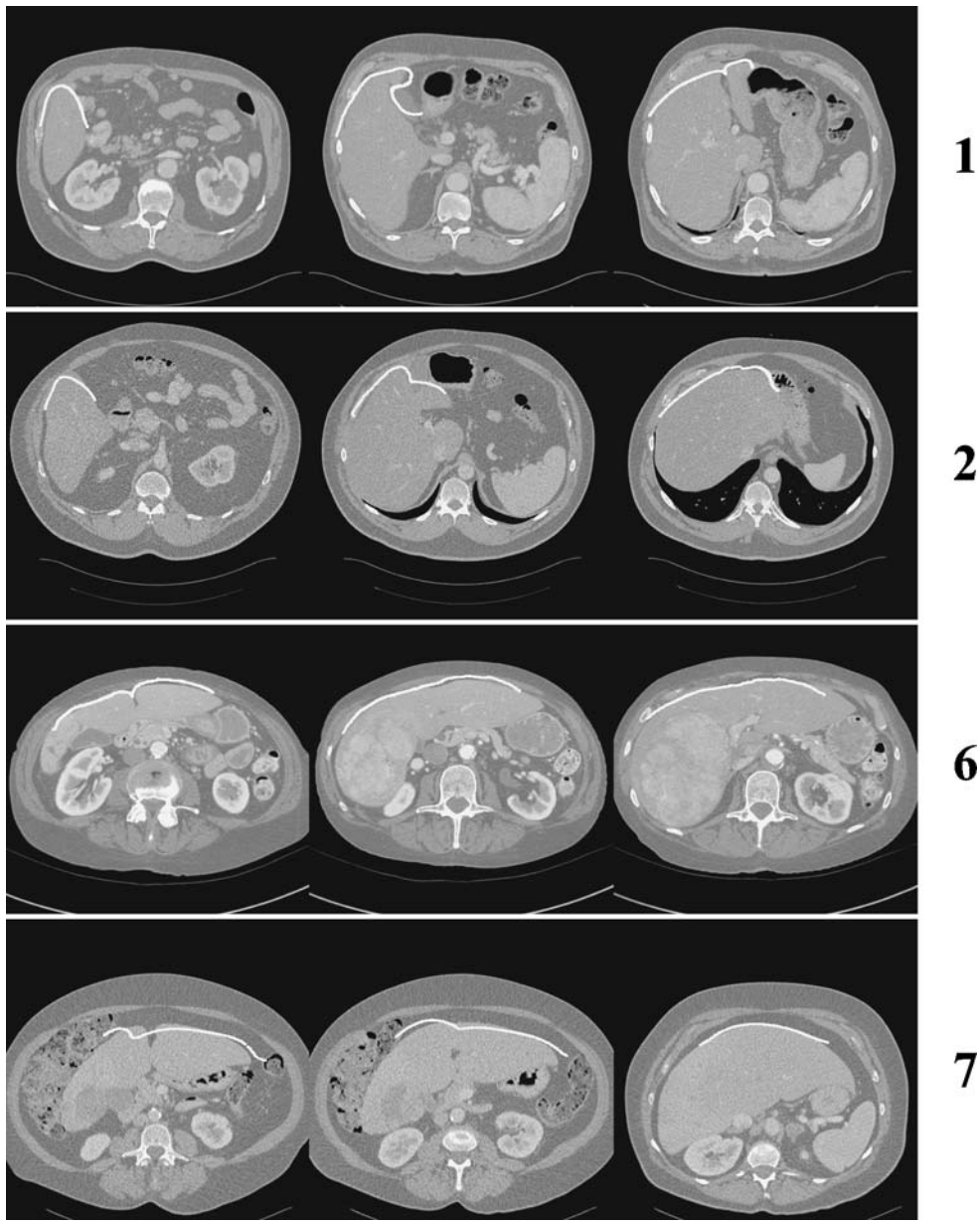


Figure 7 Iterative closest point registration results. For each case, the registered range scan data is overlaid on top of the three tomographic slices from the volume.

The final set of experiments tested the ability of the finite element model to compensate for intraoperative deformation remaining after the rigid alignment. First, a tetrahedral mesh was constructed based on segmentations of the preoperative data. Then, boundary conditions were applied to the model that represented the intraoperative conditions, fixing immobilized parts of the liver and forcing displacements in other regions that were dictated by their distance to the rigidly registered intraoperative data. Once the boundary conditions were applied, the displacements were solved using the FEM model. The resulting deformed mesh was overlaid on top of the preoperative tomograms and intraoperative data to qualitatively assess the results.

Results

Respiratory Motion

Table 1 shows the results from the PCA of respiratory motion. No respiratory data are available for case 2. Two sets of data from different time points during surgery were available for case 8. For each case, the percentage of motion that is attributed to the primary axis is shown, along with the average motion in millimeters between peak inhalation and peak exhalation that the liver moves along the primary axis. Figure 6 shows time plots of respiratory data from cases 4 and 8. The three plots represent each of

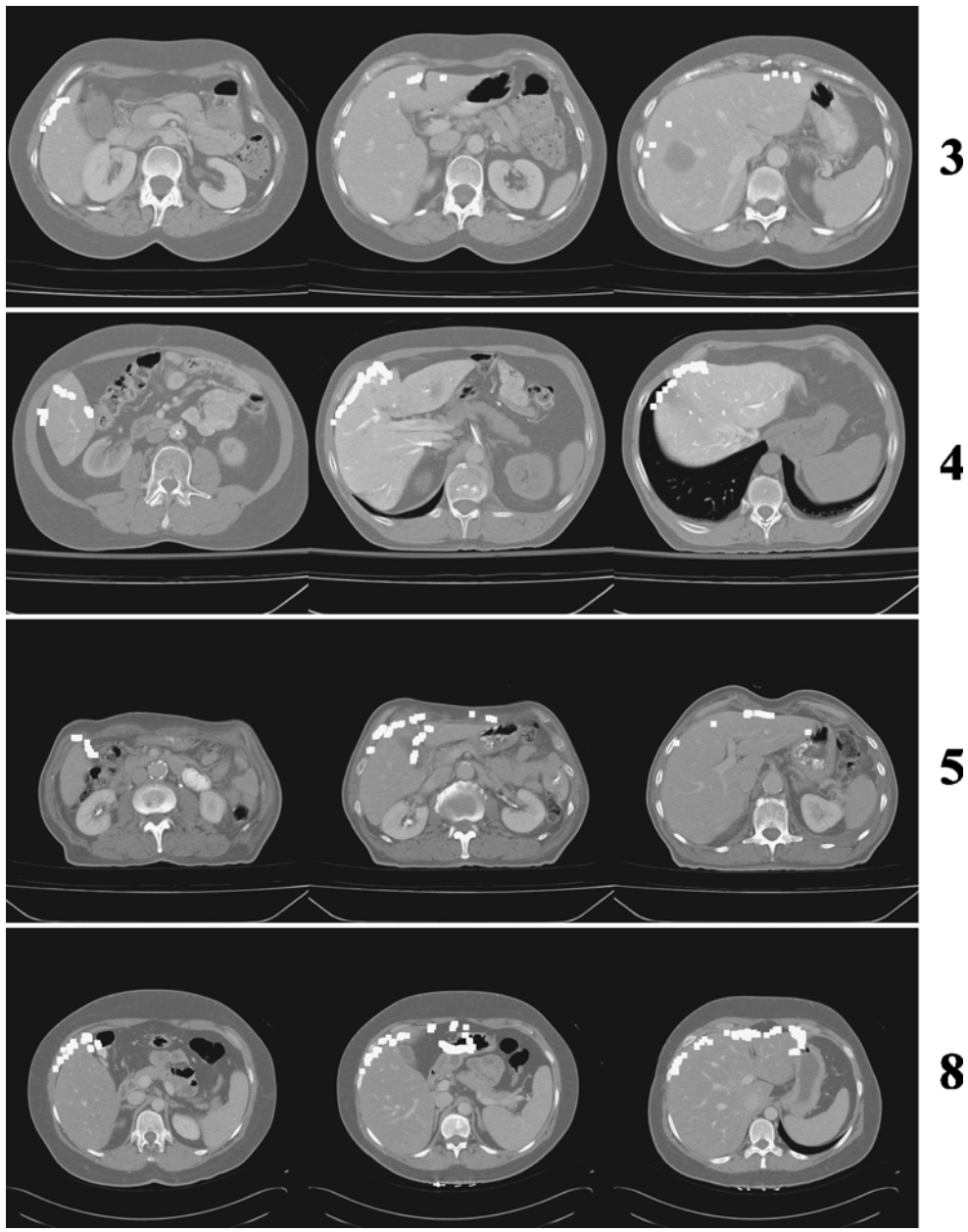


Figure 8 Iterative closest point registration results. For each case, the registered probe data are overlaid on top of the three tomographic slices from the volume.

the three primary axes as determined by PCA. The origin represents the mean position of this data.

Surface Registration

The segmented surfaces used for registration studies contained 45,000 to 80,000 vertices. However, for each individual subject, the difference between manual and level-set segmented surfaces was not greater than 3,000 vertices. Table 2 shows the results from registrations between intraoperative range scan data and preoperative tomograms, whereas Table 3 shows the results from the registrations between tracked probe data and the preoperative tomograms. In these tables, the second column indicates the number of intraoperative surface points acquired, which was rounded to the nearest 100. The values in the third and fourth columns represent the root-mean-square surface residual error (with the maximum closest point distance given in parentheses) for registrations based on the manual (registration A) and semiautomatic (registration B) segmented surfaces. This root-mean-square residual is the metric used in the minimization process of the ICP algorithm and describes the total error of fit between the two surfaces. However, sometimes, this value may be misleading with regard to accuracy in the resulting registration. The final column is the measure of similarity

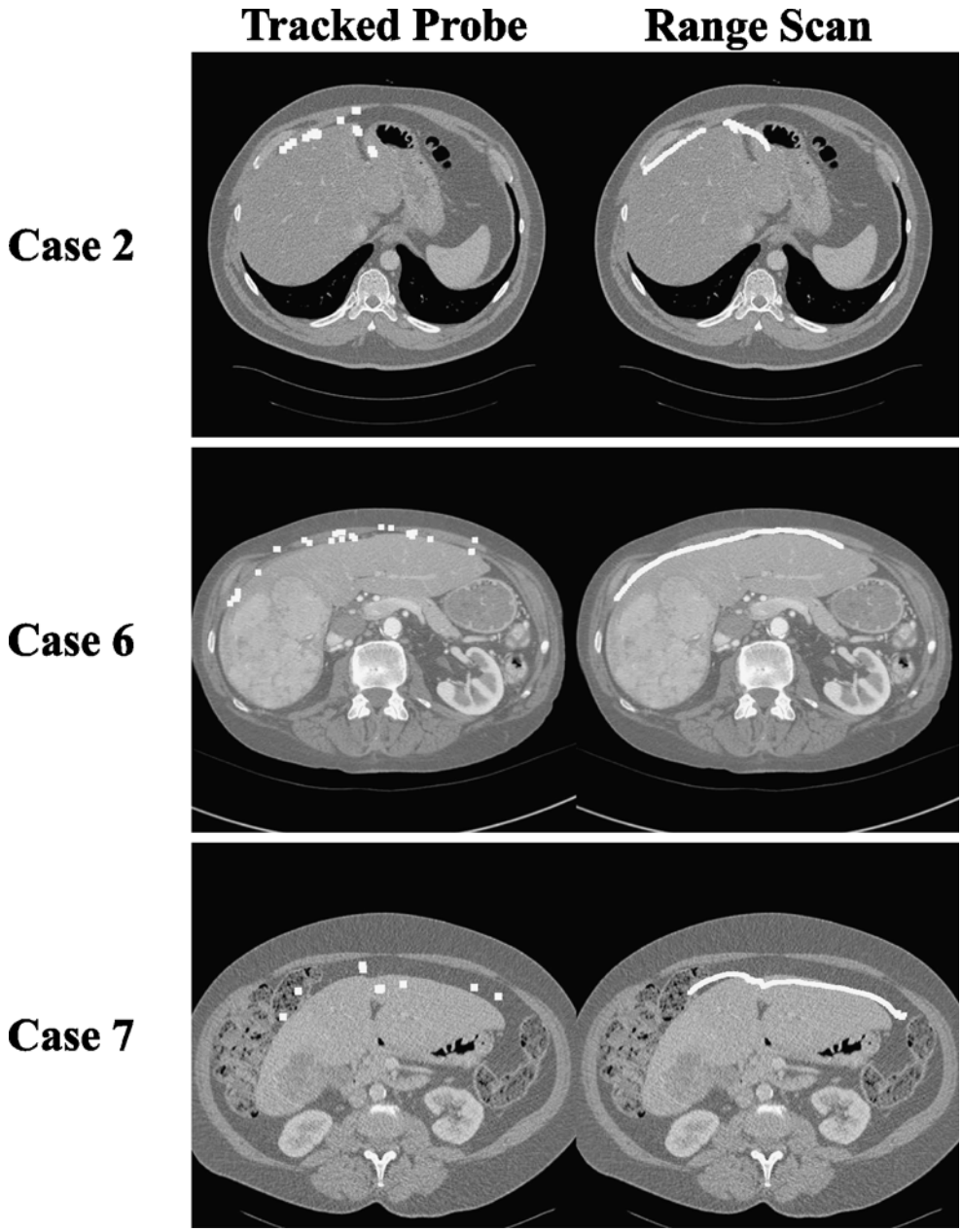


Figure 9 Comparison of surface registrations using tracked probe (*left column*) and range scan (*right column*). Both datasets are overlaid on the identical slice from the image volume.

between the registrations using these two surfaces. This measure is the root-mean-square distance that separates the resulting location of points transformed by registration A versus registration B.

Figures 7 (range scan data) and 8 (tracked probe data) show a graphical representation of the registration results. In these figures, the intraoperative data are overlaid onto the corresponding tomographic slices. In three cases, both tracked probe data and range scan data of the liver surface were available, and each modality was used for a surface registration. A comparison of the resulting registrations is shown in Fig. 9, where both datasets are overlaid on the same tomographic slice using the respective registrations.

The results of the targeting studies are found in Table 4. In each case, the inferior edge is broken into three regions (left, middle, and right), which serve as surface targets. The target regions were removed from the surfaces before registration and then used after the registration to compute two metrics: the standard root-mean-square closest point residual and the distance between points in the target surfaces along the normal vector. These two metrics are shown in the fourth and fifth columns, respectively.

Finite Element Modeling

Figure 10 shows the results from the patient model, where the displacements at each node have been used to warp the preoperative image. The deformed image is fused with the preoperative data and the registered point cloud to show the difference between the registration before and after implementation of the finite element model. The boundary conditions provide a good agreement between the deformed preoperative surface and the intraoperative surface data. The inside of the liver, where data are unavailable, is displaced in a manner that is determined by the underlying biomechanics of the finite element model.

Discussion

This study attempts to provide the framework for applying IGS concepts to liver resections. We show how this framework has been applied during initial clinical settings and analyze some of the most significant issues that could affect the surface registration. With a successful registration, the ORION system can provide powerful navigation aids to the surgeon as illustrated in Fig. 5. It can display the position of a tracked surgical instrument in relation to preoperative tomographic volumes and rendered surfaces, including important subsurface vasculature and tumors. This will allow the surgeon to have real-time quantitative information regarding the proximity of critical vascular and biliary structures as well as preoperative resection plans.

Providing navigation assistance to the surgeon using preoperative tomograms through IGS could provide some potential advantages over intraoperative ultrasound (IOUS) alone, which is the most common form of providing intraoperative navigation in liver surgery. First, accurate registration of nonvisible tumors to the operating-room environment would allow for maximum retention of healthy unaffected liver tissue by allowing tighter margins. Second, these nonrigid model-based deformation methods will not only improve tumor registration but also the underlying vascular network; that is, the methods will also allow for nonrigid alignment of computerized tomographic angiography, which is of primary importance in resective therapy. Finally, subsurface tumors can confound vascular representation in IOUS; if this method is performed in conjunction with coregistered IOUS, discrepancies in vascular ultrasound images may be corrected.

Other researchers have focused their efforts on phantom studies[25,27] and percutaneous studies,[24,28,30–32] but this work is unique in that it concentrates on acquiring and registering data from open abdominal hepatic tumor resections. Our initial work was also based on phantom studies, which resulted in registration errors of 2.9 mm and targeting errors of 2.8 mm.[23] The updated system, which was used for these studies, used the laser range scanner to reduce registration errors and target errors in phantom studies to under 0.8 and 2.0 mm, respectively.[26] The clinical findings result in higher registration errors due to the presence of a number of factors that can be eliminated during idealized phantom studies. The most important aspects are the decrease in the exposed surface region that can be acquired by the range scanner and the presence of

Table 4 Results of Targeting Studies During Surface-based Rigid Registration

Case	Target	No. of points	Mean residual (mm)	Normal distance (mm)
1	Right	1,700	5.1±3.5	4.7±2.5
	Middle	1,500	5.1±3.5	5.6±2.7
	Left	2,700	4.8±3.5	9.3±3.7
2	Right	3,000	5.0±3.7	4.5±3.7
	Middle	1,900	4.9±3.6	7.9±4.5
	Left	1,500	4.9±3.7	9.0±5.1
7	Right	1,000	4.5±2.9	5.2±4.3
	Middle	1,600	4.4±2.9	5.5±5.2
	Left	1,300	4.5±3.0	2.6±2.5

In these studies, the targets are based on the inferior ridge of the liver broken into three regions. There are two metrics listed for each target. The first metric is a closest point distance (mean±SEM) in millimeters, which is listed in the fourth column. The second is the root-mean-square (mean±SEM) distance from each point on the preoperative target surface to where its surface normal intersects with the intraoperative target surface.

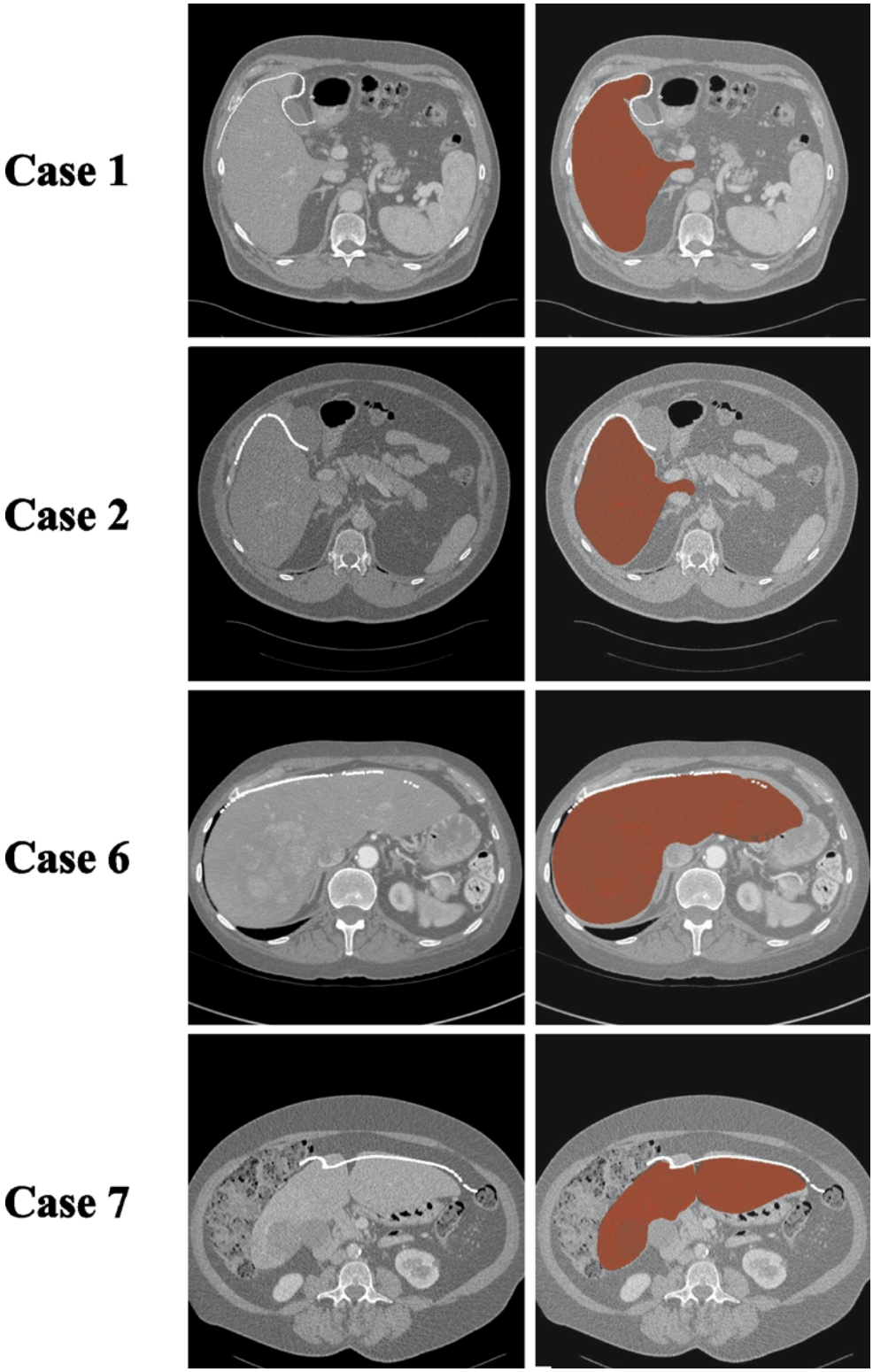


Figure 10 *Left column*—Original rigid registration of range scan data overlaid on tomograms. *Right column*—The deformed liver volume from the finite element model is overlaid in *red*. In the areas where the point cloud was used for the boundary conditions, there is improved agreement between the range scan surface and the deformed image surface.

intraoperative deformation. Other factors include the inaccuracies of the segmentation and the introduction of added noise to the range scan data caused by surrounding structures and surgical instruments located in the scanner's field of view.

This study also examined the amount of respiratory motion in the liver observed during a procedure. Our group first examined respiratory motion when Herline et al.[21] did some initial studies in two human patients. His results indicated the mean ± SEM motion of the liver during a

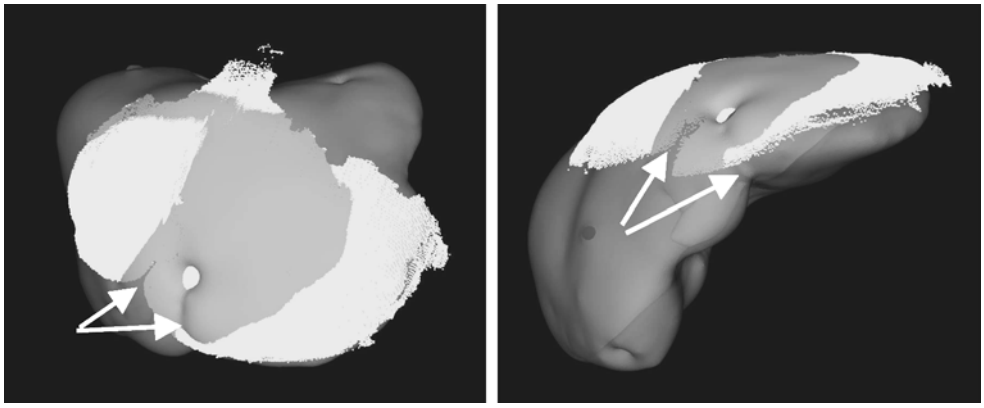


Figure 11 In case 7, the relatively planar range scan data result in misalignments during the surface-based registration. The qualitatively identified landmark, where the falciform ligament resided before surgery, is rotated clockwise as indicated by the *white arrows*.

respiratory cycle was 10.3±2.5 mm. These results are consistent with the amplitude of respiratory motion in our findings. In addition, we used PCA to determine how much of the motion is along one dimension, as it has been done in related noninvasive imaging studies.[17–20] Their results indicate periodic one-dimensional motion along the cranial–caudal axis on the order of 10–30 mm. However, in our intraoperative data, there is some misalignment present when the primary axis of the motion is transformed into image space and compared to the imaging axis that corresponds to the cranial–caudal direction. This misalignment could be caused by registration errors or patient positioning on the imaging gantry, but another significant cause could be the repositioning of the liver during surgery. Thus, the intraoperative orientation with respect to the cranial–caudal axis has been modified. This information will be valuable for future studies to account for this motion and lower the number of apneic periods.

From Table 2, the range scanner is capable of acquiring 20,000–50,000 points on the liver surface for each acquisition. Each acquisition takes approximately 20 s, with another minute for positioning as the experimental setup is not yet optimized. In comparison, using the standard rate of 40 Hz for point acquisition with the tracked probe, it would take more than 6 min to acquire the same amount of points. The results from the registration experiments indicate that the range scanner provides a better likelihood of an accurate, robust registration than does the optically tracked pen probe. In addition, the range scanner provides uniformly sampled data using a noncontact method. Both of these features limit the amount of error in surface acquisition compared to the tracked probe. These differences are showcased in Fig. 9. As a result, the range scanner provides data for a surface registration that is independent of segmentation method as indicated in Table 2. Table 3 shows the large differences in registration results with respect to segmentation method when using the tracked probe. As semiautomatic segmentation becomes less influenced by registration, hours of user interaction time can be saved before the procedure.

While the overall number of points is important to the performance of the registration, so is the information that they contain. If the range scanner captures a region that is relatively planar, then the ICP algorithm could determine multiple alignments that provide equally suitable matches. As a result, a misalignment could be determined to be equally as desirable as the correct registration. However, when geometrically unique regions of the liver are captured, many of the false matches are eliminated. The most practical feature in terms of exposure is the inferior edge of the liver near the junction of the left and right lobes at segments III, IV, and V. In case 7, there was very little information about the ridge present in the range scan, which causes a visible misalignment (shown in Fig. 11). In this figure, the notch where the falciform ligament usually resides serves as a qualitative landmark. The misalignment causes this landmark to rotate clockwise as indicated by the arrows. Also, Table 2 indicates that case 7 has the highest difference in registration between the two segmentation methods among the cases with range scan data. This is another indicator that relatively planar surfaces do not

Table 5 Approximate Time Requirements for the Tasks in Image-guided Liver Surgery

Task	Approximate time
Preoperative tasks	
Manual segmentation	3–4 h
Automatic segmentation	15 min
Marching cubes	5 min
Radial basis function Surface Fitting	5 min
Range scan calibration	5 min
Intraoperative tasks	
Landmark localization and registration*	30 s
Surface acquisition with tracked probe*	1–2 min
Range scan setup (not optimized)	1–2 min
Surface acquisition with range scanner*	15–20 s
ICP registration using *k–d* trees	1–5 min
Modeling with finite element method	2–3 min
Image deformation	2–3 min

*These tasks need to be performed during an apneic period.

produce a unique alignment and are susceptible to misregistration. To confirm the assertion that the ridge produces robust surface registrations, multiple registrations were performed on the same data while perturbing the initial alignment. The registration converged to the correct alignment over a higher range of perturbations when a pronounced ridge was present. As a result, the range scanner is now oriented at more of angle rather than an overhead perspective of the operating field, and in some cases, the liver is repositioned to make the ridge more accessible. This increases the likelihood that unique surface features are acquired from the liver.

In all cases, a significant component of the rigid registration error can be attributed to nonrigid deformation. The intraoperative forces and manipulation cause noticeable shape changes in the liver compared to the preoperative images. When deformation is encountered by the rigid ICP registration, it interprets this nonrigid motion as a registration error. In some cases, such as case 7, the change in shape may be one of the factors inducing a misalignment. In each of the four cases displayed in Fig. 10, there is strong agreement between the intraoperative data and the preoperative image surface after being deformed by the finite element model. This outcome is the direct result of the boundary conditions explicitly driving the boundary nodes to the intraoperative data. Because only an incomplete region of the liver surface is acquired during surgery, boundary conditions from these areas must recover most of the intraoperative deformations. The finite element model is desirable for this application because it determines a deformation that is based on the underlying biomechanics. In phantom studies, the FEM was able to recover deformations on the order of 3–4 cm to within a subsurface target error of 4.0 mm.[56] Currently, the finite element studies are conducted retrospectively, and future studies will determine the logistics of incorporating the required computational resources into the operating-room system.

While accuracy for image-guided systems is paramount, the amount of time required by this technology also plays a role in feasibility. Increased time under anesthesia could provide a health risk to the patient. In our framework, most of the time-consuming tasks are part of the preoperative preparation and often take place several days before the procedure. None of the intraoperative tasks takes more than a few minutes, and only surface acquisition and registration evaluation require apneic periods. Because all apneic periods are initiated at the same point of the respiratory cycle, a single surface registration should hold over many apneic periods. Major events, such as readjustment of the liver or resection, may require another registration. A summary of the events in IGS along with the time required to perform each task is located in Table 5.

Conclusions

We present some initial data regarding intraoperative surface registration for open abdominal hepatic tumor resection procedures. Respiration motion has been quantified as one-dimensional and periodic. This motion is primarily aligned in the cranial–caudal direction although the liver is slightly reoriented during the surgical process. Registrations were robust and accurate when using dense surface data acquired intraoperatively from the range scanner. Additionally, these registrations performed better when the range scan data were able to capture the unique geometric information from the ridges on the liver surface. Using the ridge as a target surface, the error calculated from average normal distance was less than 1 cm. Finally, finite element modeling was implemented to compensate for intraoperative deformation. It was shown to qualitatively improve the alignment by deforming the preoperative mesh to match the intraoperative conditions captured by the range scanner.

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Preoperative Chemotherapy for Colorectal Liver Metastases: Impact on Hepatic Histology and Postoperative Outcome

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Abstract Some investigators have suggested that preoperative chemotherapy for hepatic colorectal metastases may cause hepatic injury and increase perioperative morbidity and mortality. The objective of the current study was to examine whether treatment with preoperative chemotherapy was associated with hepatic injury of the nontumorous liver and whether such injury, if present, was associated with increased morbidity or mortality after hepatic resection. Two-hundred and twelve eligible patients who underwent hepatic resection for colorectal liver metastases between January 1999 and December 2005 were identified. Data on demographics, clinicopathologic characteristics, and preoperative chemotherapy details were collected and analyzed. The majority of patients received preoperative chemotherapy (n=153; 72.2%). Chemotherapy consisted of fluoropyrimidine-based regimens: 5-FU monotherapy, 31.6%; irinotecan, 25.9%; and oxaliplatin, 14.6%. Among those patients who received chemotherapy, the type of chemotherapy regimen predicted distinct patterns of liver injury. Oxaliplatin was associated with increased likelihood of grade 3 sinusoidal dilatation (p=0.017). Steatosis >30% was associated with irinotecan (27.3%) compared with no chemotherapy, 5-FU monotherapy, and oxaliplatin (all p<0.05). Irinotecan also was associated with steatohepatitis, as two of the three patients with steatohepatitis had received irinotecan preoperatively. Overall, the perioperative complication rate was similar between the no-chemotherapy group (30.5%) and the chemotherapy group (35.3%) (p=0.79). Preoperative chemotherapy was also not associated with 60-day mortality. In patients with hepatic colorectal metastases, preoperative chemotherapy is associated with hepatic injury in about 20 to 30% of patients. Furthermore, the type of hepatic injury after preoperative chemotherapy was regimen-specific.

Keywords Colorectal metastasis · Preoperative chemotherapy · Steatosis · Hepatic injury

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Introduction

Whereas in the past, bolus 5-fluorouracil and leucovorin had reported response rates of only about 20%,[1–5] over the past decade, additional chemotherapeutic and biologic agents have been found with significantly increased activity against colorectal cancer. Specifically, multiple authors have reported that combination therapies with oxaliplatin or irinotecan can achieve response rates of greater than 50%.[6–9] These newer agents not only have led to improved response rates, but also a notable prolongation of survival for patients with traditionally nonresectable disease. In fact, some patients with large bulky multifocal disease can have a dramatic decrease in tumor burden after treatment with preoperative chemotherapy.[10–12] This improved efficacy of chemotherapy has allowed a subset of previously unresectable patients to undergo surgery. Adam et al.[11] have reported

that about 10 to 15% of patients with initially "unresectable" disease can have significant tumor downsizing to the point that the disease can ultimately be considered resectable. As such, preoperative systemic chemotherapy may have several theoretical advantages. These include the potential to downsize tumor(s) preoperatively,[10–12] to increase curative resection rates,[13] and to convert some patients from unresectable to resectable disease.[10,12] Use of preoperative therapy as a neoadjuvant approach in patients with initially resectable metastases may also assist in identifying responders so that therapy can be tailored postoperatively based on preoperative response, as well as spare some patients who progress on preoperative chemotherapy from a nontherapeutic surgery.

Although the use of newer chemotherapeutic agents may have several potential clinical benefits, the effect that these agents have on the underlying liver parenchyma remains ill-defined. Some studies have associated the use of oxaliplatin with an increased incidence of hepatic sinusoidal obstruction,[14] whereas others have suggested that irinotecan may be associated with steatosis.[15] Fernandez et al.[15] reported that preoperative administration of oxaliplatin or irinotecan was associated with an increased risk of steatohepatitis, especially in the obese. In fact, in the report by Fernandez et al.,[15] one patient with a high body mass index (BMI) who received irinotecan died postoperatively. This study, however, included only 37 patients and needs to be confirmed in a large cohort of patients.

The purpose of the current study was to investigate the effect of preoperative chemotherapy treatment in patients undergoing curative resection of hepatic colorectal metastases. Specifically, we sought to examine whether treatment with chemotherapy before liver resection was associated with hepatic injury of the nontumorous liver and whether such injury, if present, was associated with increased morbidity or mortality after hepatic resection.

Patients and Methods

Three-hundred and thirty-six consecutive patients who underwent hepatic resection for colorectal liver metastases at Johns Hopkins Hospital between January 1999 and December 2005 were identified from our prospective institutional database. Of the 336 patients, 124 were excluded from further analyses (n=1, active hepatitis B infection of the liver; n=2, intraarterial chemotherapy before resection; n=2, hemochromatosis of the liver; n=4, severe cirrhosis; n=16, inadequate information available regarding prior chemotherapy treatment; n=44, pathology specimen unavailable; n=55, inadequate amount of nontumorous liver parenchyma in specimen for pathologic review). For the remaining 212 patients, standard demographic and clinicopathologic data were collected on each patient including sex, age, BMI, type and duration of preoperative chemotherapy, interval between last chemotherapy treatment and date of surgery, response to chemotherapy, details of the resection, characteristics of the resected tumor, and 60-day morbidity and mortality. Patients were divided into four groups based on their preoperative cytotoxic chemotherapy regimen: (1) no preoperative chemotherapy; fluoropyrimidine-based chemotherapy with (2) 5-fluoruracil (5-FU) monotherapy [5-FU with leucovorin (LV) or capcitabine], (3) irinotecan-based, and (4) oxaliplatin-based therapy. Patients who received targeted therapies (bevacizumab or cetuximab) were included and not analyzed separately. Hepatic resections were defined as major when three or more contiguous segments were resected. Response to chemotherapy was defined as "responsive" ($\geq$ 25% decrease in tumor bidimensional measurements on cross-sectional imaging), "stable" ($<$ 25% decrease in tumor bidimensional measurements on cross-sectional imaging), or "progressive" (any increase in tumor bidimensional measurements on cross-sectional imaging). Postoperative morbidity, including liver insufficiency defined as peak postoperative bilirubin greater than 6, was scored using an established grading system.[16,17]

Histologic Assessment

Histologic evaluation of the resected specimen was performed by a single attending pathologist (M.T.) with hepatobiliary expertise who was masked to the clinical data. Re-review of the specimens consisted of light microscopy examination of the original hematoxylin/eosin and Masson trichrome-stained slides. In all instances, the pathologic findings of the nontumorous hepatic parenchyma remote from the cauterized margin was examined and scored. Well-demarcated sinusoidal congestion only near the tumor or paralleling the cautery margin within the same slide was deemed as artifactual and excluded from pathologic scoring considerations.

For pathologic scoring purposes, a chemotherapy-associated liver injury (CALI) score was computed for each surgical specimen. The CALI score ranged from 0 to 16, with points being assigned for each pathologic characteristic (Table 1). In general, one point was allocated for the presence of most pathologic characteristics (e.g., biliary cholestasis, nodular regenerative hyperplasia, bile duct proliferation, peribiliary fibrosis, hepatic arterial/portal vein thickening or arterial hyalanosis, and steatohepatitis). The presence of steatohepatitis was defined according to the classification of Kleiner et al.[18] Other pathologic characteristics (e.g., portal inflammation, sinusoidal dilation/congestion, and steatosis) were scored on a graduated

Table 1 Chemotherapy-associated Liver Injury (CALI) Score

Pathologic characteristic	Point Allocation
Biliary cholestasis	0=absent 1=present
Bile duct proliferation	0=absent 1=present
Nodular regenerative hyperplasia	0=absent 1=present
Peribiliary fibrosis	0=absent 1=present
Portal chronic inflammation	0=none 1=mild 2=moderate 3=severe
Sinusoidal dilatation and congestion	0=no sinusoids involved 1=<1/3 of sinusoids involved 2=1/3 to 2/3 of sinusoids involved 3=>2/3 of sinusoids involved
Steatohepatitis	0=absent 1=present
Steatosis	1=<5% hepatocytes 2=6-30% hepatocytes 3=31-60% hepatocytes 4=>60% hepatocytes
Vascular changes	0=absent 1=present

scale (Table 1). The final CALI score was computed by summating the total number of points.

Statistical Analyses

Summary statistics were obtained using established methods. Student's *T* test was used for comparison of continuous variables with a normal distribution, whereas Mann–Whitney test was used to analyze continuous variables with a nonnormal distribution. Chi Square was used for comparing categorical variables. Multivariate analysis was performed using logistic regression. The odds ratio and the 95% confidence intervals (CI) were estimated and a p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS Version 11.5 (Chicago, IL).

Results

A total of 212 patients were included in the analysis. There were 138 (65.1%) men and 74 (34.9%) women; the mean patient age was 59.6 years (range 22 to 84). The majority of patients (n=133; 62.7%) had node-positive disease at the time of the initial colorectal resection. The presentation of hepatic metastases was metachronous in most patients (n=111; 52.4%), with the majority of these patients (n=73; 65.8%) having a disease-free interval greater than 1 year. The median number of hepatic metastases was 2 (range 1 to 15); the median size of the largest lesion was 3.3 cm (range 1 to 14 cm).

The majority of patients received preoperative chemotherapy (n=153; 72.2%) before surgical treatment of the hepatic metastases. In general, the baseline characteristics of the patients who did not receive chemotherapy and those who did receive chemotherapy were similar (Table 2). There was no difference in the number of major resections performed between the no-chemotherapy group (n=27; 45.8%) and the chemotherapy group (n=64; 41.8%; p=0.64). There was also no significant difference between groups with regard to sex, race, primary tumor stage, or the presence of diabetes (all p>0.05). Patients who received chemotherapy were, however, younger (mean age, 58.2 versus 63.1, p=0.02) and had a higher BMI (mean BMI, 28.9 versus 26.6, p=0.02).

Table 2 Patient Clinicopathologic Characteristics Stratified by Whether They Received Chemotherapy

Variable	No chemotherapy n=59 n (%)	Chemotherapy n=153 n (%)	P value
Age			
Mean (years)	63.1	58.2	0.02
Gender			
Female	24 (40.7)	55 (35.9)	0.61
Male	35 (59.3)	98 (64.1)	
Race			
Caucasian	54 (91.5)	143 (93.5)	0.89
African American	2 (3.4)	4 (2.6)	
Other	3 (5.1)	6 (3.9)	
Body mass index (kg/m^2)			
Mean	26.6	28.9	0.02
Less than 30	45 (76.3)	91 (59.5)	0.38
30 or greater	14 (23.7)	62 (40.5)	
Diabetes mellitus			
Present	7 (11.9)	24 (15.7)	0.65
Absent	52 (88.1)	129 (84.3)	
Primary lymph nodes			
Negative	25 (42.4)	37 (24.2)	0.13
Positive	29 (49.2)	104 (68.0)	
Not available	5 (8.5)	12 (7.8)	
Tumor size			
Median (cm)	3.0	3.5	0.83
Extent of hepatic resection			
Minor	32 (54.2)	89 (58.2)	0.64
Major	27 (45.8)	64 (41.8)	

Chemotherapy consisted of fluoropyrimidine-based regimens: 5-FU monotherapy, 31.6%; irinotecan, 25.9%; and oxaliplatin, 14.7%. Twenty-three (10.8%) patients received more than one chemotherapy regimen and were grouped by their most recent regimen. Of the 153 patients who received preoperative chemotherapy, the majority (n=99; 64.7%) received treatment for less than 12 weeks. Patient characteristics and operative details were stratified according to each specific chemotherapy regimen (Table 3). In general, clinicopathologic and tumor characteristics were similar among the different chemotherapy groups. However, patients who received 5-FU monotherapy were more likely to have a higher BMI (mean BMI: no chemotherapy, 26.4; 5-FU, 30.0; irinotecan, 28.1; oxaliplatin, 26.7; p=0.03). Tumor response to treatment was also higher among patients who received oxaliplatin (53.3%) or irinotecan (38.2%) compared to 5-FU (6.1%) (both p<0.001).

On final pathologic analysis of the resected specimen, the CALI score was significantly higher in the chemotherapy treated group (median 3, range 0 to 9) compared with the CALI score of patients not treated with chemotherapy (median 2, range 0 to 6; p=0.01). Specifically, steatosis >30% was identified in two (3.4%) patients who received no chemotherapy compared with 28 (18.3%) patients who were treated with preoperative chemotherapy (unadjusted odds ratio [OR]=6.38, 95% confidence interval [CI] 1.5 to 27.7; p=0.004). Steatohepatitis was noted in only three patients—all of whom received preoperative chemotherapy (Fig. 1). The proportion of grade 3 sinusoidal dilatation was also higher in patients treated with preoperative chemotherapy (4.6%) compared with patients who did not receive preoperative chemotherapy group (0%; p=0.02).

Among those patients who received chemotherapy, the type of chemotherapy regimen predicted distinct patterns of liver injury (Table 4). Specifically, steatosis >30% was associated with irinotecan (n=15; 27.3%) compared with no chemotherapy (n=2, 3.4%; OR=10.7, 95% CI 2.3 to 49.4; p<0.001), 5-FU monotherapy (n=10, 14.9%; OR=5.0, 95% CI 1.5 to 23.8; p=0.03), and oxaliplatin (n=3, 9.6%; OR=3.1, 95% CI 1.5 to 19.3; p=0.04). Similarly, irinotecan was associated with steatohepatitis, as two of the three patients with steatohepatitis had received irinotecan preoperatively. In contrast, oxaliplatin was associated with grade 3 sinusoidal dilatation compared with no chemotherapy (9.7% versus 0%; p=0.017). Of note, patients receiving oxaliplatin also tended to have a higher likelihood of severe (Rubbia–Brandt grade 3)[14] sinusoidal dilatation compared with patients who received 5-FU monotherapy (3.0%; OR=3.5, 95% CI 0.4 to 31.9; p=0.11) or irinotecan (3.6%; OR=2.5, 95% CI 0.4 to 26.1; p=0.15).

Table 3 Patient Clinicopathologic Characteristics Stratified by Type of Chemotherapy Regimen

Variable	5-Fluorouracil n=67 n (%)	Irinotecan n=55 n (%)	Oxaliplatin n=31 n (%)	P value
Age				
Mean (years)	60.6	55.9	57.1	0.05
Gender				
Female	21 (31.3)	18 (32.7)	12 (38.7)	0.77
Male	46 (68.7)	37 (67.3)	19 (61.3)	
Race				
Caucasian	64 (95.5)	49 (89.0)	31 (100)	0.82
African-American	1 (1.5)	3 (5.5)	0 (0)	
Other	2 (3.0)	3 (5.5)	0 (0)	
Body mass index (kg/m^2)				
Mean	30.0	28.1	26.7	0.03
Less than 30	33 (49.3)	18 (32.7)	8 (25.8)	
30 or greater	34 (50.7)	37 (67.3)	23 (74.2)	0.003
Diabetes mellitus				
Present	10 (14.9)	11 (20.0)	5 (16.1)	0.27
Absent	57 (85.1)	44 (80.0)	26 (83.9)	
Primary lymph nodes				
Negative	17 (25.4)	11	9	0.15
Positive	43 (64.2)	41	20	
Not available	7 (10.4)	3	2	
Tumor size				
Median (cm)	4.0	3.0	3.0	0.49
Extent of hepatic resection				
Minor	40 (59.7)	33 (60.0)	16 (51.6)	0.81
Major	27 (40.3)	22 (40.0)	15 (48.4)	

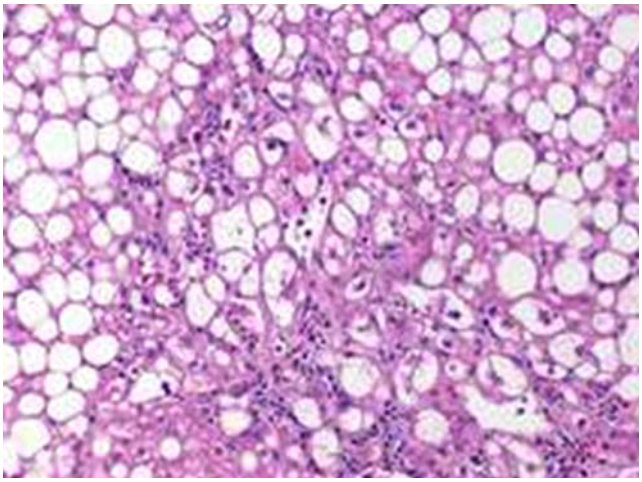

Figure 1 Features typical of steatohepatitis. Note the portal inflammation with lymphocytic infiltration, disorganized lobular parenchyma, and macrovesicular steatosis with evidence of ballooning.

When patients were stratified according to the duration of chemotherapy, patients who received<12 weeks of preoperative chemotherapy had a similar likelihood of steatosis >30% compared with patients who received chemotherapy for ≥12 weeks (17.2% versus 23.6%; OR=1.7, 95% CI 0.6 to 4.9; p=0.43). There was also no association between steatosis >30% and the time interval between cessation of chemotherapy and surgery (p=0.81). Similarly, there was no association between response to chemotherapy and hepatic injury (p=0.73).

The association between hepatic injury, diabetes, BMI, and chemotherapy was also examined. On both univariate and multivariate analyses, diabetes and BMI >30 were independently associated with steatosis >30%. The CALI score of diabetic patients was significantly higher than nondiabetics (median 4 versus 3, respectively; p=0.001); similarly, the CALI score of obese patients was higher than nonobese patients (median 4 versus 2, respectively; p=0.001). After adjusting for diabetes and BMI on multivariate analysis, irinotecan remained independently associated with steatosis >30% (adjusted OR=11.2, 95% CI 1.5 to 84.5; p=0.03). Of note, of the three patients who had steatohepatitis, two were diabetic, two had a BMI >28, and one patient was obese and had diabetes. Furthermore, both patients who were treated with irinotecan and subsequently developed steatohepatitis were obese.

The overall perioperative complication rate was 32.5% (n=69; Table 5). Twenty-three (10.8%) patients suffered from hepatic complications including liver failure (n=13), bile leaks/biloma (n=11), biliary stricture (n=1), and portal vein thrombosis (n=1). There were five (2.4%) patients with cardiovascular complications, three (1.4%) with pulmonary emboli, three (1.4%) with renal insufficiency, eight (3.8%) with a prolonged postoperative ileus, and 24 (11.3%) with postoperative infections (e.g., cellulitus, pneumonia, urinary tract infection). In the 13 patients who developed postoperative liver insufficiency, only a history of major hepatic resection was associated with an increased risk of postoperative liver insufficiency (OR=8.1, 95% CI 1.8 to 37.6; p=0.04). Overall, the perioperative complication rate was similar between the no-chemotherapy group (30.5%) and the chemotherapy group (35.3%) (p=0.79). In addition, the complication rate did not differ based on the type of chemotherapy regimen (5-FU monotherapy, 38.8%; irinotecan, 30.9%; oxaliplatin, 35.5%) (p=0.74). Furthermore, neither steatosis >30% nor the CALI score were associated with perioperative morbidity (both p>0.05). The overall median length of stay was 5 days (range 3 to 41) and did not differ between the no chemotherapy group (5 days; range 3 to 20) and the chemotherapy group (5 days; range 3 to 41; p=0.47).

Four patients died within 60 days of surgery for a perioperative mortality rate of 1.9%. Of the four deaths, one was caused by pulmonary aspiration, whereas the other three patient deaths were secondary to liver failure. There was no association between preoperative chemotherapy and the risk of postoperative mortality. In fact, no patient who died of liver failure had received preoperative chemotherapy before hepatic resection. The first patient who died of liver failure had a BMI of 34 and had not received

Table 4 Liver Injury Characteristics Stratified by Chemotherapy Regimen

	Steatosis > 30% n=30		Steatohepatitis n=3		Grade 3 Sinusoidal Dilatation n=7	
	Yes	No	Yes	No	Yes	No
No chemo	2 (3.4)	57 (96.6)	0 (0)	57 (100)	0 (0)	53 (100)
5-FU	10 (14.9)	57 (85.1)	1 (1.5)	66 (98.5)	2 (3.0)	65 (97.0)
Irinotecan	15 (27.3)*	40 (72.7)	2 (3.6)[a]	53 (96.4)	2 (3.6)	53 (96.4)
Oxaliplatin	3 (9.6)	28 (93.4)	0 (0)	31 (100)	3 (9.7)**	28 (90.3)

*p<0.001 compared to no chemotherapy; p<0.05 compared to 5-FU and oxaliplatin.
**p=0.017 compared to no chemotherapy; p=0.11 compared to 5-FU; p=0.15 compared to irinotecan.
[a] Too few events to permit meaningful statistical analysis.

Table 5 Perioperative Complications Stratified by Whether Patient Received Chemotherapy

	No Chemotherapy $n=59$	Chemotherapy $n=153$	P value*
Overall	18	51	0.746
Non-hepatic complications	16	41	1.000
Cardiovascular	4	1	
Pulmonary emboli	1	2	
Acute renal failure	2	1	
Prolonged ileus	4	4	
Postoperative infections	5	19	
Other	3	14	
Hepatic complications	8	16	0.629
Liver Failure	5	8	0.360
Bile leak/biloma	4	7	
Biliary stricture	1	0	
Portal vein thrombosis	0	1	
Length of stay (range)	5 (3–41)	5 (3–20)	0.187**

*Chi-square except when specified
**Mann–Whitney

preoperative chemotherapy. The patient underwent a right hemi-hepatectomy, wedge resection of the left lateral sector, and radiofrequency ablation of a lesion in segment 4. Postoperatively, the patient developed enterococcal bacteremia with multisystem organ failure. The patient died on postoperative day 10. Final pathology revealed >30% steatosis, mild sinusoidal congestion, and mild portal inflammation (CALI score 4). The second patient had a BMI of 30. This patient had received 11 months of adjuvant 5-FU/LV therapy after a right hemicolectomy for his primary tumor, but did not receive any additional preoperative chemotherapy before his hepatic resection. At the time of metastectomy, an extended right hepatectomy with en bloc resection of the diaphragm and a wedge resection from segment 3 was performed. This patient subsequently developed an infected biloma, had a slow rise in his bilirubin, and died on postoperative day 60 from liver failure. Pathology revealed mild steatosis, sinusoidal congestion, mild portal inflammation, and moderate portal fibrosis (CALI score 5). The third patient death from liver failure was a woman with a BMI of 26. She had received adjuvant 5-FU/LV after her colon resection, but did not receive neoadjuvant chemotherapy before hepatic resection. This patient underwent a right hemi-hepatectomy and cryoablation of a lesion in the left hemi-liver. In the postoperative period, she developed enterococcal line sepsis and a yeast urinary tract infection. The patient developed progressive liver failure with a peak bilirubin of 26.7 and she died on postoperative day 14.

Discussion

Over the last decade, advances in chemotherapy for the treatment of colorectal metastases have led to an increasing number of patients being treated with systemic therapy. In fact, many patients with colorectal hepatic metastases are now being treated with chemotherapy before the liver resection.[10,12,13,19–21] Although preoperative chemotherapy has been reported to decrease tumor burden in some patients[10–12] and may lead to improved resectability,[13] some investigators have questioned the safety of preoperative chemotherapy.[14,15,21] Specifically, Rubbia-Brandt et al.[14] reported that treatment with oxaliplatin was associated with hepatic sinusoidal dilatation and centrilobular vein fibrosis in the nontumorous liver. In the Rubbia-Brandt study,[14] however, there was no difference in the prevalence of steatosis between the group treated with chemotherapy versus the group that did not receive chemotherapy. In contrast, Fernandez et al.[15] reported an association between preoperative chemotherapy and steatosis/steatohepatitis. In the study by Fernandez et al.,[15] of the 14 patients who developed steatohepatitis, 10 had received preoperative chemotherapy with irinotecan-based therapy. The authors also suggested an association between preoperative chemotherapy, BMI, and risk of steatosis/steatohepatitis. More recently, the group from the University of Texas M. D. Anderson reported a chemotherapy-specific pattern of hepatic injury after preoperative chemotherapy for resectable hepatic colorectal metastases.[21] Specifically, oxaliplatin was associated with sinusoidal dilatation, whereas irinotecan was associated with steatohepatitis.

In the current study, we report our experience with the use of preoperative chemotherapy for resectable hepatic colorectal metastases. Similar to previous reports, we found that preoperative treatment with oxaliplatin was associated with a greater likelihood of grade 3 sinusoidal dilatation compared with no chemotherapy, 5-FU monotherapy, or irinotecan. However, although the risk of sinusoidal dilatation was higher in patients treated with oxaliplatin, the overall prevalence of grade 3 sinusoidal dilatation in patients treated with oxaliplatin was low (less than 10%). In addition, there was no difference in the rates of minor and moderate degree of sinusoidal dilatation between oxaliplatin therapy (34.9%) and all other therapies (32.9%; $P>0.05$). In contrast to oxaliplatin, irinotecan-based therapy was associated with an increased risk of steatosis >30%. Overall, the prevalence of steatosis >30% was 18.3% in the chemotherapy-treated group. However, patients who received irinotecan preoperatively were at a significantly

higher risk of steatosis >30% compared with no chemotherapy (OR=10.7) or treatment with non-irinotecan-based regimens (OR=3.1 to 5.0). Taken together, the findings of the current study provide an estimate of the expected prevalence of hepatic injury in patients receiving preoperative chemotherapy. Specifically, the data suggest that although chemotherapy associated liver injury does occur after preoperative treatment, the overall prevalence of such hepatic injury is relatively low (less than 20%). In addition, our findings confirm that there is not necessarily a "universal" type of hepatic injury secondary to preoperative chemotherapy. Instead, the phenotype of the hepatic injury is dependent on the preoperative chemotherapy regimen.

Interestingly, in the current series of over 200 patients, only three patients were noted to have steatohepatitis. Compared to previously reported series of patients treated with preoperative chemotherapy for resectable hepatic colorectal metastases,[15,21] the number of patients with steatohepatitis was lower than expected. The reason for the lower prevalence of steatohepatitis in the current study is probably multifactorial. Histological evaluation remains the only means of accurately assessing the degree of steatosis, as well as the distinct necroinflammatory lesions and fibrosis of steatohepatitis.[18] As such, distinguishing steatohepatitis from simple steatosis or steatosis with inflammation can be somewhat subjective and pathologist-dependent.[22] Despite attempts at consensus pathologic classification systems, the interrater variability between expert pathologists has been reported to be high for both steatosis and steatohepatitis.[23,24] We attempted to control for this interobserver variability by using a single pathologist with hepatobiliary expertise and by using a strict definition of steatohepatitis as defined by Kleiner et al.[18] Despite this, the histologic interpretation of the specimen probably accounted for the main reason that the prevalence of steatohepatitis was lower in our series than previous reports. Although only three individuals were found to have steatohepatitis, there were some interesting qualitative similarities among these patients: two out of the three received irinotecan, two were diabetic, and two had a BMI >28.

In the current study, both diabetes and BMI >30 were independently associated with steatosis >30%. This association between obesity and diabetes has long been recognized.[23,25–28] The pathophysiology of steatosis involves insulin resistance, [29–32] impaired β-oxidation of fatty acids,[32,33] accumulation of fatty acids within hepatocytes, [23,32] and alterations in the protein kinase C receptor.[23,34] Both obesity and diabetes are therefore associated with an increased risk of hepatic injury, as corroborated in the current study. We also report, however, that preoperative chemotherapy was an important risk factor for steatosis >30%, even after adjusting for obesity and diabetes. As such, obesity, diabetes, and preoperative chemotherapy are each independent predictors of hepatic steatosis. In particular, we found that steatosis >30% was associated with exposure to preoperative irinotecan. Given these data, use of preoperative chemotherapy may need to be more carefully considered in patients who are obese or in those who have diabetes, especially when utilizing irinotecan.

There was no association between the perioperative complication rate and preoperative chemotherapy (no-chemotherapy group, 30.5% versus chemotherapy group, 35.3%). In addition, the complication rate did not differ based on the type of chemotherapy regimen or the presence of steatosis >30%. Berhns et al.[35] similarly reported no significant difference in perioperative complications in patients with moderate to severe steatosis among patients who underwent liver resection in the era predating irinotecan and oxaliplatin. In contrast, Belghiti et al.[36] and Kooby et al.[16] did note an increase in morbidity in patients with steatosis among patients who underwent hepatic resection. Kooby et al.[16] reported an increase in surgical complications and an association between marked steatosis, chemotherapy, and BMI. Comparisons of chemotherapy, steatosis, and perioperative complications among different trials are, however, difficult. As in the current study, most studies report the degree of steatosis in a categorical, binary fashion (e.g., minimal-moderate, ≤30% versus severe steatosis, >30%). Because of this, the true underlying distribution of the severity of steatosis in each study is unknown, making direct comparisons of the relation between steatosis and complications among studies problematic. Notwithstanding, the data presented in the current study suggest that hepatic resection in select patients with steatosis >30% can be performed safely with no increase in perioperative morbidity.

Three patients died postoperatively secondary to liver failure. No patient who died of liver failure had received preoperative chemotherapy before hepatic resection. Therefore, there was obviously no association between preoperative chemotherapy and the risk of postoperative mortality. The three postoperative deaths did have a number of perioperative factors in common. Each patient had undergone major hepatic resection and two patients had also undergone concurrent ablation of the contralateral liver, thereby leaving each of the three patients with relatively little hepatic parenchymal reserve. All three patients also developed a severe infection in the postoperative period. The combination of marginal hepatic reserve and postoperative infection undoubtedly contributed to the development of liver failure and the patients' subsequent demise. Of note, we did not note an association between steatohepatitis and the risk of perioperative liver failure or mortality. In contrast, Vauthey et al.[21] have reported that patients with irinotecan-associated steatohepatitis were at an increased risk of both liver failure and postoperative death. However,

in the study by Vauthey et al.[21] every patient with steatohepatitis who died postoperatively had undergone a major hepatic resection with a concurrent ablation of the contralateral liver. The lack of association between steatohepatitis and perioperative mortality in the current study may be caused by the low number of exposure events (e.g., only three cases of steatohepatitis) and/or the fact that no patient with steatohepatitis underwent a major resection.

Conclusion

Preoperative chemotherapy was associated with an increased risk of hepatic injury to the nontumorous liver, however, the overall prevalence was relatively low (~20%). Hepatic injury after preoperative chemotherapy treatment was regimen-specific: oxaliplatin was associated with sinusoidal dilatation, whereas irinotecan was associated with steatosis >30%. In addition to preoperative chemotherapy, obesity and diabetes were associated with severe steatosis. Given this, the use of preoperative chemotherapy—especially with irinotecan—may need to be more carefully considered in patients who are obese or who have diabetes. As such, a preoperative liver biopsy in patients who are obese, diabetic, and who have received chemotherapy may help identify those patients at highest risk of perioperative complications. Future investigations will need to elucidate the pathogenesis and molecular pathways underlying the cause of chemotherapy-associated liver injury as it relates to these other known risk factors.

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Duodenal-content Reflux Into the Esophagus Leads to Expression of Cdx2 and Muc2 in Areas of Squamous Epithelium in Rats

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Abstract The molecular events responsible for the transdifferentiation of epithelial cells of the esophagus to a columnar cell type are not well understood. Cdx2 has been detected in Barrett's esophagus, so we sought evidence of Cdx2 expression during the process of transdifferentiation of the esophageal squamous epithelium into a glandular phenotype. Thirty-two rats underwent an esophago-jejunostomy to produce esophagitis of 20, 25, 30, or 35 weeks of duration. The spectrum of esophageal lesions induced by chronic reflux was examined for expression of Cdx2 and Muc2 by immunohistochemistry. Five animals developed glandular metaplasia and adenosquamous carcinoma, two developed only glandular metaplasia, and two had adenosquamous carcinoma alone. Nuclear Cdx2 expression was detected in 57% (four of seven) and 43% (three of seven) of foci of glandular metaplasia and adenosquamous carcinomas, respectively. Cdx2 staining was detectable in some squamous and some mucus secreting cells. Perinuclear and perivacuolar staining of Muc2 was detected focally in 71% (five of seven) and 57% (four of seven) of areas with glandular metaplasia and adenosquamous carcinoma, respectively. We show that duodenal-content reflux into the esophagus switches on the expression of Cdx2 protein in esophageal keratinocytic cells, promoting a mucinous transdifferentiation process with secretion of intestinal mucin Muc2.

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Introduction

Esophageal adenocarcinoma constitutes the fastest rising malignancy in the USA and some European countries.[1] Most esophageal adenocarcinomas develop from Barrett's esophagus (BE), in which intestinal metaplasia with a villiform surface, mucus glands, and goblet cells replaces the native squamous cell epithelium lining the distal esophagus.[2] The exact pathophysiology of BE is unknown, but it is thought that chronic exposure to acid and bile during reflux causes damage and inflammation in the esophageal squamous epithelium, and in a subset of patients, stem cells of squamous epithelium or associated glandular ducts undergo altered differentiation leading to the acquisition of a glandular phenotype.[3,4]

Experimental models in laboratory rodents provide a basis for understanding the developmental mechanism underlying BE pathogenesis and esophageal carcinogenesis. Previous studies have shown that duodenal-content reflux, produced by

means of an esophagojejunal anastomosis, promotes histopathological changes culminating in the development of foci of glandular metaplasia and carcinomas with mucinous differentiation (adenocarcinomas/adenosquamous carcinomas).[5–7] It is interesting to note that the incidence of both glandular metaplasia and carcinoma increased with time. Based on our studies, we suggested that these lesions arise from multipotential stem cells of the basal layer of the squamous epithelium under the effect of duodenal content secretions.[6] Because rats do not have glandular structures in the esophagus, this clearly indicates that, in this species, the differentiation program of keratinocytes can be modified by reflux to induce columnar differentiation.[8,9]

There is little understanding of the molecular genetic changes that initiate and promote the transdifferentiation of epithelial cells of the esophagus to an intestinal cell type in humans (BE), which is accompanied by the expression of intestine-specific genes including sucrase isomaltase, alkaline phosphatase, villin, Muc2, and TFF3. A gene that might induce the initial transdifferentiation to intestinal metaplasia is Cdx2, an intestine-specific transcription factor belonging to the caudal-related homeobox gene family. It is expressed in the epithelium of the small intestine and colon, where it plays a role in the regulation of cell proliferation and differentiation.[10] Cdx2 activates intestinal-specific gene transcription and may direct normal intestinal epithelial development and differentiation.[11,12] It has been suggested that Cdx2 is a master regulator of the intestinal differentiation program and is therefore not usually expressed in the stomach and esophagus, but its heterotopic expression can induce intestinal metaplasia in them.[13,14] The mucin gene Muc2 is expressed abundantly in intestinal goblet cells, and it has been shown that Cdx2 interacts with the Muc2 promoter and activates Muc2 transcription, playing an important role in the differentiation of goblet cells.[15]

Therefore, the aim of this study was to evaluate whether chronic duodenal-content reflux into the esophagus of the rat is able to induce the expression of Cdx2 and Muc2 in the squamous epithelium and areas with glandular differentiation.

Material and Methods

Animals and Experimental Design

The study was approved by the Institutional Animal Care and Use Committee of the Hospital Clinic Research Foundation, University of Barcelona. All rats received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-93 revised 1985).

Our present study is derived from the same set of animals reported in a previous publication.[6] Briefly, 32 8-week-old male Sprague–Dawley rats weighing 200–250 g were randomly divided into four groups in a time-course design and exposed to chronic duodenal-content esophageal reflux for 20, 25, 30, and 35 weeks. To induce reflux esophagitis, we performed an esophagojejunostomy with gastric preservation as previously described.[16] Eleven of the 32 rats that had been operated on were killed during the early postoperative period and were excluded from the study. These rats mostly develop respiratory complications. The remaining animals (n=21) reached the scheduled end time point and were killed 20, 25, 30, and 35 weeks after performing esophagojejunostomy with ether. At the end of the experiment period, these 21 animals were then evaluated.

Tissue Sample Preparation

Immediately after death, the entire esophagus, contiguous anastomotic site, and 5 mm of jejunal mucosa were removed and the lumen was opened longitudinally by sectioning through the dorsal aspect of the esophageal wall. With the mucosal surface upward, the margins of the specimen were fixed to a cork plate with pins for macroscopic examination, photographed, and fixed in 10% neutral buffered formalin. After 24 h of fixation, the esophagus was divided into three full-thickness segments: proximal, middle, and distal. The distal segment included the esophagojejunal anastomosis. These segments were embedded in paraffin wax, cut into 5-μm sections, and stained with hematoxylin and eosin (H&E) for histologic evaluation and with diastase periodic-acid Schiff/alcian blue for mucus characterization. Histological findings of the squamous epithelium were classified into (1) reactive changes, defined as the presence of basal cell hyperplasia, hyperkeratosis, and papillomatosis; (2) glandular metaplasia, characterized by islands of mucus-secreting cells interspersed in squamous epithelium; and (3) adenosquamous carcinoma.

Immunohistochemical Staining for Cdx2 and Muc2

Paraffin-embedded tissue sections (5 μm) were cut, deparaffinized, and rehydrated. High-temperature antigen retrieval was performed in 10 mM sodium citrate, pH 6.0, in a pressure cooker for 2 min. The slides remained in this solution for 20 min to cool. After a phosphate-buffered saline (PBS) rinse, tissue sections were treated with 0.3% hydrogen peroxide in methanol for 30 min to block endogenous peroxidase and then were washed in PBS. Primary antibodies used were as follows: anti-Cdx2 monoclonal antibody (MU 392-UC at a dilution of 1:50; Biogenex, San Ramon, CA, USA) and rabbit anti-rat Muc2 polyclonal antibody (PH497 at a serum dilution of 1:400; kindly donated by Hansson GC, Goteborg, Sweden).[17] For

Cdx2, primary antibody incubations were done at room temperature for 30 min, followed by the EnVision + System (HRP-mouse DAB+, K4007; Dako, Glostrup, Denmark) procedure for visualization. For Muc2, the primary antibody diluted in PBS-1% BSA was incubated for 90 min, followed by the EnVision + System (HRP-rabbit DAB +, K403; Dako) for 30 min, and samples were developed using DAB. Finally, sections were counterstained with GILL I hematoxylin for 2 min and viewed under light microscopy. Cells were considered positive for Cdx2 when nuclear staining was evident. We analyzed the pattern of Cdx2 expression in the jejunal epithelium as a positive control, and examined areas of normal squamous epithelium, squamous hyperplasia, glandular metaplasia, and adenosquamous carcinoma. The staining pattern for Muc2 was strictly cytoplasmic.

Results

Histological Examination (H&E Staining).

Histological findings in this study are summarized in Table 1. Reactive changes characteristically associated to reflux esophagitis were seen in all rats, almost always accompanied by extensive ulceration of the mucosa. These findings mostly involved the middle and lower thirds of the esophagus. A single layer of surface columnar epithelium and tubular mucosal glands extending <4 mm above the esophagojejunostomy was observed in the distal esophagus in >80% of the rats. Columnar cells had features of both mucous secretory and absorptive cells with interspersed goblet cells. Glandular metaplasia and/or adenosquamous carcinoma were observed in nine animals. Two of them developed only glandular metaplasia and another two animals developed adenosquamous carcinoma alone, whereas in the remaining five animals, a coexistence of these two lesions was detected in the esophagus. Foci of benign glandular metaplasia located at the basal layer of the squamous epithelium showing Alcian blue/PAS-positive cells (Fig. 1a) were first detected at 20 weeks after surgery. Adenosquamous carcinomas, characterized by the presence of both mucinous and squamous malignant cells showing mural infiltration, were present from week 20 to week 35 (Fig. 1b). These carcinomas had no specific macroscopic features, being characterized by irregular ulcerations in the mucosa and submucosa. Most adenosquamous carcinomas were located in the middle and distal segments of the esophagus.

Immunohistochemical Staining of Cdx2 and Muc2

Cdx2 immunostaining was always strong in the nuclei of the enterocytic and goblet cells of the jejunal glands adjacent to the esophagojejunal anastomosis. Cdx2 protein expression was always absent in the nuclei of cells of the squamous epithelium in the most proximal part of the esophagus not exposed to the duodenal-content reflux.

Table 1 Histological Findings

	20 weeks (n=6)	25 weeks (n=5)	30 weeks (n=5)	35 weeks (n=5)
Reactive changes	6	5	5	5
Glandular metaplasia	1	1	2	3
Adenosquamous carcinoma	2	1[a]	2[a]	2[a]

[a] These animals developed both foci of glandular metaplasia and adenosquamous carcinoma in the esophagus

Table 2 shows the expression of Cdx2 and Muc2 according to the type of esophageal lesion over the time course. There was variability in staining for Cdx2 in the esophagus exposed to reflux; three areas of glandular metaplasia were devoid of Cdx2 expression, whereas four foci exhibited Cdx2 positivity. Seven areas of carcinomas with mixed squamous/mucinous phenotype were evaluated for Cdx2 expression. Cdx2 nuclear staining was observed in 3/7 cases (43%). In one case, strong nuclear staining of the surface squamous cells was observed for Cdx2 (Fig. 1c), whereas the remaining two cases of adenosquamous carcinoma showed focal staining. Isolated foci of normal appearing keratinocytes on the surface (Fig. 1d) and deeper were seen to express Cdx2 immunoreactivity. Within the adenosquamous carcinoma, Cdx2 nuclear staining was detectable in some squamous (Fig. 1e) and some mucus secreting cells (Fig. 1f). Muc2 staining was always detected in the enterocytic and goblet cells of the jejunal glands. Additionally, Muc2 perinuclear and perivacuolar cytoplasmic staining was observed focally in 5/7 cases and in 4/7 cases of glandular metaplasia and adenosquamous carcinoma respectively (Fig. 1g). No Cdx2 expression was observed in any of the lesions at 20 weeks, whereas all three glandular metaplasia foci and two adenosquamous carcinomas found at 35 weeks showed Cdx2 immunoreactivity. Coexpression at a cellular level between Cdx2 and Muc2 could not be demonstrated because these staining protocols cannot be combined on individual sections.

Discussion

In this study, we describe the tissue expression pattern of the transcription factor Cdx2 and one of its dependent gene products, Muc2, during the development of foci of

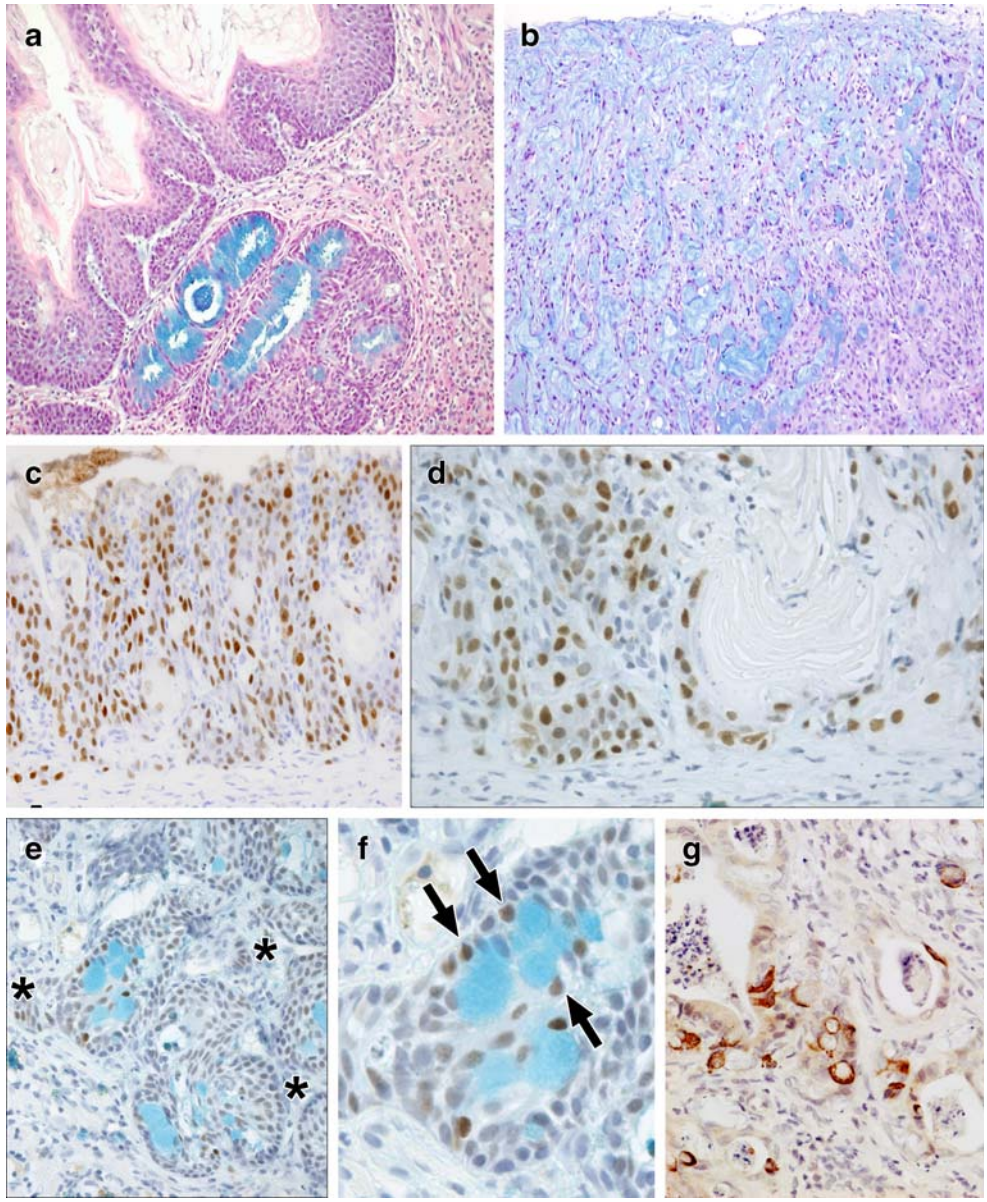

Figure 1 **a** A prominent focus of glandular differentiation with mucus secreting cells inside areas of squamous epithelium. **b** Extensive infiltration of the esophageal wall by a carcinoma with mucinous differentiation and malignant squamous component on the right side (H&E plus Alcian blue, original magnification ×100). **c** Diffuse and strong expression of Cdx2 in the nuclei within squamous areas of adenosquamous carcinoma lining the esophagus. Immunoperoxidase with anti-Cdx2 monoclonal antibody plus hematoxylin. **d** Cdx2 expression is seen here to extend through a patch of cells with stratified keratinocyte phenotype. **e** Adenosquamous carcinoma showing positivity for Cdx2 in the nuclei of squamous cells (*asterisks*) and also at higher magnification (**f**) in the nuclei of mucus secreting cells (*arrows*). Immunoperoxidase with anti-Cdx2 monoclonal antibody plus Alcian blue + hematoxylin, ×100 original magnification. **g** Marked perinuclear and perivacuolar staining for Muc2 in the glandular component of adenosquamous carcinoma. Immunoperoxidase with anti-rat Muc2 monoclonal antibody plus hematoxylin.

glandular metaplasia and carcinomas with mucinous differentiation in the esophagus of rats. We show that keratinocytes, after a chronic duodenal content-reflux esophagitis without the administration of a carcinogen, are able to express nuclear Cdx2 in the vicinity of areas with mucinous differentiation, either in foci with well-differentiated glandular features or in adenosquamous carcinomas. Areas with mucinous differentiation sometimes expressed Muc2 focally; although several glands did not express Muc2 at all, these might represent glands with a gastric differentiation as the cells sometimes appeared to contain double locules of mucous, and it has been recognized previously that glands of pseudopyloric phenotype develop in this model.[18]

Controversy exists as to the origin of the columnar intestinal epithelial cells during the metaplastic process that culminates with the development of BE as these cells may originate from squamous cell transdifferentiation. There has been considerable discussion as to whether stem cells in the basal layer of the esophageal squamous epithelium have the capacity to give rise to glandular epithelial cells.[8] The pathophysiology of columnar re-epithelialization of the distal esophagus (BE) is related to a chronic gastroesophageal mixed reflux of acid and bile secretions, and supporting this observation, several experimental studies have shown that duodenal-content reflux can trigger a glandular transdifferentiation in the esophagus of rats that increases over the time course.[5,6]

Scanning electron microscopy of squamocolumnar junctions in patients who have BE has revealed a distinctive type of multilayered epithelium (ME) that shows morphologic

Table 2 Expression of Cdx2 and Muc2 in the Spectrum of Esophageal Lesions

	20 weeks	25 weeks	30 weeks	35 weeks	Total
GM (n=7)					
+*ve* Cdx2	0/1	1/1	0/2	3/3	4/7 (57%)
+*ve* Muc2	1/1	1/1	1/2	2/3	5/7 (71%)
ASC (n=7)					
+*ve* Cdx2	0/2	1/1	0/2	2/2	3/7 (43%)
+*ve* Muc2	0/2	1/1	1/2	2/2	4/7 (57%)

GM = glandular metaplasia, ASC = adenosquamous carcinoma

and ultrastructural features of squamous and columnar epithelium.[19] This epithelium consists of four to eight layers of cells that seem squamous in the basal aspect and columnar in the superficial portion. By immunohistochemical analysis, ME expresses a pattern of mucin and cytokeratin expression similar to that of columnar epithelium in BE.[20] These data provide evidence that mucosal duct epithelium or the basal layer of the squamous epithelium may contain progenitor cells that can give rise to ME.

Cdx2 is a gene that might induce the initial trans-differentiation to intestinal metaplasia, an intestine-specific transcription factor belonging to the caudal-related homeobox gene family. It is expressed throughout the small and large intestine, where it plays a role in the regulation of cell proliferation and differentiation.[12] It has been suggested that Cdx2 is a master regulator of the intestinal differentiation program and is therefore not usually expressed in the stomach and esophagus. The Cdx2 homeobox gene exerts a homeotic function during morphogenesis of the gastrointestinal tract, as assessed by the gastric-like heterotopia resulting from local loss of Cdx2 expression in the pericaecal region of $Cdx2^{+/-}$ mice, and by the intestinal-like transdifferentiation of the gastric mucosa in transgenic mice expressing Cdx2 in the stomach.[21,22] Recently, aberrant expression of Cdx2 has been identified in areas of the stomach and esophagus containing intestinal metaplasia.[13,14,23–25] Moons et al.[24] used immunohistochemistry and semiquantitative reverse transcription polymerase chain reaction to detect Cdx2 protein and mRNA, respectively, in biopsy specimens of both columnar- and squamous-lined esophagi. Cdx2 immunostaining was positive in all specimens of intestinal metaplasia. Interestingly, Cdx2 mRNA expression was also found in the esophageal squamous epithelium in six of 19 specimens from patients with BE. This finding suggests that Cdx2 expression by squamous cells may precede the development of BE.[26] In our study, we see areas of stratified keratinocytes that express nuclear Cdx2; these may be well-differentiated islands of adenosquamous carcinoma or esophageal keratinocytes that have begun a conversion towards columnar phenotype.

Marchetti and colleagues showed that chronic acid exposure of mouse esophageal keratinocytes under defined culture conditions can induce expression of Cdx2.[27] More recently, Kazumori et al. showed that cholic acid dose-dependently increased activity of the Cdx2 promoter and Cdx2 protein production in cultured rat esophageal keratinocytes.[28] Perhaps such an effect of bile reflux contributes to the generation of Cdx2-expressing keratinocytes in our rat model of duodenal-content reflux esophagitis. Cdx2 protein nuclear expression in the esophageal keratinocytes was detected in 57 and 43% of the areas with glandular metaplasia and adenosquamous carcinoma, respectively. Interestingly, the lack of expression of Cdx2 at 20 weeks in our time course and the positive staining in all cases of metaplasia and carcinoma at 35 weeks suggest that long-term duodenal-content reflux is necessary to induce the expression of this transcription factor. These results provide evidence that chronic acid exposure can modify the fate of esophageal keratinocytes towards an intestinal program. This may be a key step in the development of intestinal metaplasia (BE) often observed in the distal esophagus in humans. Using a similar rat model, Tatsuta et al.[29] detected Cdx2 by RT-PCR and by immunohistochemical staining in specialized columnar epithelium; those observations, however, were confined to the distal few millimeters of the distal esophagus—very close to the esophagojejunal anastomosis. They also detected the expression of Cdx2 by immunohistochemistry in a few columnar cells of some foci of glandular metaplasia in the basal layer of the squamous epithelium and not in squamous epithelial cells. In our study, we were able to detect Cdx2 expression in the squamous epithelium far away from the anastomosis, and additionally detected the presence of perinuclear and perivacuolar cytoplasmic Muc2 in areas with mucinous differentiation. This original observation is supported by recent evidence showing that transfection of a Cdx2 expression vector into cultured rat esophageal keratinocytes induced the production of intestinal type mucin, Muc2, in cells that expressed Cdx2.[28] The fact that Muc2 immunoreactivity was detected more readily than Cdx2 might be due to the relative ease of access to epitopes in the mucin rather than the nuclear protein, or perhaps even to the relative volumes of mucin-containing vs Cdx2-containing structures; it is clear that Cdx2 immunoreactivity is not present in all cells of mucousphenotype in our study or in that of Tatsuta et al.[29]

In summary, our results in vivo support the concept that squamous epithelium has the potential to transdifferentiate into a mucinous phenotype by the effect of a chronic reflux of duodenal contents through the expression of Cdx2.

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Mild Acute Biliary Pancreatitis vs Cholelithiasis: Are There Differences in the Rate of Choledocholithiasis?

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Abstract The rate of choledocholithiasis at the time of elective surgery after mild acute biliary pancreatitis is still unclear because it decreases rapidly after the onset. The aims of this study are as follows: (1) To investigate whether the incidence of choledocholithiasis in mild biliary pancreatitis is higher than in patients with symptomatic cholelithiasis. (2) To evaluate the usefulness of intraoperative cholangiography in the diagnosis of unsuspected choledocholithiasis in mild pancreatitis. Prospective study including 130 patients undergoing laparoscopic surgery and classified into two groups: mild biliary pancreatitis (n=44) and symptomatic cholelithiasis (n=86). Choledocholithiasis was evaluated by endoscopic cholangiopancreatography, magnetic resonance, and intraoperative cholangiography. Preoperatively, choledocholithiasis was identified in five patients with symptomatic cholelithiasis and two with biliary pancreatitis (5.81 vs 4.54%; p=0.472). In 117 cases (90%), intraoperative cholangiography was successfully performed, identifying unsuspected choledocholithiasis in five patients of the colelithiasis group and in three in the group of pancreatitis (5.81 vs 6.81%; p=0.492). The total number of patients with choledocholithiasis in the whole series was 15 (11.5%); 11.6% in colelithiasis group vs 11.4% in biliary pancreatitis group; p=0.605. The rate of choledocholithiasis was not significantly different between the groups of patients with mild acute biliary pancreatitis and symptomatic cholelithiasis. Intraoperative cholangiography identified unsuspected choledocholithiasis in 6.81% of patients with mild acute biliary pancreatitis.

Keywords Choledocholithiasis · Acute biliary pancreatitis · Cholelithiasis

Introduction

Gallstone pancreatitis is a frequent complication of cholelithiasis related with the passage of bile-duct stones through the ampulla of Vater. Cholecystectomy during the same hospitalization after recovery of the episode or as soon as possible after discharge is the standard treatment of mild acute biliary pancreatitis (ABP) to prevent the risk of recurrent acute pancreatitis.[1]

Approximately 45–70% of patients with ABP have common bile duct (CBD) stones found on endoscopic retrograde cholangiopancreatography (ERCP) or at surgery performed within 72 h of admission.[2–7] However, the stones pass on spontaneously within days, remaining in a minority of patients.[8–11]

Nowadays, laparoscopic cholecystectomy is the gold standard for the treatment of gallstone pancreatitis and cholelithiasis. Most authors do not perform routinary intraoperative cholangiography (IOC) in patients presenting cholelithiasis and low risk of choledocholithiasis operated upon elective means.[12–14] However, the majority of surgeons would recommend the performance of IOC in gallstone pancreatitis to rule out the persistence of CBD stones (CBDS).[15–17]

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For years we have performed routinary IOC in cases with gallstone pancreatitis in the belief that this is by itself a risky factor for choledocholithiasis. This experience led us to the impression that the rate of retained CBDS in ABP was not different from that found in simple biliary lithiasis and, therefore, that the routinary use of IOC in gallstone pancreatitis was not more useful than in cholelithiasis.

This study was designed to elucidate whether the rate of choledocholithiasis is higher in gallstone pancreatitis than in simple cholelithiasis at the time of elective surgery. An additional but related secondary aim of the investigation is whether the performance of IOC in ABP is really useful compared with its utility in cholelithiasis.

Patients and Methods

One hundred and thirty consecutive patients were included in the study from April 1 2002 to April 1 2004. Data were collected prospectively and entered into a patient database. Inclusion criteria were patients with mild ABP and patients with symptomatic cholelithiasis (SC) in the form of biliary colic; both groups were fit for elective surgery. During the same period several cases of severe acute pancreatitis were also treated at our institution, but these were excluded from this study. The diagnosis of acute pancreatitis was made on admittance in the emergency room based on the clinical presentation and elevated serum total amylase level higher than three times the normal range. The biliary etiology was established by ultrasonography during the period of hospitalization or demonstrating the presence of microlithiasis by the Meltzer–Lyon test. All the laboratory parameters were obtained within the first 48 h of admittance. The definition of the episode as mild was established according to the criteria of the Atlanta classification:[18] minimal dysfunction, uneventful recovery with prompt normalization of physical signs and laboratory data, and absence of organ failure or local complications. All cases of mild ABP were treated according to the standards of the Gastroenterology Department of the University Clinic of Valencia[19] coordinated with the Department of Surgery to program the cholecystectomy during the same admission or as soon as possible. The presurgical waiting time was defined as the interval elapsed between clinical recovery and the date of operation, independently of whether the patient was discharged or operated on within the same hospitalization period.

The patients with SC were treated on an outpatient basis and programmed for surgery following the order of the waiting list. Only patients with typical biliary colics were included in the group of cholelithiasis, and cases with atypical symptoms, severe biliary colics, and acute cholecystitis requiring emergency surgery were rejected.

Before surgery, all patients included in the study were specifically investigated for choledocholithiasis by clinical history and physical examination, laboratory parameters, and ultrasonography, regardless of whether the patient had gallbladder pancreatitis or colelithiasis. They were then classified according to the risk of choledocholithiasis in high (history of acute cholangitis, jaundice, bilirubin level higher than 1.5 mg/dl and alkaline phosphatase >150 U/l, or demonstration of choledocholithiasis on ultrasonography), intermediate (laboratory alterations and CBD greater than 8 mm, but no jaundice nor previous history of cholangitis), or low risk (all parameters within the normal range and no dilatation of the CBD).[20,21] Patients with low risk of choledocholithiasis were programmed for surgery without any additional exploration. Patients with intermediate or high risk of choledocholithiasis underwent a magnetic resonance imaging (MRI) and, if the choledocholithiasis was confirmed, an ERCP with sphincterotomy and clearance of the CBD was performed before surgery.

All patients included in the study underwent laparoscopic cholecystectomy, and in all cases, an IOC was attempted with a double light Reddick cholangiogram cathether® (LeMaitre Vascular, Burlington, MA, USA). All patients included in the study signed the appropriate consenting forms to undergo risky diagnostic (imaging techniques) or therapeutic procedures (sphincterotomy and cholecystectomy).

Postoperative follow-up consisted of clinical evaluation and laboratory parameters (bilirubin level, transaminases, and alkaline phosphatase). In those cases in which IOC was not possible due to technical difficulties and there was no preoperative imaging of the bile duct, a postoperative MRI was performed to rule out an unsuspected stone at the biliary tree (Fig. 1).

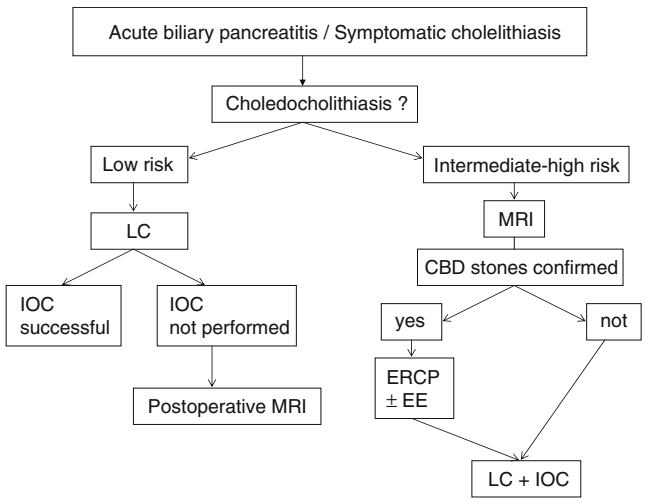

Figure 1 Management algorithm of the study. *LC*, laparoscopic cholecystectomy; *EE*, endoscopic sphincterotomy.

Sample Size and Statistical Analysis

The primary endpoint of the study was to compare the rate of choledocholithiasis between mild ABP and cholelithiasis at the time of elective surgery. A secondary objective was to determine the usefulness of IOC. Thirty-nine patients per group was the necessary minimum sample size. The parameters used to calculate the size were the following: choledocholithiasis variability of 20%, an α error of 5%, and a β error of 20%. Results are presented as percentages or mean and standard deviation. Categorical data were analyzed by the X^2 test and the two-tailed Fisher's exact probability test when cell numbers were too small for the X^2 test. For continuous variables, the two-tailed Mann–Whitney U test was used. p values were indicated as exact values and assumed to be significant at $p<0.05$.

Results

During the period of study a total of 130 patients were included and divided into two groups according to the surgical indication: mild ABP ($n=44$) and SC ($n=86$). Both groups were homogeneous in age (ABP=61±14 years, SC=58±14 years; $p=0.184$) and sex (ABP 48% males and 52% females, SC 33% males and 67% females; $p=0.068$). Presurgical waiting time was shorter in the ABP group than in SC group (median, 46 vs 151 days; $p=0.023$). The recurrence rate of acute pancreatitis while waiting for surgery was 11.3% (five patients). All such cases recurred with mild episodes without any severe episode nor other gallstone complications.

Nineteen preoperative MRIs (14.6%) were performed in patients classified as high or intermediate risk of choledocholithiasis: nine in the SC group (four intermediate and five high risk) and 10 (six intermediate and four high risk) in the ABP group. Magnetic resonance imaging was highly suggestive of choledocholithiasis in 11 patients who thereafter underwent ERCP and sphincterotomy: eight in the SC group vs three in ABP. The number of choledocholithiases finally confirmed preoperatively was five in the SC group and two in the ABP group (5.81 vs 4.54%; $p=0.472$).

One hundred and seventeen IOCs (90%) were successfully performed (90.7% in SC vs 88.6% in ABP; $p=0.465$), demonstrating unsuspected choledocholithiasis in five patients of the SC group and in three in the ABP group (5.81 vs 6.81%; $p=0.492$). The most frequent cause of unsuccessful IOC was a cystic size smaller than the diameter of the cholangiography catheter (2 mm).

In three cases with a preoperative low risk of choledocholithiasis and unsuccessful IOC, a postoperative MRI was performed confirming the absence of choledocholithiasis. This exploration was carried out to rule out unsuspected choledocholithiasis because there were neither pre- nor intraoperative imaging data. After a follow-up of 418±207 days, residual choledocholithiasis was not found in any case.

Table 1 Choledocholithiasis Rate in ABP and SC

Choledocholithiasis	ABP ($n=44$)	SC ($n=86$)	p value
Preoperative diagnosis	2 (4.54%)	5 (5.81%)	0.472
Intraoperative diagnosis	3 (6.81%)	5 (5.81%)	0.492
Total	5 (11.4%)	10 (11.6%)	0.605

Summarizing the results, the total number of patients with choledocholithiasis in the whole series was 15 patients (11.5%), 10 patients in SC group (11.6%) vs five patients in ABP group (11.4%), $p=0.605$. In the said series, seven choledocholithiases were identified preoperatively and eight by IOC (Table 1).

Discussion

Cholecystectomy has been, for years, the appropriate treatment for SC and to prevent recurrence in gallbladder pancreatitis, and it still is. At present, this operation is performed by laparoscopic means and, due to its clear advantages over the open approach, has become the gold standard. Nevertheless, the performance of IOC in laparoscopic cholecystectomy as a routinary procedure is still a matter of concern. For some authors, IOC should be performed with three specific aims: to rule out the presence of unsuspected choledocholithiasis, to identify a bile duct injury, and to acquire appropriate training for cases in which the IOC is mandatory. However, many others authors do not advocate for it, with the argument that it is both time-consuming and technically challenging.[13]

Different strategies have been proposed for the diagnosis of CBDS in ABP in terms of cost-effectivity: for a low probability of choledocholithiasis (<15%), observation with IOC is the preferred method; at intermediate risk (15–58%), endoscopic ultrasonography is the recommendable method; and for a high risk (>58%), ERCP is the preferable strategy.[16] Our approach includes ERCP only for therapeutic purposes, and therefore, we use MRI to confirm the presence of CBDS prior to the endoscopic procedure, a reasonable preoperative diagnostic choice for patients with ABP according to several studies.[22,23]

Biliary pancreatitis is considered to be triggered by the passage of stones through the papilla of Vater. Despite the fact that most CBDS pass on spontaneously, a variable number of stones remain in the common duct.[4,6,24–26] The wide range of CBDS found in ABP by different diagnostic

methods seems to depend on the time at which CBDS are investigated: early investigation shows a higher rate.

As part of the usual treatment of gallbladder pancreatitis, for years we have performed routinary IOC at the time of elective surgery. The subjective impression that the rate of CBDS in ABP was similar to that found in cholelithiasis led us to design this study.

In this series no cases with severe biliary colic requiring emergency surgery or acute cholecystitis have been included. We believe that this selection of the cases results in a relatively homogeneous population of gallbladder lithiasis differing only in their main clinical manifestation: one group presenting biliary colics and the other mild pancreatitis.

Our results show that the incidence of choledocholithiasis in ABP is no higher than that in simple cholelithiasis, and in accordance with these results, to consider ABP as a risk factor for choledocholithiasis at the time of elective surgery is questionable. The relation of cases between ABP and SC in our study, with almost one of every two included presenting ABP, may seem surprising. This can be explained by the fact that, in our center, the patients with ABP have priority over the patients with SC and are therefore operated on sooner than the patients with SC, as reflected in a shorter waiting time. Despite our attempts to even further minimize the time between the episodes of ABP and surgery, there is still a long mean period of 46 days, which explains the 11.3% recurrence rate of acute pancreatitis.

An important concern while designing the study was the possibility that our subjective low rate of CBDS in ABP was due to the performance of ERCP before elective surgery. To avoid this bias, we designed the study in a prospective manner and only indicated ERCP when a choledocholithiasis was identified by MRI independently of the ABP or SC group to which the patient belonged. The use of MRI as an imaging tool for the diagnosis of choledocholithiasis was chosen due to its high sensitivity and specificity[22,23] and its noninvasive nature. In patients with low risk of choledocholithiasis and unsuccessful IOC, postoperative MRI was negative in all cases, and therefore, we do not advocate its use in this particular group.

In summary, our results indicate that the rates of choledocholithiasis in ABP and SC at the time of elective surgery are similar. Therefore, we cannot maintain ABP per se as a risk factor for choledocholithiasis. Thus, the criteria to perform IOC should not be different in SC and mild ABP. In our study, the performance of IOC has demonstrated an incidence of 6.81% of unsuspected CBDS in ABP.

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Fast Track—Different Implications in Pancreatic Surgery

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Abstract Concepts in "fast-track" surgery, which provide optimal perioperative care, have been proven to significantly reduce complication rates and decrease hospital stay. This study explores whether fast-track concepts can also be safely applied and improve the outcomes of major pancreatic resections. Perioperative data from 255 consecutive patients, who underwent pancreatic resection by means of fast-track surgery in a high-volume medical center, were analyzed using univariate and multivariate models. Of the 255 patients, 180 received a pancreatic head resection and 51 received distal, 15 received total, and 9 received segmental pancreatectomies. The patients were discharged on median day 10 with a 30-day readmission rate of 3.5%. The in-hospital mortality was 2%, whereas medical and surgical morbidities were 17 and 25%, respectively. Fast-track parameters, such as first stools, normal food, complete mobilization, and return to normal ward, correlated significantly with early discharge ($p<0.05$). Patients' age, operation time, and early extubation proved to be independent factors of early discharge, shown through multivariate analysis (odds ratio: 4.0, 2.0, and 2.8, respectively; $p<0.05$). Low readmission, mortality, and morbidity rates demonstrate that fast-track surgery is in fact feasible and safe and promotes earlier discharge without compromising patient outcomes.

Keywords Pancreatectomy · Pancreatic surgery · Fast-track · Postoperative therapy

Introduction

During the past century, pancreatic resection has been considered to be a high-risk procedure with mainly terminal outcomes. However, within the last three decades, advancements in modern surgery have evolved pancreatic resection into a safe procedure with acceptable morbidity and low mortality. Today, elective pancreatic resections, performed at specialized high-volume medical centers, show mortality rates under 5%.[1–7]

It is believed that careful preoperative diagnostics and preparation, sound surgical techniques, and qualified postoperative care are crucial factors that lead to safe pancreatic surgery.[8] Surgical advancements in procedures such as pancreatic anastomosis, which was the key cause of death for patients undergoing pancreatic surgery in the past, can now be safely performed and are responsible for the positive development of pancreatic resection in the last 30 years. This is reflected in current trends showing that more patients are dying from systemic rather than surgical complications.[4]

Postoperative morbidity after pancreatic resection, however, still remains high with rates between 30 and 60%, leading to a prolonged hospital stay. The postoperative stay after pancreatic resection is usually 12 to 17 days at high-volume centers.[1,3–7,9–12] Postoperative complications such as pancreatic fistulas, delayed gastric empting, and biliary complications proved to be the main reasons for the prolonged stay. However, by increasing experience and case load, a significant decrease in length of stay was achieved at single institutions.[2,8,13]

In the last decade, many new scientific studies appeared, which focused on optimal perioperative care and led to the development of a new concept known as "fast-track surgery."[14] By reducing the common known stress responses in

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surgery, complication rates are reduced and rapid recovery is achieved. Comprehensive programs, aimed to reduce postoperative hospital stay, were developed through a coordinated effort of patient education, newer anesthetic and analgesic methods, pharmaceutical interventions, focused nursing, and mobilization actions.[15] Several studies have in fact shown that "fast-track" programs result in significantly reduced postoperative hospital stay. Several studies examining the outcomes of fast-track colon resection showed reduced postoperative stay by 2–4 days, lower complication rates and reduction in total hospital costs.[16–23] However, despite strong clinical evidence and proven success of fast-track programs, a recent survey across Europe and the US looking at aftercare of colon operations showed that many of the fast-track principle are still not applied in clinical practice.[24] Safety may still remain the primary concern for many surgeons, and therefore, major randomized trails are needed to confirm these positive results.

To date, no data exists proving whether such concepts could also be safely applied to complex and major abdominal surgery such as pancreatic resection. This study reviews the outcomes of a single-center survey regarding the application of the new "fast-track surgery" concept and its effects on patients who underwent pancreatic resections.

Patients and Methods

Between January 1 2004 and December 31 2004, pancreatic resections were performed in 283 consecutive patients at the Department of General Surgery, University of Heidelberg. Pre- and intraoperative outcome data were prospectively recorded in a standard form. Specific "fast-track" parameters were gathered, such as device removal (abdominal drains, nasogastric tube, and urine catheter), medications, etc. Twenty-eight patients were excluded because of incomplete medical records for analysis.

All patients received a single shot of antibiotic prophylaxis, a weight-adapted thrombosis prophylaxis with low-molecular-weight heparin combined with compression stockings, and a pancreatic secretion inhibitor (octreotide, 300–600 μg/day subcutaneously for 5–7 days). All pancreatic resections were performed in accordance with standardized procedures described elsewhere. The operations were performed by a team of 12 surgeons. Most patients were monitored in the intensive or intermediate care unit for at least one night. Occasionally, in uncomplicated cases, patients were transferred directly to the ward after an observation time of 6 h.

Postoperative pain treatment was performed by peridural or patient-controlled analgesia, followed by stepwise dose reduction and, finally, transition to nonopioid medication (metamizol four times 0.5–1 g/day) or paracetamol four times 0.5–1 g/day). Gastrointestinal tubes and intra-abdominal fluid drains (Easy Flow, Dahlhausen, Cologne, Germany) were used routinely. Intra-abdominal drains were removed between days 1 and 3. Oral intake of clear liquids was started 6 h after extubation, as soon as the effects of anesthesia disappeared. The increase of oral intake followed a stepwise plan from liquid, mashed, light, and finally normal food. Increase in food intake was monitored and determined by the treating physicians on the ward, based on the assessment of gastrointestinal function. Pharmacological support for early gastrointestinal function was introduced. According to the fast-track concept, at postoperative day 1, metoclopramid (60 mg/day) was used to prevent nausea, and magnesium (200 mg/day) and lactulose (3×10 g/day) were applied to support early start of normal bowel function, which was stopped with the first stool.

Mortality was defined as the total number of in-hospital deaths. Gastric emptying delay was defined as the necessity to leave in the nasogastric tube for more than 10 days after surgery or the need for nasogastric tube reinsertion after day 10. A pancreatic fistula was defined as persisting secretions of more than 30 ml/day of drainage fluid with a high level of amylase (>5,000 U/ml) for more than 10 days or the later reoccurrence of amylase-rich fluid in a drained intra-abdominal abscess. A biliary fistula was diagnosed when fluid with high level of bilirubin (>3 times bilirubin serum level) was secreted for more than 5 days. Postoperative bleeding was defined as the necessity to transfuse more than two units of packed red blood cells more than 24 h after surgery or the need for an additional operation due to hemorrhage.

Statistical analysis was performed using SPSS® for Windows release 11.0.0 (SPSS, Chicago, IL, USA). Univariate analyses between groups were conducted using χ^2 or Fisher's exact test for categorical variables and Mann–Whitney U test for nonparametric continuous variables. $p<0.05$ was considered statistically significant. Testing all the factors in univariate analysis was the first step in the explorative data analysis. Variables with $p<0.05$ were included in multivariate analysis performed by stepwise logistic regression. Ninety five percent confidence intervals were computed to estimate the precision of the odds ratio. The potential correlates of interest were tested using Spearman rank correlations.

Results

Demographics and Intraoperative Variables

The analyzed patient group showed a median age of 59 years (range 13 to 83 years). A high-risk comorbidity profile (ASA III–IV) was seen in 32.5% of the patients. One hundred eighty (70.6%) resections were performed for pancreatic

tumors: 159 operations (62.3%) for malignant tumors and 21 operations (8.2%) for benign tumors of the pancreas. Of the resections, 29.5% were completed in patients with chronic pancreatitis. One hundred eighty pancreatic head resections (70.6%), 15 total pancreatectomies (5.9%), 51 distal pancreatectomies (20%), and 9 segmental pancreatectomies (3.5%) were performed. Pancreatic head resections included 128 pylorus-preserving Whipple resections (50.2%), 27 classical Whipple resections (10.6%), and 25 duodenum-preserving pancreatic head resections (9.8%). The overall median operating time was 5 h and 45 min (range 73 to 643 min). Blood loss was at a median of 700 ml (range 50 to 5,500 ml) and 26% of the patients needed blood transfusion therapy. A median of zero units of packed red blood cells were used (range 0–16 units). According to the resection type, significant differences were found: Classical Whipple resection (median 1,100 ml) and total pancreatectomy (median 1,000 ml) showed significantly higher blood loss in comparison to the duodenum-preserving pancreatic head resection (median 400 ml), distal pancreatectomy, and pancreatic segment resection (both with a median of 500 ml) ($p<0.05$). The operations were performed by 12 surgeons; 82% of the resections where completed by specialized pancreatic surgeons ($n=5$) and the remaining 18% by general surgeons who received their training in pancreatic surgery ($n=7$) (Table 1).

Table 1 Demographics and Intraoperative Data

	$n=255$
Age (years)[a]	59 (13–83)
Gender	
Male	153 (60)
Female	102 (40)
ASA grade	
I	11 (4.3)
II	162 (63.5)
III	82 (32.2)
IV	1 (0.3)
BMI (kg/m^2)[a]	24 (15–40)
Underlying disease	
Pancreatic tumor	180 (70.6)
Chronic pancreatitis	75 (29.4)
Type of surgery	
Classical Whipple resection	27 (10.6)
Pylorus-preserving Whipple	128 (50.2)
Duodenum-preserving pancreatic head resection	25 (9.8)
Distal pancreatectomy	51 (20)
Segmental pancreatectomy	9 (3.5)
Total pancreatectomy	15 (5.9)
Operation	
Operating time (min)[a]	345 (73–643)
Blood loss (ml)[a]	700 (50–5,500)
Transfusion (units of PRBCs)[a]	0 (0–16)
Surgeon's education level	
Pancreatic surgeons ($n=5$)	210 (82)
Fellows in pancreatic surgery ($n=7$)	45 (18)

PRBCs=packed red blood cells
[a] Values are median (range). Other values in parentheses are percentages

Table 2 Postoperative Course

	$n=255$
Intensive care unit	176 (69)
Duration of stay (days)[a]	1 (1–32)
Readmission rate	23 (9)
Intermediate care unit	162 (63.5)
After ICU	103 (40.9)
Duration of stay (days)[a]	2.5 (1–12)
Readmission rate	17 (6.7)
Return to normal ward (days)[a]	2 (0–38)
Discharge (days)[a]	10 (4–115)
Transfer rate	30 (11.8)
Readmission rate (30 days)	9 (3.5)
Hemorrhage	1
Ileus	2
Intra-abdominal abscess	4
Others	2

ICU=intensive care unit
[a] Values are median (range). Other values in parentheses are percentages

Postoperative Course

Typically, patients were transferred to the ICU (69%) after the operation where they stayed a median of 1 day (range 1–32 days). Of the patients, 40.9% were transferred thereafter to an intermediate care unit, where they stayed for additional median of 2.5 days (range 1–12 days). However, 31% of the patients were directly transferred from the recovery room to the intermediate care unit or even to the ward (22.4 and 8.4%, respectively). Overall, patients returned to the ward after a median of 2 days (range 0–38 days) (Table 2).

On average, patients were discharged after 10 days (range 4–115 days). Of the patients, 88.2% were discharged home, whereas 11.8% were transferred to another department or a different hospital (Table 2, Fig. 1). The 30-day inpatient readmission rate was 3.5%. Four patients were readmitted due to an intra-abdominal abscess, two patients due to ileus, and one patient due to an acute upper GI bleeding.

Anesthesia and Pain Management

At the end of the operation, normothermia was achieved in 69.4% of the patients, whereas 78 patients (30.6%) revealed hypothermia. Of the patients, 50% were extubated on the operation table. Another 40% were extubated a few hours later but still on the day of the operation. Twenty-seven patients (10.6%) needed to be ventilated for longer than 1 day (Table 3).

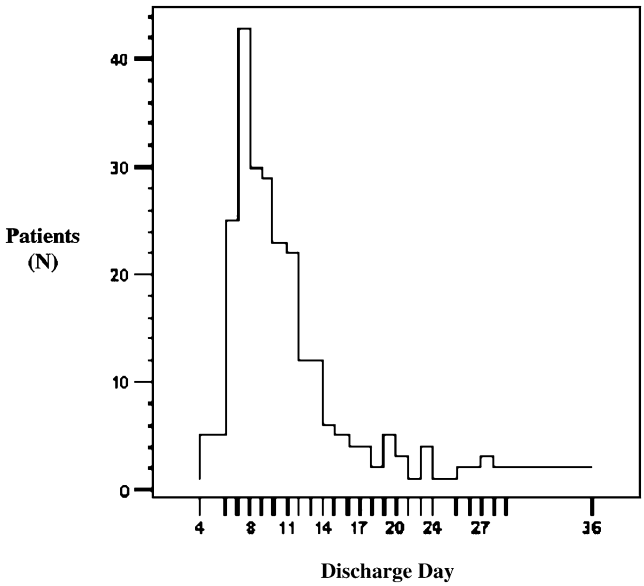

Figure 1 Discharge course.

One hundred thirty patients (51%) received epidural analgesia, whereas the epidural catheter was removed on median day 5 (range 0–11 days). In 19 patients (14.6%), there was failure of the epidural analgesia system and pain management was changed to patient-controlled or on-demand analgesia. In total, 46.3% of patients were treated with patient-controlled analgesia and 11% received on-demand analgesia (11%) (Table 3). Of the patients, 49% did not receive epidural analgesia due to several reasons, such as participation in a pain study, which prohibited the use of epidural analgesia, refusal by the patients, and some abnormalities of the coagulation system.

Table 3 Anesthesia and Pain Management

	n=255
Core temperature (°C)[a]	36.2 (34.4–37.8)
Normothermia (36–38°C)	177 (69.4)
Hypothermia (<36°C)	78 (30.6)
Extubation	
Immediate	126 (49.4)
Operation day	102 (40)
Later	27 (10.6)
Pain management	
Methods	
Epidural analgesia	130 (51)
Patient-controlled analgesia	118 (46.3)
On-demand analgesia	28 (11)
Peridural anesthesia failure rate	19 (14.6)
Course	
Peridural catheter removal (days)[a]	5 (0–11)
Opioids removal—WHO III (days)[a]	5 (1–70)
Analgesia removal—WHO I (days)[a]	9 (2–78)
Discharge with analgesia	112 (43.9)

[a] Values are median (range). Other values in parentheses are percentages

Table 4 Gastrointestinal Function

	n=255
Nasogastric tube	
Removal operation day	205 (80.4)
Removal first postoperative day	34 (13.3)
Removal later	16 (6.3)
Reinsertion rate	29 (11.4)
Feeding	
First liquid (days)[a]	1 (0–6)
Complete oralization (days)[a]	5 (1–24)
Parenteral feeding rate	55 (21.6)
First stool (days)[a]	4 (1–9)
Pharmacological support	
Antiemetics	
Metoclopramid	191 (75)
Dimenhyrinate, dolasteron	53 (20.8)
Prokinetics	
Lactulose	159 (62.4)
Oral magnesium	175 (68.6)
Erythromycin	48 (18.8)
Prostigmine	18 (7)

[a] Values are median (range). Other values in parentheses are percentages

Gastrointestinal Function and Mobilization

Nasogastric tubes were removed from most patients immediately after the end of the operation (80.4%) or during the first postoperative day (13.3%). The only reasons for a delay of the removal of the nasogastric tube were longer ventilation, early neurological dysfunction, or respiratory problems, which mandated postoperative continuous positive airway pressure therapy. However, 29 patients (11.4%) needed a reinsertion of the nasogastric tube later during the postoperative course. This occurred on median day 6 (range 1–13 days). Overall, 23 patients (9%) required a gastric tube after day 6. In 18 patients, reinsertion of the nasogastric tube was due to delayed gastric emptying, whereas the remaining two patients with delayed gastric emptying refused the nasogastric tube reinsertion.

On median day 1 (range 0–6 days), patients received clear liquid, and on median day 5 (range 1–24 days), they

Table 5 Device Removal and Mobilization

	n=255
Devices	
Intra-abdominal drain removal (days)[a]	3 (0–19)
Urinary catheter removal (days)[a]	5 (1–49)
Central venous line removal (days)[a]	6 (1–49)
Mobilization	
In the patients room (days)[a]	1 (0–9)
Complete (days)[a]	3 (1–46)

[a] Values are median (range). Other values in parentheses are percentages

Table 6 Postoperative Complications

	n=255 (%)
Surgical complication rate	63 (24.7)
Gastric empting delay	20 (7.8)
Wound infection	12 (4.7)
Fistula	12 (4.7)
Pancreatic (anastomosis)	4
Stump insufficiency	6
Biliary	1
Enteral	1
Hemorrhage	19 (7.5)
Medical complication rate	42 (16.5)
Pneumonia	10 (3.9)
Myocardial dysfunction	6 (2.4)
Renal failure	4 (1.6)
Urinary infection	6 (2.4)
Neurological dysfunction	3 (1.3)
Others	13 (5.1)
Reoperations	23 (9)
Hemorrhage	14
Fistula pancreatic	3
Fistula others	2
Others	4
Mortality	5 (2)
Anastomosis leak	3
Others	2

returned to normal food. Of the patients, 21.6% needed transient parenteral nutrition support (median duration 4 days, range 1–60 days). First defecation occurred on median day 4 (range 1–9 days).

According to the fast-track concept, most of the patients would receive, upon the first postoperative day, pharmacological support to initiate early normal gastrointestinal function: 75, 62.4, and 68.6% of the patients received metoclopramid, lactulose, and oral magnesium, respectively. The use of these medications had no significant influence on the occurrence of the first stool or early discharge. In contrast, the use of routine metoclopramid correlated negatively with early discharge ($p<0.01$). Other antiemetics (20.8%), such as dimenhyrinate and dolasteron, or prokinetics, such as erythromycin (18.8%) and prostigmine (7%), were applied only when clinical signs of delayed gastric empting or atony were present (Table 4).

All the patients had one or more intra-abdominal drains placed during the operation, but only sporadically subcutaneous drainage was applied (11/255 patients, 4.3%). The intra-abdominal drains were removed on median day 3 (range 0–19 days). Only 31% (79 patients) still had a drain in place beyond day 3. The bladder catheter was removed on median day 5 (range 1–49 days). Finally, the central venous line was removed on median day 6 (range 1–49 days) (Table 5).

First mobilization (out of the bed) was achieved on median day 1 (range 0–9 days), and on median day 3 (range 1–46 days), patients were mobile on their own in the ward (Table 5).

Postoperative Complications

In total, there were five in-hospital deaths (2%), two due to insufficiency of the pancreatic anastomosis, one due to pancreatic stump insufficiency after distal pancreatic resection, one due to insufficiency of the jejunal anastomosis, and one due to unexplained sepsis with multiorgan failure. Surgical morbidity occurred in 24.7% of the operated patients. Postoperative hemorrhage (7.5%) and delayed gastric empting (7.8%) were the most frequent postoperative complications, followed by wound infection (4.7%) and fistulas (4.7%). Fourteen of 19 postoperative hemorrhages and 5 of 12 fistulas (three pancreatic fistulas) needed operative revision. Overall, 9% of the patients received a relaparotomy. Forty-two patients (16.5%) demonstrated

Table 7 Fast-Track Variables, Correlation with Early Discharge

Fast-track Parameters	Rho	*p*
First stool	0.160	0.011
Normal food	0.406	<0.001
Complete mobilization	0.434	<0.001
Return to ward	0.336	<0.001
Intra-abdominal drain removal	0.147	0.019

Spearman's rank-order coefficient, rho. $p<0.05$

Table 8 Predictors of Early Discharge

Patients factors		*p*
Age[a]	(<60, ≥60)	<0.001
ASA[a]	(≤2, >2)	0.015
Sex[a]	(M, F)	0.124
BMI[a]	(<25, ≥25)	0.034
Disease[a]	(Benign, malign)	<0.001
Surgical factors		
Operating time[a]	(<6 h, ≥6 h)	0.002
Blood loss[a]	(<1 l, ≥1 l)	0.008
Transfusion[a]	(No, yes)	0.003
Resection type[b]		0.046
Surgeons[a]	(Pancreatic surgeon, fellow)	0.201
Anesthesia factors		
Core temperature[a]	(<36°C, ≥36°C)	0.786
Extubation[a]	(day 0, ≥day 1)	0.004
Pain management[a]	(PDA, no PDA)	0.316

PDA=peridural analgesia

[a] Univariate analyses between groups conducted using Fisher's exact test for categorical variables. $p<0.05$

[b] Univariate analyses between groups conducted using χ^2 test for categorical variables. $p<0.05$

Table 9 Multivariate Analysis on Factors Affecting Early Discharge

	Coefficient (*b*)	SE	Wald χ^2	Odds ratio	95% CI	*p*
Age	1.40	0.29	22.85	4.06	2.28–7.20	<0.001
Operating time	0.69	0.30	5.38	1.99	1.11–3.55	0.020
Extubation	1.03	0.51	4.06	2.80	1.03–7.64	0.044

Multivariate analysis performed by stepwise logistic regression. 95% confidence intervals (CI) were computed to estimate the precision of the odds ratio. $p<0.05$
CI=confidence intervals, SE=standard error

medical morbidity—11.4% showed major complications such as pneumonia ($n=10$, 3.9%), cardiac complications ($n=6$, 2.4%), renal insufficiency ($n=4$, 1.6%), urinary infection ($n=6$, 2.4%), and neurological disorders ($n=3$, 1.2%). The rest were minor complications such as pleural effusion, hypertension, and hyperglycemia (Table 6).

Factors Influencing Fast-Track Surgery

Known fast-track parameters, such as the occurrence of the first stool, normal food, complete mobilization, and transfer to the ward, correlated significantly with early discharge, defined as <10 days (Spearman's rank-order coefficient, rho, $p<0.05$) (Table 7). Moreover, the early removal of intra-abdominal drains also correlated with early discharge (Spearman's rank-order coefficient, rho, $p<0.05$) (Table 7).

Using univariate analysis to detect significant predictors of early discharge, several patient-related parameters, such as age <60 years, low ASA score (I and II), BMI <25, and the presence of benign disease, were associated with early discharge ($p<0.05$). In addition, surgical factors such as short operation time (<6 h), low blood loss (<1,000 ml), and the absence of blood transfusion led to early discharge ($p<0.01$). Univariate analysis also revealed that the resection type had a significant influence on the discharge ($p=0.046$, Chi square test). More extensive resection in combination with more complicated reconstruction (Whipple resections, segmental resection) was associated with later discharge. The extent of the surgeon's experience in pancreatic surgery did not influence the duration of the hospital stay. Finally, early extubation of the patient was the only significant anesthesia factor ($p<0.01$), normothermia or the use of epidural analgesia was not associated with early discharge (Table 8). Moreover, there were nonsignificant differences between the use of epidural analgesia or other pain management strategies and the occurrence of the first stool, return to normal food, or complete mobilization (Mann–Whitney U, $p=0.65$, $p=0.9$, and $p=0.49$, respectively). Multivariate analysis identified age <60 years (odds ratio 4.06, $p<0.001$), short operating time (odds ratio 1.99, $p<0.05$), and early extubation (odds ratio 2.8, $p<0.05$) as significant independent factors of early discharge (Table 9).

Discussion

Advances in modern surgery have made pancreatic resection into a safer procedure with mortality rates under 5% at specialized high-volume centers. However, postoperative morbidity still remains high with rates between 30 and 60%.[1,3–7,10–12,25,26] This is associated with dramatic physiological and psychological stresses during the perioperative period.[14] Recently, comprehensive perioperative programs, called "fast-track surgery," were developed to counteract these stressors, to reduce potential complications, and to promote early discharge.[14,27] Upholding surgical traditions and inspired by the promising results of fast-track concepts in colon surgery, our postoperative care regiment was adapted to achieve three major goals:[14] early transfer to the normal ward, early normal gastrointestinal function based on normal food intake and passing of stool, and early complete mobilization. This study demonstrates that, in pancreatic surgery, these three factors correlate highly with rapid recovery of the patient and that consequent early discharge at median day 10 with a low readmission rate of 3.5% can be achieved, as demonstrated with other surgical procedures.[16–18,20,21,28,29] Moreover, with a discharge on median day 10, we report a shorter postoperative stay in comparison to other high-volume centers (12 to 17 days)[1,3,5–7,9–12] and to our own historical controls of 14 to 16 days.[4,30]

Complete mobilization is known to be a crucial factor, as prolonged bed rest results in increased muscle loss, impaired pulmonary function, and increased risk for thromboembolic events.[31] Therefore, early and complete mobilization of patients on median day 3 was achieved by quick removal of nasogastric and respiratory tubes, intra-abdominal drains, urinary catheter, central venous lines, and optimized postoperative pain management.

The routinely placed nasogastric tube was removed from the majority of the patients on the day of the operation. Recent data even demonstrates that nasogastric tube placement is, in fact, unnecessary in elective abdominal surgery and leads to pulmonary complications.[32] Because only 11% of the patients need a transient reinsertion of the nasogastric tube, usually much later in the course (median day 6), early removal seems to be practical and justified.

Ninety percent of patients were extubated on the day of the operation, which was made possible by keeping a majority of the patients' core temperature normothermic during the operation (69%). Importantly, the multivariate analysis shows that early extubation is the only independent postoperative factor to influence early discharge.

Routinely placed abdominal drains were removed on median day 3. A recent prospective randomized trial demonstrated that routinely placed drains during pancreatic resection do not help to reduce mortality or morbidity.[33] In contrast, long-remaining drains were shown to be associated with significantly more abscesses or fistulas during the postoperative course.[33] In the event of an occurring fistula, interventional CT-guided puncture and drainage can be performed for successful treatment. Only 5 of 12 fistulas (42%) needed reoperation in this study. Moreover, the early removal of the abdominal drains was significantly associated with an earlier discharge and is therefore a crucial factor in the fast-track concept in pancreatic surgery.

The urinary catheter and the central venous line were removed during the first week, which was determined by the duration of epidural analgesia and the use of IV fluid infusion. A recent study in colonic surgery showed that, despite epidural analgesia, the urinary catheter can be removed earlier to allow free mobilization.[34] However, in pancreatic surgery, higher analgesic doses are needed for a longer time period. This might lead to a higher reinsertion rate. As we mainly use suprapubic drainage, we face only very few postoperative urinary infections.

Finally, epidural analgesia showed, in several studies, favorable effects in attenuating the perioperative endocrine-metabolic response and in shortening postoperative ileus.[15,35–37] However, in this study, no significant difference was seen between the use of epidural and peripheral analgesia concerning the duration of patient recovery and discharge time. That may be explained by the fact that epidural analgesia has a smaller effect on the endocrine-metabolic response in upper abdominal surgery.[15] However, efficient pain control, which may be achieved through epidural but also by patient-controlled analgesia, remains a key element in the fast recovery of the patient. This allows not only fast mobilization but also proper respiratory function and, therefore, prevention of postoperative pulmonary infection.

Besides mobilization, early recovery of normal gastrointestinal function also helps to deter postoperative morbidity in pancreatic surgery. Next to the common problem of postoperative intestinal atony, delayed gastric emptying leads to serious discomfort of the patient after pancreatic resection and results in significant prolongation of the hospitalization.[1,4,5] This study demonstrates that early normal food intake can also be achieved in pancreatic surgery. However, the routine use of antiemetic and prokinetic medications, which are strongly promoted in fast-track concepts, was shown not to correlate with normal gastric empting or early stool passage. Upper gastrointestinal procedures may have other postoperative physiological effects compared to lower gastrointestinal operations, and therefore, these fast-track interventions may be of less significance.[15] However, only prospective randomized studies that further test these interventions may provide a final answer. The low rate of delayed gastric emptying (7.1%) in comparison to reported results (14 and 70%)[1,3–7,9–12,25,26,38] is probably due to the reconstruction by antecolic duodenjejunostomy for patients undergoing Whipple procedures. This surgical adaptation was shown to significantly lower the delayed gastric emptying rate in comparison to the often-used retrocolic duodenjejunostomy.[39]

In fast-track colon surgery, some higher readmission rates were reported, leading to a controversial discussion regarding the safe recovery of patients, meaning the risk of higher readmission rates and the occurrence of severe complications after discharge.[20] In this study, the readmission rate was low, at 3.5%. Furthermore, no increase of postoperative morbidity was observed compared to a historical control.[4] Surgical and medical complication rates were the same or even slightly lower (25.9 vs 26% and 16 vs 18%).[4]

Conclusion

A fast and safe operation is still the most important factor influencing early discharge, mortality, and morbidity. However, fast-track parameters, such as early feeding, early first stool, early drain removal, and forced mobilization, seem also to promote earlier discharge and maybe even lower medical complication rates. Furthermore, the fast-track approach is safe with low hospital readmission and unchanged surgical mortality and morbidity rates.

The classical fast-track interventions, such as the use of epidural analgesia and pharmacological support of the gastrointestinal function, seem not be of great significance in pancreatic surgery. Further studies are needed to evaluate the fast track approach further and to elucidate whether obvious differences between fast-track surgery in upper and lower abdominal surgery exist.

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Portal Vein Interposition Using Homologous Iliac Vein Graft during Extensive Resection for Hilar Bile Duct Cancer

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Abstract Although autologous vein grafts have been used for portal vein (PV) reconstruction after long-segment portal vein resection during surgery for hilar bile duct cancer, their procurement prolongs operation time and increases morbidity. Less is known regarding the use of homologous vein grafts. The feasibility of homografts for PV reconstruction was preliminarily evaluated in two patients who underwent curative resection for hilar cholangiocarcinoma. Both patients underwent left lobectomy, caudate lobectomy, bile duct resection, and segmental PV resection and interposition vein graft reconstruction. The iliac vein homografts were obtained from deceased organ donors and stored for 1–2 days in cold preservation solution without freezing. Neither immunosuppression nor anticoagulation was attempted. One patient has shown good PV patency for 27 months. The second patient, who had received adjuvant chemoradiotherapy, showed an asymptomatic waisting at the proximal PV anastomosis site after 4 months, which was relieved by percutaneous balloon dilatation, and has been doing well for 12 months. In conclusion, our preliminary experience with these two patients suggests that cold-stored iliac vein homografts can be considered as PV substitutes after long PV segment resection during extensive hepatobiliary surgery.

Keywords Hilar bile duct cancer · Portal vein · Homograft

Abbreviations

CT	Computed tomography
LDLT	Living donor liver transplantation
PV	Portal vein

Introduction

Hilar bile duct cancer often involves the portal vein (PV) and hepatic artery in the hepatoduodenal ligament because of their anatomical proximity to the bile duct. Extensive surgery for hilar bile duct cancer has often included resection of the PV bifurcation.[1] End-to-end anastomosis is usually attempted after PV resection if adequate length of PV is still available after the resection of a small segment of PV. When direct anastomosis does not appear feasible, interposition of a vein graft is performed, usually using autologous large-caliber veins, such as the external iliac, left renal, and internal jugular veins.[2–5] Spiral winding of the greater saphenous vein patch can provide a large-caliber vein segment.[6]

Procurement of autologous vein grafts, however, prolongs time in surgery and may increase the operative risk to patients undergoing major liver resection. Thus, it may be more feasible to use homologous vein grafts. To date, however, there are few reports on the use of homografts as PV substitutes during non-transplant hepatobiliary surgery.[7] We herein report two patients who underwent segmental PV resection and iliac vein homograft interposition for curative resection of hilar bile duct cancer.

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Case Report

Case 1

A 49-year-old male patient had intraductal and periductal infiltrative cholangiocarcinoma involving the left hepatic duct and extending to the hepatic hilum (Fig. 1A). Obstructive jaundice was decompressed with percutaneous transhepatic biliary drainage. Percutaneous cholangioscopic biopsy revealed well-differentiated papillary adenocarcinoma. Dynamic liver computed tomography (CT) suggested left PV encasement involving the confluence portion (Fig. 1B). Left lobectomy with caudate lobe resection and bile duct resection were planned. Dissection of the hepatoduodenal ligament revealed, a 3-cm-long segment of PV around the hilar confluence was encased by the tumor, requiring 4 cm of PV segment resection. Despite full mobilization of the remnant right liver and extensive dissection of the main PV around the neck of the pancreas, direct anastomosis did not appear feasible without excessive tension at the anastomotic site.

A living donor liver transplantation (LDLT) using a modified right lobe graft was performed by our surgical team. An iliac vein homograft procured from a deceased donor 2 days before was used to reconstruct the middle hepatic vein on the right lobe graft. This homograft was preserved in cold solution for less than 48 h without freezing. The excess vein left over after the MHV reconstruction in the living donor right graft was used for the PV interposition graft for the hilar cholangiocarcinoma resection. However, the homograft was not ABO compatible. This situation was expected (CT demonstrated the encasement of the PV) and prior permission and consent was obtained from the patient and the family for the use of homograft for reconstruction of the resected portal vein segment.

The left lobe mass, including the involved PV, was removed as an en bloc resection, and the iliac vein homograft was interposed to replace the 4-cm-long defect between the right and main PV stumps. PV reconstruction was performed in end-to-end fashion using 6-0 Prolene sutures. Arterial flow was maintained to the remnant right lobe while PV reconstruction was performed. A significant growth factor was incorporated after the completion of the portal vein anastomosis to prevent portal vein stenosis. A bilioenteric anastomosis was fashioned via a Roux-en-Y hepaticojejunostomy to drain the four bile duct openings on the remnant right lobe of the liver. The histopathologic examination of the resected enbloc specimen showed that it was an R0 resection. In the postoperative period, no immunosuppressants or anticoagulants were used.

Doppler ultrasonography was performed twice during the first week and dynamic liver CT scans was performed twice during the postoperative period of 15 days (Fig. 1C). Routine follow-up with dynamic liver CT, repeated every 3 months, did not detect any change in the caliber of the

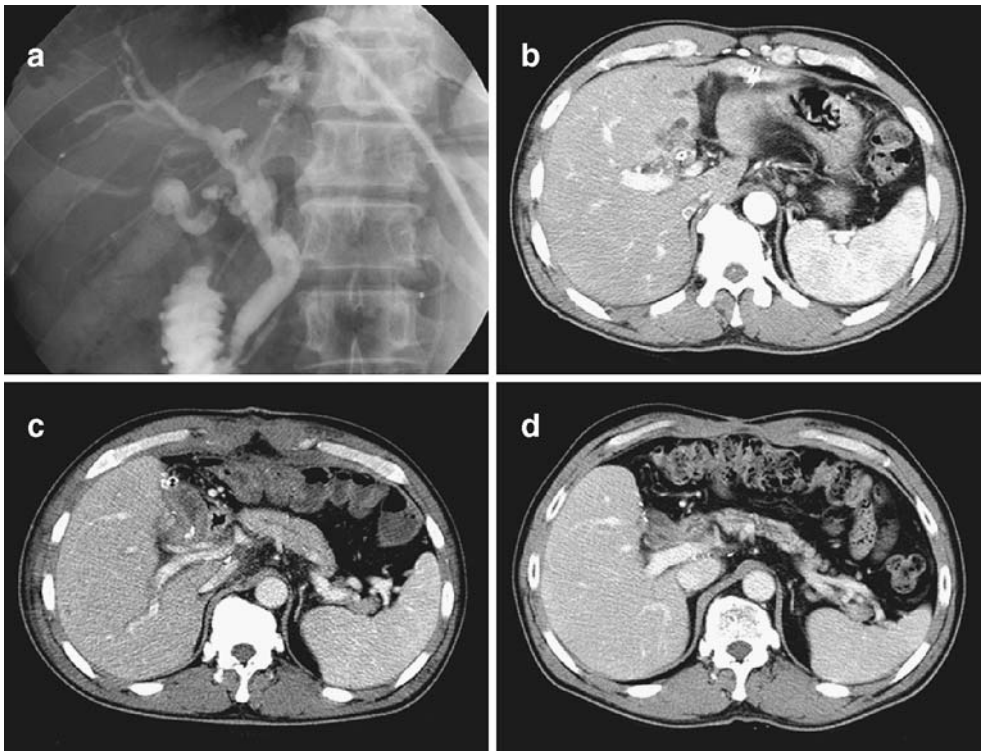

Figure 1 Imaging studies of the case 1. **a** Preoperative tubogram showing the extent of intraluminal mass. **b** Preoperative CT showing encasement of the PV bifurcation. **c** At 1 week after operation, the PV appeared rather narrow and elongated. **d** After 24 months, there was no morphological abnormality at the interposed PV homograft.

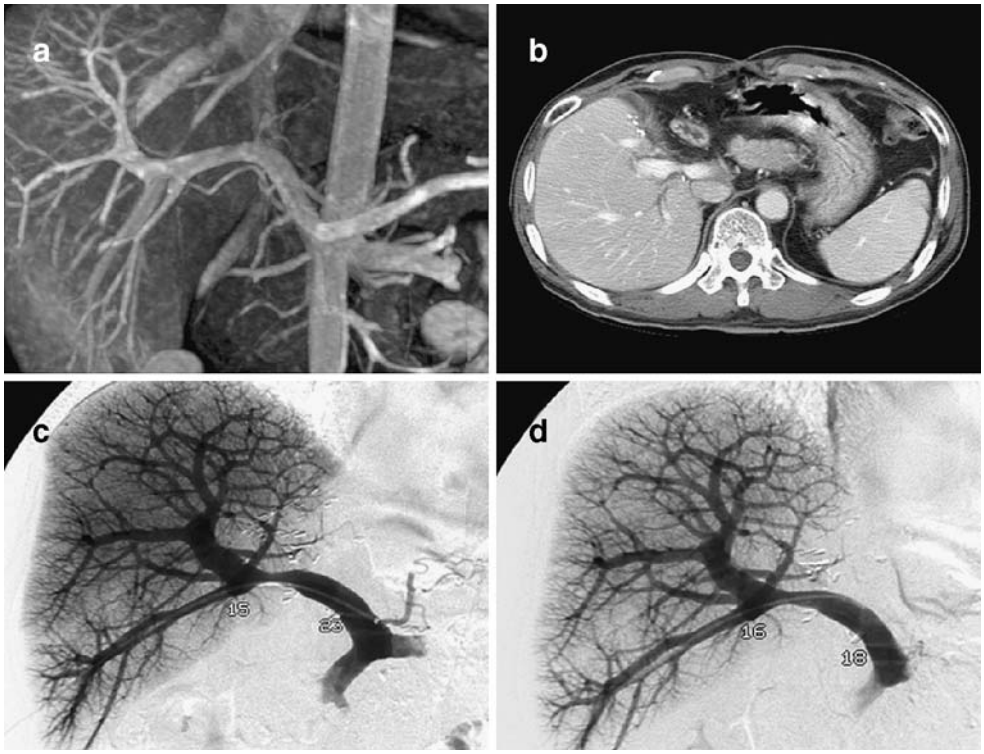

Figure 2 Imaging studies of the case 2. **a** Preoperative magnetic resonance imaging showing encasement of PV bifurcation. A 4-cm-long PV segment was resected due to heavy adhesion and direct infiltration by the tumor. **b** At 4 months after surgery, a waist was detected at the proximal anastomosis of PV. **c** After 6 months, percutaneous balloon dilatation was attempted. There was a pressure gradient of 8 mm H_2O across the PV wasting. **d** After balloon dilatation, the pressure gradient was reduced to 2 mm H_2O.

portal vein reconstruction site. (Fig. 1D). At the last followup (27 months after the liver resection), the patient is doing well with no evidence of tumor recurrence.

Case 2

A 56-year-old male patient had hilar bile duct cancer of Bismuth-Corlette type IIIb. Obstructive jaundice was decompressed with bilateral percutaneous transhepatic biliary drainages. Left PV encasement was identified on imaging studies (Fig. 2A). Left lobectomy with caudate lobe resection, bile duct resection, and PV segmental resection was planned. After dissection of the hepatoduodenal ligament, a 3-cm-long segment of the PV was found to be encased by the tumor, requiring segmental PV resection of up 4 cm. Despite liver mobilization and PV dissection around the neck of the pancreas, direct anastomosis did not appear feasible.

A cold-stored iliac vein homograft was found to be available from concurrent LDLT operation like in the situation of case 1. This vein homograft was ABO blood group-compatible and had been stored for only 1 day. Because potential use of homograft was approved by the institutional ethical committee and consented by the patient before operation, a 3-cm-long homograft was transferred to this patient. The left lobe mass including the involved PV was resected, and the iliac vein homograft was interposed between the right and main PV stumps (Fig. 3). Reconstructive procedures for the bile duct were the same as for case 1. Pathologic examination revealed that the operation was an R0 resection. Postoperative management for the 18 days admission after surgery was the same as for case 1. This patient was administered adjuvant chemoradiotherapy. Four months after surgery, follow-up CT showed a waisting at the proximal PV anastomosis site, but without abnormal liver function. This PV waisting appeared to have progressed slightly at the 6-month CT scan (Fig. 2B), but Doppler ultrasonography revealed no significant disturbance of the portal flow. To prevent further progression of PV stenosis,

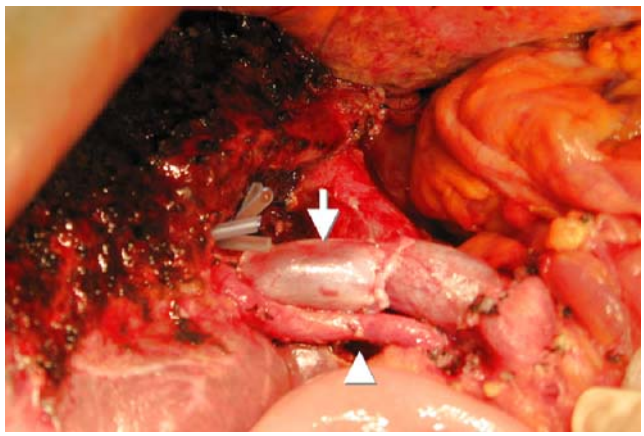

Figure 3 Intraoperative photograph of the case 2. The arrow indicates the interposed iliac vein homograft, whereas the arrowhead indicates the replacing right hepatic artery originating from the superior mesenteric artery. Four short silastic tubes were inserted into the transected bile duct openings.

percutaneous balloon dilatation was performed, and the pressure gradient across the PV stenosis was reduced (Fig. 2C). The last followup (12 months since the liver resection) showed no evidence of tumor recurrence. (Fig. 2D).

Discussion

Extensive resection for hilar bile duct cancer includes concurrent PV resection in a considerable proportion of patients.[1] It is generally accepted that segmental PV resection combined with major liver resection, up to 3–4 cm in length, can be directly reconstructed and can be elongated after concurrent pancreatoduodenectomy. In practice, when the right lobe is removed, the PV becomes rather redundant, and end-to-end anastomosis can be readily performed after segmental PV resection of up to 3–4 cm. For resection of the left lobe, however, the permissible length of PV resection for primary anastomosis becomes shorter because of the morphological anatomy of the right PV and position of the right liver.[3]

When approximation of the PV stumps fails or excessive tension is expected, it is mandatory to interpose a vein graft. Various kinds of autologous vein grafts have been harvested, but procurement of large-caliber vessels carries risks. In our institution, the external iliac vein graft has occasionally been harvested, with or without reconstruction of the excised portion using synthetic material. This procedure can induce bleeding complications in the lower abdomen and leg edema. Harvesting of the left renal vein also carries some potential risks of functional impairment of the left kidney. We have not yet attempted to procure the internal jugular vein. Because the diameter of the greater saphenous vein is too small for PV replacement, spiral winding is necessary to enlarge its diameter.[6] Outcomes using these autologous vein grafts are very favorable, despite prolongation of time in surgery and some donor site complications.

Our experience in performing LDLT has led to several changes in general hepatobiliary surgery. Because we have performed more than 200 adult LDLTs per year, our use of vascular homografts for middle hepatic vein reconstruction is very common. Furthermore, it is not uncommon for surgical teams at our institution to perform LDLT and general hepatobiliary operations concurrently. This unique situation has provided us with the opportunity to use iliac vein homografts instead of autografts.

Inasmuch as very little is known about the use of homografts in non-transplant hepatobiliary surgery, we have been very cautious in approaching this problem. Because there is a potential risk of pseudoaneurysm and thrombosis after using cryopreserved vein grafts, we have avoided their use.[9] Rather, we used homografts preserved for short periods in the cold storage, thus avoiding any potential tissue damage caused by prolonged cold storage and freezing–thawing of cryopreserved grafts.

PV reconstruction using homografts is not unusual in liver transplantation. In patients with severe PV stenosis, PV jump grafts from the superior mesenteric or left renal vein have been performed. Most of these jump grafts, however, were fresh vein grafts from deceased donors or the recipients themselves, making the former identical to the native portal vein of the graft liver.[4]

In literature, using cryopreserved iliac veins and saphenous vein homografts for PV interposition in seven liver transplant patients has resulted in aneurysm formation in four, stricture in one, and thrombosis in one.[9] Moreover, the 5-year primary patency rate of cryopreserved veins as PV substitutes has been reported to be only 58%, indicating that their use should be limited.[10] When performing LDLT surgery, we do not use cryopreserved vessel graft for PV reconstruction. Rather, we usually delay LDLT operation until an adequate deceased donor vessel is available. Unfavorable outcomes from the use of cryopreserved iliac vein homografts indicate that their use in both liver transplantation and general hepatobiliary surgery is not recommended.[9–11]

In contrast to cryopreserved homografts, vascular grafts stored in cold preservation solution usually keeps the vessel in very good quality. Based on our experience of LDLT, cold storage for up to 48 h did not seriously weaken or degrade iliac vein grafts. In fact, such cold preservation method permits 2 weeks storage.[11] We arbitrarily define fresh vein grafts as being in cold storage for less than 48 h. Thus, both vessel grafts in cases 1 and 2 are fresh grafts.

The use of homografts in these two patients constitutes a type of reutilization rather than sharing. These vessels would have been discarded because segments as short as 3 cm are usually useless for next LDLT operation. We took special care not to contaminate these vessel segments during manipulation for concurrent LDLT operation.

In case 1, our use of a cold-stored iliac vein homograft resulted in a favorable outcome, comparable to that using an autograft. In case 2, however, anastomotic stenosis developed and progressed within 6 months. Because we were familiar with this type of PV reconstruction, we suspected that anastomotic stenosis was a sequela of radiotherapy rather than a technical problem.[12,13] This finding suggests that homografts can be equally or more vulnerable to radiation injury, comparing with autografts.

Because interposition of a vein graft requires two sequential anastomoses, axial twisting must be avoided because kinking may occur. This can be achieved by maintaining precise anterior–posterior orientation when placing vascular clamps.[14] Drawing of a longitudinal line at the midline of the exposed PV was also helpful for keeping the anastomosis axis correct, even during reapplication of vascular clamps.

When using a homograft as a conduit vessel, there may be no need to meet ABO-blood-group compatibility, as in cardiac valve homograft replacement. It is unlikely that antigenicity of the homologous vascular endothelium seriously increases the risk of luminal thrombosis. Immunosuppression is also not necessary.

Although anticoagulation may be beneficial for preventing luminal thrombogenesis, major hepatectomy often results in a temporary impairment of the coagulation profile, which may help to maintain PV flow without anticoagulation. Because the PV is a medium-velocity but high-volume vessel, we do not think that anticoagulation is essential to prevent thrombosis, unless the patients has an unusual state of hypercoagulability. Because of the mechanisms of new intimal formation, short-term anticoagulation may be beneficial on a case-to-case basis.[6]

Finally, we think that this use of homograft in non-transplant surgery should be evaluated objectively from the viewpoint of gains and losses. The gain is definitely proven because it makes donor vein harvest unnecessary. The potential problem is that the outcome of homograft usage may be inferior to that of autograft usage. Although this risk has not been fully evaluated in literature, we think from our limited experience it may be low enough not to be considered as experimental. However, until large-volume studies with long-term follow-up prove its efficacy, it may be reasonable to receive informed consent and to keep on special surveillance on the patency of homograft.

In conclusion, our preliminary experience with these two cases indicates that cold-stored iliac vein homografts can be considered as PV substitutes during extensive hepatobiliary surgery.

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Viability of Endoscopic and Excisional Treatment of Early Rectal Carcinoids

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Abstract With the advent of endoscopy, the incidence of rectal carcinoid tumors has not only risen, but the majority are localized at presentation. This has led to excisional and/or ablative therapy in lieu of radical resections. A single institute's experience with rectal carcinoids was reviewed to determine the impact this approach has had on outcomes, and evaluate any selection criteria for optimizing patient survival. A single institute's tumor registry was retrospectively queried, identifying 14 patients with rectal carcinoid tumors over a 28-year period. The mean age at diagnosis was 52.1±14.4 years. Six of the 14 patients were female. Presenting symptoms included a change in bowel habits in six (38%), rectal bleeding in six (38%), and abdominal pain or distention in five (31%) patients. No patient had symptoms consistent with carcinoid syndrome. The rectal carcinoids were a mean 9.2±3.4 cm from the anal verge and a mean 9±6 mm in size. Endoscopic and/or transanal excision/fulguration techniques treated 11 (79%) patients, whereas two (14%) patients underwent a low anterior resection (LAR). Surveillance entailed periodic endoscopy for a median 65 months (range 8–281). No patient developed recurrent carcinoid disease for a 20-year overall survival of 70%.

Keywords Rectum · Carcinoid tumors · Treatment

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Introduction

Slatykow is recognized as reporting the first rectal carcinoid, identified during an autopsy, publishing the result in 1912.[1] This was followed in 1928 by Masson describing the cell of origin for carcinoid tumors to be the chromaffin cell, and later characterizing carcinoids as containing neurosecretory granules.[2] Histologically, these granules are evidence of their ability to secrete peptide and nonpeptide hormones, hence their classification as an amine precursor uptake and decarboxylation (APUD) tumors. Despite this endocrine function, only half of patients with carcinoid tumors manifest a clinical hormonal syndrome. Rectal carcinoids are notoriously hormonally silent, with the report of carcinoid syndrome in patients with rectal carcinoids being rare. In 1982, Soga published an extensive review of the literature and found at most 12 reported cases of carcinoid syndrome associated with a rectal carcinoid tumor.[3] More recently, four combined rectal carcinoid series reported only 1 of 199 (0.5%) patients experienced symptoms consistent with carcinoid syndrome.[4–7]

From recent analysis of the SEER data base, the incidence of rectal carcinoid tumors has risen to 4.2 cases per million

persons.[8] The gastrointestinal carcinoid tumor distribution involves the small bowel 41.8%, rectum 27.4%, and stomach 8.7% of the time.[8] Of all rectal tumors, carcinoids account for 1.1–1.3% of these tumors.[9,10]

Rectal carcinoids comparatively have a good prognosis with a 5-year overall survival (OS) of 88%.[11] This reflects largely the early stage at diagnosis with 82% localized, 2.2% having regional disease, and only 1.7% with metastases at the time of diagnosis. The 5-year OS for localized, regional, and metastases is 91, 49, and 32%, respectively.[11] Prognostic factors evaluated have included size, depth,[4,5,10,12,13] and histology.[4,14–17] The objective of this study was to determine the outcome of localized treatment for early rectal carcinoid tumors. Secondarily, prognostic variables used to select patients for localized treatment were evaluated.

Methods

A retrospective chart review was performed of all patients referred to a single institute between January 1, 1975 and December 31, 2003, with a confirmed or subsequently diagnosed rectal carcinoid. The study was approved and performed within the guidelines of the Institutional Review Board.

Patient demographic data, symptoms on presentation, and mode of diagnosis were recorded. The ensuing treatment and outcomes were reviewed, as were each patient's pathology slides. Not only was the pathology reexamined to confirm the carcinoid diagnosis, but also to assess the presence of any atypical histological features. Survival was calculated by Kaplan–Meier methods.

Results

Fourteen patients were identified with a carcinoid tumor within 15 cm of the anal verge. The series consisted of six females and eight males. The median age was 50.5 years (range 35–85) at diagnosis, whereas the mean was 52.1± 14.4 years. The mean tumor size and distance from the anal verge was 9±6 mm and 9.2±3.4 cm, respectively. Five (36%) patients had at least one additional cancer diagnosis, two (14%) of which were synchronously diagnosed with rectal adenocarcinoma. The remaining three (21%) patients had a metachronous cancer diagnosis that included breast carcinoma, colon adenocarcinoma, and one patient with both floor of the mouth and lung squamous cell carcinoma diagnosed at different times. The demographic and tumor characteristics are listed in Table 1.

The most common symptoms on presentation were a change in bowel habits (six patients, 43%), rectal bleeding (six patients, 43%), and abdominal pain or distention (five patients, 36%). Two patients (14%) were diagnosed on screening endoscopy. Retrospective pathologic review showed all carcinoid tumors to have typical histology. There were no atypical features such as cellular pleomorphism, mitotic figures, anaplastic appearance, mucin production; or invasion of the vessels, lymphatics, or perineurium.

Table 1 Rectal Carcinoid Patient Demographics and Clinical Features

Total number of patients	n=14
Median age	50.5 years (range 35–85)
Gender	
Female	n=6
Male	n=8
Presenting symptoms	
Change in bowel habits	n=6
Rectal bleeding	n=6
Abdominal pain or distention:	n=5
Mean distance from anal verge	9.2±3.4 cm
Size of rectal carcinoid	9±6 mm
Depth of invasion	
No greater than the submucosa:	n=10
Beyond the submucosa:	n=1

The median follow-up of all 14 patients was 65 months (range 8–281). The 20-year OS calculated by Kaplan-Meier methods was 70%; see Fig. 1. Treatment entailed endoscopic removal with or without ablation of the rectal carcinoid in nine patients, low anterior resection (LAR) was performed in two patients (one for concomitant rectal adenocarcinoma), and two had a transanal excision (TAE) of the rectal carcinoid. Transanal endoscopic microsurgery was not employed in this series of patients. The final patient, with concomitant metastatic breast carcinoma, refused further evaluation or treatment of her rectal carcinoid tumor. Of the nine patients treated endoscopically, four had undefined biopsies or polypectomies, two had a biopsy and fulguration, two had cold biopsies, and the final patient underwent a snare polypectomy for definitive treatment. Five patients received their definitive therapy from referring institutes, one LAR and four endoscopic biopsy procedures. They were referred for further therapy recommendations, all of which entailed surveillance in addition to having their pathology reviewed. All patients treated endoscopically or via TAE (11 patients) had no evidence of disease (NED) for a median 71 months (range 22–231). Of the two patients treated via LAR, one had two lymph nodes positive for carcinoid disease and subsequently received adjuvant chemoradiation therapy for a synchronous rectal adenocarcinoma. This patient was NED after 25 months of follow-up, whereas the second patient treated with LAR (performed at an outside institute) for a localized rectal carcinoid was NED after 281 months of follow-up.

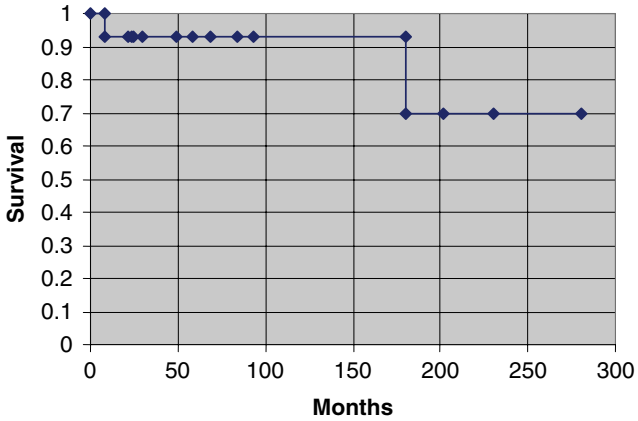

Figure 1 Kaplan–Meier survival curve for all (n=14) rectal carcinoid patients. The estimated 20-year survival is 70%.

The 10 patients with their rectal carcinoid not invading beyond the submucosa, were all NED for a median 78 months (range 27–281). The one patient where the primary rectal carcinoid invaded beyond the submucosa and into the subserosal, had regional disease in two perirectal lymph nodes. This patient received adjuvant chemoradiation therapy for the synchronous rectal adenocarcinoma and was NED after 25 months of ongoing follow-up. Data on the depth of invasion was not available for three patients.

Besides depth of invasion, patient outcomes were stratified with respect to the size of the primary rectal carcinoid. Seven patients had primary rectal carcinoids ≤1 cm, four had primary rectal carciniods >1 and ≤2 cm, whereas in three patients the primary tumor size was unknown. For the seven patients with tumors ≤1 cm, all were NED after a median 89 months (range 22–202). One of the four patients with the carcinoid >1 and ≤2 cm had regional lymph node disease cleared by a LAR and was NED after 25 months of follow-up. The remaining 3 of 4 patients with a primary rectal carcinoids >1 and ≤2 cm were NED after follow-up of 27, 30, and 49 months.

Discussion

The absolute incidence of rectal carcinoid tumors is rare; however, the incidence has risen from 0.4 to 4.2 cases per million people.[8] This increasing trend has been postulated to be the result of a change in reporting guidelines of carcinoids, and the introduction of endoscopy in the 1980s.[18] As one would expect after the introduction of endoscopy, not only the incidence of rectal carcinoids has increased, but the percentage of patients with localized disease has risen.[11] With a higher proportion of early rectal carcinoid tumors identified, the literature has tried to stratify these carcinoids into benign or malignant behaving tumors. The benign early rectal carcinoids have been managed safely with local excision either by endoscopic techniques or via transanal excision (TAE), limiting the morbidity of a radical resection.

Commonly, rectal carcinoids are diagnosed in the sixth decade with an equal gender distribution.[5,6,11,19–23] The demographic characteristics of this series were similar, with a median age of 50.4 years and 6 of 14 patients being female.

Depth of invasion and size are two important prognostic factors for carcinoid tumors to distinguish between a clinically benign versus malignant course. In 1983, Naunheim and colleagues[5] found rectal carcinoid size to be a statistically significant prognostic marker for developing metastatic disease, $p<0.001$. In their review of the literature, 13 of 388 (3.4%) rectal carcinoids ≤1 cm either had metastatic disease on presentation or progressed to metastatic disease. Similarly, 14 of 125 (11%) rectal carcinoids 1.1 to 1.9 cm, and 61 of 82 (74%) rectal carcinoids ≥2 cm had metastatic disease or progressed to have metastases. In 1992, Jetmore et al. reported their experience over 32 years with rectal carcinoids. For sizes <1 cm, 0 of 56 patients developed metastatic disease, whereas two of 28 (7%) patients with tumors 1 to 2 cm led to the eventual diagnosis of metastatic disease. For this same series, all patients (5 of 5) having rectal carcinoids >2 cm had metastatic disease on presentation.[6] Matsui et al. and Higaki et al. found no recurrences after excision of primary rectal carcinoids <2 cm in a total of 37 patients.[24,25] Sauven et al. reported OS over a median 33.5 month follow-up for rectal carcinoids <1 cm (7 of 8, 88%), 1.0 to 2.0 cm (12 of 15, 80%), and >2.0 cm (0 of 20, 0%).[13] Comparably, in this current series, all seven patients with primary rectal carcinoids ≤1 cm were NED for a median 89 months (22–202). For early primary, rectal carcinoids >1 cm and ≤2 cm, 4 of 4 survived for a median 28 months (range 25–49). One of the four patients with a primary >1 and ≤2 cm did have regional lymph node involvement.

If one segregates outcome in relation to depth of carcinoid invasion after excision, it is apparent that carcinoids invading beyond the submucosa have a worse prognosis. Naunheim et al. found 12 of 313 (3.8%) patients with invasion limited to the submucosa had metastatic disease on presentation. For those rectal carcinoids that had invaded beyond the submucosa, 66 of 88 (75%) had metastatic disease.[5] Matsui et al. and Higaki et al. found no recurrence for rectal carcinoids limited to the submucosa for their combined experience with 37 patients [24,25]. Higaki et al. reported the only rectal carcinoid of the two series to have invaded beyond the submucosa (muscularis propria), and this patient ultimately died of the disease.[24] Sauven et

al., for a median 33.5 month follow-up reported an OS of 100% (0 of 16 patients), with rectal carcinoids limited to submucosa. For those patients with carcinoid invasion into the muscularis propria, the OS was 75% (3 of 4 patients), and 0% (0 of 19 patients) for rectal carcinoids invading beyond the muscularis propria.[13] This is very consistent with the current reported series having an OS of 90% (9 of 10 patients) for rectal carcinoids limited to the submucosa over a median 78 months (27–281). The one death was caused by metastatic breast carcinoma without any evidence of recurrent carcinoid disease.

The literature has suggested that size and depth of invasion are codominant in relation to prognosis. This is exactly what Stindl and colleagues found in their series where size and depth were correlated with the risk of lymph node involvement, distant metastases, and death.[16] However, size and depth of invasion are not perfect prognostic indicators. This is emphasized by case reports of rectal carcinoid tumors less than 1 cm with lymph node involvement, and even a rectal carcinoid less than 0.5 cm with hepatic metastatic disease.[26,27] Therefore, atypical histology has been assessed to determine which early rectal carcinoids may demonstrate a clinically malignant behavior.[4,14–17]

For example, atypical carcinoids are defined as having cellular pleomorphism, frequent mitotic figures, anaplastic appearance, mucin production, or invasion of the vessels, lymphatics, perineurium or muscularis propria, and have a prognosis that is worse than typical carcinoids lacking these features. Quan et al.[15] noted rectal carcinoids with anaplastic nuclei tended to be larger (45% greater than 1.5 cm) and have metastases (45%). Federspiel et al. found in their series 4 of 35 patients with colorectal carcinoid developed metastases. Of these, four patients that developed metastases, three had ≥2 mitosis per 10 high-powered fields (hpf), and invaded the muscularis propria. All four patients with carcinoid metastases were also found to have ulceration of the primary carcinoid.[14] Mitosis and ulceration as prognostic factors reported by Federspiel et al. are clouded by the presence of muscularis propia invasion by the carcinoid, i.e., depth. Soga was very clear on his recommendations that the malignant categorization of rectal carcinoid tumors should be based entirely on histologic evidence, without regard to size or depth of invasion.[3] Schindl et al. classified typical (benign) rectal carcinoids as having a uniform cell pattern, <2 mitosis/hpf, growth in solid nests or strands, no perineural or lymphovascular infiltration. Atypical (malignant) carcinoid tumors were pleomorphic or demonstrated local invasion (perineural or lymphovascular). They found the tumor's size, depth, and histology (atypical vs. typical) significantly correlated to the risk of lymph node involvement, distant metastases, and death.[16] Looking outside tumor size and depth as prognostic factors, Tsioulias et al. examined DNA ploidy to predict metastatic potential. They reported on 22 patients with rectal carcinoids, 19 with disease localized to the rectal wall, with all having a diploid pattern on DNA analysis. The three remaining patients of the series with metastatic disease had an aneuploid pattern.[28] However, this relationship is tempered by Fitzgerald et al. who did not find any correlation between DNA ploidy and prognosis.[12] None of the 14 rectal carcinoid tumors reported in this series had any atypical histologic findings.

Conclusion

Finally, as seen in this series the rate of synchronous lesions was 14% similar to 13% seen in the SEER data base, and therefore, any patient diagnosed with a rectal carcinoid tumor should undergo a screening colonoscopy evaluating for synchronous lesions.[18] In light of the patient outcomes in this series, it is reasonable to consider primary rectal carcinoid tumors ≤2 cm, invasion limited to the submucosa, and having typical histology to be benign. None of the rectal carcinoid tumors meeting this definition of benign, treated with local excision and ablation (endoscopically or via TAE), experienced any type (local or metastatic) of recurrence. Therefore, local excision and/or ablative techniques are viable therapeutic modalities for early, benign rectal carcinoid tumors.

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Intestinal Malrotation Discovered at the Time of Laparoscopic Roux-en-Y Gastric Bypass

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Abstract Four morbidly obese women who met the NIH criteria for bariatric surgery had laparoscopic Roux-en-Y gastric bypass. At operation, each was found to have intestinal malrotation. Two cases were completed laparoscopically, and two were converted to open operation because of difficulty defining the anatomy. All four operations were successful with no immediate complications and patients tolerated the procedures well. We present the four cases and offer recommendations should this unusual congenital defect be discovered at the time of laparoscopic gastric bypass.

Keywords Morbidly obese · Laparoscopic Roux-en-Y gastric bypass · Intestinal malrotation

Introduction

The incidence of intestinal malrotation among adults is estimated to be 0.2–0.5%, and few among this small number become clinically evident.[1] In fact, the actual incidence of malrotation in adults is unknown because this condition may not result in symptoms that would bring it to medical attention.[2] These facts make diagnosing this congenital defect difficult except at the time of operation, imaging studies ordered for other reasons, or at autopsy. In the extreme manifestation of intestinal malrotation with volvulus, patients may present with a high-grade bowel obstruction and intestinal ischemia. However, many patients with intestinal malrotation without volvulus may be mistakenly presumed to have irritable bowel syndrome, peptic ulcer disease, biliopancreatic disease, or psychiatric diseases.[1]

Between 2002 and 2004, we operated total of 503 gastric bypass surgeries, out of which 493 were laparoscopic, 7 were open, and 3 were converted to open. Among them we fortuitously discovered four cases of intestinal malrotation of various degrees at the time of laparoscopic gastric bypass (LGB) in morbidly obese women. This manuscript presents these cases, discusses the embryology, anatomy, and classification of these malrotations and intraoperative decision making. Recommendations are offered in the event this anomaly is encountered at the time of bariatric surgery.

Case Reports

Case 1

A 49-year-old white woman (weight 265 lbs, BMI 42) with obstructive sleep apnea, hypertension, hypercholesterolemia, and gastroesophageal reflux disease (GERD) underwent LGB. The 20 cc gastric pouch was created as usual without difficulty, but while attempting to identify the ligament of Treitz, the proximal small intestine was not found in its usual location at the base of the transverse mesocolon. Despite extensive exploration, the anatomy could not be clearly defined laparoscopically. Therefore, the procedure was converted to open at which time the

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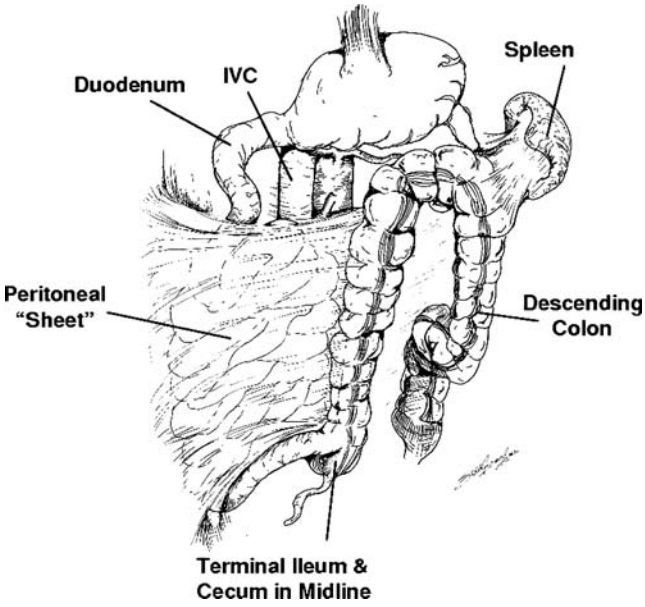

Figure 1 Malrotation in case 1.

cecum was identified in the midline of the pelvis, and the entire small intestine was covered in a peritoneal sheet (broad "Ladd's band") stretching from the right abdominal wall to the misplaced right colon. After cutting this sheet of peritoneum, the duodenum was seen emerging from the retroperitoneum to the right of the aorta and proceeded caudally parallel to inferior vena cava. The jejunum was in right upper quadrant and extended down the right side of the abdomen to join the cecum in the midline of the pelvis. The colon ascended in the midline, and the "hepatic" flexure was to the left of midline. There was essentially no transversely oriented colon, and the descending colon was suspended at the spleen. The remaining colon maintained its usual course to the sigmoid and rectum (Fig. 1).

The jejunum was transected 40 cm distal to the point from where it emerged from the retroperitoneum. One hundred centimeters was measured distally from this point where a stapled jejunojejunostomy was created. The jejunal Roux limb was brought up to the gastric pouch in an antegastric position. It did not cross the colon because the rotation defect left the colon to the left of the midline. The gastrojejunostomy was created using a 25-mm circular stapling device. Methylene blue test confirmed the integrity of the anastomosis, and a drain was placed in the left upper quadrant. The patient made an uneventful recovery and at 33 months has lost 100 lbs with resolution of obstructive sleep apnea, hypertension, and hypercholesterolemia.

Case 2

A 45-year-old white woman (weight 216 lbs, BMI 42) with hypertension, diabetes mellitus-type 2, hypercholesterolemia, and GERD underwent LGB at which time intestinal malrotation was discovered after creating a 20-cc gastric pouch. The cecum was found near the ligament of Treitz, which was in its usual location, and the terminal ileum was located cephalad to the ligament of Treitz. The ileum swept around to the left of the proximal jejunum resulting in a partial or mixed malrotation. After ensuring the exact location of ligament of Treitz we proceeded with the LGB operation and completed it in the previously described fashion. This resulted in the jejunal Roux limb lying anterior to the stomach and terminal ileum because the colon was fixed to the left of the course of the Roux limb (Fig. 2).

Case 3

A 54-year-old white woman (weight 210 lbs, BMI 41) with arthritis, sleep apnea, and hiatal hernia underwent LGB. After creating the 20-cc gastric pouch, it became apparent that the patient had intestinal malrotation when the ligament of Treitz could not be identified in its usual location. Because of unclear anatomy, the operation was converted to open. The cecum was in left lower quadrant and ascending colon made an oblique path up into right upper quadrant where it was attached anterior to the duodenum. The first and second portions of the duodenum were in their normal positions, but the third and fourth portions never crossed the midline. Most of the small intestine was in the right lower abdomen and pelvis. The small intestine had to be freed from adhesions in the pelvis because of previous hysterectomy. The peritoneal bands in the right upper quadrant (Ladd's bands) were lysed, thus mobilizing the ascending colon and hepatic flexure away from the duodenum. At this time it became apparent that the

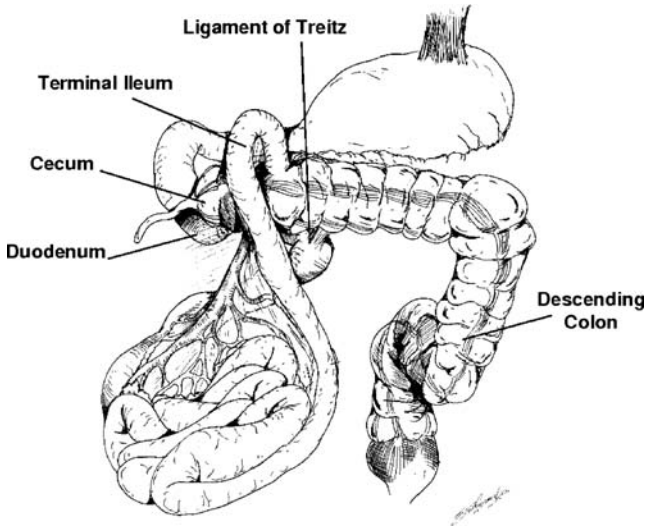

Figure 2 Malrotation in case 2.

transverse colon traveled retroperitoneally behind the superior mesenteric artery (SMA) and anterior to the aorta at the root of the small bowel mesentery. The splenic flexure of the colon emerged from the retroperitoneum and continued in its usual course down the left lateral abdomen. Further efforts to mobilize the transverse colon were abandoned because resection would have been necessary to place it in its normal position. After creating the Roux limb in the usual manner, it was brought into approximation to the gastric pouch in the retrocolic–retrogastric fashion through the space of Riolan. Cecopexy to the right lower abdominal wall was done to prevent volvulus of right colon along with appendectomy. A gastrostomy tube was placed in the bypassed segment of the stomach, and the operation was completed. The patient tolerated the procedure well and was discharged after she started taking gastric bypass soft diet on postoperative day 2. No further complications have been evident in the follow up period of 2 years (Fig. 3).

Case 4

A 29-year-old black woman (weight 358 lbs, BMI 62) with GERD, back pain, obstructive sleep apnea, and migraine headaches underwent LGB. At the time of the operation, malrotation of intestines was noted after gastric transection. The duodenum turned caudad at the junction of the second and third portions and never crossed the midline. The entire small intestine was in the right side of abdomen. The cecum and colon were overlying the sigmoid colon, and the appendix was in left lower quadrant (nonrotation, similar to Fig. 1). There were no Ladd's bands or peritoneal coverings of intestines. The operation was completed laparoscopically in the usual manner, and appendectomy was performed. The patient recovered well and was discharged home on postoperative day 2 in excellent condition. No complications have become apparent to date.

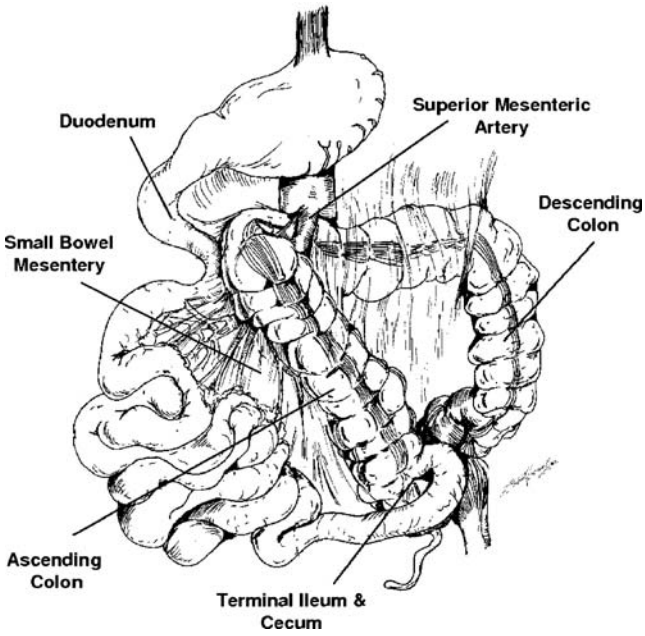

Figure 3 Malrotation in case 3.

Discussion

Intestinal malrotation is a congenital anomaly that presents in a wide variety of clinical manifestations based on diverse anatomic configurations ranging from not-quite-normal intestinal position, to complete nonrotation, to reverse rotation.[3] Malrotation of the intestines also results in abnormal fixation of the mesentery. The normally broad attachment of small intestine mesentery from the ligament of Treitz to the ileocecal valve is usually narrowed depending on the extent of malrotation. This fact predisposes the patient to midgut volvulus around the SMA with resulting small bowel obstruction and potential intestinal ischemia. Ladd's bands are congenital adhesive bands that typically attach from the right posterolateral retroperitoneum to the right colon or cecum and can compress the duodenum causing partial proximal bowel obstruction. These bands can also be the boundary of internal hernias.[2,4]

Understanding the embryology and development of the midgut is essential in understanding and treating the rotational defects of the intestines. The duodenojejunal loop in the embryo is in the same position as the adult stomach, proximal and cephalad to the SMA. In order for it to reach its adult position, the duodenojejunal loop must lengthen and rotate 270° counterclockwise around and posterior to the axis of the SMA. The cecocolic loop lies distal and inferior to the SMA in the embryo and also must undergo 270° counterclockwise rotation to come to lie on the right and anterior to the SMA as in adulthood.

This rotational process occurs in three steps. First, the midgut herniates into celom of the body stalk at sixth week of gestation. As this loop pushes into the body stalk, it undergoes a counterclockwise rotation of 90° so that the duodenojejunal loop lies on the right and the cecocolic loop lies to the left of SMA axis. The second stage occurs during the 10th gestational week when the midgut returns to the abdomen as there is now more space because of the relative decrease of the size of the liver. During this process, the midgut completes its 270° of counterclockwise rotation. The cephalad part of the midgut enters the abdomen first to the right of the SMA, thus displacing the abdominal portion of the colon to the left. Then colon, cecum, and terminal prearterial segments enter the abdomen. Thus the transverse colon lies in front of SMA, and the cecum is at the level of the iliac crest on right side. The third stage begins at the 12th week and continues well after birth. In the third stage, further descent of the cecum, ascent of the hepatic flexure,

and fixation of the ascending and descending mesenteries take place. Any aberration in this process leads to malrotation and malfixation of the intestines.[5,6]

There are several broad categories of rotational defects. First, nonrotation occurs when the midgut rotates 90° as it enters the body stalk, but there is no further rotation when the viscera returns to the abdominal cavity. In the second stage of development when the midgut reenters the abdomen the postarterial segment enters first. Therefore, the colon lies on left, the cecum lies in the midline, and the small intestines come to lie on the right. This was the defect that was discovered in cases 1 and 4. The most dangerous complication of this defect is midgut volvulus around the narrowed mesenteric base with resulting ischemia and necrosis of the bowel.

Second, incomplete or mixed rotation occurs when only partial rotation (180°) occurs during the second stage. This results in terminal ileum reentering the abdomen first in the second stage of development. With the final 270° rotation failing to occur, the cecum is located in a subpyloric position and is fixed to the right lateral abdominal wall by thickened peritoneal bands (Ladd's bands), which can compress the duodenum. This compression may cause partial duodenal obstruction, and more importantly, midgut volvulus can occur because of the narrowed mesenteric base. Case 2 in this series demonstrated this rotational defect. However, no Ladd's bands were seen in this case. This resulted in the Roux limb lying anterior to the stomach and terminal ileum and to the right of the colon.

The third category of rotational defects is reverse rotation in which the first 90° of counterclockwise rotation is followed by 180° of clockwise rotation. The prearterial or postarterial segment can enter the abdomen first. If the postarterial segment enters first, then the colon lies behind the SMA, and the small intestine is anterior to the artery and colon. If the prearterial segment enters first, then the small intestine lies in front of artery and fills the left side of the abdomen while the colon lies to the right with the cecum in the midline. Rarely, the duodenum can be in reverse rotation with the colon in normally rotated position. Internal hernias can occur as complication in such cases.[7]

Case 3 demonstrates an unusual rotation in that the cephalad portion is in nonrotation and the caudad portion is in reverse rotation. Perhaps this occurred because of attachment of the future colonic hepatic flexure to the duodenum while it was in the body stalk. When the duodenum underwent its first 90° counterclockwise rotation, the caudal part rotated 90° in the clockwise direction because of this attachment. If there is no rotation afterward, then the prearterial segment will be in nonrotation and the postarterial segment will be in reverse rotation as seen in this case. This would explain the fact that the transverse colon is behind the SMA and in the retroperitoneal space.

From these cases we have learned several lessons. First, bariatric surgeons must remain aware of potential undiagnosed congenital anomalies that can affect the procedures they are undertaking. We failed to remove the appendix in several of the cases presented because of a lack of complete understanding of the anatomical defect and being surprised by the findings. In retrospect, appendectomy should have been accomplished in each patient. Second, depending on the anatomy and experience of the surgeon, LGB can be safely completed after performing the Ladd's procedure (division of the lateral peritoneal bands and mobilization of the duodenum and jejunum to the right side of the abdomen, division of adhesions around the SMA to broaden the mesenteric base by mobilizing the right colon to the left side of the abdominal cavity, and an appendectomy). However, conversion to open surgery should be entertained if the anatomy is unclear or the surgeon is uncomfortable with continuing laparoscopically. Patient safety must take first priority in these situations. Third, depending on the type of malrotation encountered, the Roux limb may traverse unusual structures as it is brought into apposition with the proximal gastric pouch (cases 1, 2, and 4). This should not be of major concern as long as the mesentery is positioned so there is no volvulus around its base or twisting of the Roux limb. Modification of the position of the Roux limb may be needed to accommodate the rotational defect (antegastric [case1] or retrocolic–retrogastric [case3]).

The incidence of intestinal rotational anomalies in the morbidly obese population is small so that upper GI barium series, the standard for detection of intestinal malrotation,[2] is neither necessary nor cost-effective.[8,9] In the hands of an astute, experienced bariatric surgeon, these rotational defects should be manageable laparoscopically without long-term sequelae for the patient.

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Risk Factors for Mortality and Postoperative Complications After Gastrointestinal Surgery

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Abstract
Background Predictors of a poor surgical outcome are numerous, of which some are well-defined. We aimed to assess risk factors predictive of poor surgical outcome across different gastrointestinal operations related to the patient, the disease, the treatment, and the organization of care.
Methods Data from 5,255 unselected patients undergoing open gastrointestinal surgery from 1995 through 1998 was prospectively recorded in a clinical database and validated. The database embraced variables related to patient history, preoperative clinical condition, operative findings and complexity, and the surgeon's training. Variables predictive of mortality and complications occurring within 30 days after surgery were assessed by multiple logistic regression analysis.
Results After elective operation, the 30-day mortality was 2.8% and major complications occurred in 11.5% of the patients. The corresponding figures in emergency surgery were 13.8% and 30.1%. Independent of elective or emergency surgery, dependent functional status, and type of operation were associated with postoperative mortality. Comorbidity, type of operation, blood loss, and reoperation were predictors of complications regardless of elective or emergency operation. In elective surgery, predictors of poor surgical outcome were high age, comorbidity, malignancy, and the surgeons training, whereas abnormal vital signs values and peritonitis were predictors of poor outcome after emergency surgery.
Conclusion Premorbid factors, characteristics of the disease, the patients' preoperative condition, operative factors, and the surgeon's training are all associated with surgical outcome across different gastrointestinal operations and should be assessed when auditing surgical outcome.

Keywords Risk factors · Mortality · Postoperative complications · General surgery · Gastrointestinal surgery

Introduction

Postoperative mortality and complications constitute a risk to all patients undergoing surgery. Several reports have documented factors predictive for mortality and complications after specific operative procedures,[1–5] but across different operations in gastrointestinal surgery reports are missing.

To assess the surgical outcome of the various operations performed at a large university-affiliated department of surgical gastroenterology serving a population of 280,000, a clinical database for operative risk and complications was introduced.[6] This initiative was inspired by the work of Copeland *et al.* on the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM).[7] Subsequent reports have documented the relevance of physiological and operative severity variables to assess the risk of postoperative complications after gastrointestinal surgery.[8] This database comprised similar variables as the POSSUM scoring system. In addition, a literature search was performed and variables reported as predicting surgical outcome related to organization of care

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and patient factors were also included. Thus, the database embraced all four aspects related to patient outcome (the patient, the disease, the treatment, and the organization).[9]

The aim of this study was to assess factors predictive of postoperative mortality and complications after open gastrointestinal surgery when adjusting for potential confounders through multiple logistic regression analysis.

Patients and Methods

From January 1995 through December 1998, a cohort of 5,255 consecutive patients operated on for gastrointestinal disease were evaluated. The operations were performed electively or as emergency operations (within 24 h after admission) at the Department of Surgical Gastroenterology, Bispebjerg Hospital. The operations included herniotomy, cholecystectomy, and gastroduodenal surgery, as well as operations on the small bowel, appendix, colon, and rectum. Laparoscopic, anal, and perianal operations were not included.

Variables as listed in Table 1 with possible relation to postoperative complications were assessed. Data regarding patient history (family status, employment, and dependent functional status [need of help for daily hygiene], smoking and drinking habits, and comorbidity [concurrent medical disease]) were collected from questionnaires completed

Table 1 Baseline Characteristics

	Elective operations n=3,388		Emergency operations n=1,867	
Anamnestic variables				
Age (median, interquartile range)	61	(46–74)	61	(32–77)
Male gender	2,043	(60.3)	887	(47.5)
Family status[a]	1,216	(35.9)	867	(46.4)
Employed	1,244	(36.7)	528	(28.3)
Dependent functional status[b]	258	(7.6)	343	(18.4)
Smoker	1,403	(41.4)	791	(42.4)
Alcohol abuser (more than five drinks per day)	141	(4.2)	101	(5.4)
Diabetes, cardiovascular disease, or lung disease	1,074	(31.7)	646	(34.6)
Liver cirrhosis or previous myocardial infarction or stroke	231	(6.8)	175	(9.74)
Vital signs variables[c]				
Systolic blood pressure (<110 or >130 mmHG)	402	(11.9)	241	(12.9)
Pulse (<50 or >80 beats per minute)	1,109	(32.7)	1007	(53.9)
Electrocardiogram (not sinus rythm)	166	(4.9)	175	(9.4)
Hemoglobin (<6.8 or >10.2 mmol/l)[d]	235	(6.9)	336	(18.0)
Leukocyte count (>10.1 or <4.0 billions/l)[d]	190	(5.6)	1078	(57.7)
P-Kalium (<3.5 or >5.0 μmol/l)[d]	219	(6.5)	460	(24.6)
P-Natrium ((<135 μmol/l)[d]	169	(5.0)	346	(18.5)
P-Creatinine (>125 μmol/l)[d]	108	(3.2)	225	(12.1)
Operative variables				
Herniotomy	1,915	(56.5)	130	(7.0)
Cholecystectomy	666	(19.7)	122	(6.5)
Gastroduodenal surgery	63	(1.9)	233	(12.5)
Small bowel surgery	139	(4.1)	453	(24.3)
Appendectomy	0	(0.0)	647	(34.7)
Colorectal surgery	578	(17.1)	285	(15.3)
Operative complexity (difficult or very difficult)	593	(17.5)	528	(28.3)
Multiple operations	220	(6.5)	287	(15.4)
Blood loss (>100 ml)	750	(22.1)	662	(35.5)
Peritonitis (serous fluid, local, or diffuse)	57	(1.7)	566	(30.3)
Malignancy	511	(15.1)	222	(11.9)
Specialist surgeon	1,232	(36.4)	308	(16.5)
Reoperation	182	(5.4)	234	(12.5)

Values are number of operations (with percentages in parentheses) unless stated in brackets.
[a] Single or widow
[b] Need of help for daily hygiene
[c] Latest updated value before surgery
[d] Values deviating from reference interval

before operation by the patient or surgeon at admission or at referral to the outpatient clinic. These data and data from the clinical record was recorded on a database sheet by the surgeon pre- or postoperatively.

Postoperative mortality or complications were considered if the patient died or had a complication within 30 days after surgery. Major complications were defined as severe, potentially fatal, or as complications requiring a reoperation. This category included deep wound infection, intraabdominal abscess, septicemia, wound- or facial rupture, anastomotic leakage, intestinal fistulas, significant stoma problems, venous thromboembolism, stroke, myocardial infarction, or renal or lung insufficiency needing intensive care. In addition, admission to the intensive care unit for other reasons or admittance for more than 15 days was considered as indicators of a major complication. Minor complications included wound hematoma, superficial wound infection, pneumonia, urinary tract infection, unexplained fever, or postoperative hypotension.

Postoperative complications and reoperations were recorded by the surgical staff at patient discharge or death. Complications occurring after discharge, but within 30 days after surgery were recorded on readmission. In case of admission to other departments of the hospital within 30 days, data were extracted from retrieved clinical records and discharge letters. Thus, only complications needing hospitalization were recorded.

The data were entered into the database by use of the EPI-INFO 6.0 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Entry of data was ensured by continuous control procedures. In addition, data from patients operated in 1995 or 1996 (n=2,036) were validated by specific procedures contained in the EPI-INFO software and selected cases were matched with the patient's clinical

Table 2 Postoperative Complications

	Elective operations n=3,388		Emergency operations n=1,867		p value[a]
Mortality[b]	88	(2.8)	226	(13.8)	$p<0.01$
Major complications					
Intraabdominal hemorrhage[c]	37	(1.1)	45	(2.4)	
Deep wound infection[c]	47	(1.4)	60	(3.2)	
Intraabdominal abscess[c]	41	(1.2)	84	(4.5)	
Septicemia[d]	20	(0.6)	65	(3.5)	
Wound- or facial rupture[c]	29	(0.9)	70	(3.7)	
Anastomotic leakage, intestinal fistula, or significant stoma problem[c]	77	(2.3)	112	(6.0)	
Thromboembolism, myocardial infarction, or stroke[e]	26	(0.8)	69	(3.7)	
ICU admittance because of renal insufficiency	21	(0.6)	65	(3.5)	
ICU admittance because of lung insufficiency	42	(1.2)	175	(9.4)	
ICU admittance for other reasons	86	(2.5)	288	(15.4)	
Postoperative admission > 15 days	248	(7.3)	327	(17.5)	
Total	674	(20.0)	1,360	(72.8)	
One or more major complications	390	(11.5)	562	(30.1)	$p<0.01$
Minor complications					
Wound hematoma[f]	165	(4.9)	35	(1.9)	
Superficial wound infection[f]	69	(2.0)	90	(4.8)	
Pneumonia[g]	67	(2.0)	178	(9.5)	
Urinary tract infection or unexplained fever[h]	43	(1.3)	36	(1.9)	
Postoperative hypotension	49	(1.4)	148	(7.9)	
Other	82	(2.4)	141	(7.6)	
Total	475	(14.0)	628	(33.6)	
One or more minor complications	424	(12.5)	494	(26.5)	$p<0.01$

Values are number of operations (with percentages in parenthesis).
[a] Chi-square (two-sided)
[b] Analysis based on the patient's first operation as reoperations were excluded.
[c] Reoperation performed
[d] Positive blood culture
[e] Positive radiology, CT, ECG, or blood values
[f] Observation or local treatment
[g] Positive radiology
[h] Positive urine culture or sustained fever for more than 3 days

record. Data from patients operated on in 1997 or 1998 (n=3,260) were validated by matching data from all cases with the patients' clinical records.

The data were analyzed by multiple logistic regression using the SAS 8.02 software (SAS Institute Inc., Cary, NC, USA). Separate analyses were conducted on elective and emergency operations with postoperative death, major complications, and minor complications as dependent variables. As the database embraced patients operated on more than once, different strategies were used. For the analysis of mortality, the first recorded operation was included in the material, because of the fact that the patient had to have survived the first operation to be at risk of dying of a subsequent one. For the analysis of complications, Generalized Estimating Equations (GEE) were used to adjust for dependent complications occurring in patients undergoing surgery more than once.

In each analysis, a univariate analysis was performed with patient age and gender as fixed covariates. A linear spline function was used to check if the assumption of linearity in the continuous variable "patient age" was fulfilled. This was the case in models involving elective operations, but in the models of emergency operations nonlinearity was found and "patient age" was modeled piecewise-linear accordingly.

Based on the univariate models, the odds ratio (OR) of each variable was estimated. The multivariate models were achieved by a forward selection procedure where variables likely to be associated with outcome ($p<0.2$) were included. In these models, all variables not significantly associated with outcome ($p>0.05$) were discarded by backward elimination. Finally, interaction terms between the variables were examined. All results were described with odds ratio and 95% confidence interval.

Results

A total of 5,296 operations entered the database of which 3,388 (64.4%) were elective and 1,867 (35.5%) emergency operations. Forty-one operations (0.8%) were discarded because of missing patient identification numbers. After elective surgery, the mortality was 2.8% and the incidence of major and minor complications were in 11.5% and 12.5%, respectively (Table 2). After emergency operations, the mortality was 13.8% and major and minor complications occurred in 30.1 and 26.5% of the patients, respectively (Table 2).

The multivariate regression analyses disclosed that high age, dependent functional status, comorbidity, malignancy, type of operation, and operation performed by a nonspecialized

Table 3 Variables Associated with Postoperative Mortality Analyzed by Logistic Regression—the Final Model

	Elective operations		Emergency operations	
	Multivariate		Multivariate	
	OR	95% CI	OR	95% CI
Anamnestic variables				
Age	1.04	1.01–1.06	–	
Male gender	–		1.61	1.03–2.51
Dependent functional status	3.54	2.07–6.28	1.79	1.10–2.90
Diabetes, cardiovascular disease, or lung disease	2.31	1.36–3.93	–	
Vital signs variables[a]				
Pulse <50 or >80	–		1.55	1.00–2.41
Abnormal ECG	–		2.09	1.26–3.44
Impaired sensorium (Glasgow Coma Scale <15)[b]	–		3.03	1.72–5.34
Hyponatriemia (<135 μmol/l)[b]	–		1.63	1.05–2.54
Operative variables				
Appendectomy[cd]	–		–	
Cholecystectomy[cd]	–		0.48	0.17–1.36
Small bowel surgery[c]	0.72	0.30–1.72	1.49	0.87–2.56
Colorectal surgery[c]	0.20	0.10–0.43	1.63	0.93–2.85
Malignancy	2.80	1.74–7.01	–	
Nonspecialized surgeon	2.02	1.16–3.51	–	

Only variables significantly associated with mortality are listed.
[a] Latest updated value before surgery
[b] Values deviating from reference interval
[c] Reference: gastroduodenal surgery
[d] Appendectomy and elective cholecystectomy were excluded from the analysis because of sparse cells

surgeon were associated with mortality after elective surgery (Table 3). After emergency operations, male gender, dependent functional status, and operation together with indicators of poor physiologic condition at the time of surgery (abnormal pulse, abnormal ECG, impaired sensorium, hyponatremia, and hypercreatinemia) were predictive of postoperative death (Table 3).

Factors associated with major complications after all operations were comorbidity, type of operation, blood loss, and reoperation (Table 4). High age was associated with complications after elective operations as well, whereas abnormal hemoglobin, hyponatremia, hypercreatinemia, peritonitis, multiple operations, and operation performed by a specialist surgeon were predictive of major complications after emergency operations (Table 4). Abnormal leukocyte count was inversely associated with major complications after emergency operations.

Minor complications were associated with high age, comorbidity, and type of operation in elective surgery (Table 5). Comorbidity was a predictor of minor complications after emergency operations in addition to abnormal pulse, peritonitis, and reoperations (Table 5). Abnormal blood pressure, leukocyte count, and abnormal P-Kalium levels were negatively associated with minor complications.

Lifestyle factors and factors related to family and employment status were neither associated with a poor surgical outcome nor a prolonged hospital stay.

Discussion

This study demonstrates that in an unselected population of patients undergoing open gastrointestinal surgery, the mortality within 30 days after surgery is five times higher after emergency than elective operations. Likewise, major and minor postoperative complications occur two to three times as often in emergency surgery. These findings confirm the surgical literature.[1–3,10–12]

Table 4 Variables Associated with Major Complications Analyzed by Logistic Regression—the Final Model

	Elective operations		Emergency operations	
	Multivariate		Multivariate	
	OR	95% CI	OR	95% CI
Anamnestic variables				
Age	1.02	1.01–1.03	–	
Diabetes, cardiovascular disease, or lung disease	1.40	1.08–1.83	1.53	1.11–2.10
Vital signs variables[a]				
Hemoglobin (<6.8 or >10.2 mmol/l)[b]	–		1.50	1.03–2.19
Leukocyte count (>10.1 or <4.0 billions/l)[b]	–		0.69	0.51–0.95
Hyponatriemia (<135 μmol/l)[b]	–		2.01	1.32–3.06
Hypercreatinemia (>125 μmol/l)[b]	–		1.81	1.27–2.56
Operative variables				
Appendectomy[cd]	–		1.49	0.64–3.45
Cholecystectomy[c]	2.96	1.77–4.96	1.51	0.59–3.84
Gastroduodenal surgery[c]	13.13	6.47–26.65	4.30	1.89–9.78
Small bowel surgery[c]	12.14	7.12–20.70	3.13	1.41–6.94
Colorectal surgery[c]	10.83	6.76–17.35	6.61	2.89–15.10
Serous peritonitis	–		1.22	0.83–1.80
Localized peritonitis	–		2.15	1.33–3.46
Diffuse peritonitis	–		2.10	1.31–3.38
Blood loss (100–500 ml)	2.12	1.47–3.03	1.38	0.98–1.96
Blood loss (>500 ml)	4.17	2.75–6.33	2.93	1.79–4.77
Multiple operations	–		2.32	1.41–3.82
Specialist surgeon	–		1.97	1.35–2.88
Reoperation	3.34	1.67–6.69	2.09	1.15–3.80

Only variables significantly associated with major complications are listed
[a] Latest updated value before surgery
[b] Values deviating from reference interval
[c] Reference: Herniotomy
[d] Elective appendectomy excluded from the analysis because of sparse cells

Irrespective of elective or emergency operation, dependent functional status was a strong predictor for postoperative death. This association has not previously been found by surgical outcome studies, but our findings confirm other reports.[13] The type of operation was associated with postoperative mortality and with gastroduodenal operation as the strongest predictor in elective surgery, and colorectal surgery as the strongest predictor in emergency surgery. The latter finding may account for perforated diverticulitis or colonic obstruction, being emergency conditions known to have a high postoperative mortality.[14] Like other surgical outcome studies, high age, comorbidity, and malignancy were associated with postoperative mortality after elective surgery.[1,4,15–17,5,12] Comorbidity includes concurrent diabetes, cardiovascular disease, and lung disease and thus correspond with a high ASA score (American Association of Anesthesiologists physical status classification), which also has been shown to be associated with a poor postoperative outcome.[1,11,18,19]

Common to the majority of risk factors associated with mortality after emergency operation were characteristics of a poor preoperative clinical condition. Abnormal pulse, abnormal ECG, hyponatremia, hypercreatinemia, impaired sensorium, and peritonitis all indicate severe acute illness.[1,5,20] As shown by others, male gender was an independent risk factor for postoperative death after emergency operation as shown by others.[2,4,21–24]

Postoperative complications were associated with comorbidity, type of operation, perioperative blood loss, and reoperation irrespective of elective or emergency operation.[3,25,26] High age was only significantly associated with complications after elective surgery, whereas abnormal paraclinical values, peritonitis, multiple operations, and reoperations were predictors of complications after emergency operations. These findings illustrate the importance of the patient's clinical condition at the time of operation, suggesting that a poor clinical condition and a high operative complexity apparently conceal risk factors otherwise significant in elective surgery.

The surgeon's experience was a predictor of postoperative outcome. Although it is a poorly described factor in most surgical outcome studies, the significance of the surgeons experience is illustrated by the fact that even experienced surgeons vary with respect to complication

Table 5 Variables Associated with Minor Complications Analyzed by Logistic Regression—the Final Model

	Elective operations		Emergency operations	
	Multivariate		Multivariate	
	OR	95% CI	OR	95% CI
Anamnestic variables				
Age	1.02	1.01–1.03	–	
Diabetes, cardiovascular disease, or lung disease	1.46	1.16–1.84	1.42	1.06–1.92
Liver cirrhosis or previous myocardial infarction or stroke	–		1.69	1.14–2.52
Vital signs variables[a]				
Systolic blood pressure (<110 or >130 mmHG)	–		0.67	0.51–0.88
Pulse (<50 or >80 beats per minute)[b]	–		1.34	1.02–1.76
Leukocyte count (>10.1 or <4.0 billions/l)[b]	–		0.64	0.48–0.84
P-Kalium (<3.5 or >5.0 μmol/l)[b]	–		0.72	0.53–0.97
Operative variables				
Appendectomy[cd]	–		–	
Cholecystectomy[c]	1.07	0.73–1.58	–	
Gastroduodenal surgery[c]	2.95	1.60–5.42	–	
Small bowel surgery[c]	1.93	1.15–3.23	–	
Colorectal surgery[c]	2.89	2.19–3.82	–	
Serous peritonitis	–		1.28	0.91–1.81
Localized peritonitis	–		2.14	1.43–3.21
Diffuse peritonitis	–		2.19	1.44–3.34
Reoperation	–		2.37	1.51–3.71

Only variables significantly associated with major complications are listed
[a] Latest updated value before surgery
[b] Values deviating from reference interval
[c] Reference: Herniotomy
[d] Elective appendectomy excluded from the analysis because of sparse cells

rates.[27,28] Like others, we found that elective patients operated by nonspecialized surgeons had a nearly twice as high risk of postoperative death.[2] In contrast, specialist surgeons performing emergency operations were associated with a 50% higher risk of major complications. This finding, however, is interpreted as a selection phenomenon, signifying that the specialist was called in to perform the more difficult operations.

In this study, we achieved a high validity of data through different prospective and retrospective validation procedures. These measures were taken as the validity of data in clinical databases collected on a routine basis is poor unless a rigorous validation procedure is employed.[29]

The reported mortality and complication rate may seem high, but our findings are in line with reports from other centers with an unselected population.[1] Our definition of a 30-day limit of postoperative death and complications is in accordance with previous reports.[1,7] Both aspects may account for the higher mortality and complication rate compared to reports from other centers operating on selected populations and with in-hospital death only.

We did not find sociodemographic and lifestyle factors to affect surgical outcome. This finding contradicts some reports suggesting that excessive alcohol intake and smoking affect postoperative complications.[30,31] However, as smoking for instance appears to have the highest impact on wound complications,[32,33] the pooling of surgical outcome in groups of major and minor complications may conceal the significance of these lifestyle factors.

In conclusion, premorbid factors, characteristics of the disease, the patients' preoperative condition, operative factors, and the surgeon's level of training all predict a poor surgical outcome. Our findings provide variables for the development of risk scores and preoperative identification of patients with a high risk of postoperative mortality and complications in elective and emergency surgery.

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Enterocolitis due to Simultaneous Infection with Rotavirus and *Clostridium difficile* in Adult and Pediatric Solid Organ Transplantation

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Abstract Diarrhea is a well-known complication of immunosuppression but is also frequently caused by pathogens such as *Clostridium difficile* (CD) and rotavirus (RV). Three adult and five pediatric solid organ recipients (SORs) developed diarrhea with simultaneous identification of CD and RV. Rotavirus was identified using an immunochromatografic- or enzyme-linked immunosorbent assay; CD was identified using a rapid immunoassay or enzyme immunoassay. One adult renal, one adult kidney–pancreas, one adult liver, and five pediatric liver recipients were affected. Onset of RV/CD infection ranged from 2 weeks to 4 years posttransplant. All patients presented with enterocolitis causing significant fluid and electrolyte loss. In adults, CD was treated with metronidazole and in children with oral vancomycin. RV infection was treated with fluid/electrolyte replacement. During diarrhea, a significant rise in tacrolimus serum level was noted. All patients cleared CD. One child developed recurrent episodes of RV infection and died from bacterial sepsis; the renal recipient died 6 months posttransplant from myocardial infarction. The remaining six patients are currently alive with well-functioning grafts. Simultaneous infection with CD and RV may lead to severe diarrhea in SORs. Both pathogens should be considered in SOR presenting with diarrhea.

Keywords Diarrhea · Transplantation · *Clostridium difficile* · Rotavirus · Immunosuppression

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Introduction

Diarrhea is a common symptom in patients undergoing solid organ transplantation. It is a frequent side-effect of immunosuppressive therapy but also can be caused by a multitude of infectious agents, including bacteria, fungi, protozoa, and viruses[1–7]. In solid organ recipients (SORs), the spectrum of pathogens is more diverse than in immunocompetent hosts[6]. *Clostridium difficile* (CD) is a common anaerobic microbe in human bowel, side by side with other microbes, and can cause a toxin-mediated invasive colitis of characteristic clinical symptoms, including watery diarrhea with fluid loss, abdominal pain, fever, nausea, and malaise. The clinical spectrum ranges from diarrhea to fulminant hemorrhagic pseudomembranous colitis or even toxic megacolon[8,9]. A toxic megacolon and paralytic ileus are signs of severe illness and may result in colonic perforation with peritonitis. Mortality in cases of toxic megacolon ranges from 24 to 38%. On colonscopy, colitis with pseudomembranes and a vulnerable mucosa are typically found[8,9]. *Clostridium difficile* colitis has been attributed to a variety of antibiotic agents including

clindamycin, cephalosporins, and extended-spectrum penicillins. These agents can also cause enteritis unrelated to superinfection with CD[8,9]. Recently, CD colitis was also recognized in patients without antibiotic exposure[10,11].

Rotavirus (RV) is the most common cause of viral enteritis in infants and young children[7,12]. In adult immunocompetent individuals, RV only causes a mild disease; in immunosuppressed patients, hospitalization is often necessary for excessive fluid loss[7]. Debilitating disease during end-stage organ failure combined with the operative trauma, immunosuppressive therapy, and applied antibiotics cause severe impairment of host defense and an imbalance of the natural gut flora. Therefore, SORs are particularly prone to acquire intestinal infections and coinfection with multiple pathogens. Rapid detection of enteric pathogens is essential to initiate optimal treatment, as diarrhea during the early posttransplant period can cause severe secondary complications[1–3,7,8,11–13]. In this study, the epidemiology and clinical significance of simultaneous infection with CD and RV in pediatric and adult SORs was investigated.

Patients and Methods

Within this series, eight patients developed simultaneous CD and RV enteric infection. Patients were included in the study if they presented with acute enteritis/colitis and if both pathogens could be identified from stool within a period of a maximum of 2 weeks. Other enteric or opportunistic pathogens were excluded as causative organisms based on the results of repetitive microbiological cultures or detection assays. Demographic data of the eight patients are shown in Table 1.

Perioperative Management

At the time of pretransplant evaluation, all potential recipients were screened for *Cytomegalovirus* and *Epstein–Barr virus* antibodies. Pretransplant stool was examined for common enteric pathogens but not for RV or CD.

Surgical technique and perioperative management were performed according to standard techniques. Routine immunosuppression consisted of Calcineurin inhibitor-

Table 1 Demographic Data

Initials	Gender	Underlying disease	Transplanted organ	Age at time of transplant	Date of transplant/ retransplant	Immunosuppressive therapy	Induction therapy	Rejection before enteritis
LT	Male	Polycystic nephropathy	Kidney: living related	72	May 2003	Tacrolimus, mycophenolate mofetil, steroides	No	Yes
BE	Male	Diabetic nephropathy	Cadaveric kidney/ pancreas	32	Oct 2003	Tacrolimus, mycophenolate mofetil, steroides	Antithymocyte globulin	No
MJ	Male	Alcoholic liver cirrhosis	Full-size liver	59	Nov 2004/ March 2005	Tacrolimus, mycophenolate mofetil, steroides	No	No
DS	Female	Extrahepatic biliary atresia	Liver: segmental graft	2	Jan 1995	Cyclosporin, azathioprine, steroides	Antithymocyte globulin	Yes
TD	Male	Aagenes syndrome	Liver: living related	0.3	March 1999	Tacrolimus, azathioprin, steroides	Basiliximab	Yes
WJ	Male	Extrahepatic biliary atresia	Liver: living related	1	Jan 2002	Tacrolimus, mycophenolate mofetil, steroides	Basiliximab	No
MT	Male	Cystic fibrosis	Full-size liver	7	Dec 1999	Cyclosporine, azathioprine, steroides	No	No
OL	Male	Extrahepatic biliary atresia	Liver: living related	0.4	Feb 2003	Tacrolimus, mycophenolate mofetil, steroides	Basiliximab	No

based triple-drug therapy. Antithymocyte globulin or interleukin-2 receptor antagonist induction was used following cardiac, lung, intestinal, pancreas, islet, and composite tissue allograft transplantation and in subsets of liver and kidney recipients. Perioperative antibiotic prophylaxis consisted of piperacillin/tazobactam (4.5 g q 8 h for 48 h) for the majority of intestinal, liver, pancreas, and cardiac recipients and of penicillin G (2×5 million units) in combination with flucloxacillin (2×2 g) for renal recipients (single shot) and Cefepime (2 g q 8 h for 72 h) for lung recipients. The perioperative antimicrobial prophylaxis was adapted according to pretransplant microbiological findings. Stool was sent for detection of pathogens in case of diarrhea or significant abdominal discomfort.

Hospital Setting and Microbiology Laboratory

Innsbruck University Hospital is the major referral teaching hospital of the western part of Austria. The facility has a capacity of 1,608 beds, including 118 ICU beds. The transplant ward has a capacity of 26, including six ICU and two step-down beds. The microbiological laboratory processes approximately 6,000 stool samples per year.

Testing for stool pathogens including enterohemorrhagic *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., and *Yersinia* spp. were performed on a routine basis according to standard methods on selective media. Other enteric pathogens, including RV and CD, were tested for upon request. Until June 2004, for RV, an enzyme-linked immuno-sorbent assay (Ridascreen® R-Biopharm, Darmstadt, Germany) was used, and thereafter, an immunochromatographic-test was used (Rota-Strip® Coris Bioconcept, Brussels, Belgium). In children, testing for RV had been routine in all cases of diarrhea, whereas in adults, before January 2003, testing for RV was performed sporadically but became routine thereafter. *Clostridium difficile* was cultured from stool using selective media (CD agar base with selective supplement Oxoid, UK) and toxin A was detected with a rapid immunoassay (CD Toxin A test Oxoid, UK) up to the year 1995. Thereafter, an enzyme immunoassay for the detection of toxin A and B (Premier® Toxins A&B by Meridian, Cincinnati, OH, USA) was utilized.

Data Collection and Analysis

Data on all stool samples for all cardiac (n=117), lung (n=41), pancreas (n=93), and liver (n=305) recipients who were transplanted between January 1, 1994, and December 31, 1999, were retrieved from the transplant database. In addition, data of 252 consecutive kidney transplants performed between 1994 and 1997 were available. All stool samples from patients transplanted between January 1, 2000, and December 31, 2004 (n=1,300), were analyzed using the computerized databases of the microbiological laboratory and the transplant unit. In total, 497 stool samples (162 from the early and 335 from the later study period) were screened. We identified an additional patient with simultaneous CD/RV infection who had his first liver transplant in 2004. This graft failed and he had a retransplant in 2005, after which he developed the enteric infection. Hospital records of the eight patients who had simultaneous infections with RV and CD were studied in detail. Data are given as median with range.

Results

Demographic Data

Between January 1, 1994, and December 31, 2005, a total of 2,799 solid organ transplants were performed, including 1,438 renal, 651 liver, 289 pancreas, 242 cardiac, 118 lung, five combined heart/lung, 27 intestinal, 25 islet, and two hand transplants.

Amongst the recipients of the 2,799 solid organ transplants, there were 83 children (1994–2004). During the entire study period, CD was diagnosed in 36 and RV in 21 organ recipients. Rotavirus was isolated from 14 children and seven adults, including 16 liver, three renal, and two pancreas recipients. All cases of RV enteritis in adult recipients were diagnosed after January 2003, when routine testing was introduced. *Clostridium difficile* infection was detected in 11 children and 25 adults, including four lung, three cardiac, four renal, two pancreatic, two small bowel, 20 liver, and one hand recipients. Pediatric liver recipients were found at highest risk for RV infection (14 of 39 children, i.e., 33%) and CD infection (nine children, i.e., 23%). One adult heart and one adult lung recipient underwent colectomy for CD associated megacolon and both survived. No patient with RV-associated enterocolitis required surgery.

Eight SORs had simultaneous RV/CD infections (Table 2). The three adults consisted of one kidney recipient, one kidney/pancreas recipient, and one liver recipient. The five children were all liver recipients and all except one received left lateral segmental grafts in three instances from a living related donor. One child developed RV infection 6 months after CD colitis and was not included in the analysis.

Clinical Course, Treatment, Outcome

Diagnosis of enteritis and/or colitis was based on clinical symptoms including diarrhea, abdominal pain, and abdominal distention. Also, the presence of fever, leucocytosis, and elevated C-reactive protein levels were taken in

Table 2 Clinical Data

Initials	Infectious complications prior to RV/CD	Onset of RV/CD post transplant	RV test	CD toxin	CD culture	Treatment	Rise in tacrolimus levels	Infectious complications post RV/CD infection	Outcome RV/CD colitis	Outcome
LT	Peritonitis, pneumonia	50 days	Elisa	A/B	Positive	Metronidazole	Yes	None	Ok	Death with functioning graft due to cardiac arrest
BE	None	7 days	Elisa	A/B	Positive	Metronidazole	Yes	None	Ok	Well with functioning graft
MJ	CD colitis, cholangitis, intrahepatic abscesses	159 days	Elisa	A/B	Not done	Vancomycin	Yes	None	Ok	Well with functioning graft
DS	*Cytomegalovirus* disease, peritonitis	35 days	Elisa	A	Positive	Vancomycin	Yes	None	Ok	Well with functioning graft
TD	Pneumonia, peritonitis	90 days	Elisa	A	Positive	Vancomycin	Yes	Sepsis	Recurrent RV infection	Death due to sepsis and multi organ failure
WJ	None	100 days	Elisa	A/B	Positive	Vancomycin	Yes	None	Ok	Well with functioning graft
MT	Recurrent respiratory tract infections	1,450 days	Elisa	A/B	Positive	Vancomycin	No	None	Ok	Well with functioning graft
OL	Recurrent RV infection	480 days	Elisa	A/B	Positive	Vancomycin	Yes	Recurrent RV infection	Recurrent RV infection	Well with functioning graft

RV Rotavirus; CD *Clostridium difficile*

consideration. Colonoscopy was only performed in one patient to deflate the large bowel in the case of megacolon (Fig. 1).

Median onset of CD/RV enteritis was 70 days posttransplant; five of the eight patients had posttransplant infectious complications prior to the outbreak of diarrhea. When considering perioperative prophylaxis and therapy of post transplant infections, all patients had been exposed to piperacillin/tazobactam. Six of the eight patients had been exposed to multiple different antimicrobial agents prior to the outbreak of CD/RV infection. Bloody stool was seen in one adult and two children; all patients had massive watery diarrhea. Treatment of enteritis comprised intravenous fluid and electrolyte replacement, loperamid (one to two tablets and another tablet after every bowel movement), and diet. In case of CD enteritis in the adult renal and kidney/pancreas recipient, metronidazole (500 mg q 8 h) was administered intravenously, followed by oral maintenance therapy. All liver recipients received oral vancomycin (10 mg/kg q 12 h). Immunosupression was reduced temporarily in all eight patients due to a significant rise in tacrolimus (TAC) trough levels. There was no clear association with a single particular antimicrobial agent given immediately prior to CD infection; however, six of the eight patients had received piperacillin/tazobactam at some stage. In six cases, RV/CD enteritis was successfully treated without recurrence of the pathogens. In one adult recipient, CD infection relapsed. One child developed several episodes of RV enteritis, which ultimately caused bacterial superinfection, graft failure leading to multiorgan failure, and death. Another adult patient died due to cardiac arrest 6 months posttransplant with functioning graft and no evidence for RV or CD recurrence. All other patients are currently alive with functioning grafts.

Discussion

This study shows that simultaneous infection with CD and RV is a serious complication in SORs. Pediatric liver recipients were affected most commonly, but we also observed three cases in adults. In all patients, dehydration and electrolyte and protein loss required prolonged hospitalization. Diarrhea is associated with a significant rise in the trough level of TAC[13,14]. Therefore, daily monitoring and early dose reduction is mandatory[7,13,14]. Simultaneous infection with multiple viral and bacterial pathogens seems to cause an increased severity of enterocolitis. Secondary complications or repeated episodes of enteric infection can lead to life-threatening conditions.

Due to the poor pretransplant conditions associated with end-stage organ failure, the surgical trauma, and the required immunosuppression, SORs are at particularly high risk for acquiring infectious complications. As a result of repeated courses of antimicrobial therapy pre-, peri-, and posttransplant and the prolonged exposure to the hospital environment, this patient population frequently is colonized with uncommon pathogens. The gastrointestinal tract can serve as a permanent source for recurrent infections[6,8].

Diarrhea is a frequent side effect of immunosuppressive therapy, enteral nutrition, or antimicrobial treatment[1,7,13]. Most importantly, diarrhea originates from bacterial, fungal, viral, or protozoal infection[1,6,8,11,15]. Eradication of the responsible pathogen from the gastrointestinal tract and removal of toxins is the goal of any therapy. Obtaining a quick and accurate diagnosis is often difficult, as stool cultures can take up to 48 h. Sometimes, even repeated testing fails to identify pathogens[8,10,16]. Rapid detection assays should be applied in all SORs presenting with diarrhea, with the limitation that the sensitivity of tests for

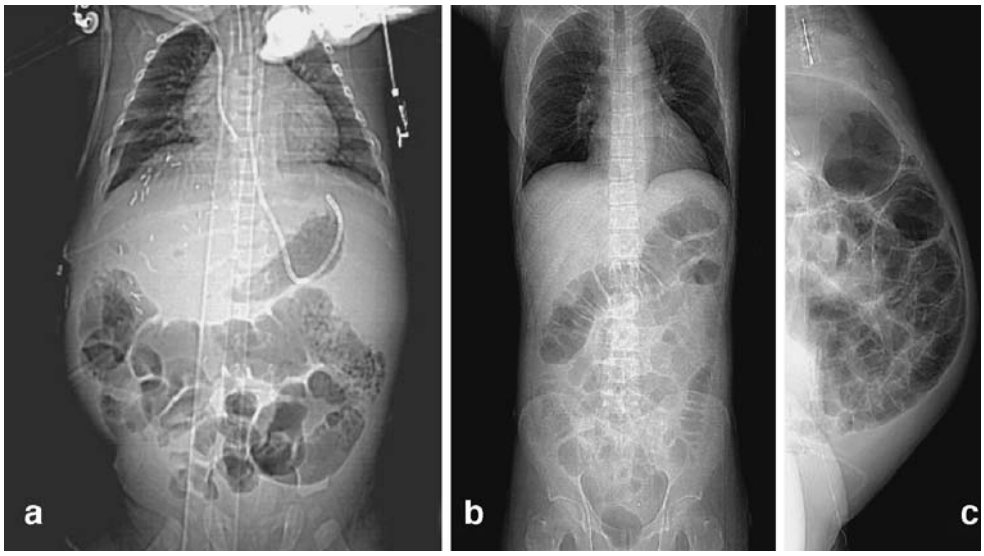

Figure 1 Megacolon: significant distension of the colon in three patients with simultaneous RV and CD infection: pediatric liver recipient (OL), adult kidney-pancreas recipient (BE), adult kidney recipient (LT).

detecting CD toxins or proteins of RV in stool are often unsatisfactorily low. Therefore, in SORs, empiric therapy of diarrhea is controversial and must be guided by both test results and clinical criteria[1,8,15,16]. One must bear in mind that quinolones potentially aggravate CD infection, whereas, in the case of RV colitis, the application of oral metronidazole or vancomycin is an unnecessary exposure to antibacterial agents.

Clostridium difficile is one of the numerous commensals of the human intestinal tract. In case of antibiotic exposure or application of immunosuppressive drugs, a shifting in the intestinal flora equilibrium results in an overgrowth of CD[8]. Systemic symptoms associated with CD infection are caused by toxin-induced inflammatory mediators, such as interleukin-8, macrophage-inflammatory protein-2, substance P, or tumor necrosis factor-Alpha. These cytokines are released locally within the colon and cause a massive inflammatory reaction, mucosal necrosis, and formation of pseudomembranes[9]. Both CD toxins increase vascular permeability due to the opening of tight junctions between cells[9].

Rotavirus is the most common enteric pathogen in children and can cause severe diarrhea. Rotavirus-related childhood hospitalizations increased from approximately 22% between 1986 and 1999 up to 39% in the year 2004. Estimated RV-related cases in children accounted for 611,000 deaths per year worldwide[17]. Usually, RV enteritis is self-limiting and only replacement of fluid and electrolytes is necessary. In the immunocompromised host, RV can cause complicated enteritis[7]. Treatment with antiviral agents or immunoglobulins is not recommended[7,18].

Our data provide evidence for a possible interaction between RV and CD. Cotransmission of both nosocomial pathogens might occur in the hospital environment; however, pathogen-specific factors can also be assumed. Following ingestion and invasion of the enterocyte, RV causes cell lysis and consecutive destruction of the mucosal layer, which promotes bacterial adhesion and invasion of the intestinal wall. Such a phenomenon has been shown for RV-infected human enterocyte-like cells, which experience an enhanced invasiveness of *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*[19]. It is tempting to assume that RV-infected gut cells are also prone for superinfection with CD[20]. Specific interactions may be responsible for bacterial colonization and penetration of virus-infected cells[21]. Nosocomial transmission of RV and CD has been well described, especially in the hospital environment, and therefore, preventive strategies such as careful hand washing and disinfection are necessary[7,8,16]. Screening for these pathogens and isolation of infected patients might be advisable[7]. We have not been able to detect any case of simultaneous RV/CD infection in nontransplant patients. This may be due to under-reporting and/or lack of routine testing for RV in adults with diarrhea. One of the pediatric patients (#7 OL) of this series was the source of an outbreak of RV in our ward[7]. For pediatric SORs when transferred to a transplant ward, testing for RV seems mandatory to avoid such outbreaks. Once RV and CD infection is diagnosed, symptomatic treatment of diarrhea becomes the most important first step. All drugs that potentially cause gastrointestinal toxicity must be withdrawn and antibiotics should be discontinued if possible. In adults, first-line treatment consists of oral metronidazole, which is given for 7–14 days. Vancomycin should be reserved for persisting CD enteritis[3,8,16]. In case of toxic megacolon, surgery might be indicated; however, surgery was reported to be associated with a very high mortality rate in particular in transplant patients[11,21,22]. In our series, two of 36 patients with CD colitis underwent colectomy and both survived. In children, thus far, oral vancomycin remains the first-line agent. For ongoing diarrhea, persistent RV infection might be responsible. Tapering or even cessation of immunosuppression might be the only option in recurrent cases. Simultaneous RV/CD infection seems to prolong hospitalization; however, none of the eight patients reported here required surgical intervention. This is one of the first series of simultaneous infection with RV and CD. Although RV in most cases causes enteritis, it also can cause severe colitis mimicking CD infection, in particular if a coinfection with adenovirus or other pathogens is present[23,24]. We strongly recommend testing for RV and CD in all SORs presenting with diarrhea. Although colonoscopy was carried out only in a single patient, the clinical presentation together with identification of two enteric pathogens make our diagnosis highly suggestive. Johal et al. suggested that, in hospitalized patients with diarrhea, flexible sigmoidoscopy may help diagnose CD infection in individuals with negative stool cultures and negative CD toxin assay[25]. Concerning identification of RV, it has been reported that blood in stool can cause false positive reaction with the RV latex agglutination test; however, in most patients in this series, including all children, RV was detected on several occasions[26,27].

Conclusion

Simultaneous infection with RV and CD should be considered in SORs presenting with diarrhea. Testing for both pathogens should be carried out in pediatric and adult SORs.

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Small Intestinal Submucosa (SIS) in the Repair of a Cecal Wound in Unprepared Bowel in Rats

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Abstract
Purpose Porcine-derived small intestinal submucosa (SIS) has been accepted as an acellular matrix for tissue regeneration. However, its use for remodeling gastrointestinal defects has been poorly investigated. Our previous study of the rodent stomach has demonstrated that the SIS stimulates regeneration of native tissue under acidic conditions. The purpose of this paper was to investigate the feasibility of using SIS as a bioscaffold for a colonic defect in unprepared bowel.
Methods A 1×1-cm whole layer was excised on the anterior wall of the cecum in 24 rats, followed by onlay repair with SIS. Measurement outcomes included animal survival, mesh stability in situ, and histologic evaluation at 3 weeks and 6 months.
Results Rats showed a significant weight gain and had no evidence of postoperative leakage. All wounds were secured and associated with either omental or other fatty adhesions. Histological findings revealed that intact mucosa covered the area of the graft in all cases 6 months after surgery and that the defect was completely replaced by the normal constituents (mucosa, muscle, and nerve cells) of the bowel wall.
Conclusions SIS was largely successful in promoting healing in a cecal wound in unprepared bowel and serving as a bioscaffold for regeneration of the native colonic tissue. Small intestinal submucosa may be useful in surgical anastomoses to promote healing and presumably prevent leakage.

Keywords Small intestinal submucosa (SIS) · Acellular matrix · Cecum defect repair

Introduction

Porcine-derived small intestinal submucosa (SIS) is a novel prosthetic, which has been recently used as a bioscaffold for the regeneration of various tissues and organs. Despite increased clinical interest in applications of prosthetic materials in the gastrointestinal surgery, few studies have assessed the use of SIS for remodeling gastrointestinal defects.[1–4] These studies investigated SIS use in the repair of the esophagus,[1] stomach,[4] small intestine,[2] and biliary tract.[3] Our previous study examining the use of SIS in repair of stomach defects[4] revealed that SIS serves as a bioscaffold and stimulates regeneration of native tissue under acidic conditions.

The purpose of the present study was to determine if SIS would adequately close a defect in the presence of bacterial contamination, and to investigate the feasibility of using SIS as a bioscaffold for a colonic defect in unprepared bowel.

Materials and Methods

Twenty-four male Sprague–Dawley rats (body weight 270–310 g, Charles River Laboratories, Raleigh, NC, USA) were housed with free access to water and chow under standard conditions (23°C room temperature, 12 h dark–light cycles). Rats were randomly divided into two groups, including a short-term study (group S) and a long-term

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study (group L). In each group rats were assigned to one of the following subgroups: (1) 1 cm full-thickness cecum defect with the preservation of the omentum and (2) 1 cm full-thickness cecum defect with omentectomy.

Each animal was restricted from any oral intake except for water 18 h before surgery. Anesthesia was induced and maintained with isoflurane in oxygen. An upper midline incision was made, and the cecum was identified and gently mobilized with atraumatic forceps. A 1×1-cm circular whole layer defect was created on the anterior wall of the cecum with scissors. After hemostasis was achieved with electrocautery, a round patch of two-ply SIS (Surgisis™ ES, Cook Biotech, Lafayette, IN, USA) was prepared by opposing two layers and cut to approximately the same size as the excised portion of the cecum. The material was immersed in sterile saline for 10 min before implantation. To be secured to the cecal wall, stitches were taken from the whole layer and placed within 1 mm of the edge of the graft with a 5-0 polypropylene running suture. In group L, additional interrupted sutures (eight to ten with polypropylene sutures) were placed to mark the site of SIS for future reference. In a subset of animals (six rats in each group), the operation was completed with an omentectomy. The skin incision was closed in two layers and animals recovered from anesthesia. Ampicillin (0.01 mg/body) (Polyflex, Fort Dodge Animal Health, Fort Dodge, IW, USA) was administered subcutaneously twice a day for 3 days. Immediately after the operation, animals were checked on a daily basis for signs of distress and were administered analgesics as needed. Weight and food intake were monitored weekly.

Rats in group S were killed 3 weeks after surgery for the short-term study. The rest of animals (group L) were killed 6 months after the operation for the long-term study. The abdominal cavity was macroscopically evaluated for adhesions. The grafted area was removed with surrounding tissues. The samples were fixed with 10% formalin embedded in paraffin, and sectioned 4 μm along with the circular muscle. The slides were stained with hematoxylin and eosin.

All aspects of this research were reviewed and approved by the Durham VA Medical Center Animal Care and Use Committee, and by the Animal Care Committee, Durham, NC, USA.

Data are expressed as the mean±SEM. Statistical analysis was performed by a paired *t* test.

Results

Clinical Signs and Macroscopic Characteristics in Short-term Study Group

All animals in group S survived for the 3-week postoperative period. They gained weight significantly (preop 293±3.1 g, 3 weeks postop 438±6.6 g) and had no evidence of postoperative leakage. At necropsy, one rat, which underwent omentectomy, developed a subcutaneous abscess.

All 12 defects patched with SIS showed no features of leakage within 3 weeks. Macroscopic examination demonstrated the omentum covering the grafted area in all animals without omentectomy. In the remaining animals in which an omentectomy was performed, the fatty tissue derived from the genital organs attached to the patched area in three out of six rats. Filmy adhesion of the small intestine to the surgical area was observed in one rat and no adhesion was seen in two instances. In two of six cases in the omentectomized group, SIS was not incorporated and was excluded into the lumen of the cecum, entwined with the polypropylene suture that had secured the SIS.

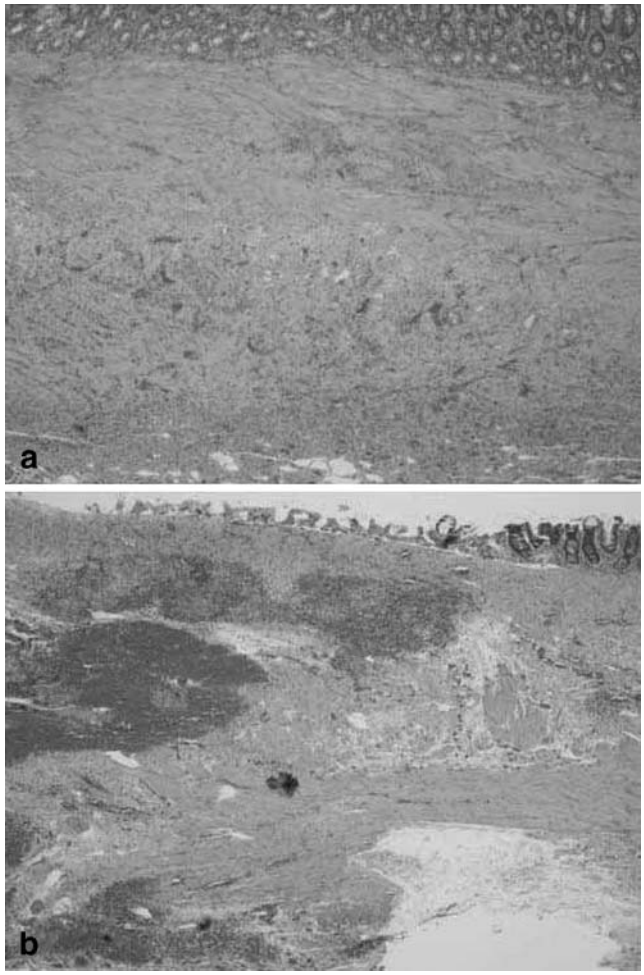

Figure 1 The SIS grafted area at 3 weeks after surgery. **a** Defects created on the cecal wall were covered by granulation tissue and early fibrosis, both with neovascularization and infiltration of inflammatory cells (magnification ×20). **b** Ulcerated mucosa was observed. Muscularis propria was replaced by a thick layer of fibrosis, granulation tissue, and chronic inflammation (magnification ×20).

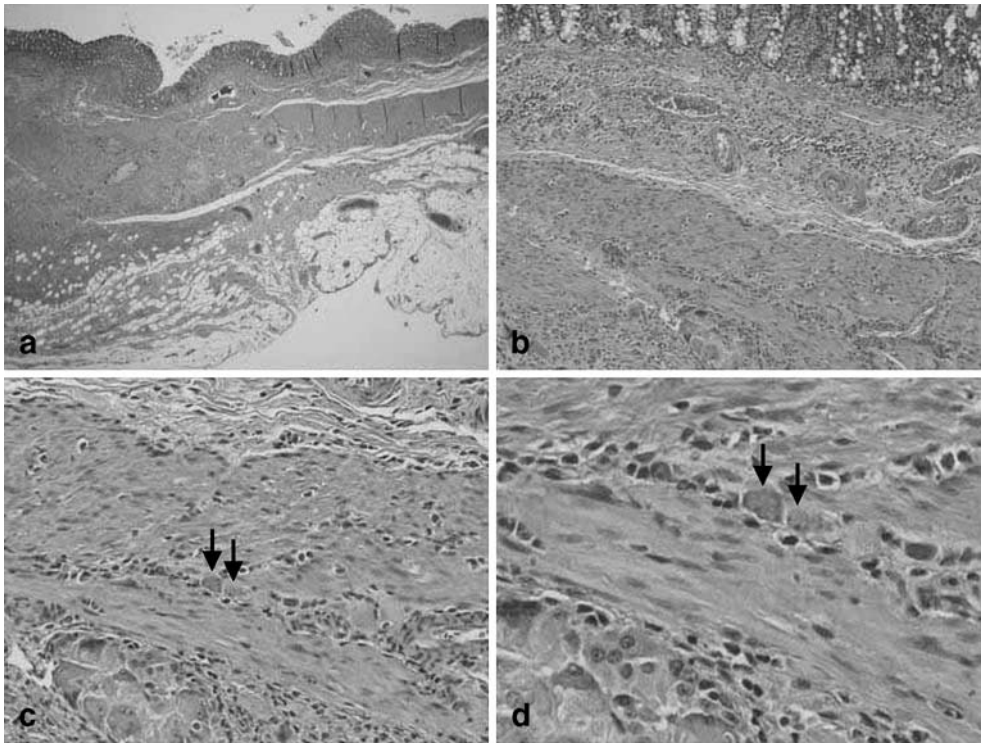

Figure 2 The defect was completely covered 6 months after surgery by regenerated mucosa, lamina propria, submucosa, muscularis propria, subserosal fat, and granulation tissue with chronic inflammation and foreign body reaction. **a** The border between the normal tissue and the SIS reorganized area (magnification ×20). Smooth muscle layers in lamina propria and muscularis propria in the normal cecum extended continuously to the regenerated area. **b** Restructure of layers of mucosa, lamina propria, submucosa, and muscularis propria was recognized (magnification ×100). **c** Regeneration of neural cells (arrowhead) was observed between smooth muscle cells (magnification ×200). **d** Regenerated neural cells (arrowhead) are morphologically quite similar to those in the normal tissue (magnification ×400).

Histological Findings in the Short-term Study

Microscopically, the defect was covered by granulation tissue and early fibrosis with varying amounts of inflammatory cells and neovascularization (Fig. 1a). An intact mucosa overlaid the defect in roughly half of the specimens, whereas ulceration of varying extent was present in others (Fig. 1b). No significant morphologic difference was seen in those specimens with vs without omentectomy, although serosal fibrovascular adhesions were common in the specimens without omentum.

Clinical Signs and Macroscopic Characteristics in Long-term Study Group

All animals in group L also survived and thrived over the 6-month postoperative period as well. They showed a significant weight gain (preop 280.1±5.1 g, 6 months postop 640.0±22.9 g) and had no postoperative complications. On gross inspection the omentum was also slightly adherent to the surface of the patched area in five of six rats with preserved omentum. On the contrary, in all rats that underwent omentectomy, genital fatty tissue covered the surface of the grafted area. The SIS-reorganized area was easily identified by detection of the remaining polypropylene suture. There was no evidence of diverticular formation and/or shrinkage in the region of the graft. Such foreign body reaction as seen in group S was not observed.

Histological Findings in the Long-term Study

All layers of the cecum wall including mucosa, lamina propria, submucosa, muscularis propria, subserosal fat, and serosa was reorganized by native tissue (Fig. 2) and/or granulation tissue with chronic foreign body reaction. Neural cells that are morphologically similar to those seen in normal tissue were observed in regenerated area (Fig. 2c, d)

Discussion

The present study demonstrated that SIS grafts could be safely incorporated to the gut with bacterial contamination in unprepared gut. Furthermore, microscopic findings revealed that intact mucosa covered the area of the graft and that all layers of the cecum were replaced by native colonic tissue with regeneration of neural cells in most animals by 6 months after surgery. We are truly aware of the fact that the major drawback of our study is the lack of a control group. As preliminary experiments, however, we had examined simple omental patch or a polyglactin mesh (Vicryl® mesh) for a defect in the stomach using three rats for each. Unfortunately, none of the rats remained alive because of severe peritonitis. From an ethical point of view, therefore, we gave up our intention of making control groups using omentum alone or of using other kinds of mesh to close a cecal defect in this series.

Small intestinal submucosa is a xenogenic extracellular matrix (ECM) obtained from the porcine small intestine. When implanted in vivo, SIS is supposed to induce cellular responses that recapitulate embryogenesis and tissue regeneration such that appropriate tissue structure and function are restored with minimal scar formation.[5,6] Small intestinal submucosa-related site-specific regeneration of tissues has been observed consistently when SIS was used as scaffolds for repair of the urinary bladder,[7] muscle tendon,[8] body wall,[9–11] and vasculature.[12] However, the exact mechanism by which SIS induces site-specific repair remains unclear. One possible aspect of this process might be related to the presence of growth factors.[13–16] Small intestinal submucosa has been reported to contain the bioactive basic fibroblast growth factor and transforming growth factor-β.[13] Interestingly, it has been reported that bioactivity is retained in the matrix after sterilization procedures and remains after prolonged storage at room temperature.[17]

Despite increased clinical attention to the applications of prosthetic materials in the gastrointestinal tract, to date, only a few studies have assessed the uses of SIS for the esophagus,[1] small intestine,[2] biliary tract,[3] and stomach.[4]

Chen and Badylak[2] evaluated the feasibility of using SIS as a scaffold for small bowel regeneration in an in situ xenograft model in dogs. After 6 months the patched region was difficult to identify by simple observation or palpation without the marking suture because the regenerated bowel appeared identical to native bowel in size, texture, and consistency. Histologic studies revealed complete absence of the SIS by 3 months. At 6 months and beyond, histologic evaluation of harvested specimens showed that the layers of the remodeled wall contained a mucosal epithelial layer, varying amount of smooth muscle, sheets of collagen, and a serosal covering and appeared nearly identical to the native bowel.

Badylak et al.[1] examined the remodeling events that occur when an ECM scaffold derived from either the small intestine or the urinary bladder is used as a resorbable scaffold for repair of esophageal defects in a dog model. The xenogenic scaffolds used for repair of the patch defects were reabsorbed completely within 30 to 60 days and showed replacement by skeletal muscle, which was oriented appropriately and contiguous with adjacent normal esophageal skeletal muscle, organized collagenous connective tissue, and a complete and intact squamous epithelium. By day 50, the ECM scaffold material could not be identified by light microscopy.

Recently, Rosen et al.[3] applied the use of SIS to the biliary tract and reported that at 5 months SIS was completely replaced with native collagen with a covering biliary epithelium that was normal caliber for canine common bile duct. They also described that a biliary epithelium covered the SIS graft as early as 2 weeks after placement with complete site-specific repair by 1 month. By 2 months, the SIS graft was replaced by an organized deposition of collagen, and at 5 months the graft was completely replaced with native collagen with a covering biliary epithelium that was normal caliber for canine common bile duct.

In the present study, we found that SIS was incorporated to the unprepared cecum and found that all layers of the cecum were replaced by native tissue with regeneration of neural cells. However, in 2 out of 24 cases SIS was eliminated into the lumen of the cecum. Some studies in which specific antibody probes were used to monitor the fate of SIS graft revealed that it was usually absorbed within 2 months in vascular[18] and urinary bladder[19,20] surgeries. In our clinical surveillance[21] of infected or contaminated hernias treated with the use of SIS, we observed recurrent hernia in 7 of 20 patients. All patients except one with a recurrent hernia had received operation for a concomitant grossly infected wound. Taken together, these findings may suggest a limitation to SIS implantation in some areas of gross bacterial contamination.

In conclusion, our findings tentatively show that SIS, as one of the foreign bodies, is well incorporated into the gastrointestinal tract in a "clean-contaminated" rat model, and that the defects created in the cecum were completely replaced by normal components of the bowel wall. This implies that SIS might provide a novel approach in surgical anastomoses to promote healing and presumably prevent leakage.

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Technical Considerations in Laparoscopic Fundoplication

How I Do It

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Abstract Gastroesophageal reflux disease (GERD) is a common disease and can be successfully treated by laparoscopic fundoplication. This article describes the technique of laparoscopic surgery for GERD with a focus on operative pitfalls.

Keywords Gastroesophageal reflux disease · Fundoplication · Laparoscopic surgery · Esophagus

Introduction

GERD is seen in up to 40% of the population.[1] If avoidance of triggers such as coffee, carbonated beverages, alcohol or fruit juice, and long-term medication with proton pump inhibitors cannot provide satisfactory results, surgery is indicated.[2,3] Since 1991, laparoscopic fundoplication has emerged as the best surgical option with superiority over other treatments.[4,5] During this experience, several lessons have been learned. The primary goal is to restore adequate LES function with an increase in resting LES pressure, fewer transient LES relaxations, increased intraabdominal esophageal length, accentuation of the angle of His, creation of a mucosal rosette, and speeding of gastric emptying.[6] In essence, the fundoplication is carried out in much the same way as for the open procedure with only minor modifications required. The steps of the procedure are described in detail, and suggestions are given how to avoid and deal with operative pitfalls.

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Surgical Procedure

Operating Room Setup

Most surgeons operate from between the legs of the patient in lithotomy position. This allows for easy access to the subdiaphragmatic abdomen and avoids twisting of the surgeon's back. The patient is placed supine in steep reverse Trendelenburg. Full muscle relaxation is of major importance to create a good intraabdominal working space. The laparoscopic procedure is performed using five 5–11 mm ports. Instrumentation includes a 0° or 30° telescope, atraumatic graspers, a Babcock grasper, a liver retractor, a small hook attached to the electrocautery, the harmonic scalpel, and two needle holders. A nasogastric tube is only inserted if there is excessive gas within the stomach. No Foley catheter is required.

Operative Technique

A vertical 1-cm incision is made above the umbilicus in the midline, the Verress needle is introduced, and a pneumoperitoneum is created. This camera port should not be placed too far inferiorly, particularly in obese patients. Further ports are placed in the subcostal area, avoiding close proximity of one port to another to avoid clashing of the hands. After placement of 5 mm ports in the upper midline, left mid subcostal area and 11 mm ports in the right and far left subcostal areas, the abdominal cavity is inspected.

In the presence of a hiatal hernia, the first step is to reduce the hernia content as far as possible and to place the

gastrohepatic ligament on stretch. This is then divided up to the right crus. The right crus is mobilized along its free edge. This is extended onto the left crus (Fig. 1). This dissection should proceed well posteriorly until the crus is seen to curve under the esophagus. Once this has been achieved, the esophagus can be elevated from the right-hand side together with the posterior vagus nerve which is usually a few millimeters posterior to the esophagus. Care must be taken not to traumatize the nerve. The crural edges are skeletonized, and this allows for the creation of a window posterior to the esophagus and below the diaphragm. This can easily be done by looking for the left crus of the diaphragm from the right-hand side of the esophagus and making a window immediately inferior to this muscular structure. The window is then enlarged, and the esophageal hiatus is dissected until clear diaphragmatic muscle is seen free of fat and connective tissue. The key to the dissection of the esophageal hiatus is to remain close to the edges of the crural muscle to avoid damage to the stomach or entry into the left pleural cavity. This will allow for easy access to the mediastinum and esophageal mobilization. Once the mediastinum has been entered, there is frequently a friendly dissection plane even in redo cases. The esophagus may need to be mobilized for some distance into the chest to obtain esophageal length. It is unusual for the esophagus not to be able to be mobilized sufficiently to allow the cardia to lie well below the diaphragm. Once there is sufficient esophageal length, the hiatus is reconstructed using interrupted nonabsorbable stitches such as Ethibond or Prolene (Ethicon, Inc., Somerville, New Jersey, USA) (Fig. 2). The first stitch should be placed immediately anterior to the point where the two crura join in front of the aorta. Care must be taken not to pass the needle into the aorta, which can cause considerable bleeding. If this should occur, the stitch should be removed, and pressure should be placed over the aorta for 10 min. Attempts to tie the stitch in the aortic wall may lead to further bleeding and to pseudoaneurysm formation. Further stitches are then placed until the esophageal hiatus appears adequate in size to accommodate the esophagus and a food bolus. Sufficient muscle should be included in the stitches to avoid tearing of the muscle. A tension-free reconstruction should be achieved, and stenosis of the hiatus around the esophagus must be avoided. To achieve this, the final stitch may be placed with a F56–60 dilator in the esophagus.

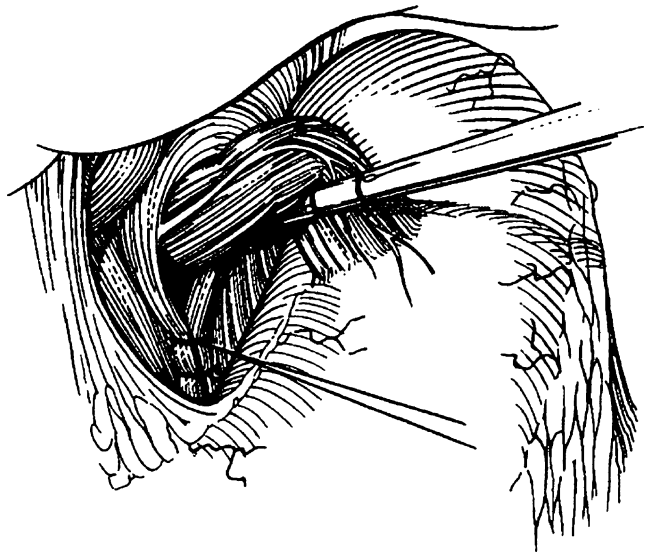

Figure 2 The right and left crura are approximated.

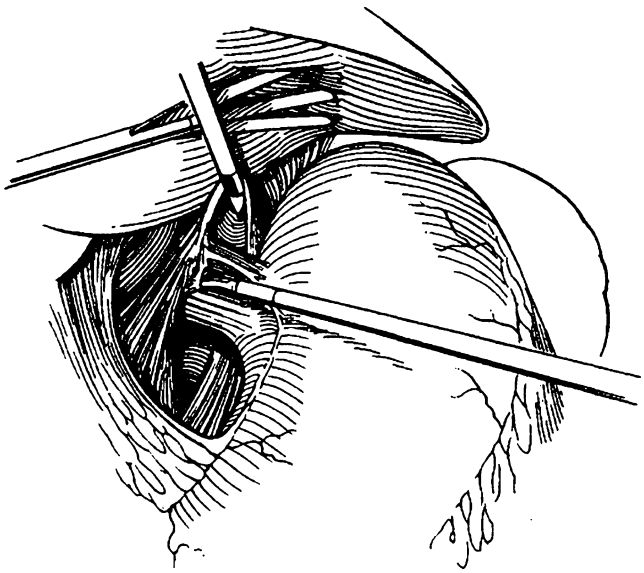

Figure 1 Laparoscopic view of the esophagogastric junction with the liver retracted.

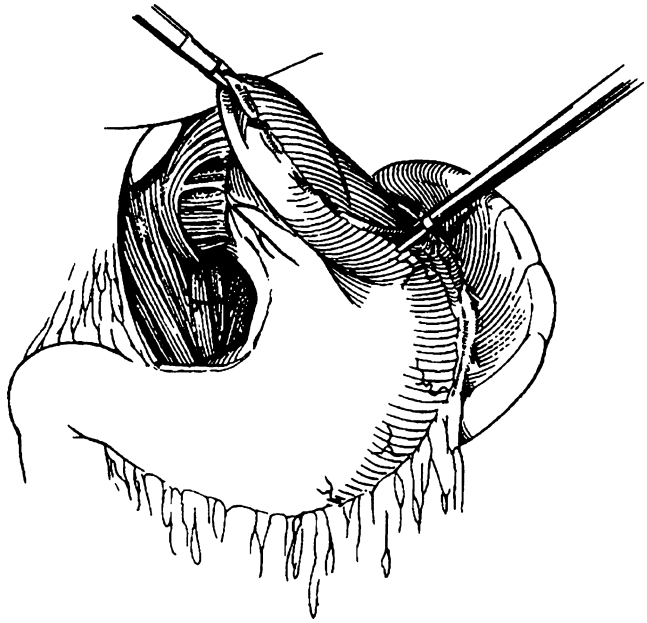

Figure 3 The fundus of the stomach is mobilized.

After the division of the short gastric vessels using the harmonic scalpel over a distance of 10–15 cm below the angle of His (Fig. 3), the procedure is completed by fashioning a 360° Nissen or a 270° Toupet fundoplication.[7–9] The decision whether to perform one or the other is based on preoperative esophageal motility. If a severe motility disorder is identified, a Toupet fundoplication is indicated. The greater curvature about 8 cm distal to the angle of His is grasped and brought behind the esophagus and the posterior vagus nerve (Fig. 4). In the case of a Nissen fundoplication, the fundus is secured to the appropriate portion of the more distal greater curvature brought anterior to the esophagus creating a 360° wrap (Fig. 5). This should be secured with several nonabsorbable sutures. The appropriate tightness of the wrap can be judged by grasping the more distal fundus over an intraesophageal bougie. With experience, the bougie may be omitted (Fig. 6). A short, floppy fundoplication is advisable, which may cause dysphasia if it is over 2 cm in length. Rosetti has suggested a modification in which the anterior part of the cardia is used for the left limb of the wrap. This is thought to cause less dysphasia; however, most surgeons use the greater curvature at the level of the short gastric vessels for the left side of the wrap. The esophageal bougie may again be advanced at this time to ensure that the wrap is not too tight. It is not advisable to secure the wrap to the diaphragm because it is more sensible to allow the stomach to move independent from the diaphragm.

In the case of a Toupet fundoplication, the wrap is first fixed to the left and right crura of the diaphragm (Fig. 7). Thereafter, three interrupted sutures are applied to the right side of the esophagus, and the left side of the wrap is then fixed to the left side of the esophagus with a further three sutures to create a partial posterior fundoplication. Care should be exercised to avoid incorporating the anterior vagus nerve in these sutures.

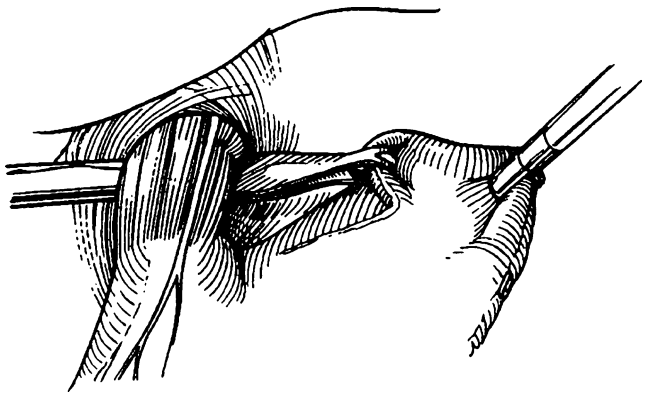

Figure 4 Grasping of the fundus of the stomach with a Babcock grasper, which is passed from the right behind the esophagus.

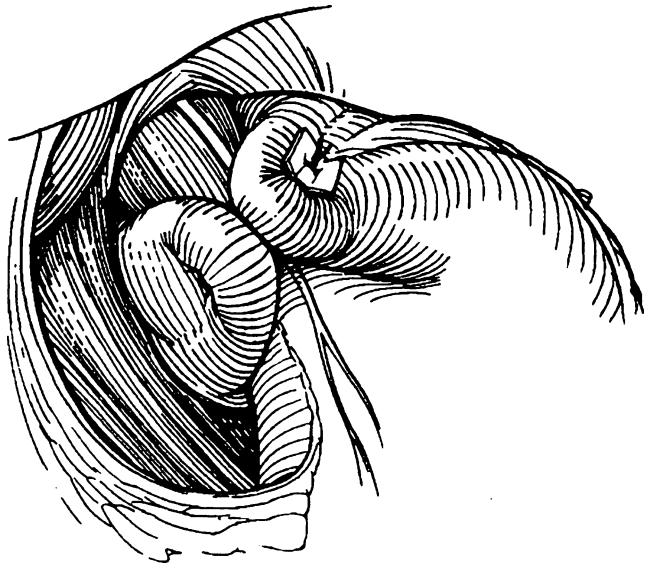

Figure 5 The completed Nissen fundoplication.

Operative Pitfalls

Fundoplication in Patients with Previous Abdominal Surgery

An increasing number of fundoplications are being performed in patients who have had previous abdominal surgery. Insertion of ports can be dangerous due to bowel adhesions to the scar, and placement at "nonstandard" sites might be necessary. If a previous midline incision is present, the Veress needle can usually be safely placed in the left subcostal area. Alternatively, the first trocar can be inserted using the Hasson or "open" technique, which is preferred by some surgeons for all cases. After division of adhesions between the parietal peritoneum and intraabdominal organs, placement of further

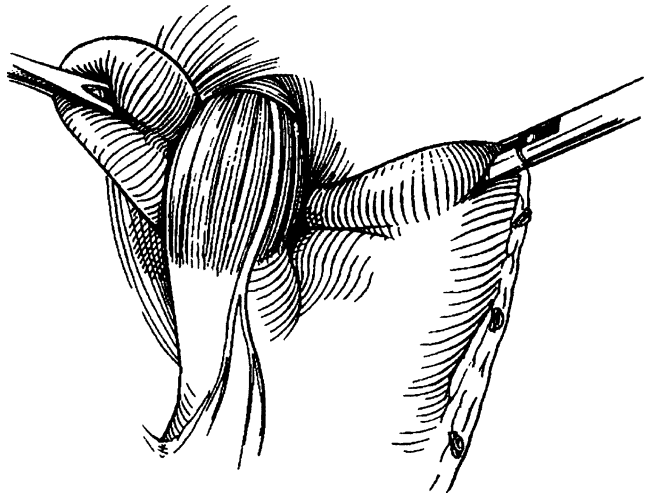

Figure 6 The fundus of the stomach is brought behind the esophagus to create the wrap.

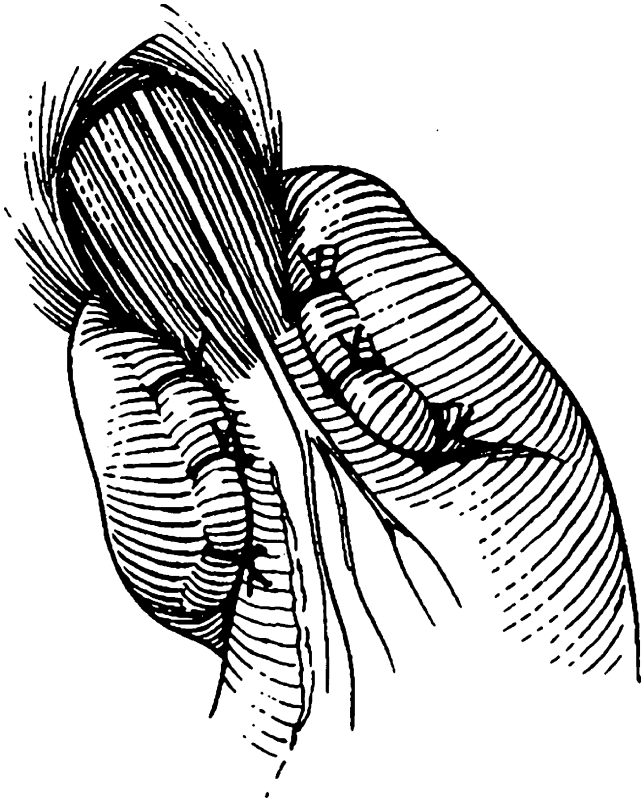

Figure 7 The completed Toupet fundoplication.

ports can be achieved. Dissection of the left liver lobe from the stomach and diaphragm may be tedious in redo operations. Conversion to laparotomy is required in 9% after a previous laparoscopic antireflux procedure but in 29% after previous open procedures.[10]

Left Accessory or Replaced Hepatic Artery

This artery originates from the left gastric artery and is found to be present in up to 25% of patients. Some accessory arteries are small and can be divided without consequence; however, large vessels suggest that there is complete replacement of the arterial blood supply to the left lateral liver segments, and the vessel should be preserved intact to avoid ischemic damage to the liver and biliary tree.[11] If access to the esophageal hiatus is truly obstructed, the vessel may be ligated after trial occlusion to check for liver blanching.

Tearing and Perforation of the Stomach and Esophagus

This may occur in the early surgical experience and is best avoided by gentle handling of tissues. Fragile tissues must be expected in elderly patients, patients with previous interventions at the gastroesophageal junction, diabetic individuals, and individuals receiving steroid treatment or other immunosuppressive agents. Small serosal tears may be oversewn and should be included in the fundoplication site whenever possible. Transmural injuries of the esophagus and stomach can be repaired laparoscopically using a stapling device or by suturing the defect. Intraoperative endoscopy can be helpful to ensure that the defect is completely closed.

Large Hiatal Hernias

The first step is to reduce the hernia into the abdomen. This is facilitated by dividing the peritoneum at the edge of the esophageal hiatus and then by pulling down on the sac to completely reduce it into the abdomen. In the case of a paraesophageal hernia (type-II and type-III hiatal hernia), this is particularly important.[12] After being reduced from the chest, a large sac is left attached to the anterior wall of the cardia and does not require to be excised. We feel that a remnant of the sac in the mediastinum might cause an effusion or could promote recurrent herniation. On dissection, care must be taken not to injure the esophagus, stomach, vagus nerves, or blood vessels. The large hiatal defect is then closed. This can be particularly difficult in some patients and may require the use of prosthetic material if the hiatus is not compliant and cannot be adequately approximated.[13] This can result in a large dissecting tear in the crura. Should this occur, there are several options. The first option is to place a strip of Teflon along the edge of the crus to strengthen this structure and to bolster the stitch. Another technique is to place a lateral release incision in the diaphragm and to cover this with polypropylene mesh, Gortex, or bioabsorbable material. It is generally best to use bioabsorbable materials. Some authors suggest the universal use of such patches to allow for a tension-free repair.[14] If necessary, the hiatal defect may be reinforced with mesh preferably denaturated animal or human tissue (Cook® SIS, Bloomington, IN, USA) fixed to the diaphragm using metallic staples or stitches. Foreign material should be avoided if possible, as this may lead to migration of the mesh into the esophagus or stomach. If mesh is used for hiatal closure, these patches should be cut with a “keyhole” defect and positioned to lie posterior to the esophagus. They must be attached to the diaphragm using staples or interrupted sutures. Diaphragmatic stitches placed anterior to the esophagus have been suggested to close large defects; however, tension is usually even greater in this area.

Division of Short Gastric Vessels

The fundus should be freed as high as possible to allow the wrap to lie in place without any tension. Several studies have been carried out to determine the need for complete division of all short gastric blood vessels. Most have come

to the conclusion that division of the short gastric blood vessels is necessary to allow for a floppy fundoplication. The use of the harmonic scalpel has shown itself to be most valuable in dividing these blood vessels. Blood vessels close to the spleen, in the tight space between the fundus and the upper pole of the spleen, can safely be divided. In paraesophageal hernias, these vessels have been sufficiently stretched by the gastric herniation to allow the fundus to be more easily brought behind the esophagus without tension.

Forward Kinking of the Esophagus

In the case of a large hiatal defect, posterior approximation of the crura might cause anterior kinking of the esophagus with obstruction as it rides up and through the hiatus. This is occasionally observed on lateral barium esophagogram but seldom causes symptoms such as dysphagia.

Short Esophagus

In type-III hernias, insufficient intraabdominal length of the esophagus has been reported after an attempted mobilization.[15] In most cases, adequate dissection of the esophagus up into the mediastinum allows for sufficient mobilization. Dissection can be performed as high as the bronchial bifurcation. If adequate intraabdominal length of the esophagus without tension cannot be obtained, an esophageal lengthening procedure such as the Collis gastroplasty followed by a fundoplication should be performed. This can be achieved laparoscopically; however, the best approach for this procedure is through the chest. DeMeester et al.[16] have reported the need for thoracotomy in over 33% of paraesophageal hernias. A novel laparoscopic approach for esophageal lengthening has recently been suggested. The fundus of the stomach is flopped to the right with a bougie in place in the lumen, and then a stapled fundectomy to a point 3 cm inferior to the angle of His is carried out. This is then stapled off along the left side of the esophagus to achieve a Collis gastroplasty.[17] The excised wedge of stomach is discarded.

Pneumothorax

This occurs more frequently on the left side and can result in a tension pneumothorax. The intraabdominal gas pressure should be decreased when a pneumothorax is created. Tension pneumothorax will result in the need for conversion to an open procedure. In most cases, no chest tube is required as the gas in the pleural space can be expelled by forceful lung inflation at the time of release of the pneumoperitoneum. In some cases, patients experience subcutaneous emphysema of the neck even if a pneumothorax is not present. This will resolve within a few hours.

Postoperative Management

For the majority of patients, a nasogastric tube is an unnecessary inconvenience. Patients are encouraged to ambulate early and to use incentive spirometry. Most patients leave the hospital the day after surgery. There have been some reports of patients being allowed to go home on the day of surgery. A routine gastrografin esophagogram is only performed if the dissection was difficult. Even in the presence of a luminal perforation, this test may not reveal the leak, and CT or further studies may be needed. During the first 24 h after surgery, pain control is satisfactorily achieved using liquid analgesics taken by mouth. We prefer to use lortab elixir (Hydrocodone/Acetaminophen, UCB Pharma, Inc., Smyrna, GA 30080, USA); however, any synthetic opioid as well as tramadol or nonsteroidal antiinflammatory drugs can be used. Metoclopramide or ondansetron are our preferred antiemetic drugs. Retching and vomiting must be suppressed to avoid stress on the repaired hiatus and fundoplication. Patients are started on a liquid diet on the night of surgery and advanced to a pureed diet as tolerated. Fresh bread, hard fruit and vegetables, and meat should be avoided for approximately 2–3 weeks. A normal diet is usually achieved within 6 weeks after surgery. About 12.2% of patients will experience early dysphagia requiring dilation.[18] This can safely be done over a guide wire using a 56–60 F bougie. Fourteen percent will experience new onset of diarrhea, and 10% will complain of gas bloat as air can be swallowed but not easily released if the fundoplication is competent. These symptoms should be treated symptomatically.

Conclusion

The principles of antireflux surgery include reducing abdominal organs from the mediastinum, gaining adequate intraabdominal length of the esophagus, narrowing the hiatus, and achieving an effective fundoplication.[6] Minimally invasive techniques offer a better treatment option at lower risk than open procedures.[19,20] Laparoscopic fundoplication should be successful if appropriate principles of operative therapy are followed.[21,22]

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Detection and Management of Extrahepatic Colorectal Cancer in Patients with Resectable Liver Metastases

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Abstract The presence of extrahepatic disease has a great effect on the management of patients with metastatic colorectal cancer in the liver. FDG-PET scanning is currently the most sensitive way of detecting extrahepatic metastases in such patients. This is supported by 10 studies, which show that FDG-PET scan will discover extrahepatic disease in about one in six patients who have completed standard imaging. Staging laparoscopy is another means of detecting extrahepatic disease. Its role remains undefined especially in patients who have had FDG-PET scans. It should probably be restricted to patients with high clinical risk scores. In terms of treatment, patients with recurrence at the primary colorectal site as well as resectable liver metastases appear to benefit from resection of both sites provided that R0 resections can be obtained. Resection of involved hepatic pedicle lymph nodes in patients with resectable liver metastases is associated with poor outcome. The situation regarding patients with peritoneal and liver metastases bears a strong resemblance to that of primary site recurrence and liver metastases. Very acceptable survival can be expected if the peritoneal disease can be eradicated. Information regarding treatment of lung and liver metastases is the most complete of any of these areas. Good results may be expected if all the disease can be cleared. Caution is required in interpreting claims of good survival when study numbers are small and confidence intervals of data are not provided.

Keywords Extrahepatic colorectal cancer · Colorectal cancer · Liver metastasis · Liver resection · FDG-PET scan · Colorectal lung metastases · Colorectal peritoneal metastases · Colorectal portal lymph node metastases

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To determine whether surgical treatment of colorectal cancer metastatic to the liver is indicated requires answers to several questions. 1. Can the hepatic tumors all be resected or ablated while leaving an adequate volume of remnant liver? 2. Has the primary tumor been resected completely or if not is this achievable? 3. Are extrahepatic metastases present, and if so, what are their size, number, and location, and should they also be resected? The second and third of these important questions involve detection and management of extrahepatic deposits of colorectal cancer, either at a primary colorectal site or in extrahepatic secondary sites. The rationales and techniques involved are rapidly evolving and of great interest to those caring for these patients. The purposes of this review are to assess current methods for detection of extrahepatic deposits of colorectal cancer in patients with apparently resectable liver metastases and to evaluate the extent to which resection of extrahepatic tumors is of benefit to patients who also have resectable liver tumors.

Detection of Extrahepatic Metastatic Deposits of Colorectal Cancer in Patients with Potentially Resectable Hepatic Metastases: Detection of Extrahepatic Cancer by Imaging Tests

Computed tomography (CT scan), magnetic resonance imaging, ultrasound, and FDG-PET scanning are the major imaging modalities for detection of extrahepatic tumors.

Because FDG-PET has been shown to be the most sensitive means of detecting *intrahepatic* metastases in three metaanalyses,[1–3] we evaluated the literature comparing the effectiveness of this test for detecting *extrahepatic* metastases to that for CT, magnetic resonance imaging, and abdominal ultrasound. To our knowledge, there is no metaanalysis of studies aimed at determining the relative effectiveness of FDG-PET in detecting extrahepatic disease in patients with apparently resectable liver metastases. We identified 10 reports, which had the following three features: (1) more than 20 patients in the study, (2) report confined to patients with colorectal cancer or cohort with colorectal cancer identifiable from other patients, and (3) report describing the utility of FDG-PET in identifying undiagnosed *extrahepatic* disease in patients with apparently resectable hepatic metastases by conventional imaging, or containing an identifiable cohort with those characteristics,[4–13]

In all 10 studies, FDG-PET was performed after "conventional" or "standard" imaging was completed. Conventional/standard imaging consisted of CT in all patients[4–6,8,9,12,13] or almost all patients.[11] Variable numbers of patients also had other forms of imaging such as MRI,[4,5,7] CT portography,[4,11] or abdominal ultrasound[4,8] before FDG-PET imaging. All FDG-PET scans were performed in the reporting institution but in some studies, a proportion of the CT scans were performed at an outside facility at a variable time of up to 2 months before the FDG-PET scan and were then reviewed in the reporting institution.[6,10,13] Chest CT was part of the conventional workup in all patients,[8,9] in some patients,[4–7,13] was not performed at all[10,12] or was performed only after the FDG-PET scan revealed disease in the lungs or mediastinum.[5,11] Confirmation of the FDG-PET finding of extrahepatic cancer was obtained either by operating on all patients regardless of the results of the FDG-PET scan or by percutaneous biopsy of a PET-positive area[4,5,7,8,11,13] or, in some cases, by following the patients until FDG-PET-positive areas were determined by other means to harbor cancer.[4–9,12,13]

It is obvious from the foregoing that these studies do not represent a uniform set of investigations. However, all have reached the conclusion that FDG-PET is the most sensitive way of detecting extrahepatic deposits of cancer in patients with colorectal liver metastases, who are being staged for surgical therapy. The results of the 10 studies are given in Table 1. The percentage of patients with extrahepatic disease discovered by FDG-PET scan in patients with apparently resectable liver metastases, after they had completed standard imaging, ranged from 10 to 32%, with the median of the 10 studies being 17%. The sites where metastatic deposits were identified only by FDG-PET were lung or mediastinum,[4–11,13] intraabdominal lymph nodes, peritoneum or retroperitoneum,[4–10,12,13] site of the previously resected primary tumor,[4,5,8,13] a new unsuspected colorectal tumor,[4,5] and bone or spine.[4,7,8] In two of the earlier studies, metastatic disease in the chest missed by a chest radiograph was detected by CT of the chest after FDG-PET was performed;[5,11] had chest CT been performed routinely in these studies as it was in others, FDG-PET scans would have appeared less effective. In most cases, extrahepatic deposits were located in the chest or in abdominal lymph nodes, retroperitoneum, or peritoneal surface. While to date most studies have evaluated the effect of free-standing PET devices, one study compared CT/PET to contrast enhanced multidetector row CT.[14] Of 36 extrahepatic metastases detected by CT/PET in lung, intraabdominal nodes, and bone, only 22 were found by contrast enhanced multidetector row CT, demonstrating a striking superiority of CT/PET in this regard.[14]

The chance that cancer will be detected only by FDG-PET seems to increase with disease severity. In this regard, a number of prognostic factors have been associated with a poor outcome after liver resection for colorectal metastases, such as the number and size of liver tumors, the stage of the primary colonic tumor, timing of recurrence, and carcinoembryonic antigen (CEA) level.[15] Certain of these factors have been assembled to create risk scores.[16,17] Three studies showed that the chance of having extrahepatic disease discovered by FDG-PET in patients with apparently resectable liver metastases is higher in patients who have unfavorable prognostic factors than in patients who do not have.[4,6,7] Two of these studies used the Fong clinical risk score as the measure of prognosis in examining this issue.[4,7] Schussler-Fiorenza et al.[7] recommended that risk score be used to select patients for FDG-PET to reduce the overall costs of managing such patients. Specifically, they recommended that FDG-PET scans be performed only in patients with a Fong risk score greater than zero as none of seven patients with zero score, had treatment altered by performance of a scan. This number of patients in this study is too small to obtain definitive recommendations, but the concept that patients with higher risk scores are more likely to have undiagnosed disease discovered by FDG-PET is logical and supported by data from these three studies.

False-positive FDG-PET scans were reported in a small number of patients; the median percentage of false-positive extrahepatic disease discovered was 2%. In some cases, this

Table 1 Studies Examining the Utility of FDG-PET in Identifying Extrahepatic Disease not Discovered by Conventional Imaging

First Author	Year of Publication	City, Country	No. of Patients in Study	No. of Patients with EHD Discovered Only by FDG-PET	Patients with EHD Discovered Only by FDG-PET (%)	No. of Patients with False-Positive FDG-PET	Patients with False-Positive FDG-PET (%)	Patients in Whom FDG-PET Altered Management (%)
Lai[5]	1996	Camperdown, AU	34	11	32	1	3	29
Vitola[11]	1996	Nashville, USA	24	4	17	1	4	25
Fong[4]	1999	New York, USA	40	8	20	2	5	40
Zhuang[10]	2000	Philadelphia, USA	28	6	21	1	2	21
Strasberg[6]	2001	St. Louis, USA	43	5	12	0	0	23
Ruers[9]	2002	Nijmegan, NL	51	7	14	1	2	20
Arulampalam[12]	2004	London, UK	28	4	15	0	0	32
Schussler-Fiorenza[7]	2004	Madison, USA	73	9	12	1	1	20
Rosa[8]	2004	Munich, GE	58	12	21	1	2	21*
Truant[13]	2005	Lille, FR	53	5	10	3	6	18
Total			432	71		11		
Mean			43.2	7.1	17.4	1.1	2.5	24.90
Median			41	6.5	17	1	2	22

EHD=Extrahepatic disease, AU=Australia, USA=United States, NL=The Netherlands, UK=United Kingdom, GE=Germany, FR=France
*As a result of discovery of extrahepatic disease only.

led to unnecessary laparotomy.[5–7] Infrequently, extrahepatic disease is missed by FDG-PET scan and is discovered only at operation (false negative); this has been explained by small tumor size (less than 1.5 cm),[4,6,9,11,13] recent chemotherapy,[12] mucinous tumors,[13] and misreading of an extrahepatic tumor as a liver tumor.[4,5,10] In our study, this occurred in 2 of 37 patients, and this is similar to most other reports.[6] An exception is the study of Schussler-Fiorenza et al.[7] who reported a false-negative rate of about 20% for extrahepatic disease; an unusual aspect of their study is that five patients with lung disease had positive conventional imaging for lung metastases but negative FDG-PET scans.

A common variable provided in the reports of this type is the percentage of patients in whom FDG-PET scans altered management. The median percentage in these studies was 25% (Table 1). Therefore, the majority of time that management was altered as a result of new information provided by FDG-PET it was due to the discovery of extrahepatic disease (approximately 17%). The discovery of extrahepatic disease by FDG-PET led to the abandonment of the planned liver resections in most patients.[4,6–12] In some cases, liver resection was performed along with resection of foci of tumor in the lungs[4,6,12,19] at the site of a previously resected primary[4] or at a new unsuspected primary site in the colon.[4,5,10,12]

The conclusion that FDG-PET is more sensitive than conventional imaging in detecting extrahepatic deposits of cancer in patients with liver metastases from colorectal cancer is indirectly supported by other studies, which have examined patients from the aspect of recurrent colorectal cancer at any site as opposed to the liver. For instance, Lonneux et al.[18] found that FDG-PET scanning is more sensitive than conventional imaging for local recurrence of the colorectal cancer at the primary site, and for metastases in the lung and at other sites. An interesting subset of such studies has examined patients whose only abnormality was elevated CEA, i.e., conventional imaging was normal in hepatic and extrahepatic sites. Five of such studies were identified[19–23] (Table 2). FDG-PET was highly effective in locating the cancer in most of these patients, both in hepatic and extrahepatic sites. The extrahepatic sites were similar to those described in the 10 studies examining the effectiveness of FDG-PET in finding extrahepatic cancer in patients with potentially resectable liver metastases described previously (Table 1).

In summary, although the available set of studies is not uniform, there are 10 studies in which FDG-PET scanning discovered unsuspected extrahepatic disease in about one-sixth of patients (median of 10 studies) with apparently

Table 2 Results of FDG-PET Scan in Patients with Elevated CEA Blood Level and Normal Conventional Imaging

First Author	Year of Publication	City, Country	Number of Patients	No. of Patients with Abnormal PET Out of All Patients with True Recurrent Disease	Patients with Abnormal PET out of All Patients with True Recurrent Disease (%)	Site of Tumor Discovered by FDG-PET (No. of Tumors)
Flanagan[22]	1998	St. Louis, USA	22	15/15	100	Liver (6), pelvis (6), peritoneum (4), chest (3), abdominal/pelvic nodes (2), spleen (2),
Flamen[21]	2001	Leuven, Belgium	50	34/44	77	Extrahepatic abdomen (17), liver (10), postsurgical site (8), lung/mediastinum (3), supraclavicular (2), brain (1), bone (1)
Libutti[19]	2001	Maryland, USA	15 (arm 1)	10/13	77	Abdominal (8), extra-abdominal (2)
Libutti[19]	2001		15 (arm 2)	15/15	100	Not available
Libutti—total study[19]			Total 30	25/28	89	Not available
Zervos[20]	2001	Columbus, USA	15	13/14	93	Extrahepatic abdomen (11), liver (5), mediastinum(1)
Liu[23]	2005	Taoyuan, Taiwan	37	25/28	89	Lung/mediastinum (9), carcinomatosis/peritoneal (9), locoregional (7), liver (4), pelvis, (2) retroperitoneal nodes,(1) bone (1), brain (1)

resectable liver metastases after conventional imaging. False-positive results were quite infrequent (2%). False-negative results were slightly more frequent and were usually due to small tumor size or reduced uptake of FDG either due to mucinous tumor type or recent chemotherapy. As is well known, chemotherapy can alter the ability of tumor cells to take up FDG without necessarily killing the tumor cells.[24] Given the power of FDG-PET to discover extrahepatic disease and alter management of patients, its routine use can be advocated. There may be some rationale to limiting the test to patients with known positive clinical risk factors for recurrence when the availability of the test is limited.

Detection of Extrahepatic Cancer by Staging Laparoscopy

Staging by diagnostic laparoscopy is another method, which is used to detect extrahepatic metastases following conventional imaging in patients with colorectal hepatic metastases. There are five reports from four different centers, which can be specifically analyzed for the benefit of diagnostic laparoscopy with ultrasound in a cohort of patients with apparently resectable liver metastases.[25–29] Unnecessary laparotomy was avoided as a result of findings at diagnostic laparoscopy in 5–21% of cases.[25–29] However, with the exception of the earliest report by Rahusen et al., only 5–10% were spared unnecessary laparotomy.[26–29] About 6% of patients were eliminated as a result of peritoneal implants and the remainder as a result of detection of new liver disease. The examination was relatively ineffective in the detection of nodal metastases.[26,28] Two reports from the same center concluded that limiting the study to patients with a high clinical risk score[16] increases the yield rate dramatically[26,28] and recommended limiting the procedure in this way.

One reason for the relatively low yield of staging laparoscopy in this disease is that many patients do not undergo a complete laparoscopy due to adhesions.[26–28] However, even with a clinical risk score of 2–3, only about 11% of patients avoided an unnecessary celiotomy in the series of Grobmeyer et al. When the risk score was 4–5, the yield did rise to approximately 22%; however, only 1 in 10 patients with apparently resectable liver metastases had a risk score of 4–5. Yields were higher when the outcome measure was detection of occult disease rather than avoidance of celiotomy, and they were also higher when the intended procedure was implantation of an arterial infusion pump, i.e., when the disease in the liver was

unresectable. Therefore, to obtain 15% or greater rate of avoidance of celiotomy in patients with apparently resectable liver disease, staging laparoscopy would have to be limited to a rather small proportion of patients.

Recently, Thaler et al.[30] reported somewhat different results regarding the value of diagnostic laparoscopy in patients with apparently isolated colorectal metastases to the liver. The yield of findings, which would have eliminated patients with apparently resectable liver metastases, was well over 20% in this study.[30] Some 8% of patients were found to have nodal metastases alone, and 11% had peritoneal metastases. The authors suggest that "comfort and facility" with laparoscopy may have contributed to their ability to achieve these high yields,[30] especially in regard to lymph-node deposits, compared to earlier studies.[26,28] However, the intended treatment of the patients in this study[30] was quite different from the other study groups.[25–29] In Thaler's report, only 14 of 100 treated patients had liver resection, and many of these were performed laparoscopically. Sixty-six patients were treated with RF ablation with or without hepatic artery infusion pump. Another 12 patients had liver resection and RF ablation. Patients in this study might have been at a later stage of the disease; this would explain both the higher yields at laparoscopy and the choice of RF ablation rather than resection on such a high proportion of patients with liver metastases isolated to the liver.

Another way of assessing the potential value of diagnostic laparoscopy is to determine the incidence of findings at laparotomy, which would preclude resection had diagnostic laparoscopy been performed. While this approach is indirect, it has been used to evaluate its potential in pancreatic cancer.[31] Our results are as follows. We have not performed staging laparoscopy since instituting routine preoperative FDG-PET scanning in patients with apparently resectable colorectal metastases to the liver. In our initial series of 43 patients, only 5% of patients were unresectable due to the findings at laparotomy including lymph-node metastases,[6] and this is our continuing experience. In terms of the value of laparoscopic ultrasound after FDG-PET, we have found that intraoperative ultrasound, which is at least as sensitive as laparoscopic ultrasonography, has rarely affected the decision to perform liver resection.[32]

The reasons for these discrepancies are unexplained. It may indeed reflect local expertise, i.e., efficacy rather than effectiveness. At present, the data available in the literature do not permit a precise evaluation of the importance of staging laparoscopy in this group of patients. All reports are noncomparative case series. To address the questions satisfactorily, a multicenter trial would be required, and this is unlikely to occur. At present, it would seem reasonable to limit the use of diagnostic laparoscopy to patients with high clinical risk scores and to make extra efforts to assess portal and celiac lymph nodes.

Treatment of Colorectal Metastases in the Liver in Patients with Extrahepatic Deposits of Colorectal Cancer

This section will deal with the treatment of colorectal metastases in the liver in patients who also have recurrence at the primary site or in secondary extrahepatic metastases. The latter mainly include lymph node, peritoneal, and lung metastases. The total number of patients with the combination of liver metastases and tumor in one of the extrahepatic sites, who have been treated by surgical resection, is very small compared to the numbers of patients treated surgically, who had disease confined to an individual site. Therefore, case series describing the results of surgical treatment of the former type of patient often contain a small number of patients. It is not unusual to find survival curves computed on 20 patients and in some cases on cohorts of fewer than 10 patients.

When examining reports of outcomes that depend upon the calculation of survival curves in small numbers of patients, it is important to recall that such data may have wide 95% confidence limits. Also, confidence limits tend to get wider as one progresses along the temporal axis of the survival curve, and more and more patients become censored. Therefore, when numbers are small and follow-up is incomplete, what may seem to be a large difference between survival curves may not be a difference at all. Furthermore, what appears to be an acceptable survival result may in fact statistically not be different from zero survival. Unfortunately, confidence limits of survival curves are not commonly presented, and so the significance of results may be indeterminable. Before engaging in an analysis of such data, the reader may wish to read Bollschweiler's review[33] of the benefits and limitations of Kaplan–Meier calculations.

Colorectal Metastases in the Liver with Recurrent Cancer at the Primary Site

Few studies have reported outcomes of treatment of recurrence at the primary site in the presence of distant metastases, and none focussed exclusively on hepatic metastases in patients with recurrence at the primary site, although this problem is commonly treated in high-volume centers. However, much can be learned from examining the results of resection of colorectal (mainly rectal) cancer in patients in whom the recurrent disease was confined entirely to the primary site. Available case series are shown in Table 3. The largest series by Hahnloser et al.[34] described 394 patients who underwent reoperation and intraoperative radiation therapy (IORT), when appropriate, for localized recurrent rectal cancer. An R0 resection was attained in 35% of patients. Some 7% had an R1 resection, 35% an R2 resection, and 23% were unresectable at the

time of reoperation due to extent of disease. Overall 5-year survival of the 304 patients who were actually resected was 25%, and for all 394 patients, it was about 20%. Five-year overall survival was affected by completeness of resection—37% after R0 resection, 22% after R1 resection, and 14% after R2 resection.[34] IORT was only beneficial if the tumor could be resected with clear margins. In other studies, the presence of microscopic or macroscopic positive resection margins (R1 or R2) was also associated with significantly poorer 5-year overall survival results.[35–37] ranging from 0 to 14% (Table 3). Yamada et al.[38] reported on 60 patients, who underwent laparotomy, of whom 37 were resected. The 5-year survival was 18%. When stratified based on the type of invasion—i.e., local, sacral, and lateral, the 5-year survival was 38, 10, and 0%, respectively. Patients with elevated CEA had a poorer outcome than those with a normal level—5-year survival of 8 vs 39%.[38] Other papers in the literature also cite CEA and preoperative pain as prognostic indicators of poor outcome. These factors and site in the pelvis likely reflect the extent of disease and ability to achieve an R0 resection.

The preceding studies did not deal with patients who had local rectal recurrence as well as hepatic metastases, but what can be garnered from these studies is that if an R0 resection is not obtained when resecting a primary site recurrence, the 5-year survival is only about 15%. Based on these numbers alone, one could reasonably predict that the 5-year overall survival of patients who had an R1 or R2 resection of a colorectal recurrence as well as a liver resection for metastatic disease would have a poor outcome, with the likelihood of a 5-year overall survival of less than 10%.

There are two case series, from Memorial Sloan Kettering Cancer Center, that have presented results of treatment of local recurrence of the primary colorectal cancer in the presence of distant metastases including liver, lung, peritoneum, lymph nodes, breast, and abdominal wall.[39,40] In the first case series, 20/44 (45%) patients had liver metastases, and 16 of these patients underwent resection of recurrence at the primary site and liver resection.[39] It appears that the 5-year overall survival in this group was about 10%. In the entire series, the 5-year survival for patients who had R0 resection at the primary site was 17%, and it was 0% for those with either an R1 or R2 resection.[39] Therefore, there seems to be some benefit to the treatment of distant metastases when R0 resection of the primary site recurrence is obtained. The second paper was confined to colonic recurrences in 76 patients.[40] Fifty patients had local recurrence only, and 26 patients had local recurrence and distant metastases. Seventeen of the latter had disease localized to the liver only, and seven had liver and lung metastases. An R0 resection of local and distant tumor deposits was achieved in 8 of the 26 patients (31%). In the remaining 18 patients, resections were R1 or R2 in 13 (50%) patients, or the resections were abandoned at the time of laparotomy due to the extent of disease. Survival data for the 26 patients with both local and distant recurrences are not provided separately from the entire series although the presence of potentially resectable distant metastases was an indicator of poor outcome. Importantly, there were 30 patients in the entire series who had either an R1 or R2 resection, and the 5-year survival rate was 5%.[40]

To summarize this area, the data are fairly strong that results of resection of recurrent primary site colorectal cancer are very acceptable in the absence of distant metastases when an R0 resection is obtained but are much poorer when margins are positive. When liver metastases are also present, results seem to deteriorate significantly even when R0 local resection and R0 liver resection are achieved. It seems reasonable to resect liver tumors in patients in whom an R0 resection of a local recurrence of colorectal cancer has been obtained. However, the evidence from this literature is that performing a liver resection when only an R1/R2 resection of a colorectal primary site recurrence has been attained is a strategy that will lead to few long-term survivors. It is to be hoped that newer forms of systemic therapy will improve the results of treatment even in patients who have R1 resections, but as yet, there is no proof that it will.

Colorectal Metastases in the Liver and Extrahepatic Lymph-Node Metastases

Colorectal cancer may spread to regional perihepatic lymph nodes from hepatic metastases. The main evidence that this occurs is that metastases are found in lymph nodes adjacent to the liver in patients without evidence of metastases in lymph nodes close to the primary tumor.[41,42] Most studies regarding nodal metastases in patients with colorectal metastases in the liver have dealt with lymph nodes in the "hepatic pedicle". The pedicle encompasses nodes in the hepatoduodenal ligament, in the adjacent retroduodenal/retropancreatic area, and along the common hepatic and celiac arteries (Fig. 1). In the Japanese numerical schema, these would be nodes at sites 8,9,12,13a and 17a (Fig. 2).[43] Elias et al.[44] divided the pedicle into several zones (Fig. 1), and Jaeck et al.[42] later grouped the zones into two "areas": one along the hepatoduodenal ligament (zones 1–4=area 1), and the other along the common hepatic and celiac arteries (zones 5,6= area 2).

Most studies have focussed on lymph nodes in the hepatic pedicle, but lymphatic drainage of the liver to primary lymph nodes is not confined just to these particular nodes. For instance, lymphatics connect through the bare area of the liver to intrathoracic lymph nodes.[45] Also,

Table 3 Relationship Between Type of Resection and Survival After Surgery for Recurrent Colorectal Cancer at Primary Site

First Author	Year of Publication	City, Country	No. of Patients	Laparotomy Only	Patients Resected	5-Year Survival of Resected Patients (%)	R0 Resection [*N* (%)]	R1 Resection [*N* (%)]	R2 Resection [*N* (%)]	R0 Resection 5-Year Survival	R1 Resection 5-Year Survival (%)	R2 Resection 5-Year Survival (%)
Garcia-Aguilar[79]	2001	Minneapolis, USA	64	13	51	NA	42 (82)	R1+R2; 9 (18)		35%	R1, R2, or laparotomy only (7)	
Yamada[38]	2001	Kagoshima, Japan	60	23	37	18	NA	NA	NA	NA	NA	NA
Lopez-Kostner[80]	2001	Cleveland, USA	NA	NA	46	32	NA	NA	NA	NA	NA	NA
Shoup[37]	2002	New York, USA	NA	NA	100	39	64 (64)	30	6	51	13	14
Hahnloser[34]	2003	Rochester, USA	394	90	304	25	138 (45)	27 (9)	139 (46)	37	22	14
Vermaas[35]	2004	Groningen, NL	NA	NA	92	~15	53 (57)	25 (27)	14 (15)	21	R1+R2 (3)	
Bakx[36]	2004	Amsterdam, NL	NA	NA	40	26	16 (40)	R1+R2 (24)		~55	R1+R2 (0)	
Wiig[81]	2005	Oslo, Norway	NA	NA	190	NA	65	NA	NA	~50	NA	NA

NL=The Netherlands

lymphatics of the left liver may drain primarily to nodes along the lesser curvature of the stomach.[46] It is likely that the site of the colorectal secondaries in the liver determines preference to metastasize to particular lymph nodes and that this is based upon the normal pattern of lymph-node drainage from various parts of the liver. For example, centrally located metastases in segments 4 and 5 seem to cause nodal metastases in the hepatic pedicle more frequently than metastases in other sites in the liver.[42] Kokudo et al.[43] noted a tendency for metastases in the right liver to metastasize to number-12b nodes and for those in the left liver to metastasize to number-8 nodes. In anatomical terms, the situation is not much different from other organs such as the colon or stomach in which the site of the primary tumor in the organ influences the site of lymph-node metastases. However, in surgical terms, there is a large difference because the primary nodes from the colon or stomach lie in the abdomen and are surgically accessible, whereas primary nodal metastases from the liver may lie in the mediastinum, and resection at the time of liver surgery is impractical.

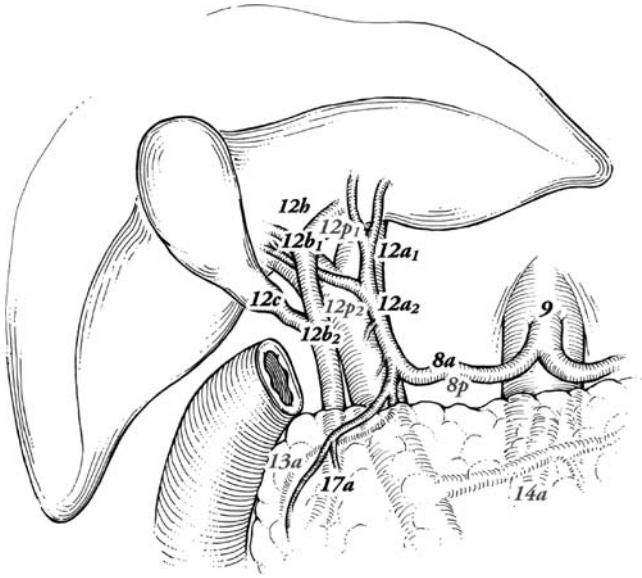

Figure 2 Lymph-node station numbers according to the Japanese Society of Biliary Surgery. Redrawn from Kokudo et al.[43] and from the classification of biliary tract carcinoma, Japanese Society of Biliary Surgery, Kanehara and Co. Ltd., Tokyo, 1994.

Microscopic vs Macroscopic Lymph-Node Metastases

Macroscopic lymph-node metastases are discovered either by preoperative imaging or intraoperative palpation and visual examination. Nodes considered to have a "suspicious" appearance and which are confirmed to harbor malignancy by frozen section should be classified as macroscopically involved. Microscopically involved lymph nodes are discovered by postoperative histologic examination of nodes from patients who have undergone protocol dissection of grossly normal lymph nodes. Because patients with macroscopically involved nodes have a larger burden of nodal disease, one would suppose that they have a worse prognosis than patients with microscopic nodal involvement.

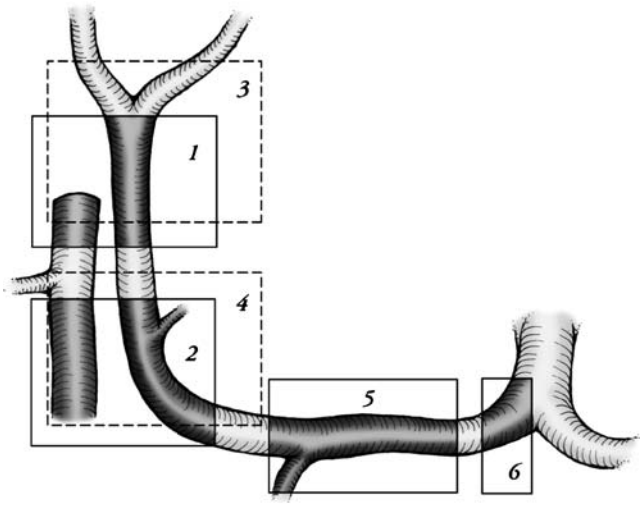

Figure 1 Division of lymph nodes of the hepatic pedicle according to Elias et al.[44] The numbers indicate zones around the hepatic artery and bile duct. Zones 3 and 4 (dashed boxes) are posterior. Redrawn from Elias et al.[44]

Results of Protocol Node Dissection for Microscopic Lymph-Node Metastases

Much of the available data on this subject come from a set of valuable studies from France.[42,44,47,48] Elias et al.[44] in 1996 reported the results of protocol node dissection in a multi-institutional trial involving seven centers, including groups from Strasbourg and from Bordeaux (see below). One-hundred patients without macroscopic node disease and in whom at least three nodes were obtained from dissection of the hepatic pedicle were described.[44] Fourteen patients were found to have 26 microscopically involved lymph nodes. Three of eight patients with involvement of nodes along the common hepatic artery (area 2 of Jaeck) did not have involvement of nodes in zone 1–4 as well. This suggests a nodal drainage pattern that went directly to these nodes perhaps through the lesser omentum as suggested by Kokudo for left liver metastases[43] or that the tumor "skipped" through the nodes closer to the liver. The presence of positive nodes in any site was significantly related to CEA level, tumor number, and "high percentage of liver involvement", which was not further defined. The dissection was described as "tedious", and seven patients had lymph leaks, all of which resolved. During the study, eight additional patients were excluded because of macroscopic

lymph-node involvement discovered at the time of surgery. Note that the incidence of macroscopic node involvement 8/108 was not much less than the incidence of microscopic node involvement 14/108.[44]

Survival data were not reported in the 1996 paper[44] but subsequently, three papers have appeared in which survival data from some[42,48] or all[47] patients in the original study have been given. Elias and Ouellet[47] in a review article briefly describe a 26% 3-year overall survival in the 14 patients with microscopically involved nodes. The 3-year overall survival in the 86 patients without involved nodes was 66%.[47] While a 23% 3-year survival rate seems quite acceptable, caution must be used in interpreting this figure as the number of patients was small, the follow-up was relatively short, and the 95% confidence limits of the estimate were not provided. The Strasbourg group independently reported institutional survival data in 160 patients who had protocol dissection.[42] Some 17 of 160 (11%) had microscopically involved nodes, and the 3-year survival rate in these patient was 19%. In eight patients, the disease was confined to area-1 nodes,[42] and in nine patients, it involved area 2 with or without area 1 (Fig. 1). None of the latter survived for more than 1 year. Two of the eight with area-1 involvement were alive after 3 years, providing 38% 3-year overall survival in this very small subgroup. Disease-free survival status at 3 years was not provided in either study, and 5-year overall survival is unreported.[42,47] Jaeck et al.[42] conclude that lymph-node involvement in zone 1 should not be considered "an absolute contraindication" for resection of colorectal liver metastases". It is difficult to disagree with such a highly qualified statement. However, the number of patients, on which the conclusion is based, was very small, the follow-up was relatively short, the data were analyzed retrospectively, and the subgroups seemed to have been established after outcomes were known. The inherent danger in doing so and the need to confirm such findings by a prospective trial before coming to conclusions are well recognized.

Laurent et al.,[48] also from an institution which participated in the original trial (Bordeaux), recently reported on 156 patients of whom 23 (15%) had lymph-node involvement. The 3- and 5-year survival rates were 27 and 5%, respectively. Notably, the 3-year survival figure is very close to that in the other two reports from France.[42,47] This is highly suggestive that the data of Laurent et al.[48] in respect to the finding of a 5-year overall survival of 5% is representative of what might be expected from resection of colorectal metastases in the liver in patients with microscopically involved nodes, who have been followed up for long enough to permit a 5-year survival analysis. The conclusion of Laurent et al. is not that protocol node dissection is therapeutic but rather that it should be performed to establish prognosis.

There are two other reports in which lymph-node dissection was performed, but in these reports, it is not possible to determine how many of the patients had macroscopically versus microscopically involved nodes in these studies. Beckurts et al.[49] from Germany routinely dissected nodes from "the hepatoduodenal ligament". Judging from the French experience routine dissection will result in roughly equal numbers of patients with microscopically and macroscopically involved nodes in a large study. Beckurts et al.[49] found that 35 of the 126 (28%) patients had positive lymph nodes. There were no 5-year survivors. Nakamura et al.[50] reported on 43 of 79 patients who had lymph-node dissection of the hepatic pedicle. Patients in the first 11 years of the 20-year study period had protocol node dissection, whereas after that resection was done only if nodes were detected at the time of surgery. Seven patients were discovered to have nodal metastases, and two survived for over 5 years but died at 62 and 66 months. A 5-year overall survival of over 40% is reported for this group. Unfortunately, this small study has been used to justify node dissection. However, the danger of basing recommendations on survival data from very small cohorts of patients must be emphasized, particularly when 95% confidence limits are not available. Other studies in this area do not provide information regarding microscopic node disease. The study of Kokudo et al.[43] deals with lymph-node sampling of nodes which were visibly enlarged and palpably harder than normal at least for the positive nodes, i.e., macroscopically involved nodes. In summary, based on the best available information,[48] protocol lymph-node dissection of the hepatic pedicle in association with resection of colorectal liver metastases can be expected to discover microscopic cancer in nodes in about 15% of cases with a 5-year survival of about 5% in those with microscopically positive nodes.

Macroscopic Lymph-Node Metastases

The English-language literature on this subject was thoroughly reviewed by Rodgers and McCall in 2000.[51] Of 185 studies in the literature describing liver resection for colorectal cancer, they identified 15 studies, which reported survival rates when metastatic disease was found in hepatic lymph nodes at the time of surgery. One-hundred forty-five of about 2,800 patients in these 15 studies had involved nodes. About 30% of the total number of 2,800 patients came from the American-based Registry of Hepatic Metastases.[52] The survival rate was very low when nodal disease was present. Only 5 of 145 patients with macroscopic node involvement were alive at 5 years: one was alive without disease, two had recurrence, and the status of disease was unknown in two patients.[51] Eighty-three of the 145 patients underwent formal lymph-node dissection, and

four individuals survived for 5 years. However, not all of the operated patients were followed up for 5 years;[51] therefore, the overall 5-year survival rate was *at least* 5%, but the actual 5-year survival rate could not be determined. Of the remaining 62 patients who apparently did not have a lymph-node dissection, only one was living after 5 years of follow-up. In the subgroup of 862 patients in the Registry study, 25 were found to have lymph-node involvement, and there was one 5-year survivor.[52] The only other report of a large number of node-positive patients who underwent simultaneous node and liver resection was by the French Association of Surgery (Association Francaise de Chirurgie or AFC), which was published in a monograph in 1992, rather than a peer-reviewed publication,[53] This publication was not available to us. However, secondary sources[47,51] report that this study, which came from 85 institutions, described 104 patients treated by simultaneous node and liver resection and that patients were followed up for 5 years.[47,51] The 5-year survival rate was 12%.[47,51] Elias and Ouellet[47] in a recent review refer to unpublished data from their center in 12 patients with disease limited to the liver and hilar lymph nodes. After liver and node dissection, the 5-year survival rate in this small group of patients was 27%; three patients survived disease-free beyond 5 years.[47] Noted again are the studies of Beckurts et al.[49] and Nakamura et al.[50] in which some patients had macroscopic node involvement and Kokudo et al. in which all nine patients had macroscopically involved nodes. All patients in these three studies were dead 5.5 years after surgery. In summary, based on the information from the largest studies, lymph-node dissection in the presence of macroscopic lymph nodes in the hepatic pedicle in association with resection of colorectal liver metastases can be expected to result in a 5-year survival of 5–12%. Note that this is not different for the results in patients with microscopic node involvement.

In summary, this is a particularly difficult area to obtain good data, and the attempts do so have involved considerable effort. The results of resection of lymph-node metastases at the time of hepatic resection hover between 5 and 10% 5-year overall survival, and this figure is based upon the studies with very small numbers of patients. Consequently, at this time, it cannot be confidently concluded that hepatic pedicle lymph-node dissection alters the outcome of the disease. It might be suggested that we have now entered a new era of effective chemotherapy for colorectal cancer and of improved localization of disease with FDG-PET and that node dissection would now be able to contribute to better outcomes in patients with involved lymph nodes—e.g., isolated to the hepatoduodenal ligament on PET. Indeed, it is predictable that improved survival rates will be reported in patients who are treated both with newer chemotherapy and node dissection, but the challenge will be to prove that the node dissection has contributed to that outcome. This is an issue that seemingly could be answered only by a very large randomized controlled trial.

Colorectal Metastases in the Liver and Peritoneal Metastases

The treatment of peritoneal metastases from colorectal cancer has advanced considerably in the past decade. Sugarbaker[54] pioneered and recently reviewed results of cytoreduction combined with intraoperative hyperthermic intraperitoneal instillation of peritoneal chemotherapy (HIPEC). A number of phase-2 trials suggested that this approach extends life in these patients. Now, convincing data are available from a randomized controlled trial performed in the Netherlands in which 105 patients were randomized to receive systemic chemotherapy with 5FU and leucovorin or cytoreduction combined with HIPEC[55] and adjuvant chemotherapy with the same agents. The trial was discontinued when it was found that the HIPEC group had much better results.[55] The HIPEC-treated patients had a 2-year overall survival of about 45%, which was twice that in the control group treated with systemic chemotherapy alone. Follow-up results in the treated group were recently reported; the 5-year overall survival rate was 19%.[56] Results were highly dependent on the completeness of the resection. Fifty-nine patients in whom no gross residual tumor was detectable at the end of the cytoreduction had a 5-year overall survival rate of 43%, whereas no patient with any gross residual disease survived for 5 years. Note that the extent of resection in these studies is not framed by the terms R0, R1, and R2 but by complete resection, minimal residual disease, and gross residual disease. The latter two are macroscopic levels of residual disease and would otherwise be rated as R2. Stated otherwise in this area, the extent of resection tends to be rated as R0 and the two types as R2. Complications were frequent. Fifteen percent developed intestinal fistula. However, the complications tended to occur in patients with diffuse intraperitoneal disease in whom disease complete gross resection of disease was usually not possible. Patients with liver metastases were not treated.

We were able to identify only one study in which substantial numbers of patients were actually treated for liver and peritoneal metastases. In this important study, 506 patients from 28 institutions were treated between 1987 and 2002 by cytoreduction of intraperitoneal tumors and perioperative intraperitoneal chemotherapy.[57] Sixty-one patients underwent simultaneous liver resection. The 5-year overall and disease-free survival rates were 19 and 10% respectively in the entire series. Completeness of resection was a key determining factor in the outcome. The 5-year overall survival in 271 patients with resection of all gross

disease was 31% with a median survival of 32 months. For 106 patients with minimal gross disease (no residual nodule >5 mm), the 5-year survival was 15% with a median survival of 24 months, and there were no 5-year survivors in 129 patients when residual nodules were >5 mm.[57] Simultaneous resection of liver metastases was a highly significant negative prognostic marker in multivariate analysis ($p<0.008$). Further information regarding this subgroup is not given in the paper, but in a personal communication from one of the authors (FN Gilly), it was learned that the median survival in the patients who had liver resection as well as treatment of the peritoneal metastases was 17 months, a figure which likely would place the 5-year survival between 0 and 15%, although that data is not available. The authors conclude that the presence of peritoneal and liver metastases usually indicates disseminated disease.

To summarize this area, certain persistent surgical investigators have now shown that the peritoneal surface should be regarded as an organ much as the liver or lung in respect to colorectal metastases. Metastases confined to the peritoneum can be treated with an impressive degree of success provided that complete gross resection is obtained. The presence of concomitant liver metastases degrades these results. To obtain reasonable results of combined liver and peritoneal cytoreduction, it is likely that complete *gross* resection of the peritoneal secondaries and R0 resection of the liver metastases are required.

Colorectal Metastases in the Liver and Lung

Compared to the sites covered above, there is a much more extensive literature covering the surgical treatment of pulmonary metastases from colorectal cancer and also much more information pertaining to the surgical treatment of patients with both liver and lung metastases. While 15–20% of patients with liver metastases are eligible for resection,[58] only 2% of patients with lung metastases are resectable.[59] Nonetheless, resection of isolated pulmonary metastases is associated with an impressive 21–43% 5-year survival.[59,60] Encouraging results of treatment for colorectal metastases isolated to liver or lung have stimulated the use of surgical resection in highly selected patients with both hepatic and pulmonary metastases. When compared to the total number of surgically treated patients with isolated liver or isolated lung metastases, the number of patients who undergo resection of both organs is small. For instance Headrick et al.[61] found that of 804 patients who underwent hepatic resection and 264 patients who underwent pulmonary resection for metastatic colorectal cancer only 58 (5.4%) had resection of lesions in both organs.

The clinical presentation of patients with liver and lung metastases, who have resection of both organs, is quite variable. Some individuals present with metastases at both sites and synchronously with the primary colorectal tumor. Others present with one synchronously involved secondary site with the other secondary site presenting metachronously. However, the commonest pattern of presentation in surgically treated patients seems to be metachronous presentation at both sites, and often, these presentations are sequential rather than simultaneous. Multiple types of presentations complicate comparisons of results, and a further impediment is the fact that many patients undergo additional resections in the same organ for second or third recurrences.[62,63] Some studies report all types of presentations, but others originating from thoracic units consist purely of patients who had pulmonary resections after having had hepatic resections.[63,64]

There are about 20 reports of this type in the literature. Table 4 focuses on nine case series in which 25 or more patients are presented.[61–63,65–70] Mortality has been very low, and morbidity has been acceptable. Eight of these series report 5-year overall survival. Five-year overall survival ranged from 9 to 74%, but in five of the eight series, the 5-year overall survival ranged from 27 to 51%. The latter figures compare favorably to the results of treatment of tumors isolated to one of the organs only. The variability in the results appears to be a reflection of the means of calculating survival and of case selection. Survival is variably presented as from the first or last metastasectomy or some time point between (Table 4). The apparently good results at 5 years have to be tempered by the fact that many of the patients may be alive with disease at 5 years rather than cured[62,66] and that overall survival at longer time periods than 5 years appears to decline much more than that in the series of patients with metastases isolated to the liver. For instance, in the study of Shah et al., the 5-year overall survival after the first metastasectomy was 74%, but the DFS was about 10%.[62] The fact that these patients with metastatic colorectal cancer are living so long and paradoxically seem to do better if they have more than one pulmonary metastasectomy[63] suggests that an unusual favorable tumor biology accounts at least in part for the good results. How much can be attributed to the biology of the disease and how much to its attempted extirpation is incalculable and cannot be determined by clinical trials because of the rarity of the problem. However, resection must contribute substantially because few patients with even single metastases in either organ survive for 5 years. Robinson et al.[67] reported on a nonresection group of 23 patients who had undergone colon resection and who had metastases limited to liver and lung, and none survived for more than 4 years. This group had more advanced disease, but using the shapes of the hazard functions of the two groups, Robinson et al.[67] were able to conclude that resection provides a survival advantage.

Table 4 Results of Liver and Pulmonary Resection for Metastatic Colorectal Cancer

First Author	Year of Publication	No. of Patients	Liver Metastases	Lung Metastases	5-Year Overall Survival (%)	Statistically Significant Indicators of Poor Outcome	Statistically Significant Indicators of Good Outcome
Murata[65]	1998	30	20 solitary, 10 multiple	18 solitary, 12 multiple	44*	Synchronous metastases, bilateral pulmonary metastases	
Regnard[63]	1998	43	25 solitary, 18 multiple	Median 2 (range, 2–12)	11*	Elevated CEA, early metachronous pulmonary metastases	More than one pulmonary metastasectomy
Kobayashi[66]	1999	47	30 solitary, 17 multiple	21 solitary, 26 multiple (9 bilateral)	31*	Simultaneous detection pulmonary and hepatic metastases	Solitary pulmonary metastasis, small number of hepatic metastases
Robinson[67]	1999	25	15 solitary, 10 multiple	10 solitary, 15 multiple (8 bilateral)	9*	Synchronous, resections, older age, multiple liver metastases, short disease-free interval	
Headrick[61]	2001	58	33 solitary, 25 multiple	31 solitary, 27 multiple	30†	Elevated CEA >5 ng/ml, mediastinal lymph node involvement.	
Nagakura[68]	2001	27	15 solitary, 12 multiple	9 solitary, 18 multiple	27‡	Simultaneously detected hepatic and pulmonary metastasis (within 1 month), extrahepatic metastases at initial hepatectomy	
Mineo[69]	2003	29	17 solitary, 12 multiple	21 solitary, 8 multiple	51*	Elevated CEA, elevated CA19-9, positive mediastinal lymph nodes	
Reddy[70]	2004	26	Average 1.4 (range, 1–5)	Average 1.7 (range, 1–6)	Mean, 34 months		
Shah[62]	2006	39	31 patients with ≤4 tumors, 8 patients with >4 tumors	24 solitary, 25 multiple	74‡	None	None

*Calculated from second metastasectomy
†Calculated from first pulmonary resection, which was usually the second metastasectomy.
‡ Calculated from first metastasectomy

Most authors suggest that liver resection should precede lung resections for colorectal metastatic disease when both are diagnosed at the same time. This is based on the fact that extrahepatic intraabdominal disease may be discovered at laparotomy that would preclude either liver or lung resection. Also, because liver function recovers completely after resection, unlike pulmonary function, it would seem reasonable to perform thoracotomy after laparotomy rather than the reverse. Good results have also been obtained in some series by doing both resections under the same anesthetic,[65,66] and this seems reasonable depending on the patient and the magnitude of resection required. Most studies in the literature include only patients in whom preoperative workup suggested that complete resection of tumor was possible[62,69] although in some reports, patients with positive hepatic surgical margins are included.[71] Several studies include patients who required multiple hepatic or pulmonary resections for recurrent disease.[61–63,71] The literature may reflect a changing management strategy as repeat resections become more widely accepted. In 1998, Regnard et al.[63] reported that 16% of their patients underwent repeat pulmonary resections for recurrence, wherease in 2006, Shah et al.[62] reported the same for 49% of the patients in their series. A majority of patients who underwent both hepatic and pulmonary resections for metastatic colorectal cancer receive adjuvant therapy.[61,67,72–74]

Multiple attempts have been made to refine patient selection by identification of prognostic indicators. These analyses are limited by the small numbers of patients available for analysis.[61,62,65,67–72] Elevated CEA has been identified in several studies as a negative prognostic indicator.[61,63,69,70,72] The presence of positive thoracic lymph nodes has also been reported as a negative prognostic indicator.[61] Several groups have evaluated simultaneous versus sequential detection of hepatic and pulmonary colorectal metastases as a prognostic indicator. Regnard et al.[63] found that a short interval between metastasectomies was of borderline negative significance. A later study by Nagakura et al.[68] found that patients who presented with sequential liver and lung colorectal metastases had 44% 3-year survival after resection, whereas patients who presented with simultaneous metastases had 0% 3-year survival. They concluded that patients who present with simultaneous metastases in both liver and lung are not candidates for resection even if all gross tumor appears resectable. Robinson et al.[67] reported that patients with metachronous resections survived longer than patients with synchronous resections, with median survival of 70 versus 22 months from resection of their primary colorectal cancer. Other variables that have been identified as prognostic indicators include the number of pulmonary or hepatic metastases, distribution of pulmonary or hepatic metastases, patient age, extrahepatic metastases diagnosed at hepatectomy, and elevated CA19-9 (Table 4). Robinson et al. divided their patients into two groups, an ideal group consisting of younger patients with a single liver lesion and a long interval of 4 years between the colon resection and the appearance of the lung metastasis and a nonideal group of older patients with multiple liver metastases and synchronous lung metastases.[67] The predicted 5-year OS in the former was 50%, and the predicted 2-year OS in the former was 0%.

In summary, in selected patients, the resection of colorectal metastases limited to liver and lung seems to provide very acceptable 5-year OS rates with low mortality and acceptable morbidity.

Colorectal Metastases in the Liver and Multiple Extrahepatic Sites

Most of papers in literature examining management colorectal liver metastases associated with extrahepatic metastatic disease have evaluated results of treatment of the liver and one specific extrahepatic site such as lung, peritoneum, or lymph nodes. Recently, in a series of papers, Elias et al.[75–78] reported results of treatment of sets of patients with liver plus one or more other extrahepatic sites including those above as well as ovary, adrenal, and other sites. They showed that the 5-year OS of a mixed group of patients is about 20%,[78] and in those in whom an R0 resection was obtained, the 5-year OS was 28%.[77] In one paper, they reached the rather provocative conclusion that the total number of metastases, whether inside or outside the liver, was an important determinant of outcome, and the localization, whether inside of outside the liver, "does not matter".[75] The methods adopted in these studies deserve close scrutiny. One might ask what the expected 5-year OS would be if one lumped small groups of patients with liver metastases and extrahepatic metastases at different sites, some with predictable good outcome such as lung and peritoneum, and others with predictable poor outcome such as lymph nodes and examined for 5-year OS in the patients as a whole. One would expect survival rates somewhere between the reported results for the individual sites. Also, if the individual groups were small, failure to find statistical difference among sites within such a study would not be surprising due to the possibility of an error of the second kind. Some of the groups in these studies have been quite small; for instance, in one paper, the group of patients with "multiple extrahepatic sites" consisted of only 11 patients.[78] Furthermore, in regard to total number of metastases versus localization of metastases, the statistical methods used confound the site and number of metastases,[75] and the conclusion that there is a difference is based unfortunately upon the comparison of *p*-values of sets of curves.[75] We have recently commented on this problem in detail.[76] The reason to be cautious in accepting these conclusions is that their acceptance could lead to an overly aggressive approach to patients with colorectal cancer at multiple extrahepatic sites as well as within the liver. This is especially concerning in countries such as the USA in which treatment of these patients is not regionalized.

Summary and Conclusions

This analysis supports the following conclusions. FDG-PET scanning is currently the most sensitive way of detecting extrahepatic metastases in patients with colorectal cancer, who have potentially resectable liver lesions. Its routine use is advisable. Restricting its use to patients with higher risk scores will increase the probability of a positive scan. This would reduce the overall cost of using FDG-PET at the expense of missing extrahepatic disease in a few patients. The role of staging laparoscopy remains undefined especially in patients who have had FDG-PET scans. Its use should probably be restricted to patients with high clinical risk scores.

Patients who have recurrence at the primary colorectal site as well as resectable liver metastases appear to benefit from resection of both provided that R0 resections can be obtained. When they are diagnosed synchronously, an attempt should be first made to resect the recurrence at

the primary site because in more than 50% of patients, an R0 resection will not be obtained. At present, there seems to be little benefit in surgical treatment of the liver component unless an R0 resection is accomplished at the primary site. Frozen section evidence of a complete resection of the primary site recurrence is sufficient to proceed with treatment of the hepatic lesions under the same anesthetic in a stable patient.

Microscopic or macroscopic hepatic pedicle lymph-node involvement is associated with poor outcomes in patients with resectable liver lesions. The 5-year OS is probably at a 10% level at best. Whether such patients should be offered surgical therapy is a difficult question. To answer it would require definition of the acceptable lower limit of 5-year OS for a complex and costly surgical treatment. Can the treatment of 10 or more patients to obtain one long-term survivor be justified? Certainly, the cost effectiveness of such a strategy must be very poor. While the question cannot be easily answered, it is important that surgeons provide patients in this situation with very realistic expectations of outcome. It is likely that many would opt for less invasive approaches after being completely informed. It is to be hoped that combination therapy using newer drugs and surgery will lead to better results, but that remains to be determined. Also, because newer drugs, especially monoclonal antibodies to receptors controlling angiogenesis, are resulting in dramatic improvement in results in stage-4 colorectal cancer, it will be necessary to prove that surgery is contributing to the results when disease is located in the liver and extrahepatic sites.

The situation regarding patients with peritoneal and liver metastases bears a strong resemblance to that of primary site recurrence and liver metastases. Very acceptable survival can be expected if the peritoneal disease can be eradicated or almost eradicated. Therefore, it seems reasonable to resect the liver disease once that has been accomplished but not to do so when macroscopic peritoneal implants remain. As in the case of primary site disease, the effect of treatment of the peritoneal disease in terms of completeness of resection is less predicable than that for the liver resection. Consequently, the peritoneal surgery should come first followed by the liver surgery. As with primary site recurrence, this may be done during the same laparotomy.

Information regarding treatment of lung and liver metastases is the most complete of any of these areas. Good results may be expected if all the disease can be cleared. Unlike primary site recurrence and peritoneal disease, when liver and lung metastases are present simultaneously, it is advisable to perform the liver surgery first because laparotomy may disclose unknown intraperitoneal disease. Again, both procedures may be done under the same anesthetic depending on the magnitude of the procedures required and the health and stability of the patient.

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Thyroid Artery Erosion by Esophageal Cancer: Management with Interventional Radiology

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Abstract Management of upper gastrointestinal bleeding because of erosion of vessels by esophageal cancer may be challenging. We present herein the angiographic images of a 49-year-old patient who was admitted with massive bleeding from a tumor-eroded inferior thyroid artery. Attempts to control the bleeding by means of flexible endoscopy and insertion of a Sengstaken–Blakemore tube had failed. The diagnosis was impressively demonstrated by multislice computed tomography with intravenous contrast in the arterial phase and multiplanar reconstructions (computed tomography angiography) and by digital subtraction angiography. The bleeding was successfully treated with superselective catheterization and coiling of the eroded vessel.

Keywords Sengstaken–Blakemore tube · Esophageal cancer · Tumor bleeding · Inferior thyroid artery · Embolization · Coiling · Interventional radiology

Introduction

Management of upper gastrointestinal (GI) bleeding because of erosion of vessels by esophageal cancer may be challenging. We present herein the angiographic images of an esophageal squamous cell cancer in the upper esophagus, which eroded the inferior thyroid artery and caused massive upper GI bleeding. The diagnosis was impressively demonstrated with computed tomography (CT) angiography (see Fig. 1a) and digital subtraction angiography (DSA; see Fig. 1b) and was successfully managed with superselective embolization (see Fig. 1b, insert).

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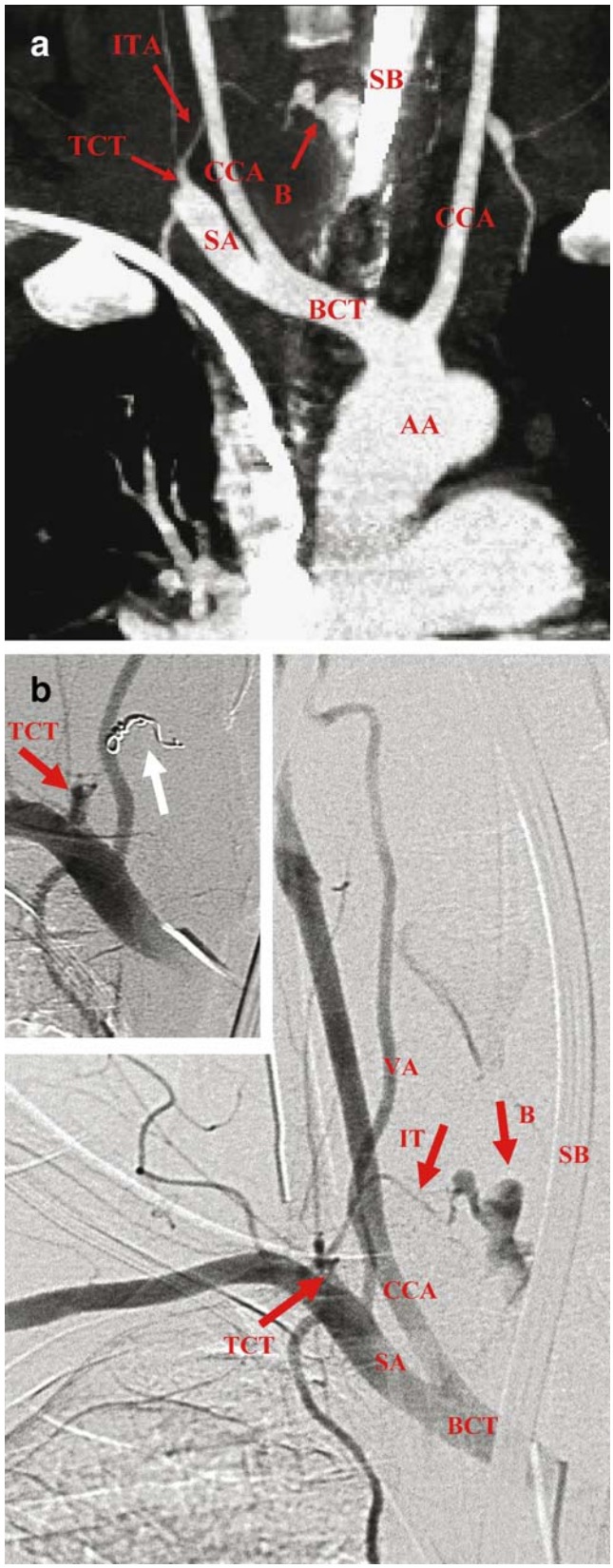
Case Report

A 49-year-old patient was admitted to the Dept. of Surgery, Technical University of Munich with massive bleeding from the upper GI tract and suspicion of esophageal cancer as origin of the bleeding. The patient was in a bad general condition, suffering from severe hemorrhagic shock (systolic blood pressure 90 mmHg, pulse 120 bpm, and hemoglobin 6.0 mg/dl after transfusion of six erythrocyte concentrates). For the interhospital transfer by helicopter the patient had received analgosedation and endotracheal intubation with mechanical ventilation. A Sengstaken–Blakemore tube had been inserted with the aim to control the bleeding.

At our institution, repeated flexible endoscopy confirmed a lesion in the supracarinal esophagus, highly suspicious for advanced esophageal cancer, which was the origin of active arterial bleeding. It was neither possible to stop the bleeding with endoscopic interventional techniques, nor was it possible to determine the exact



localization. A multislice computed tomography (MSCT) of neck, chest, and abdomen with intravenous (i.v.) contrast in arterial and portal venous phase with multiplanar reconstructions and CT angiography was performed (Sensation Cardiac 64, Siemens Medical Solutions, Erlangen, Germany). This investigation revealed an advanced esophageal cancer in the upper esophagus with active bleeding from the right inferior thyroid artery (see Fig. 1a).

Digital subtraction angiography was performed subsequently for further evaluation and interventional treatment. Digital subtraction angiography confirmed active bleeding from the inferior thyroid artery (see Fig. 1b). The contrast medium entered the esophageal lumen along the Sengstaken–Blakemore tube, being fully inflated and in proper position. A 2.7-F microcatheter (Progreat, Terumo Corporation, Tokyo, Japan) was directed into the bleeding vessel. Immediate successful embolization was achieved by using four microcoils (Hilal coils 2/20 and 4/20, William Cook Europe, Bjaeverskov, Denmark) with complete stagnation of the bleeding (see Fig. 1b, insert).

After this procedure the patient received further treatment on the surgical ICU for stabilization of vital parameters. In total the patient had required transfusion of 22 erythrocyte concentrates and 18 fresh frozen plasmas. The patient experienced a complicated course, with prolonged respiratory insufficiency because of aspiration, requiring prolonged mechanical ventilation for several days. Pleural effusions were treated with intermittent insertion of chest tubes. After 6 days the patient could be discharged from the ICU.

Subsequently the patient underwent a standard work-up for esophageal cancer staging, revealing a locally advanced squamous cell carcinoma of the proximal esophagus with multiple liver metastases. The interdisciplinary tumor conference decided on systemic chemotherapy as palliative treatment.

Discussion

Upper GI bleeding is a rare but well-known complication of esophageal cancer.[1] In a historical analysis, Barrie and Goodner have calculated a frequency of upper GI bleeding

Figure 1 **a** CT angiography with i.v. contrast suggestive for active bleeding from the inferior thyroid artery because of erosion by supracarinal esophageal squamous cell cancer. **b** DSA confirming the diagnosis of active bleeding from the inferior thyroid artery. Treatment of the bleeding by superselective catheterization and coiling without further evidence of bleeding (see white arrow on insert). VA = Vertebral artery, CCA = common carotid artery, BCT = brachiocephalic trunk, SA = subclavian artery, SB = Sengstaken–Blakemore tube, AA = aortic arch, TCT = thyrocervical trunk, ITA = inferior thyroid artery, B = bleeding.

of 5.1% in a large series of esophageal cancer patients (n= 1,859 cases treated at the Memorial Sloan–Kettering Cancer Center, New York, between 1926 and 1965). At that time hematemesis was considered "one of the early warning signs of esophageal cancer," whereas nowadays—like in our case—it is regarded as a sign of advanced disease, associated with a poor prognosis.

Gastrointestinal bleeding occurs when vessels are eroded by the invading tumor. Tumor invasion may affect minor vessels, or rarely major vessels, like the aorta[2] or the inferior thyroid artery, as in the case presented.

But bleeding because of esophageal cancer does not necessarily result from erosion of one definite vessel. Diffuse (occult) bleeding (because of incipient angiogenesis) from the well-neovascularized tumor tissue is a much more frequent condition and a potential cause of chronic tumor anemia. Bleeding of esophageal cancers is nowadays sometimes seen in association with endoscopically placed stents, which are frequently used for palliation.[3] It has been suggested that bleeding as a complication in association with stent placement is more frequent in tumors after previous antineoplastic therapies (chemotherapy or irradiation), but the literature regarding this is controversial (e.g., see Raijman et al.[4]).

Gastrointestinal bleeding from the inferior thyroid artery does not necessarily, as presented herein, have to be because of esophageal cancer. Other causes, like true and false aneurysms and trauma, have been reported in the literature (e.g., see Habib[5]). Interventional radiology with superselective catheterization and application of coils (like presented herein), glue, or embolic particles is the treatment of choice for tumor-associated and nontumor-associated problems with these supraaortic arteries. The use of these tools is nowadays considered standard when attempts to stop the bleeding by means of endoscopy have failed or are not suitable as definitive treatment.

The Sengstaken–Blakemore tube is used as a tool for management of bleeding esophageal varices (e.g., see Hermann and Traul[6]). The principle is compression of bleeding from the varices by balloon tamponade. Although the pressure in the portal system may be exceedingly high under these circumstances with portal hypertension, it is not very likely that a Sengstaken–Blakemore tube will sufficiently control massive arterial bleeding (e.g., from an eroded thyroid artery). This can be derived from our case in which active bleeding could be demonstrated with both CT and DSA, although the Sengstaken–Blakemore tube was in proper position and fully inflated.

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