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Surgical Education to Improve the Quality of Patient Care: the Role of Practice-Based Learning and Improvement

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Abstract Health care is going through immense change, and concerns regarding the quality of patient care and patient safety continue to be expressed in many national forums. A variety of stakeholders are demanding greater accountability from the health care profession. Education is key to supporting surgeons' efforts to provide high-quality patient care during these challenging times. Educational programs for surgeons should be founded on principles of continuous professional development (CPD) and practice-based learning and improvement (PBLI). CPD focuses on the specific needs of individual surgeons and involves lifelong learning throughout a surgeon's career. It needs to form the basis of PBLI efforts. PBLI involves a cycle of four steps—identifying areas for improvement, engaging in learning, applying new knowledge and skills to practice, and checking for improvement. Ongoing involvement in PBLI activities to address specific learning needs should positively impact a surgeon's practice and improve outcomes of surgical care.

Keywords Surgical patient safety · Quality of surgical care · Practice-based learning and improvement in surgery · Continuous professional development of surgeons · Continuing surgical education

Introduction

Health care is going through a period of momentous change. Reports of the Institute of Medicine have drawn significant national attention to issues relating to the quality of health care and patient safety.[1–3] A variety of stakeholders, including payors, large consumer groups, and the public, are demanding greater accountability from the health care profession and are seeking specific data relating to the patient care outcomes of individual surgeons. Furthermore, ongoing development of new procedures and technologies has raised concerns about the safe introduction of these procedures and technologies into surgical practice. Surgeons need to provide the best care to patients in the midst of these challenges. Education can be very helpful in this regard. The important role of education in changing physicians' practices and improving the quality of patient care has been the subject of much recent attention. The Accreditation Council for Continuing Medical Education has changed its standards for accreditation of providers of continuing medical education to include evaluation of the impact of educational interventions on physicians' practices and health care outcomes.[4]

Advances in the science of continuing education have resulted in recognition of the new paradigm of continuous professional development (CPD), which needs to replace the traditional model of continuing medical education (CME).[5] Traditional CME has generally been episodic and has focused on the needs of groups of learners. The principal focus of the educational programs has been clinical, and the activities have usually been teacher centered and teacher driven. Lecture formats have commonly been used to address learning objectives, and educational programs have mostly been conducted in formal settings. In contrast, CPD focuses on lifelong learning needs of individual physicians. It is learner centered, and individual learning needs drive participation in educational programs. Alignment of the learning needs

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of individual physicians with educational programs is important in changing practices and improving outcomes of patient care. The learning needs of individuals are defined through ongoing and systematic analyses of their practices. Educational programs should include formative assessments that are coupled with specific and timely feedback to improve performance. CPD is comprehensive and encompasses professional activities beyond direct clinical care. It includes focus on practice management, health care systems, communication skills, professionalism, teamwork, and leadership. A variety of learning formats and media are used to achieve optimum outcomes. CPD may be conducted in various venues that extend beyond the traditional conference settings. Ready access to educational programs through the Internet is important in bringing educational resources close to practice locations, which should facilitate the use of the resources to positively impact patient care. The goal of CPD should be to help physicians achieve requisite levels of competence and performance using supportive and nonpunitive measures.

Both the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties have defined the same six core competencies for all residents and practicing physicians, one of which is practice-based learning and improvement (PBLI).[6,7] Residents need to acquire skills in PBLI, which should bear them in good stead after residency training when PBLI becomes the principal driver of continuing performance improvement. CPD needs to be the basis of PBLI efforts. Most surgeons have not engaged in structured PBLI activities and need support to participate in such efforts.

PBLI involves a cycle of four steps—identifying areas for improvement, engaging in learning, applying the new knowledge and skills to practice, and checking for improvement.[5,8]

Practice-Based Learning and Improvement in Surgery

Step One

A surgeon should identify areas for improvement through ongoing and systematic gap analyses. Such analyses involve assessing the outcomes of one's practice and comparing these with national, regional, and local benchmarks, and with the best available evidence. Collection of data relating to outcomes is important in conducting gap analyses because self-assessments alone may not be sufficient. Evidence from the literature suggests that physicians are not good at assessing themselves.[9] Several research studies have demonstrated little, no, or inverse relationships between self-assessments and external measures of physicians' competence. Poor correlations between these measures have been found across the specialties, as well as across different levels of training and experience. Furthermore, the worst correlations have been found among physicians who are least skilled or most confident. These findings are disconcerting because of the potential for negative impact on patient care. Thus, surgeons need to be provided user-friendly tools to systematically assess their practice outcomes.

A number of programs of the American College of Surgeons (ACS) are available to surgeons to assess outcomes of their care. These include the National Surgical Quality Improvement Program (NSQIP), the National Trauma Databank, the Bariatric Surgery Database, and the Case Log System. The ACS Case Log System has been especially designed to support PBLI efforts. The system involves voluntary self-reporting of operative case data. It is compliant with requirements of the Health Insurance Portability and Accountability Act. Surgeons are able to access their own data, which are collected by an intermediary, and the ACS database contains only de-identified aggregate information. Surgeons can enter information using a personal digital assistant or the Internet. In addition to the demographic information on individual patients, surgeons are able to record the comorbidities and whether the surgical procedure was elective or emergency in nature. Relevant information relating to outcomes, including morbidity and mortality data, are subsequently entered by the surgeon. Thirty-day morbidity and mortality statistics for specific operations can be generated by the system, and comparative data from the cohort of surgeons enrolled in the system are available to surgeons for comparison. NSQIP data for specific operations will soon be available for benchmarking. Although the NSQIP data are risk adjusted and are collected by third-party reviewers, this information along with the aggregate data from surgeons enrolled in the ACS Case Log System should be useful for comparison. Such benchmarking is vital in conducting gap analysis and defining individual learning needs. The same process for entering data and benchmarking performance may be used by surgeons to evaluate the impact of participation in educational programs.

The ACS Case Log System was launched in October 2005 and, currently, over 1,000 users are enrolled in the program. More than 140,000 cases have been entered in the system, and over 500 cases have been entered by 20 or more users. The ACS has recently completed negotiations with the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) to merge the ACS Case Log database with the SAGES Outcomes Initiative to create a National Surgical Outcomes Database, which should be helpful in pooling de-identified data from the two databases to support the educational efforts of surgeons on a large scale.

Use of the best evidence from the surgical literature is important in conducting gap analyses and supporting surgeons' decision making. Evidence from the literature needs to be placed within the context of the surgeon's experience and patients' preferences to provide optimum patient-centered care. Evidence is also helpful to surgeons in assessing the efficiency and safety of a new surgical procedure or technology. This evidence needs to be considered by the surgeon along with the needs of the patient population served and the local support available while making a decision whether to adopt the new procedure or technology into surgical practice.[10] The ACS has partnered with the Canadian Association of General Surgeons to jointly offer an Internet-based program, "Evidence Based Reviews in Surgery," to enhance knowledge and skills in evidence-based surgery. This program provides learners access to especially paired clinical and methodologic articles from the current surgical literature. A list of questions relating to the articles prepares learners for the subsequent listserv discussion with experts in the clinical arena and research methodology. This program has been well received by both practicing surgeons and surgical residents.

Step Two

The second step in the PBLI cycle involves engaging in learning. Motivation is key to encouraging surgeons to pursue educational programs. Although educational theory suggests that adults are inherently motivated to learn, a variety of factors may discourage participation in further education. The additional time and effort needed are obvious deterrents, especially if the surgeon needs to take substantial time away from his or her busy practice to participate in the educational program. Motivation of learners may be enhanced by a variety of intrinsic and extrinsic drivers. The primary intrinsic drive comes from the desire to provide the best care to patients. Thus, analyzing the outcomes of one's practice and benchmarking these results as outlined in "Step One" of the PBLI cycle is important. Extrinsic drivers include the need to remain competitive in a challenging health care environment, reimbursements, and external regulations. Both intrinsic and extrinsic drivers are important in motivating surgeons to participate in educational programs.

Once a surgeon has decided to pursue further education, an appropriate educational program needs to be selected. Research has demonstrated that traditional, teacher-centered continuing educational programs that are delivered in didactic formats usually result in little or no impact on a physician's performance. Interactive and sequenced programs are more likely to positively impact physicians' practices and patient care outcomes.[11] Furthermore, educational programs that provide enabling materials, such as patient education resources for use after the program, are helpful in changing physicians' practices. In spite of the concerns regarding the limited efficacy of didactic continuing educational programs in changing physicians' practices and improving patient care outcomes, they do have a role. Didactic programs may help in sharing information and updating learners about the latest advances in their fields of interest. Such programs can also assure learners that their practices are within acceptable guidelines and can stimulate the learners' interest in the topic. In addition, learners may benefit from the opportunity to meet experts. Didactic programs are useful in preparing physicians for subsequent experiential programs that are likely to change their practices and improve patient care outcomes.

Distance education delivered through the Internet is useful in bringing educational programs close to physicians' practices, which should encourage participation. A variety of educational programs are currently available on the Internet, but their quality varies immensely. Factors that encourage participation in on-line continuing education include the quality of content, case-based and interactive formats, ease of accessibility and use, and convenience in obtaining continuing education credits.[12]

Educational interventions that are designed to achieve competence and develop expertise in performing new surgical procedures and using new technologies should be founded on special principles of skills acquisition.[13–15] Acquisition of new surgical skills is influenced by the innate ability of the learner, the complexity of the skill, and the quality of the educational intervention. The development of expertise requires deliberate practice and specific and timely feedback.[16] Continuous improvement in performance results from establishment and achievement of goals that exceed current levels of performance. Research has demonstrated that distributed training over a period of time is more effective in retention of surgical skills, as compared to massed training conducted through a single intervention.[17] Simulations and simulators are key to acquiring new surgical skills, maintaining existing skills, and achieving expertise. They provide opportunities for training in structured, individually tailored, and safe environments where learners are able to practice skills repeatedly and receive constructive feedback.

Surgical advances and changes in practice patterns of surgeons necessitate acquisition of new knowledge and skills. Acquisition and maintenance of surgical skills after residency training present a host of unique challenges and opportunities. Surgeons continue to face difficulties in locating suitable educational opportunities to address their learning needs and obstacles resulting from the need to take time away from busy practices discourage participation.[14] Unlike the model of residency education, post-residency

education is often not well structured. Traditional skills courses available to surgeons generally involve short interventions that are insufficient in helping surgeons acquire new skills. In addition, valid and reliable assessment of surgeons' knowledge and skills are conducted infrequently, and preceptoring and mentoring necessary for the safe transfer of the new knowledge and skills to patient care are often not available. The surgeon needs to seek and participate in educational programs that have addressed these traditional shortcomings. A disease-based approach rather than a technology-driven approach needs to be used to acquire new skills. The educational program should address all aspects of surgical care and not just the technical competence.[13] Furthermore, training and credentialing of the entire surgical team are necessary to promote optimum care.

The ACS is pursuing a number of major initiatives to address the problems outlined above. Ongoing horizon scanning is used to evaluate evidence regarding the efficacy and safety of a new surgical procedure or technology. If introduction of the new procedure or technology into surgical practice is supported by sufficient evidence, a postgraduate course is designed, with the help of experts, to provide surgeons the opportunity to acquire the requisite knowledge and skills. ACS offers a spectrum of postgraduate courses, many of which involve use of simulations. Mechanisms to offer preceptoring after the course are currently being explored.

The ACS has implemented a new program for verification and documentation of surgical knowledge and skills. This verification program includes five levels: verification of attendance, verification of satisfactory completion of course objectives, verification of knowledge and skills, verification of preceptorial experience, and demonstration of satisfactory patient outcomes.[13] This program was launched at the ACS Clinical Congress in October 2006, and each postgraduate course was reviewed and assigned an appropriate verification level. Currently, there are only a few ACS courses that include valid and reliable assessments of knowledge and skills to fulfill requirements for Level III verification. Attempts are being made to introduce changes in all ACS courses to offer higher levels of verification. The verification program will permit ACS to provide appropriate documentation to individual surgeons after participation in postgraduate courses, which should be helpful in local decisions regarding credentialing and privileging.

Another new initiative of the ACS involves bringing contemporary surgical education close to surgeons' practices through the Accreditation Program for Education Institutes. The overarching aim of this program is to improve the quality of surgical care and promote patient safety through simulation. The program is especially designed to provide regional support for surgical education and help in the safe transfer of the newly acquired knowledge and skills to practice. This program should facilitate implementation of state-of-the-art educational programs, support sharing of scarce educational resources, and promote collaborative research to advance the field of simulation-based surgical education. This program was launched in October 2005 and involves the use of three Standards—the Learners, the Curricula, and Technologic Support and Resources—to accredit institutes at one of two levels, Level I (Comprehensive) and Level II (Basic).[18] After review, ten institutes were accredited at Level I in 2006 and another eight were accredited at Level I in June 2007. The consortium of ACS-accredited Education Institutes will continue to be expanded, as new applications for accreditation are received, and additional institutes are reviewed and accredited.

Step Three

The third step in the PBLI cycle involves applying the new knowledge and skills to practice. An important approach to facilitating application of new knowledge and skills to practice is to use reinforcing strategies and reminders after participation in the educational program. In addition, motivation and confidence in one's knowledge and skills are important in applying new skills in practice. Because of the difficulties associated with accurate self-assessment, valid and reliable assessment of knowledge and skills can yield valuable information relating to the surgeon's competence and help to increase the confidence of a surgeon.

Local support from preceptors and mentors is crucial in facilitating the safe transfer of the newly acquired surgical skills to practice. Such support may be provided by a senior partner in one's practice or by other experienced colleagues. There are a variety of models to offer effective preceptoring to surgeons. The preceptor may work with the learner at the learner's institution; the learner may work with the preceptor at the preceptor's institution; or structured teaching and learning experiences may be offered through mini-fellowships.[13] Each model has advantages and disadvantages. Evaluation of the specific needs of the learner and consideration of local factors are essential while selecting the best approach to meet the needs of individual surgeons. Telementoring and teleproctoring may be helpful in the transfer of new knowledge and skills to practice if in-person preceptoring and mentoring is difficult to arrange.[10]

Step Four

The final step in the PBLI cycle is checking for improvement once the new knowledge and skills have been applied to practice. This involves assessing the impact on learning,

performance, and patient care outcomes. The impact on learning may be evaluated through reassessment of the surgeon's knowledge and skills using valid and reliable evaluation tools. Assessment of a surgeon's interpersonal and communication skills, teamwork, and leadership may be conducted through 360-degree evaluations. Assessment of the surgeon's performance in simulated settings should yield useful information; however, assessment of performance in real settings is desirable. Systematic practice audits and ongoing assessment of surgical outcomes are useful in this regard. The process used to assess a surgeon's practice in "Step One" of the PBLI cycle should yield valuable data relating to outcomes in this step of the PBLI cycle as well. In addition, data from institutional quality assurance programs may be helpful in evaluating a surgeon's performance.

A system to document PBLI activities is needed to support surgeons' educational efforts aimed at improving the quality of surgical care. The ACS has recently launched a system to help surgeons document their PBLI efforts. Data relating to verification of attendance in educational programs of ACS are now seamlessly transferred from several programs to the individual surgeon's "My CME" page on the ACS Web Portal. The program will be expanded to include transfer of such data from all ACS programs, as well as from educational programs that are jointly sponsored by the ACS and other national organizations. Furthermore, opportunities to record verification levels achieved through participation in educational programs will be available to surgeons, along with the option to record personal notes regarding the PBLI efforts. Thus, an individualized portfolio may be created by a surgeon on his or her "My CME" page to support PBLI efforts and help in addressing external requirements, such as those relating to Maintenance of Certification, Maintenance of Licensure, credentialing, and privileging.

Closing Remarks

Education designed to support PBLI should change surgeons' performance and improve patient care outcomes. The educational programs need to be different than the traditional programs that have been offered over the years. Educational interventions should be tailored to the individual needs of surgeons based on ongoing and systematic assessment of outcomes and comparison of these data with external benchmarks. This requires a major change in the culture of surgery. Collaboration across various national, regional, and local organizations is necessary to support PBLI efforts of surgeons and positively impact surgical care on a large scale.

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Clinical Impact of Lymphadenectomy Extent in Resectable Esophageal Cancer

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Abstract Esophageal cancer (EC) frequently presents with advanced stages and is associated with high recurrence rates after esophagectomy. The value of an extended lymph node dissection (ELND) remains unclear in this setting. An EC data set was created from the Surveillance, Epidemiology, and End-Results 1973–2003 database. Relationships between the number of lymph nodes (LNs) examined and overall survival (OS) were analyzed. From a cohort of 40,129 EC patients, 5,620 individuals were selected. The median age was 65 (range: 11–102), and 75% were men. The median tumor size was 5.0 cm (0.1–30). On multivariate analysis, total LN count (or negative LN count, respectively) was an independent prognostic variable, aside from age, race, resection status, radiation, T category, N category (all at $p<0.0001$), and M category ($p=0.0003$). Higher total LN count (>30) and negative LN count (>15) categories were associated with best OS and lowest 90-day mortality ($p<0.0001$). The numeric LN effect on OS was independent from nodal status or histology. Greater total and negative LN counts are associated with longer EC survival. Although the mechanism remains uncertain, it does not appear to be limited to stage migration. ELND during potentially curative esophagectomy for EC can be supported by the data.

Keywords Lymphadenectomy · Resectable esophageal cancer · Lymph nodes · N staging · Survival

Background

Esophageal cancer (EC) continues to represent a significant therapeutic challenge, with an increasing incidence and death rate, and a mere 16% overall survival (OS) rate.[1,2] Despite its potential to induce significant morbidity, esophagectomy can lead to better OS results than any other treatment modality alone, especially when performed in a high volume setting that is linked to a lower postoperative mortality[3] and superior long-term survival.[4] Many high-volume surgical centers preferably perform extended resections, such as en-bloc esophagectomies or two- or three-field dissections, which may contribute to better regional disease control because of removal of metastatic lymph nodes (LNs), and may be linked to better survival.[5–9] However, neither the minimum number of LNs to be removed during curative intent esophagectomy nor the optimum LN count that could be linked to the best survival results have been well established. Recommended minimum LN counts range from 12 for a greater than 90% staging sensitivity[10], over 16 for greatest survival benefit[11], to 18 for optimal staging accuracy.[12] Few clinical studies have comparatively addressed outcomes after various degrees of LN dissections (LND). A randomized controlled trial (RCT) examined upper mediastinal and cervical LND in patients with squamous cell cancer (SCC) of the mid-esophagus; mean LN counts were 82 compared to 43 in the comparison group, and the OS at 5 years was 66% compared to 48%.[13] A RCT comparing transthoracic with

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transhiatal esophagectomy (THE) yielded 31 versus 16 LNs and a 5-year OS of 39% versus 29%.[14] A case-control study of patients with T3N1 EC undergoing en-bloc esophagectomy compared to transhiatal resection resulted in total LN counts of 52 versus 29 and an OS of 32% compared to 9%.[15] Finally, a nonrandomized European study of two-field LND with THE versus THE alone reported 17 and 5 LNs, respectively, with a disease-free survival at 5 years of 41 and 10%.[16] Thus, it appears that in all studies that compare different operative approaches to EC resection that are associated to different LN counts, survival results are superior for patients in whom more extensive LNDs have been performed, as evidenced through higher LN counts.

We have previously investigated the impact of LN counts on survival after operative therapy for various gastrointestinal cancers, including gastric cancer of early and advanced stages,[17,18] extrahepatic cholangiocarcinomas,[19] and pancreatic cancer.[20] In all instances, population data revealed a strong association between increasing total or negative LN counts and better survival. The rationale for this study was to determine possible associations of LN counts and survival after esophagectomy for EC. To address this question, we resorted to US population information from the Surveillance, Epidemiology, and End-Results (SEER) data set published by the National Cancer Institute.

Patients and Methods

An EC data set was created through structured queries to the public version SEER 1973–2003 database, which includes combined records from multiple cancer registries representative of the US population. EC stage information was created according to the sixth edition American Joint Committee on Cancer tumor–node–metastasis (TNM) criteria,[21] with the exception that metastatic involvement of LNs was classified as N1 disease only, as detailed information on extraregional nodal location was lacking. From 40,129 individuals with EC, 5,620 were extracted based on sufficient information regarding disease extent, operative treatment administered, and known survival outcomes. Those patients who received adjuvant radiation treatment were kept within the analysis; information on chemotherapy is not provided in the SEER data. Patients with incomplete resection information, such as "surgery, not otherwise specified," were kept in the analysis, as long as sufficient information was available to document that resection of the primary tumor had taken place, such as through details in the pathologic findings. Several variables were recategorized or computed anew, such as the negative LN count (from total and positive LNs) and the LN ratio (positive to total LNs removed).

OS was the primary outcome component of interest. OS information in the SEER database reflects time from diagnosis to last follow-up (death or last contact) in monthly increments; censoring criteria were generated accordingly. Actuarial survival was analyzed via the Kaplan–Meier method, for the entire cohort, and for node-negative or node-positive groups separately. To eliminate early postoperative mortality and to determine the impact of LN counts on long-term survival, a conditional OS analysis was performed, only including patients who were alive at least 6 months or beyond. Univariate group comparisons utilized the log-rank test. Cox regression was used for multivariate analysis, with a backward elimination model for all covariates; we selected a threshold for keeping a variable in this elimination model at $p=0.05$. All continuous variables were entered into this analysis as continuous data. Variables included into this multivariate calculation were grade (high versus low), T stage category (T1 versus T2 versus T3+T4), total number of LNs examined (and/or number of negative LNs), N stage category (N0 versus N1), and/or number of positive LNs, race, age, gender, tumor size, year of diagnosis, presence of metastases, and tumor location (overlapping, upper, middle, or lower third). A projected 5-year survival analysis was performed based on a linear projection model as described earlier.[17,18] Simple group data comparisons based on parametric statistics were done via *t*-test; for categorical parameters, chi-square testing was used. Significance of differences was assumed at p values of less than 0.05. Calculations were performed using the SAS 8.2 statistical software package (SAS, Cary, NC) or StatView 5.0.1 software for Macintosh computers (SAS Institute).

Results

Patient Demographics

From a cohort of 40,129 patients with an EC diagnosis within SEER, disease extent information was available in 15,417, and sufficient treatment and survival information was available for 12,102 individuals to calculate actuarial OS as postoperative outcome. Completeness of LN staging information could be identified for 5,620 individuals, which were included in the first multivariate analysis. Of these, 3,568 patients had undergone a resection. After exclusion of unspecified categories, 2,597 cases remained, which served as cohort for subsequent analyses relevant to LN count questions. The median age within the cohort was 65 years (range: 11–102), and 75% of patients were men. Ethnic information identified white patients in 82%, black patients in 12%, and other racial groups in 6% of cases. The location of the primary tumor could be classified as upper esophagus for 4%, middle esophagus for 18%, lower

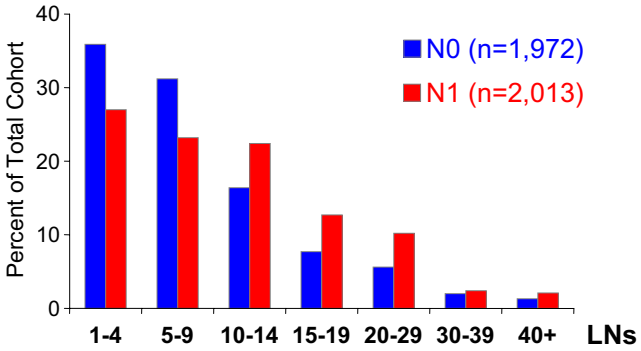

Figure 1 Frequency of categorized number of total lymph nodes examined by N stage category.

esophagus for 71%, and overlapping or unspecified for 7% of patients. The median tumor size was 5.0 cm (range: 0.1–30). Adenocarcinomas encompassed 57% of cases, and squamous cell carcinomas 43%. Of the resected patients with at least one LN examined, the median total LN count was 8 (range: 1–77), the median positive LN count 1 (0–46), and the negative LN count 6 (0–72). Differences were observed in the frequency of categorized number of total LNs examined when separated by N stage category (Fig. 1); patients classified as N0 tended to have fewer LNs identified more frequently than those classified as N1. The median follow-up was 15 months (range: 0–188), with a median follow-up for survivors of 25 months.

Multivariate Survival Analysis

On multivariate analysis, the total LN count was an independent prognostic variable, aside from age, race, resection status, radiation, T category, N category (all at $p<0.0001$), and M category ($p=0.0003$). Parameter estimates and risk ratios for all patients selected on the basis of this Cox proportional hazards model are listed in Table 1. Total LN counts were exchangeable for negative LN counts in this model, at a similar significance level with $p<0.0001$. A second multivariate model based on patients with complete pathologic staging and LN count information yielded the same prognostic variables, in addition to positive LN counts, tumor size, and race (Table 2). Again, negative LN counts were exchangeable with total LN counts. With the second model, grade and tumor location were entered into the model, but the presence of each of these factors forced the resection factor to become nonsignificant above the 0.05 level. It was difficult to interpret this conditional relationship, and so, we chose to report the model in which resection was significant.

Table 1 Parameter Estimates and Risk Ratios for all Patients Selected on the Basis of the Cox Proportional Hazards Model ($n=5,620$)

Factor	*N* (percent)	Median (range)	Hazard ratio	Lower 95% CI	Upper 95% CI	*p* value
Total LN number (*n*, continuous)	N/A	3 (0 to 80)	0.982	0.977	0.988	<0.0001
Age (years, continuous)	N/A	65 (11 to 96)	1.016	1.013	1.019	<0.0001
Resection YN		N/A				<0.0001
No resection	2,133 (38)		Baseline	Baseline	Baseline	
Resection	3,487 (62)		0.785	0.752	0.820	
Radiation YN		N/A				<0.0001
No radiation	2,689 (48)		Baseline	Baseline	Baseline	
Radiation	2,931 (52)		0.854	0.825	0.884	
T Stage		N/A				<0.0001
T1	1,199 (21)		Baseline	Baseline	Baseline	
T2	963 (17)		1.058	0.997	1.122	
T3–T4	3,492 (62)		1.504	1.434	1.577	
N stage		N/A				<0.0001
N0	1,647 (29)		Baseline	Baseline	Baseline	
N1	1,643 (29)		1.383	1.307	1.463	
N unstaged	2,330 (42)		1.032	0.968	1.100	
Metastases		N/A				0.0003
M0	5,246 (93)		Baseline	Baseline	Baseline	
M1	374 (7)		1.134	1.070	1.201	
Race		N/A				<0.0001
White	4,609 (82)		Baseline	Baseline	Baseline	
Black	661 (12)		1.179	1.099	1.264	
Other	350 (6)		0.957	0.879	1.042	

N/A Not applicable

Table 2 Parameter Estimates and Risk Ratios for all Staged Patients Selected on the Basis of the Cox Proportional Hazards Model (n=2,597)

Factor	*N* (percent)	Median (range)	Hazard ratio	Lower 95% CI	Upper 95% CI	*p* value
Total LN count (*n*, continuous)	N/A	8 (1 to 74)	0.966	0.959	0.973	<0.0001
Positive LN count (*n*, continuous)	N/A	1 (0 to 28)	1.073	1.055	1.091	<0.0001
Tumor size (mm, continuous)	N/A	40 (1 to 300)	1.004	1.002	1.006	<0.0001
Age (years, continuous)	N/A	64 (11 to 90)	1.018	1.013	1.023	<0.0001
Resection Y/N		N/A				0.0341
No resection	210 (8)		Baseline	Baseline	Baseline	
Resection	2,387 (92)		0.917	0.847	0.992	
Radiation Y/N		N/A				<0.0001
No radiation	1,615 (62)		Baseline	Baseline	Baseline	
Radiation	982 (38)		0.850	0.806	0.897	
T stage		N/A				<0.0001
T1	517 (20)		Baseline	Baseline	Baseline	
T2	519 (20)		1.130	1.035	1.234	
T3–T4	1,561 (60)		1.441	1.333	1.557	
N stage		N/A				<0.0001
N0	1,254 (48)		Baseline	Baseline	Baseline	
N1	1,343 (52)		1.279	1.205	1.358	
Metastases		N/A				0.0117
M0	2,468 (95)		Baseline	Baseline	Baseline	
M1	129 (5)		1.144	1.034	1.265	
Race		N/A				0.0293
White	2,227 (86)		Baseline	Baseline	Baseline	
Black	208 (8)		1.171	1.034	1.326	
Other	162 (6)		0.921	0.803	1.056	

N/A Not applicable

Univariate Survival Analysis of Lymph Node Count Impact

Higher total LN counts (up to >30) and negative LN counts (up to >15) categories were associated with the best OS ($p<0.0001$) and the lowest 30- and 90-day mortality ($p<0.0001$). The numeric total LN count effect on OS is depicted in Fig. 2. It was observed for both N0 and N1 stage subgroups, but appeared to be linked to greater OS differences for N0 EC in comparison to N1 EC (Fig. 3). A similar effect of better OS outcomes with higher total LN counts was observed for both squamous cell and adenocarcinoma EC histologies (data not shown). Negative LN counts demonstrated a strong association with OS as well. The actuarial OS for patients with EC dependent on various negative LN count categories is displayed in Fig. 4. This negative LN count impact persisted when the cohort was split by nodal status and appeared to present in a similar magnitude of OS differences (Fig. 5). Median survival and long-term OS (in percent) are listed in Table 3.

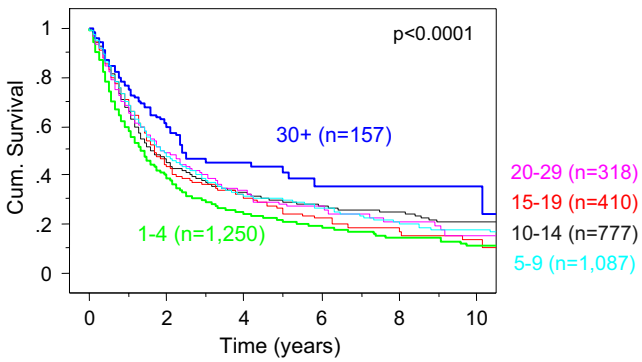

Figure 2 Actuarial overall survival curve for patients with esophageal cancer by various total lymph node count categories.

A cutpoint analysis intended to detect the total LN number related to the greatest OS differences. As tabulated in the same table, the highest chi-square statistic representing greatest group differences was observed at low LN counts: one for the overall cohort and five for N0 and N1 resected patients. However, significant differences were still encountered for cutpoints above 30 total LNs, always in favor of the group with higher total LN counts. The highest significant cutpoints were at 45 for N0 and at 35 for N1 disease stages.

Early Postoperative Deaths Based on Lymph Node Numbers

To separate esophagectomy-related (early) mortality from long-term survival in the analysis of LN count associations, we analyzed early mortality associations and conditional long-term OS separately. Death within 30 days occurred to 3% of N0 and 5% of N1 patients ($p=0.0004$). Similarly,

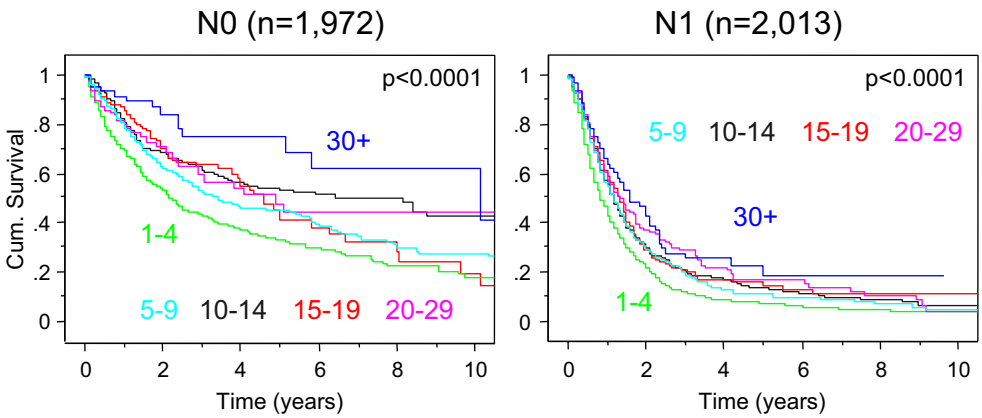

Figure 3 Actuarial overall survival curve for patients with esophageal cancer by various total lymph node count categories and separated by N category.

mortality at 30 days after resection was 5%, but 14% without resection ($p<0.0001$); the corresponding 90-day mortality was 13% versus 30% ($p<0.0001$). Significant relationships between mortality and LN counts existed for total LN counts, LN ratio, and negative LN counts, always with the lowest mortality rate for the higher LN count categories. Figure 6 depicts such mortality within 90 days by total LN count categories, LN ratio categories, and negative LN count categories. A long-term survival impact of LN counts was examined after excluding all deaths within 6 months after diagnosis. Figure 7 depicts actuarial conditional OS curves for patients with EC by various total LN count categories. Survival differences are less obvious, but still evident especially at LN counts of >30.

Projected Numeric Lymph Node Impact on Overall Survival

Plots of actuarial OS at 5 years and at 10 years were generated for various total LN count categories (Fig. 8). The highest OS results were invariably observed at the highest LN count categories for the overall patient cohort as well as for adenocarcinoma and squamous cell carcinoma histologies. Based on a resulting linear regression model, the projected numeric total LN impact on 5-year OS was calculated for the entire cohort and separately by histologic type (Table 4). The results show a relative increase in OS at 5 years for every ten LNs identified of between 4 and 5%.

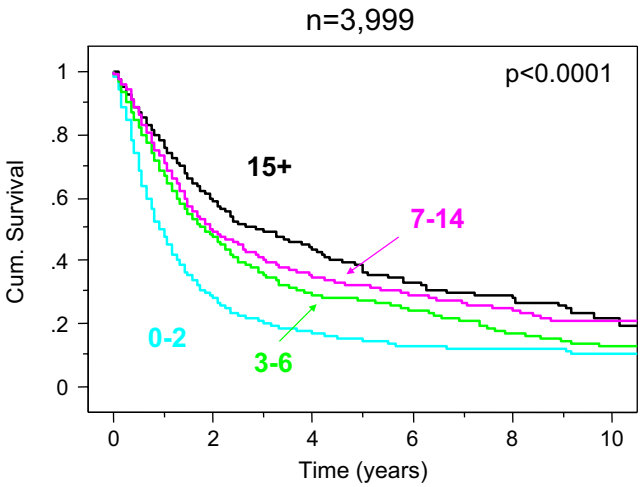

Figure 4 Actuarial overall survival curve for patients with esophageal cancer by various negative lymph node count categories.

Implications of Lymph Node Ratio

The ratio of metastatic to total LNs (LN ratio), a previously reported prognostic parameter for EC survival, showed a strong association with OS results. When divided into quintiles, the lowest LN ratio (0.01 to 0.19) associated with the best survival (median=1.75 years) and the highest LN ratio (0.8 and greater) with the worst OS (median=0.67 years; $p<0.0001$) in nodal positive patients. To examine the implications of total LN counts on LN ratio, we assessed median OS relationships with various LN ratio categories, again excluding 0 (i.e., N0 patients). Separation between OS outcomes of different LN ratio categories was greatly enhanced in settings of higher total LN counts, as displayed in Fig. 9.

Discussion

The results show a strong association between postoperative LN counts and survival after esophagectomy for EC. Invariably, higher total LN counts or negative LN counts are linked to better OS, which is observed in both N0 and N1 stage groups, as well as in both main histologic types of EC. These findings are perhaps even more profound, as they are derived from population data, with an anticipated mix between providing hospitals and surgeons regarding esophagectomy volume. Best survival after esophagectomy is usually obtained in high-volume settings, where more extensive resections including extended LNDs are the norm.[5–7] Our findings would therefore generally corrobo-

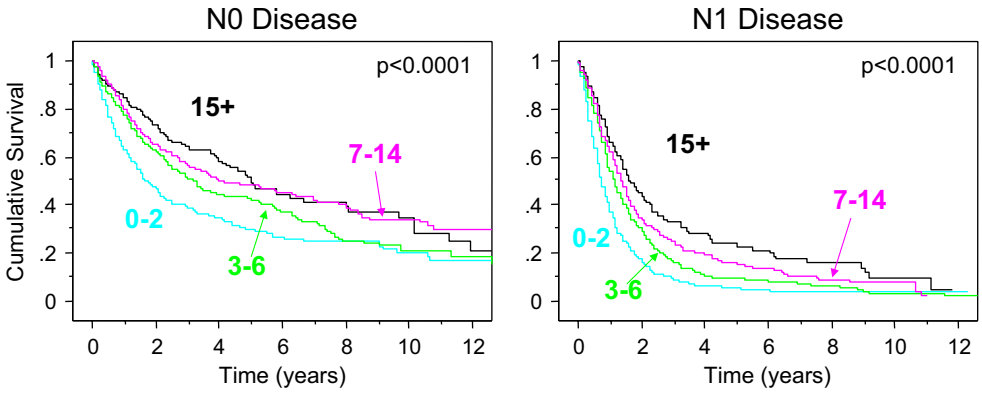

Figure 5 Actuarial overall survival curve for patients with esophageal cancer by various negative lymph node count categories and separated by N category.

rate those reports of others in which resection techniques linked to larger LN counts are associated with better OS results.[13–16] From available reports, it remains unclear which EC patients might benefit most from more extensive dissections with greater LN counts. Accordingly, among subsets that have been reported to benefit are patients with N0 SCC,[22] N0 adenocarcinoma,[23] T3N1 adenocarcinomas when less than nine LNs are involved,[15] early SCCs where distant LN spread is more common that in early adenocarcinoma,[24] or in those midthoracic lesions for which cervical and/or abdominal LND is included.[6,25–27] Although, in our results, the total LN count impact was more obvious in N0 than N1 disease, the observed benefits of greater LN counts are not restricted to any specific patient subsets and have thus to be explained as a more general phenomenon.

Whereas a therapeutic benefit of removing more LNs with potential metastatic disease is assumed to partake in this phenomenon, it cannot be proven from the available

Table 3 Overall Survival by Total LN Count, by Nodal Staging Category

LN Count	Number	Median OS (years)	3-year OS (%)	5-year OS (%)	Log-rank χ square statistic
All patients (n=12,102)					
0 nodes	8,113	0.66	14	9	*930.9*
1 node	370	1.08	24	18	907.2
2–4 nodes	777	1.58	34	25	701.1
5–9 nodes	1,184	1.75	36	28	368.1
10–14 nodes	774	1.67	37	29	184.6
15–19 nodes	408	1.67	36	24	113.8
20–29 nodes	318	1.83	40	28	55.0
30+ nodes	158	2.42	45	41	20.9
N0 patients, at least 1 LN examined (n=1,972)					
1 node	220	1.75	38	28	32.2
2–4 nodes	487	2.42	46	35	*49.5*
5–9 nodes	615	3.42	52	45	38.0
10–14 nodes	324	8.17	62	53	13.4
15–19 nodes	152	4.58	63	41	12.4
20–29 nodes	110	4.92	60	48	11.8
30+ nodes	64	10.17	75	75	5.4
N1 patients, at least 1 LN examined (n=2,013)					
1 node	150	0.67	6	4	34.0
2–4 nodes	290	0.91	14	9	*36.3*
5–9 nodes	569	1.17	18	10	21.9
10–14 nodes	450	1.17	20	13	16.5
15–19 nodes	256	1.33	21	15	13.5
20–29 nodes	206	1.33	29	17	7.0
30+ nodes	92	1.58	26	19	2.9

Cutpoint analysis for detecting the total lymph node number related to greatest overall survival differences
The log-rank χ square statistic corresponds to the maximum within the range for that group versus the minimum within the next group of total LN counts. For example, "5–9 LNs log-rank χ square statistic" compares the K–M curve between 0–9 LNs examined (or 1–9 LNs examined for N0 and N1) versus 10+LNs examined. The italicized value corresponds to the cutpoint with the largest χ^2 statistic, i.e., the greatest detectable survival differences within the entire cohort. The χ^2 statistic in the 30+ rows reflect 39 or fewer LNs versus 40 or more LNs. A χ^2 statistic of more than 4 is accompanied by a p value of less than 0.05.

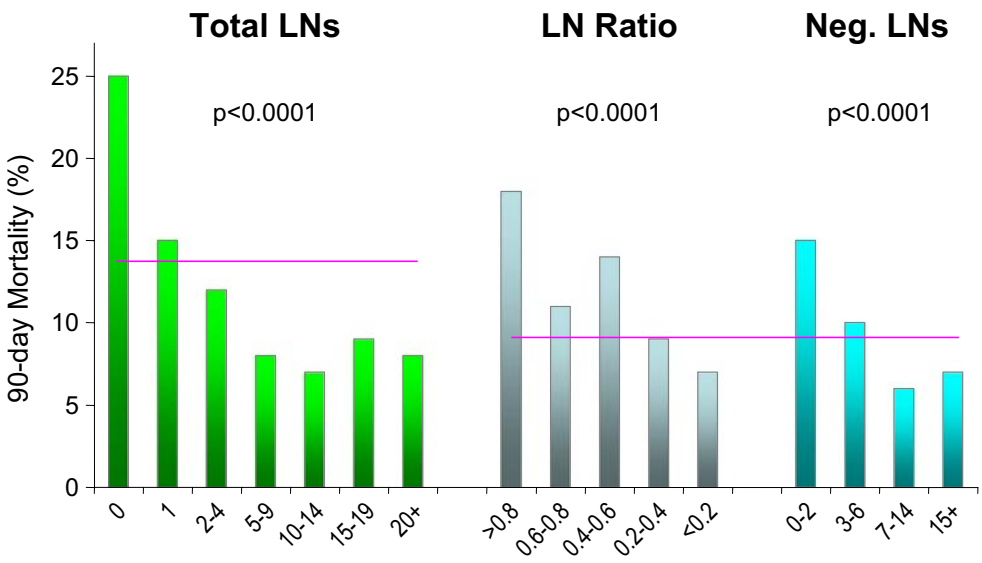

Figure 6 Mortality within 90 days by total LN count categories, LN ratio categories and negative LN count categories. The *horizontal bars* mark the average 90-day mortality for that patient cohort.

information. The numeric total LN effect in N1 patients, the benefit of negative LN counts in patients with more than 1 positive LN, and the conditional survival benefits of LN counts beyond 6 months, all usually within a range of 10 to 20% when comparing lowest and highest LN count groups, let us suspect some therapeutic effect because of better regional disease control. Multiple studies have described a high rate of immunohistochemically identified micrometastases to regional LNs, with generally negative prognostic implications, even when standard histopathologic examination would not reveal evidence for LN involvement.[28–30] Removing more of these LNs at risk may reasonably reduce avenues for subsequent oncologic progression.

There are, however, numerous caveats that need to be respected in the interpretation of our results. The large SEER population database has not been established to analyze specific surgical technical questions, and therefore, significant limitations in information accompany this analysis. Firstly, patients with sufficient information are highly selected from within the database, and coding errors or potential omissions cannot be ruled out. The selection process is necessitated in part by identifying patients who underwent surgical therapy, but also because of lack of complete data among surgically treated individuals. Naturally, this selection could introduce bias, if cases with complete data differ from others by treatment or other survival hazards; however, such potential bias cannot be controlled for in the context of numeric LN analyses. Furthermore, we lack data on LN location, the exact operative technique for local and regional dissections, any margin status, any chemotherapy given, or any response to preoperative chemoradiation. Other parameters that have been linked to post-esophagectomy survival are equally unknown, such as the institutional volume, surgeon volume, the patient's performance or nutritional status, and the quality of macroscopic and histopathologic examination, all of which could possibly influence the LN status entered into the database. Is the total LN count or the

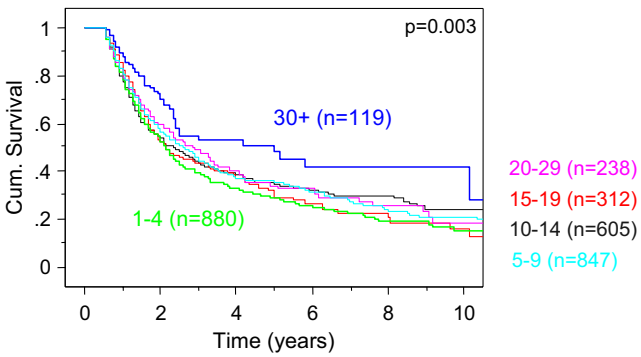

Figure 7 Actuarial conditional overall survival curves for patients with esophageal cancer by various total lymph node count categories. Included are only individuals alive at least 6 months from diagnosis.

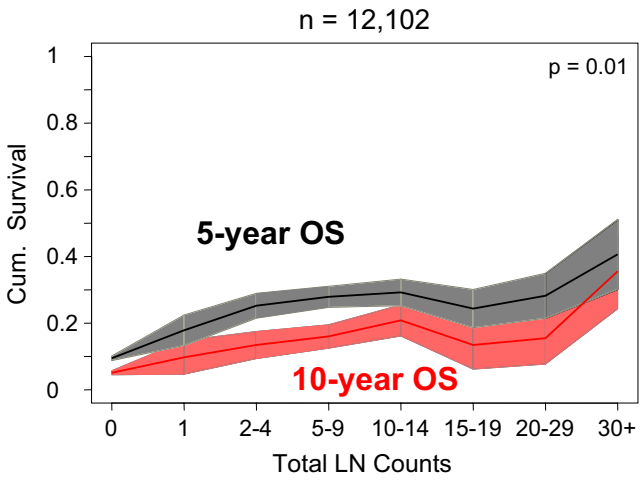

Figure 8 Plots of actuarial overall survival at 5 and 10 years by total lymph node count categories. The *shaded areas* represent the 95% confidence intervals.

Table 4 Projected Numeric Total Lymph Node Impact on 5-Year Overall Survival, by Histologic Type

Stage subgroup	Patients (*n*)	Baseline 5-year survival (based on 0 LNs examined for all groups; %)	For every ten extra LNs examined, survival improved by (%)	*p* value
All patients	12,102	18	5.0	0.0115
N0 subgroup, 1+ LNs examined	1,972	32	10.0	0.0075
N1 subgroup, 1+ LNs examined	2,013	8	3.0	0.006
Adenocarcinomas	5,695	21	3.2	0.1123
Squamous cell carcinomas	5,740	11	10.7	0.0007

The baseline 5-year survival in this linear projection model is based on the *y*-intercept and thus represents a hypothetical survival number for the groups shown. Accordingly, if a squamous cell carcinoma patient had only seven LNs examined, his expected 5-year overall survival would be 11%+7×1.07=18.5%. If an adenocarcinoma patient had 27 LNs dissected, his expected 5-year overall survival would be 21%+27×0.32=29.6%.

negative LN count not just a result of more extensive regional dissection, but perhaps a surrogate for a healthier patient, or a better patient selection reflective of a high-volume, higher quality healthcare setting where better survival can be expected without actual better oncologic control of the underlying cancer? The SEER data alone do not allow controlling for volume–outcome relationships. However, high esophagectomy volume institutions frequently subscribe to standardized, wider regional dissection extents, and much of the undisputable volume–survival relationship may in fact already result from a greater lymphadenectomy extent alone.[4] It is thus plausible that a large component of the LN count effects observed in the population data represents the spectrum from low-volume institutions in low LN count categories to high LN counts obtained in many high-volume settings. Obviously, LN numbers do not always equate to the true lymphadenectomy extent, but they certainly are the best surrogate available. Nevertheless, all these questions have to be considered carefully before possibly any practical implications of the results can be claimed.

Total and negative LN counts appear to be rather important for survival prediction of EC, and this information extends beyond predictive information from the TNM staging criteria. Limitations of the TNM staging system have been highlighted by others, but outside the number of positive LNs, LN counts have not been suggested as clinical staging criteria.[31,32] The LN ratio does obviously reflect total LN counts aside from positive LN number. The LN ratio has been reported as prognostic variable in EC,[5,32,33] including in one study based on the SEER data for EC between 1988 and 1997.[34] We did not intend to merely duplicate this earlier effort with our analysis, but had a specific practical interest to define an optimal LN number to be removed at the time of esophagectomy, which would preferably represent a valid numeric target even for N0 disease, which the LN ratio is not. A definable number of LNs known preoperatively as target, to be removed by the surgeon and to be identified by the pathologist, would likely serve as a standard goal of EC care, irrespective of ultimate nodal involvement, in a system where standards throughout the population appear rather variable. Undoubtedly, wider LND influences the quality of staging,[12,35] and the LN count impact on OS in N0 disease will reflect a mechanism of stage migration to a large extent. This is certainly corroborated by our findings of nodal stage assignment linked to different LN count profiles, and the largest cutoff point differences in low LN count ranges. Irrespective of the contributing mechanism being a result of better staging and/or better disease control, total LN counts of 30 or higher would appear to represent this preoperative target that can be linked to optimal survival results in our analysis. It should be noted, however, that the recommended total LN count of 30 is merely reflective of a desirable practical target; the observed numeric LN count impact is not an all-or-nothing phenomenon, but a gradual effect of a continuous biologic variable, i.e., the involved LN count. Complex biologic tumor and patient heterogeneity would suggest that the risk for residual positive LNs is not eliminated at a certain total or negative LN count, but rather likely to decrease gradually with increasing counts.

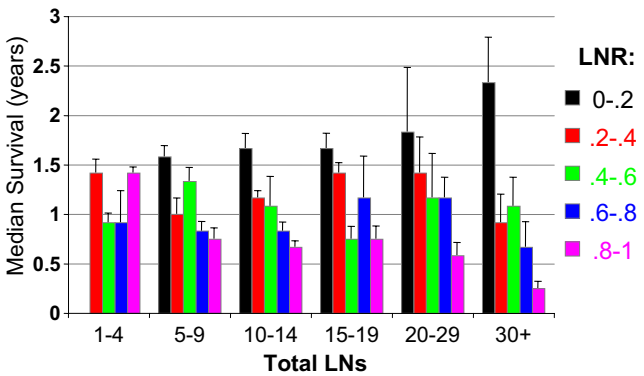

Figure 9 Median actuarial overall survival by various lymph node ratio and total LN count categories. The *bars* represent the standard error. *LNR* lymph node ratio. Only N+ patients are included.

Evidence for a continued numeric LN effect at higher LN count ranges and for nodal positive patients, is perhaps the strongest argument in favor of a true lymphadenectomy–survival relationship that can be extracted from the available data. In addition, these population-derived observations corroborate the findings of the few available RCTs mentioned earlier.[13,14,16]

Our results suggest that larger total LN counts are linked to better outcomes, with an optimal number of 30 or greater. This putative dissection goal is derived from standard LN evaluation techniques and may indeed change with qualitative analysis of LN involvement, such as through the sentinel LN technique.[36] Other factors that may influence a wider LND goal in the future may be the development of specific and reliable staging criteria for early stage disease or major responses to preoperative chemoradiation,[37] which could render the need for LN removal superfluous. For now, however, we interpret the findings as supportive for a more extended LN retrieval at the time of esophagectomy and recommend to obtain 30 or more LNs to expect an optimized quality of numeric EC staging, an optimal ability for survival prediction, and an optimized regional disease control with its potential for improved EC survival.

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DISCUSSION

Jeffrey H. Peters, M.D. (Rochester, NY): A wise man, his name is Tom DeMeester, once told me that medicine is a field that is forced to be practiced before it can be proven or completely understood. This aphorism could not be more true than in the debate about lymphadenectomy and cancer. We could spend the rest of the week trying to answer the question of its benefit.

That said, the 20-something years now of my career and data such as this convince me, that given solid tumors of the GI tract, this author is correct: There is a benefit to lymphadenectomy in esophageal cancer, probably in gastric cancer, and probably also in colon cancer. Proving it is of course the challenge, a big challenge. This is a well-written manuscript by the way, which critiques itself very nicely. I come away with the thought that this is not sloppy science, but rather well thought through data.

With these caveats in mind, let me then ask you a couple of questions. In yours, as well as similar published data, a dose response is often observed. Why? This study and others like it in the colon and the stomach clearly show a dose response. I would expect that there would be a threshold response, not a dose response. One would suspect that there would be a point, at 20 nodes or 30 nodes or 40 nodes or 50 nodes that you would not find any more benefit, and that is not what we see here.

Secondly, you mentioned it a little bit, but I wonder if you could pinpoint the few key rebuttals to the criticism that this does not prove anything, and that such data is simply an epiphenomenon. I am convinced that it does prove that there is a benefit here somewhere, even though some of the benefit may be due to stage migration or other factors. What are the key rebuttals of that criticism?

And finally, it strikes me that there may be a very real correlation between the number of lymph nodes removed and high volume, high quality multi-specialty centers. Do you have the center data and can you refute this potential confounding factor.

Again, there is beginning to be a preponderance of similar data that I believe is swinging the pendulum back, in tumors of the GI tract, toward the recognition that lymphadenectomy is indeed of benefit. We are a long way from proving it, but at some point each of us must decide how you are going to practice.

Very good paper, I enjoyed it very much. Thank you for the opportunity to discuss it.

Roderich E. Schwarz, M.D. (Dallas, TX): Thank you very much, Dr. Peters. It is nice to be supported by a grateful review, and I appreciate it. In fact, the rationale, in part, was brought forth by an excellent symposium that you had put on at the American College meeting that discussed the same question, and it was an attempt to provide at least more data than are currently available in the literature, and because you mentioned the wise man, a wise answer to complex part of statements would be not to answer too much in detail.

Why is there no cutoff? I think it is, in part, statistical and it is, in part, that we truly have a mixture of different phenomena at play. Therefore, it is not a simple oncologic phenomenon or therapeutic phenomenon. We do not have a natural distribution or bell-shaped distribution of lymph node counts in here. Therefore, a lot of what we see is a continuous variable that increases possible effects as the counts go up, and really, there is no single cutoff, primarily for statistical reasons. If one does a cutoff analysis, which we have attempted in the manuscript, you see that the

higher you go with the cutoff, you continue to see significant differences up to counts between 35 and 40. Therefore, I think it is, in part, a biologic phenomenon, it is, in part, by how the data were accumulated, and that the majority of data are actually in the very low lymph node number counts.

A key rebuttal is difficult because we have really only an ability to speculate on mechanism. We just have no insight, because certainly taking information from this database, which lacks a lot of detailed information such as you mentioned on volume of the institution or maybe even individual surgeon's volume, et cetera, leaves that open to criticism. I think the key is that we see an effect that is measurable and statistically significant in nodal positive disease. That does not rule out the presence of stage migration, but it is much less of a mechanism in stage migration than if you just look at nodal negative disease, and that is perhaps the key response for rebuttal to that part of the criticism.

And your final point to the institutional volume, I think it is very important. Of course, certain high volume institutions, such as your former institution, are included in the database. Therefore, it may be that all the patients in the total 30+ total lymph node category are in fact your former patients from USC, and that could well be, but that does not exclude that there is an oncologic benefit to a certain defined subset of patients who have primarily limited disease in the regional distribution and are at low risk ultimately for systemic disease. That is perhaps the best answer I can come up with on that point.

John G. Hunter, M.D. (Portland, OR): I too enjoyed your paper and I think I learned quite a bit from it. I do not fundamentally disagree with Jeff, but I do have a little sort of bone to pick on the final conclusion, which was that harvesting more than 30 lymph nodes confers survival benefit. In your several graphs of LN harvest and survival, there was little difference between 5 and 29 negative lymph nodes and then it jumped up in the 1930s. My interpretation is that there are just a few expert centers harvesting >30 nodes/specimen, and this is only a surrogate for the quality and care in those centers and does not have anything to do with the lymph node resection rate. I noticed USC is one of these centers.

Therefore, the question I have then is: How many centers are represented in that "over 29 lymph node" category and how much confidence do you have that the improved survival of these patients reflects lymph node harvest rather than the other factors that accrue around a "center of excellence"?

Dr. Schwarz: Thank you very much. Those are excellent points. We do not have the ability from this data set to deduce the actual institution at which the operation or the treatment took place. Patients are categorized by their residence more than anything else. Therefore, this is difficult to analyze. I do not have a good answer to your question.

The recommendation to shoot for a target number of 30 or more is somewhat imprecise. I agree with you. It would be much easier to look at the negative lymph node counts and come up with at least a number of 15 or more, because there the separations between the curves are more obvious. The problem is that I think for the variability in the standards of care for this disease in the population, it is good to have a preoperative target that the surgeon knows about and that the pathologist in fact knows about, hence, that can only be set by the total lymph node count. Therefore, if I try to get 30 lymph nodes during my esophagectomy and if my pathologist is being told by me, I want 30 lymph nodes, your likelihood to achieve 15 or more negative lymph nodes gets much higher. Therefore, I think it is a bit more practical recommendation. But you are absolutely right, the data would be in stronger support for negative lymph nodes that show a bit more obvious progression as the counts increase.

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Esophagectomy—It's Not Just About Mortality Anymore: Standardized Perioperative Clinical Pathways Improve Outcomes in Patients with Esophageal Cancer

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Abstract

Background Esophageal resection (ER) remains the standard therapy for early esophageal cancer; however, because of concerns regarding high levels of morbidity and mortality reported in analyses of national databases, many patients are relegated to less effective endoscopic or chemotherapeutic approaches.

Methods All patients undergoing esophagectomy by a single surgeon for cancer or high-grade dysplasia between 05/91–05/06 were prospectively entered into an IRB-approved database. All aspects of work-up and treatment were guided by an evolving standardized perioperative clinical pathway.

Results Three hundred forty consecutive patients, mean age of 64 (33–90), underwent ER for Barrett's esophagus (17) or invasive cancer stages I-87, II-133, III-94, IV-9. One hundred thirty-nine (41%) had neoadjuvant therapy. Sixty-three percent were American Society of Anesthesiologists class III or IV, and five different operative approaches were used. Patient were managed intraoperatively with a "fluid restriction" protocol. Mean intraoperative blood loss was 230 cc. 99.5% of patients were extubated immediately, and mean ICU and hospital stays were 2.25 (1–30) and 11.5 (6–49) days, respectively. Postoperative analgesia was managed with patient-controlled epidural analgesia in 98.5%, and 86% were mobilized on day 1 after surgery. Complications occurred in 153 patients (45%), most commonly atrial dysrhythmia (13%), and postoperative delirium (11%). Anastomotic leaks occurred in 13 patients (3.8%). Mortality occurred in one patient (0.3%). No significant differences were seen in length of stay, operative time, blood loss, or complications in patients receiving neoadjuvant therapy. For stages I, II, and III, patients between 1998–2004 Kaplan–Meier 5-year cumulative survival was 92.4, 57.1, and 34.5%, respectively.

Conclusions Surgical treatment of esophageal cancer can be done with moderate morbidity and very low mortality, and the expectation of improved levels of survival, especially in early-stage patients. Standardized perioperative clinical pathways can provide the infrastructure for the treatment of these patients and should include increased efforts to minimize blood loss and transfusions, improve postoperative pain control and extubation rates, and facilitate early mobilization and discharge. ER, as sole therapy or in combination with radiation/chemotherapy, should remain the standard of care in patients with early and locoregional esophageal cancer.

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Keywords Esophagectomy · Esophageal neoplasms · Clinical pathways

Introduction

Esophageal resection has been an important component of treatment for many patients with early and regionally advanced cancers of the esophagus and proximal stomach. It has gained a well-earned reputation for being a formidable

operation with high levels of associated morbidity and mortality. Multiple recent analyses of the results of esophageal resection have indicated that outcomes are closely related to the numbers of esophageal resections done by individual surgeons and medical centers.[1–7] Assessments within the last decade have documented mortality rates in low-volume centers, ranging between 9.2 and 20.3% with high-volume centers demonstrating improved mortality rates ranging from 2.5 to 8.4%. Some of these same studies also demonstrate improvements in complications and costs at high-volume centers.[3–5,8]

As a result of this data, many surgeons, insurers, and other independent groups such as Leap Frog (http://www.leapfroggroup.org), would advocate that esophageal resection be done only in high-volume centers with some advocating that the minimal volume to achieve "high-volume status" should be 20 resections per year.[9]

In an era in which patients and non-surgical physicians have increasing options for managing early as well as regionally advanced esophageal cancers, surgeons should be able to demonstrate significantly better outcomes involving mortality, morbidity, and quality of life than is currently reported even in many "high-volume" medical centers. Endoscopic management of dysplastic Barrett's esophagus[10] and even definitive radiochemotherapy for early cancer[11–13] is being increasingly advocated and will receive a receptive medical and consumer audience unless currently available morbidity and mortality rates are improved and post-resectional survival and quality of life is assessed and verified to be superior to other treatment modalities.

Results of esophagectomy for cancer has typically focused on the surgical team and issues such as mortality, complications and length of stay. Other important surgical issues such as fluid management, blood loss, and transfusion requirements have not been as closely assessed. Surgical management and outcomes reporting must review and assess a wider range of perioperative issues such as extubation rates, pain management and achieving early mobilization and nutritional goals. Perioperative management currently involves a diverse multi-specialty team. To coordinate this team, standardized perioperative clinical care pathways can provide an infrastructure for patient management and set standard goals for workup and surgical treatment to improvement efficiency and outcomes.

Patients and Methods

All patients undergoing esophagectomy by a single surgeon for high-grade dysplasia or cancer between May 1991 and May 2006 had information prospectively entered in an IRB-approved database. Data collection included preoperative demographics including comorbidities, clinical stage as well as specifics regarding neoadjuvant therapy. Detailed documentation of intraoperative issues such as blood loss and fluid administration was recorded as well as all postoperative complications. Patient management was directed by a standardized perioperative clinical pathway that was initiated early in the series and modified over the period of study. See Table 1.

The study population comprises 340 consecutive patients, 17 with high-grade dysplasia in Barrett's esophagus, and 323 with invasive cancer (adenocarcinoma, 81%; squamous cell carcinoma, 17%; others, 2%). The mean age was 64 years (range, 33–90) with 241 (83% being male). Most common presenting issues were dysphasia at 66% and weight loss at 47%. Clinical stage and American Society of Anesthesiologists (ASA) status are shown in Table 2, with 68% presenting with stages II and III disease, and 63% being ASA 3 or 4. All patients were presented at multidisciplinary tumor board. Neoadjuvant therapy was used in the 139 patients (43% of those with invasive cancer), with chemoradiation used in 63% and chemotherapy alone in 36%.

All patients had placement of a thoracic epidural catheter preoperatively and patient-controlled epidural anesthesia (PCEA) was the major postoperative pain management system. Specific goals within the standardized clinical pathways included targets such as conservative intraoperative fluid administration, immediate postoperative extubation, and mobilization in the hall postoperative day 1 with the current discharge goal of days 7–8. Statistical analysis was done using the chi-square test to compare differences in nominal variables. Continuous variables were analyzed with Student's *t* test. Kaplan–Meier survival was calculated from the date of surgery to the date of death or date last known alive.

Results

Operative approach was chosen according to individual patient and tumor characteristics. Table 3 demonstrates the five resectional approaches utilized in this series. The most common operation was a left thoracoabdominal in 63%. Patients had a secondary operation in 111 cases (33%), most commonly involving wedge resection of the lung (9.7%), cholecystectomy (6.8%), and a wedge biopsy of the liver (4.7%). Two patients required emergent operations, both involving acute perforation of malignant strictures. The anastomoses was cervical in 204 (60%). Only 4% of patients had pyloric emptying procedures. Conduit was stomach in 98%, and a jejunostomy feeding tube was inserted in 83% of patients.

Operative issues, such as length of procedure, blood loss, intraoperative fluid administration, and length of stay, were

Table 1 Esophageal Resection Standardized Clinic Pathway

- Initial Contact: (Referral):
  - Interview patient within 48 hours
  - Verbal Review (telephone interview)
    - PMH
    - Current Symptoms → Swallowing/Wt Loss
    - Current Investigations
    - Travel Arrangements – Seattle accommodations
    - Initial description of surgery/VM
  - Patient Appointment made with respect to patient/referring physician wishes, patient symptoms/status, patient availability
- Prior to VM Appointment
  - Arrangements for previous notes, investigations, films, path sent or brought to VM
  - Arrange patient tailored schedule – which is forwarded to patient
- Initial encounter (completed within 2-3 working days)
  - Consultations
    - Thoracic surgery
    - Medical oncology
    - Radiation Oncology
    - Cardiology (>50 y.o. (risk factors))
  - Path Review
  - Investigations
    - Contrast CT
    - PET/CT
    - EGD/EGD US – attended by surgeon
- Presentation at thoracic tumor board (next conference following initial appointment)
  - Patient contacted with recommendations day following tumor board – reports sent to referring MD
- Pre-Op Arrangements
  - Initiate chemotherapy or chemoradiotherapy
  - Referral for neoadjuvant therapy
  - Reassessment following completion of neoadjuvant therapy
    - CT scan
    - EGD US
    - ± PET scan
  - Reassessment done 2-4 weeks prior to operative date
  - Individualized operative approach according to
    - Tumor/Barrett's characteristics
    - Patient Physiology
    - Previous Surgery
- Surgery
  - Thoracic epidural placed pre-operatively
  - Minimize blood loss/transfusions
  - Conservative intra-operative fluid administration
  - Immediate extubation
  - Post-op anesthesia – PCEA
  - Admit to ICU
- Post-Op
  - Patient sits up and dangles evening of surgery
  - Patient walks in hall morning POD #1
  - Discharge from ICU 12-18 hours post-op
  - Walks the ward 3-4 x each day
    ± Physical therapy consult
  - Chest tube 1 removed Day 2
  - Chest tube 2 removed Day 3, 4 or 5
  - Jejunostomy tube nutrition initiated Day 3
  - Gastrografin/Barium swallow Day 4 or 5
  - NG tube removed Day 5 or 6
  - Switch to oral/J-tube analgesics Day 5 or 6
  - Dietary/Home Health Consult Day 5 or 6
  - Discharge Day 7 or 8
- Represent at next available tumor board following completion of path results
- Review recommendations with patient within 24 hours
- Forward recommendations to referring/outside MDs

Table 2 Clinical Stage and American Society of Anesthesiologists (*ASA*) Status

Clinical Stage			ASA Level	
I	-	87	I	1
II	-	133	II	126
III	-	94	III	204
IV	-	9	IV	9

seen to significantly improve over time (Table 4). Operative approaches were chosen according to tumor and physiologic issues but also to optimize exposure to facilitate tumor resection and adequate lymphadenectomy under direct vision and minimized blood loss. Mean blood loss was 229 cc, and 30 patients (8.8%) required intra- or postoperative transfusions. Seventeen of the 30 (57%) patients receiving blood transfusions had received neoadjuvant therapy. Achievement of specific goals within the clinical pathways included pain management with PCEA in 335 (98.5%), immediate extubation, in 338 (99.5%), and patients being mobilized in the hall on postoperative day 1 in 292 (85.9%).

A total of 260 complications was documented in 153 out of 340 patients (45%). Most common complications were atrial dysrhythmia (13%) and postoperative delirium (11%; Table 5). Anastomotic leaks occurred in 13 patients (3.8%), chyle leaks occurred in 14 patients (4.1%), and reoperations were required in 10 patients (2.9%) (anastomotic leak 2, chyle leak 6, bleeding 2). In-hospital and 90-day mortality occurred in one patient who had a combined esophagectomy and right upper lobectomy for synchronous cancers for an overall mortality rate of 0.3%.

Of the 139 patients receiving neoadjuvant therapy, 25 (18%) were found to have complete responses after resection. Overall (p=0.273), cardiac (p=0.667), and pulmonary (p=0.535) complication rates in patients receiving neoadjuvant therapy were not significantly different from complication rates observed among patients without neoadjuvant therapy. Five-year Kaplan–Meier survival in stages I, II, and III patients operated on between 1998 and 2004 was 92.4, 57.1, and 34.5%, respectively. See Fig. 1a and b.

Table 3 Operative Procedures

Left Thoracoabdominal	214	
Ivor Lewis	91	
Transhiatal	24	
Right Thoracotomy/Transhiatal	8	
Retrosternal	3	
Secondary Procedures	111	(33%)

Discussion

The outcomes of esophageal resection is undergoing increasing scrutiny, not only within the medical community but also by patients and payors. Increasing assessment of statewide[2,3,6] and national[1,5,7] databases demonstrate a direct relationship between volume of esophageal resections and outcomes, particularly mortality rates. The reasoning for this scrutiny is easily understood when, in spite of reports documenting improved outcomes over time,[1,14,15] a study within the last 5 years assessing mortality between 1994 and 1999 in the Medicare population show rates in very low-volume hospitals to be approximately 20% but even high-volume hospitals demonstrating a cumulative mortality rate of 8.4%.[7]

The current series demonstrates a mortality of under 1%, which is not unique but uncommon in any review of the literature involving large series of esophageal resections. We credit this outcome to a number of issues including a high volume of esophageal resections while, at the same time, recognizing that high-volume practice invariably is associated with an organized institution-wide infrastructure working toward optimizing outcomes in esophageal cancer patients. This has resulted in the evolution of a standardized clinical care pathway for patients undergoing esophageal resection, which provides performance goals and guidelines involving initial assessment, procedure selection, intraoperative management, and postoperative care (Table 1). These guidelines have evolved over the period of the study but now provide a "best-case" infrastructure that guide the management of esophagectomy patients. Previous reports have demonstrated that standardized clinical care pathways can reduce length of stay and costs in not only esophagectomy patients[16] but in a wide variety of major thoracic operations.[17] We would agree and go farther that they can improve outcomes and efficiency during all aspects of patient assessment and treatment.

Highlights of the current standardized pathway include the goal of interviewing all patients within 48 h of referral and before arrangements are made for initial consultation. Initial encounters are tailored to patient requirements and culminate with presentation at multi-disciplinary tumor board with a thoracic oncology nurse coordinator reporting back to the patient within 24 h regarding recommendations. Operative approach is individualized according to individual patient and tumor characteristics and, based on adhering to appropriate cancer principles with a paralleling goal of minimizing blood loss, conservative perioperative fluid administration and maximizing postoperative analgesic management to promote immediately mobilization whenever feasible. The ability to achieve these goals is demonstrated in rates of immediate extubation, patient-controlled epidural analgesia utilization, and instance of day 1 mobilization of 99.5, 98.5, and 85.9%, respectively.

Table 4 Operative Detail and Lenght of Stay Changes Over Time

Group Label	Time Frame	N	Mean OR Time, in minutes (s.d.)	Mean OR Blood Loss, in cc (s.d)	Mean OR Fluids, in cc's (s.d.)	Mean LOS, in days (s.d.)
All Patients	May 1991 – May 2006	340	399.1 (64.7)	230.6 (167.7)	4410.3 (1437.1)	11.5 (5.6)
Cohort 1	May 1991 – April 1996	77	411.6 (94.5)	374.7 (265.5)	5019.5 (1643.6)	13.7 (8.3)
Cohort 2	May 1996 – April 2001	116	403.8 (56.7)	201.6 (97.0)[a]	4393.5 (1367.8)[a]	11.5 (4.5)[a]
Cohort 3	May 2001 – May 2006	147	388.9 (48.2)[c]	178.1 (82.4)[b]	4108.5 (1278.6)[b,c]	10.4 (4.3)[b]

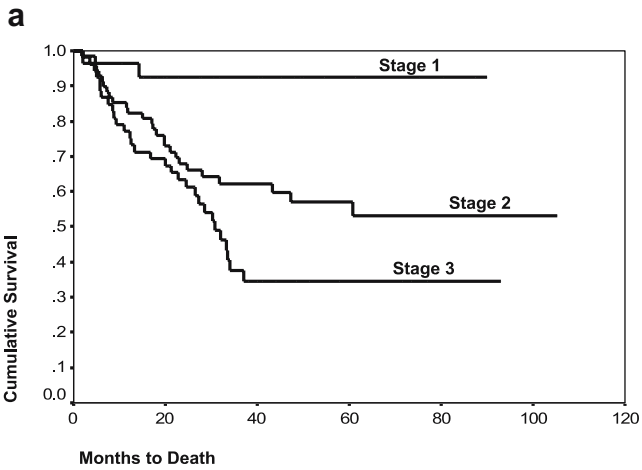
[a] vs. Cohort 1: Operative blood loss (p = .000); Operative fluids (p = .005); LOS (p = .034), by t-test.
[b] vs. Cohort 1: Operative blood loss (p = .000); Operative fluids (p = .000); LOS (p = .002), by t-test.
[c] vs. Cohort 2: Operative time (p = .022); Operative fluids (p = .035), by t-test.

Surgeons have tended to favor a particular surgical approach that can readily be appreciated by an examination of many of the large historical series. The effect of a thoracotomy and the recognized relationship of major pulmonary complications on morbidity, costs, and mortality[14,15,18–22] has encouraged some surgeons to avoid thoracotomies and utilize minimally invasive approaches whenever feasible. Actual assessments of both randomized[23,24] and non-randomized[25–28] trials comparing transhiatal and transthoracic procedures have shown subtle or no differences in morbidity, mortality, or quality of life.[29] We select operative approaches to optimize exposure to facilitate a standardized cancer operation but also to minimize intraoperative fluid and blood requirements. Virtually all patients in this series had patient-controlled epidural analgesia, supervised by a pain management team for a mean of 5 days postoperatively.[30] This approach has previously been shown to improve outcomes in esophageal resection[18,31] and decrease pulmonary complications in a wide variety of surgical procedures.[32] We believe that the evolving goals in our standardized clinical pathway is the major reason we have demonstrated significantly improved perioperative parameters over time (Table 4). It is also a contributing factor to our previous report demonstrating that postoperative quality of life can be equal to the general population in patients undergoing esophageal resection for high-grade dysplasia and intramucosal cancer.[33] The outcomes in this series equal or exceed results reported in series of minimally invasive esophageal resections. These outcomes, in addition to quantity of life data, can serve as a benchmark for future comparisons.

The incidence of pulmonary complications in this series was 17.1% overall. Pneumonia was the most common individual respiratory complication (5.9%), although rates of reintubation and acute respiratory distress syndrome

Table 5 Perioperative Complications

Patients with complications		153 (45%)
Total number of complications		260
		TOTAL
Cardiac		53 (15.6%)
Atrial Dysrhythmia	46	
Ventricular Arrhythmia	3	
Congestive Heart Failure	3	
Myocardial Infarction	1	
Respiratory		58 (17.1%)
Pneumonia	20	
Pneumothorax That Required Treatment	11	
Pleural Effusion That Required Treatment	11	
Re-Intubation	7	
Pulmonary Embolus	5	
Prolonged Air Leak	2	
Respiratory Failure (acute respiratory distress syndrome)	2	
GI		34 (10%)
Ileus	16	
Urinary		29 (8.5%)
Urinary Tract Infection	20	
Vascular		5 (1.5%)
Deep Vein Thrombosis	3	
Other		81 (23.8%)
Post Operative Delirium	36	
Wound Infection	10	



b

	(N)	Kaplan-Meier 5-Year Survival	Overall Survival (Mean)	Confidence Interval
Stage I	27	92.4%	83.7 Mo	75.49-91.97
Stage II	72	57.1%	66.27 Mo	55.09-77.44
Stage III	55	34.5%	44.8 Mo	34.1-55.52

Figure 1 **a** Survival curves. **b** Results: survival 1998–2004.

(ARDS) were low at 2.0 and 0.6%, respectively. Early aggressive pain management, extubation, and mobilization are important factors as are minimizing intraoperative fluids and blood loss. We and others have previously demonstrated that intraoperative fluid administration algorithms are unnecessary and "fluid restriction" is feasible, safe, and can improve outcomes,[30,34,35] especially with respect to respiratory complications.[36] Although operations in this series took an average of over 6 h, mean blood loss, as assessed by anesthesia, was 229 cc and intraoperative fluid administration was under 4.5 l. These parameters were also seen to improve over the course of the study (Table 4). As a result, in spite of the fact that 41% of patients had neoadjuvant therapy, only 30 patients (8.8%) required transfusion at any point during their hospital stay. When it has been a component of the analysis, significant blood loss has been an issue in esophageal resection with previous reports commonly demonstrating mean blood loss over 500 cc[26,37–41] and transfusion requirements in over 50% of patients.[38,39] Increasingly, blood loss has been shown to be an important factor in operative outcomes including mortality[15,28,40,42–44] and survival.[38,39,41,45]

The ultimate place of neoadjuvant therapy in the treatment of patients with esophageal cancer is still not clear.[46] However, preoperative chemotherapy or radiochemotherapy continued to form a component of the treatment of the majority of patients with locoregional esophageal and esophagogastric junction cancer. In this series, 43% had neoadjuvant therapy with 18% demonstrating a complete response. Our results agree with previous studies[47,48] that neoadjuvant therapy does not significantly impact complications or perioperative outcomes.

An examination of large national databases will demonstrate that even modern-day mortality rates for esophageal resection for cancer range between 8 and 20%.[7,49] Although individual series of resections from high-volume centers can demonstrate significantly improved survival rates, it is this data which has encouraged centers to critically examine the place of surgery in the treatment of early[12] and locally advanced esophageal cancer.[11,13] Portale and colleagues have recently demonstrated that modern surgical survival, with or without combined modality treatment, can result in 5-year survival rates in stages I, II, and III patients as high as 81, 51, and 14%, respectively.[50] Our results support these findings demonstrating stages I, II, and III 5-year survival rates of 92.4, 57.1, and 34.5%, in addition to confirming that large series of resections can be done with very low mortality, in this case, with an in-hospital and 90-day mortality rate of 0.3%.

Conclusions

In an era in which appropriate therapy for patients with esophageal cancer will come under increasing reassessment, surgeons should continue to review technical approaches and critically analyze outcomes. Continuing advances in non-surgical treatment of esophageal cancer should not be compared to current national mortality rates of between 5 to 20% and morbidity rates exceeding 50%. Standardized perioperative clinical care pathways can provide an infrastructure to set goals and improve results. This will lead to improvement in morbidity and mortality and also facilitate ongoing assessment of costs and quality of life to provide a more pertinent impression of modern-day surgical results of the treatment of esophageal malignancy.

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DISCUSSION

Jeffrey H. Peters, M.D. (Rochester, NY): Following on Dr Traverso's Presidential address, as a high volume report from a single surgeon, it is of course not the average of the average. Nevertheless, Bill, there is still much to be gleaned from studies like this. Dr Low did a good job of outlining why the data are important, not the least of which is because controlled studies are so rare in this area of major resections; as such we are always comparing ourselves to yesterday and not to today. So it is important that we have modern outcome data. It also is quite true, as the title points out, it is not all about mortality anymore, more patients are surviving longer, and being cured.

I will ask you one simple and one conceptual question, Don. The first is, do you think we can do without the ICU post-esophagectomy. This thought has crossed my mind from time to time, as we may be getting into an era where ICU stays are no longer necessary in most, if not all, of these patients.

More conceptually, are the boundaries of the morbidity and mortality of the various treatment options coming close enough together so that, as Bill so nicely pointed out in his presidential address, we should stop focusing on the extent of the treatment, and start focusing more on the environment that the treatment takes place in? Is this true given our endoscopic, minimally invasive and/or open surgical treatment options? Great paper, Don. I enjoyed it you very much and thank you for the opportunity to discuss the data.

Donald E. Low, M.D. (Seattle, WA): Dr. Peters, thank you very much. With respect to the ICU, I think that part of the answer can be taken from the fact that in 1992 our goal was to discharge patients from the ICU in 48 to 72 h. Now our goal within the pathway is to discharge patients from the ICU in 12 to 18 h. Can it be eliminated? Yes, I think it can. However, I believe that we have to make sure that we have developed specialized units within our hospital to make sure that the nursing care and the other ancillary support infrastructure that we have to manage these patients immediately after surgery is in place on the ward. Selected patients do not require the same level of monitoring but do require experienced personnel to be involved in their immediate post-operative care.

The second question I think is extremely intuitive and probably the most important question that we should address. Does it matter how we are doing these operations? Although we should be able to diversify our approach, the basic answer is probably no. The corollary of that is, we must know our individual results. We must know what our outcomes are, including mortality, morbidity, survivorship, and quality of life. This will be particularly important as minimally invasive surgical approaches continue to evolve.

John G. Hunter, M.D. (Portland, OR): Don, again, a very nice paper. What you have shown is that as mortality has fallen out as your largest problem, your number one complication now is atrial dysrhythmia, and in order to get better we take our number one complication and we go to work on it. You and I both believe, I know, that this is a complication unto itself and not a harbinger of some other complication as has been reported by the Hong Kong group. What are you doing about that, any pretreatment, post-treatment? How are you working on this problem?

Dr. Low: Thank you for that lead-in, because I think your starting comment was right: If we are going to continue to improve our results we must take the problems that are afflicting us most and analyze them separately. Currently in front of our IRB is a proposal for a randomized clinical trial in which we are going to start utilizing antiarrhythmic medications prior to esophageal resections. We are specifically proposing a trial utilizing amiodarone in an attempt to decrease the incidence of post-operative atrial dysrhythmias. We have not observed that atrial fibrillation is a problem which indicates that something more ominous is going on. It is, however, a major issue in a certain component of our patient population which delays discharge and increases costs.

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Return of Esophageal Function after Treatment for Achalasia as Determined by Impedance-Manometry

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Abstract
Background Treatment for Achalasia is aimed at the lower esophageal sphincter (LES), although little is known about the effect, if any, of these treatments on esophageal body function (peristalsis and clearance). We sought to measure the effect of various treatments using combined manometry (peristalsis) with Multichannel Intraluminal Impedance (MII) (esophageal clearance).
Methods We enrolled 56 patients with Achalasia referred to the University of Washington Swallowing Center between January 2003 and January 2006. Each was grouped according to prior treatment: 38 were untreated (untreated achalasia), 10 had undergone botox injection or balloon dilation (endoscopic treatment), and 16 a laparoscopic Heller myotomy. The preoperative studies for 8 of the myotomy patients were included in the untreated achalasia group. Each patient completed a dysphagia severity questionnaire (scale 0–10). Peristalsis was analyzed by manometry and esophageal clearance of liquid and viscous material by MII.
Results Mean dysphagia severity scores were significantly better in patients after Heller Myotomy than in either of the other groups (2.0 *vs*. 5.3 in the endoscopic group and 6.5 in untreated achalasia, $p<0.05$). Peristaltic contractions were observed in 63% of patients in the Heller myotomy group, compared with 40% in the endoscopic group and 8% in untreated achalasia ($p<0.05$ for both treatment groups *vs*. untreated achalasia). Liquid clearance rates were significantly better in both treatment groups: 28% in Heller myotomy and 16% in endoscopic treatment compared to only 5% in untreated achalasia ($p<0.05$). Similarly, viscous clearance rates were 19% in Heller myotomy and 11% in endoscopic treatment, *vs*. 2% in untreated achalasia ($p<0.05$). In the subset of patients who underwent manometry/MII both pre- and postoperatively, peristalsis was observed more frequently postoperatively than in preop studies (63% of patients exhibiting peristalsis *vs*. 12%), as was complete clearance of liquid (35% of swallows *vs*. 14%) and viscous boluses (22% of swallows *vs*. 14%). These differences were not significant, however. In the patients who had a myotomy the return of peristalsis correlates with effective esophageal clearance (liquid bolus: r=0.46, $p=0.09$ and viscous bolus: r=0.63, $p<0.05$). There is no correlation between peristalsis and bolus clearance in the endoscopic treatment group.
Conclusions With treatment Achalasia patients exhibit some restoration in peristalsis as well as improved bolus clearance. After Heller Myotomy, the return of peristalsis correlates with esophageal clearance, which may partly explain its superior relief of dysphagia.

Keywords Achalasia · Heller myotomy · Esophageal motility · Multichannel intraluminal impedance

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Introduction

Achalasia is an esophageal motility disorder defined by a loss of distal esophageal peristalsis as well as impaired

relaxation of the lower esophageal sphincter (LES) upon swallowing. It is relatively rare, with an incidence in the general population of approximately 1 person out of every 100,000.[1] Treatment for achalasia is aimed at eliminating the LES obstruction, and three modalities are most commonly employed. Pneumatic dilation refers to mechanical disruption of the muscle fibers of the LES using a rigid balloon dilator. Another non-surgical method involves injection of botulinum toxin into the LES.[2] With surgical treatment, most commonly Heller myotomy, the muscle fibers of the LES are directly divided, resulting in a wide-open esophagogastric junction.[3, 4]

While all of the methods described above can effectively address the functional impairment of the LES, there is no treatment specifically directed at the dysfunction of the esophageal body, which is a defining feature of achalasia. Relief of dysphagia after treatment is assumed to be the result of eliminating this functional obstruction of the distal esophagus. However, although the return of peristalsis after both balloon dilation[5] and Heller myotomy[6] has been described, there is little in-depth analysis of the effect of treatments for achalasia on esophageal body function.

Multichannel intraluminal impedance (MII) is a relatively new technology which uses the change in resistance to electrical current across two electrodes to indicate the passage of either a liquid or viscous bolus. Pairs of electrodes (impedance channels) are arrayed along the length of an esophageal manometry catheter so that as a bolus is swallowed, changes in impedance at each pair in turn are converted into a display which represents the transit of that bolus through the esophageal body. It is easy to perform and is recorded simultaneously with manometry, thus permitting the analysis of both peristalsis and bolus clearance without the need for radiation exposure or additional instrumentation.

Using esophageal manometry with MII, we examined the effect of these three treatments on esophageal body function. We attempted to define in greater detail the relationship between symptomatic improvement after treatment for achalasia and changes in esophageal body function.

Materials and Methods

We retrospectively reviewed simultaneous manometry/MII studies on 56 patients with achalasia referred to the University of Washington Swallowing Center between January 2003 and January 2006. Each patient was sorted into one of three groups based upon treatment status. The first group included 38 patients without any prior treatment (untreated achalasia). The second group consisted of 10 patients who had either undergone botulinum toxin injection or pneumatic dilation, who in essence formed a partially treated group, as they had returned for workup of recurrent symptoms. The third group had undergone Heller Myotomy (N=16), and were studied as part of their routine six-month follow-up after surgery as practiced in our institution. The untreated achalasia group includes the preoperative studies of 8 patients who subsequently underwent Heller Myotomy, thus were included in both groups.

Each patient completed a questionnaire that rated the severity of dysphagia using a ten point visual analog scale, with a score of one indicating “mild” symptoms and ten representing the “most severe” symptoms; patients circled “zero” if they were asymptomatic. After signing an informed consent form for the study, each patient also underwent simultaneous esophageal manometry and MII testing using a specially designed solid-state catheter system (Sandhill Scientific Inc., Highland Ranch, CO). The catheter includes four pairs of impedance sensors separated by 5 cm intervals and five manometric sensors spaced 5 cm apart, and has been previously described.[7] Testing was done with the patient positioned 30° from the supine position. The MII-manometry catheter was inserted transnasally to a distance of 60 cm from the nares. The length and proximal position of the lower esophageal sphincter (LES) were determined via a station pull-through technique. Then the catheter was positioned such that the manometry and impedance sensors were 5, 10, 15, and 20 cm above the sphincter. Each patient was given 10 swallows of 5 cc aliquots of saline, and another 10 swallows of 5 cc aliquots using a viscous material with a jelly-like consistency (Sandhill Scientific Inc., Highland Ranch, CO). Adequate time was given between each swallow to allow completion of the previous swallow ($\geq$ 20 sec).

Manometrically, a swallow was defined as normal if the mean contraction amplitude at the two most distal sensors was greater than or equal to 30 mmHg with normal propagation in the four esophageal body sensors.[8]

MII detects the entrance and exit of a swallowed bolus between paired sensors by measuring a drop in resistance to alternating current. Ionic concentrations around the catheter correlate with the measured changes in electrical impedance. When the impedance drops 50% from its baseline, the bolus has entered between the sensor pairs; the exit occurs when impedance recovers to the baseline.[9] A successful swallow consecutively enters and exits all four pairs of sensors. For the purposes of this study, esophageal clearance of both liquid and viscous boluses was expressed as the percentage of swallows during which the bolus completely traversed the esophageal body. Normal esophageal clearance for a given patient is defined as complete bolus transit in 80% or more liquid swallows and 70% for viscous swallows.

Data analysis was performed using SPSS for Windows (SPSS, Chicago, Illinois). Unpaired *t*-test and chi-squared analysis were used to assess differences in variables.

Pearson's correlation was used to determine associations between peristaltic frequencies and percentages of complete bolus transit, as well as symptom duration and these esophageal function parameters. A p-value of less than 0.05 was considered statistically significant. The study was approved by the University of Washington Institutional Review Board (HSD# 05–7136–E/A 01).

Results

Patient demographics are listed in Table 1. Similar ratios of male to female patients were present in each group, and there were no significant differences in their mean ages. The mean duration of symptoms for the untreated achalasia patients was 89 months, compared with 135 months in the non-surgical group and 72 months in the myotomy group (p= NS) (Table 1).

After Heller Myotomy, the mean dysphagia severity score was 2.0, which was significantly better than those of both the endoscopic treatment and the untreated achalasia groups, with means of 5.3 and 6.5, respectively ($p<0.05$) (Fig. 1). Manometric parameters in each of the three groups are listed in Table 2. The mean lower esophageal sphincter pressure (LESP) for the Heller myotomy group was significantly lower than that of the other two groups. The mean percentage of intact peristaltic swallow sequences was significantly greater in both the Heller myotomy patients (20%) and the endoscopic treatment group (18%) compared to the untreated achalasia group (2%). The percentage of patients exhibiting any intact peristaltic sequences was significantly higher in both treatment groups (40% after endoscopic treatment and 63% after Heller Myotomy) when compared to untreated achalasia ($p<0.05$) (Table 2).

Impedance results demonstrated significantly better clearance of both liquid and viscous boluses in both the Heller myotomy and endoscopic treatment groups when compared to untreated achalasia. The mean percentages of swallows in which liquid and viscous boluses were cleared in each group are listed in Table 2. Heller myotomy patients demonstrated higher clearance rates than those in the endoscopic treatment group for both liquid (28% vs. 16%) and viscous boluses (19% vs. 11%), but these differences were not significant. Normal esophageal clearance was not observed in any individual patient in either the untreated achalasia or the endoscopic treatment groups. Four of 16 (25%) of the Heller Myotomy patients had normal liquid clearance and one of 16 (6.2%) had normal viscous clearance.

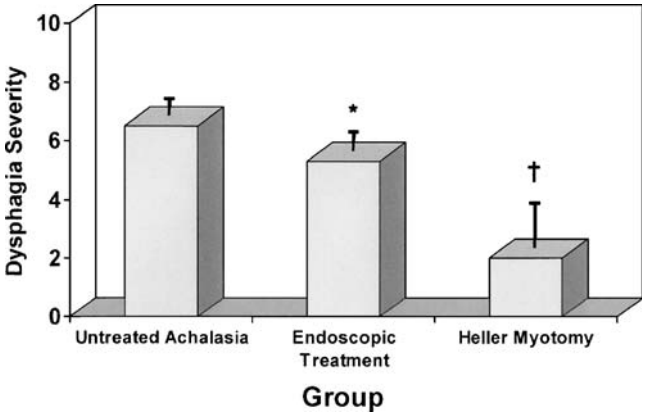

Figure 1 Mean dysphagia scores for untreated achalasia, endoscopic treatment, and Heller myotomy. *$p<0.05$ vs. untreated achalasia; †$p<0.005$ vs. untreated achalasia and endoscopic treatment.

Subanalysis was performed in the subset of 8 Heller Myotomy patients that participated in both pre-operative and post-operative esophageal manometry and MII testing. Higher clearance rates were seen post-operatively (35% liquid, 22% viscous) in comparison to the pre-operative results (13.9% liquid, 13.6% viscous). However, this subset of patients was too small to demonstrate statistical significance.

Peristalsis was compared to both liquid and viscous clearance in the endoscopic treatment and the Heller myotomy groups to determine whether or not the improvement in peristalsis correlated with improved liquid and viscous clearance. No correlation was demonstrable between peristalsis and clearance in the endoscopic treatment group. However, in the Heller myotomy group liquid clearance was weakly correlated with peristalsis (r=0.456; $p=0.09$; Fig. 2), and viscous clearance was strongly correlated with peristalsis (r=0.663; $p<0.05$; Fig. 3). No correlation between the duration of symptoms (in months) and the level of esophageal function was observed for patients with untreated achalasia, endoscopically treated patients, or Heller myotomy patients. Specifically, the presence or absence of peristaltic activity and rates of liquid and viscous bolus clearance were independent of the duration of disease and there was no observable impact of the timing of treatment (relative to symptom onset) upon esophageal function.

Table 1 Patient Demographics

	Untreated Achalasia	Endoscopic treatment	Heller Myotomy
N	38	10	16
Mean Age	52	53	56
Male : Female	21 : 17	5 : 5	8 : 8
Symptom Duration (months)	89	135	72

Table 2 Esophageal Manometry and MII Data

	LESP (mmHg) Mean+/−SEM	Mean % of Swallows with Peristalsis	% of Patients With Peristalsis	% of Swallows with Complete Liquid Clearance	% of Swallows with Complete Viscous Clearance
Untreated Achalasia	28.0+/−3.0	2%	8%	5%	2%
Endoscopic Treatment	22.4+/−4.5	18%*	40%*	16%*	11%*
Heller Myotomy	9.7+/−1.3	20%*	63%*	28%*	19%*

*$p<0.05$ vs. Untreated Achalasia

Discussion

While manometry has for decades been used as the primary measure of esophageal body function, it is only able to evaluate the character and strength of peristalsis. Esophageal transit and bolus clearance, which are the functional purpose of the esophagus, are not assessed by this technique. Esophageal impedance adds this dimension to the manometric measurement of peristalsis in the analysis of esophageal function. This study demonstrates, for the first time, the affect of achalasia and the most widely practiced therapies for this disease on both esophageal peristalsis and esophageal clearance. In doing so we have shown that there is a nearly complete absence of function (both of peristalsis and clearance) in untreated achalasia, with incremental improvement with increasingly effective therapy. Heller myotomy in fact results in the greatest reduction in LES resting pressure and return of peristalsis, which correlates with improved esophageal clearance. These findings lend credence to both the overall effectiveness of Heller myotomy, as well as impedance technology as a reliable adjunctive measure of esophageal function.

Previous reports have compared the results of endoscopic balloon dilation with Heller myotomy in terms of symptom relief and long-term efficacy.[10–12] Though the success rates of both procedures vary widely, particularly over time, Heller myotomy is typically associated with more consistent dysphagia relief than dilation at both short and long-term follow-up. Further, while the incidence of subsequent intervention is not insignificant after either procedure, it is lower after myotomy.[11] The effects of Botulinum toxin injection are universally transient,[13] and this treatment is more commonly recommended for elderly or high-risk patients.[14] Because of the relatively small numbers in the endoscopic treatment group, together with the fact that many of these patients represent treatment failures to some degree, it is difficult to make any conclusions with regard to the superiority of Heller myotomy over endoscopic therapy on the basis of the current study. However, the addition of MII to manometric assessment in these patients after treatment does demonstrate some parallels with results of other reports comparing outcomes. While significant, if somewhat modest, improvements in esophageal transit are demonstrated in both the

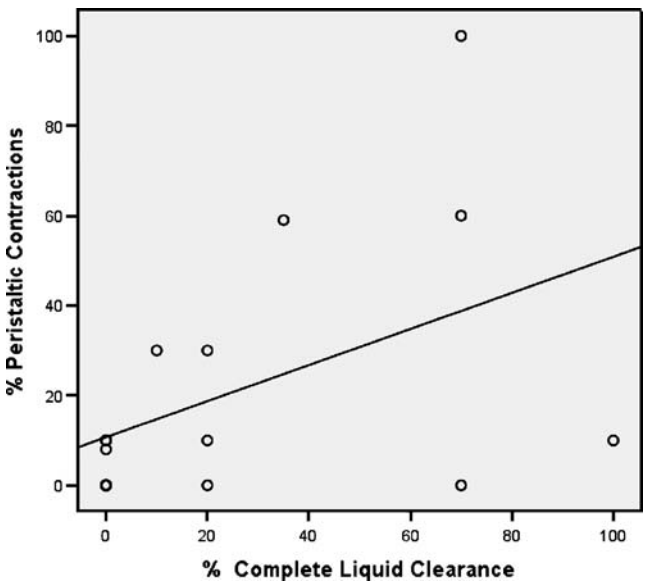

Figure 2 Correlation between rates of successful peristalsis and liquid bolus clearance in patients after Heller myotomy; r=0.456; $p=0.09$.

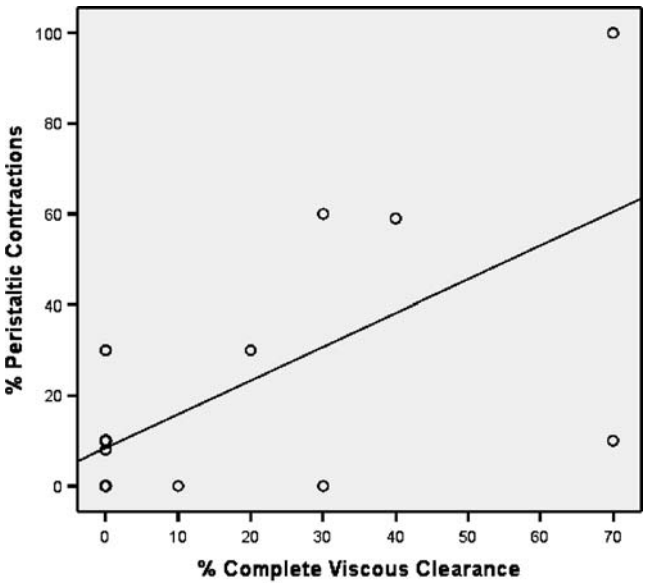

Figure 3 Correlation between rates of successful peristalsis and viscous bolus clearance in patients after Heller myotomy; r=0.663; $p<0.05$.

endoscopic treatment and Heller myotomy groups, clearance rates of liquid and viscous boluses are higher after Heller myotomy than after endoscopic treatment. Again, this must be tempered in light of the fact that the endoscopic treatment group consists of patients presenting with recurrent symptoms, in effect a partial treatment group, and does not truly represent all patients who have undergone non-surgical therapy for achalasia.

The concept that esophageal function can improve after treatment for achalasia has been explored for some time. Scattered individual cases of recovery of esophageal peristalsis after either pneumatic dilation[15] or surgical myotomy[16, 17] may be found in the literature from the last three decades. Series of patients undergoing dilation indicate a rate of peristaltic return post-procedure ranging from 20–25%;[5, 18] those series involving surgical patients report rates in the range of 8–26%.[6, 19–22]

Interestingly, the proportion of patients exhibiting peristalsis after treatment observed in this series (40% of patients who had undergone either botox or dilation and 63% of those who had undergone Heller myotomy) are higher with those reported by other authors. The reason for the discrepancy between our results and those of other series is unclear, as standard criteria for peristaltic sequences (wave progression and distal esophageal contraction amplitude > 30 mmHg) were used to identify those patients with peristaltic activity in this study. It is possible that different manometric techniques, criteria, and/or the relatively small sample sizes of the post-treatment groups reported here could explain the higher numbers of patients observed to have peristaltic sequences in the present work.

Esophageal clearance after Heller myotomy has been previously examined in a report by Finley *et al*. They performed radionuclide esophageal emptying studies in 67 patients both before and after laparoscopic Heller myotomy, finding a decrease in liquid retention over 10 minutes from 70% to 48% between the pre- and postoperative examinations.[23] These data are consistent with the findings of the present study, although we have employed a very different technique to assess esophageal transit. This is the first study to use multichannel intraluminal impedance in the evaluation of patients after treatment for achalasia. Tutuian and Castell reported a comparison of various primary esophageal motility disorders using MII. As one might expect, in distinction to nearly all of the other disorders, no patients with achalasia were observed to have normal esophageal bolus transit, as defined by complete clearance of at least 80% of liquid boluses and 70% of viscous boluses.[8] This is quite similar to the data for the 38 patients with untreated achalasia reported here. Impairment in clearance was seen in the majority of patients in each treatment group as well, although significantly higher rates of bolus transit were demonstrated in each. Further, 25% of myotomy patients had normal clearance rates for liquid boluses, and one of the sixteen had normal viscous bolus clearance.

Results for the subset of eight patients who had undergone both pre- and postoperative manometry/MII studies were consistent with those of the larger group of Heller myotomy patients. Substantial improvement in the mean rates of peristalsis, liquid clearance, and viscous clearance was observed in this subset, although none of these differences reached the level of statistical significance because of the relatively small sample size. With a larger number of patients completing manometry/MII both before and after Heller myotomy, it will likely be possible to draw more definitive conclusions about the implications of this procedure for the improvement or recovery of esophageal function.

The reasons why esophageal function may return after treatment for achalasia remain uncertain. It is possible that the loss of peristalsis observed in idiopathic achalasia is to some degree secondary to the functional obstruction of the LES and subsequent esophageal dilatation. This has been supported by animal models of achalasia in which the LES has been functionally restricted, resulting in aperistalsis.[24, 25] Schneider *et al*. experimentally induced the features of classic achalasia in 16 cats using a surgically-placed band to restrict the LES. Once the band was subsequently removed, peristaltic activity fully returned in all of the animals.[24] Using a similar technique in opossums, Khajanchee and colleagues demonstrated manometric return of peristalsis after relief of distal esophageal obstruction in response to electrical vagal stimulation in nearly half of all swallows studied.[25] This supports the concept that the functional esophageal obstruction itself contributes to the defect in peristalsis observed in achalasia, and that to some degree, this is reversible with LES-directed therapy.

It is, however, unclear why certain patients have been observed to recover esophageal function after treatment as in this study and in other case series,[5, 6, 22, 26] whereas others do not. Variants of achalasia exist in which some peristalsis is observed, including vigorous achalasia, characterized by higher-amplitude simultaneous contractions in the distal esophagus in conjunction with a non-relaxing LES, and short-segment achalasia, in which the proximal esophageal segment retains peristaltic activity. These may represent an early stage in the progression of the disease,[27] and as such, these patients would seem to be most likely to recover esophageal function after relief of the relative distal esophageal obstruction. In one series of 45 patients undergoing surgery reported by Parilla and colleagues, 46.6% of patients demonstrated the return of peristalsis in the proximal esophagus after surgery, but only 8.8% were observed to have peristaltic sequences progressing to the distal esophagus. Those patients with either a shorter duration of dysphagia or less esophageal dilatation preoperatively were more likely to recover peristaltic activity.[22]

However, in the report of 41 patients undergoing Heller myotomy by Patti *et al*., which included 10 patients with vigorous achalasia, no association between the timing of surgery relative to symptom onset and recovery of morphologically normal esophageal peristalsis was observed.[6] Similarly, in our series the duration of symptoms prior to therapy was not associated with the presence or absence of peristaltic sequences or the ability to clear either liquid or viscous boluses in either treatment group. Based upon the available evidence, including the results of the present work, it remains impossible to predict which patients will most likely recover esophageal function after treatment.

The fact that, after Heller myotomy, the improvement in esophageal peristalsis correlates with the success of esophageal bolus transit is an important finding. It stands to reason that esophageal peristalsis and bolus transit are intimately associated, yet many patients have reportedly adequate relief of dysphagia in the face of persistent aperistalsis after surgical management of achalasia. For many (possibly all) patients, the effect of gravity no doubt plays a major role in clearance. However, the significant though modest improvement in esophageal function demonstrated by manometry combined with MII in this study may in part explain why dysphagia is so consistently relieved by Heller myotomy.

Conclusion

Both surgical and non-surgical therapies produce relief of dysphagia in achalasia. Using esophageal manometry to assess motility combined with multichannel intraluminal impedance to evaluate esophageal bolus transit, modest but significantly better esophageal body function can be demonstrated in patients who have undergone either endoscopic treatment (botox injection or balloon dilation) or surgical management (Heller myotomy) compared to patients with untreated achalasia. Although bolus clearance rates and the percentage of patients with at least some peristaltic sequences after myotomy are statistically similar to those after endoscopic treatment, peristaltic contraction rates correlate with liquid and particularly viscous clearance only after myotomy. These findings also suggest the utility of manometry/MII in the post-treatment follow-up of patients with achalasia. An assessment of esophageal body function may help clarify situations in which symptoms persist despite manometrically adequate ablation of the LES. Ultimately, larger sample sizes, particularly of patients both before and after treatment, would likely increase the strength of the conclusions presented here and perhaps reveal further insight into esophageal body function after treatment for idiopathic achalasia.

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High Resolution Anoscopy in the Planned Staged Treatment of Anal Squamous Intraepithelial Lesions in HIV-Negative Patients

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Abstract Anal dysplasia (low-grade squamous intraepithelial lesions, LSIL; high-grade squamous intraepithelial lesions, HSIL) is a challenging disease for the surgeon. We reviewed 42 patients that underwent high-resolution anoscopy (HRA)-targeted surgical therapy of anal dysplasia in the past 10 years. Patients were followed up in the Anal Neoplasia Clinic with physical examination, cytology, HRA, and biopsy if indicated. Patients with disease amenable to local therapy were treated with office-based HRA-directed therapies. There were 30 men (mean age 39 years, range 21–63) and 12 women (mean age 50 years, range 31–71) included in the study. HSIL was present in 33, with four undergoing planned staged treatment due to circumferential disease. HSIL recurred in 45%, and most were re-treated successfully in-office. Progression to HSIL was seen in one patient with LSIL and to squamous cell carcinoma in one patient with HSIL despite therapy. No patients with LSIL had dysplasia at last follow-up. Minor complications occurred in three patients. HRA-targeted surgical therapy coupled with surveillance and re-treatment with office-based therapies offered an effective method in controlling anal dysplasia in the immunocompetent patient. Morbidity is minimal, and our progression to cancer rate is low (2.4%).

Keywords High-resolution anoscopy · Anal dysplasia · Surgical treatment · Low-grade squamous intraepithelial lesions · High-grade squamous intraepithelial lesions

Introduction

Anal dysplasia is an uncommon, challenging disease for the practicing surgeon. Its management is controversial, as many treatment options are available with different degrees of morbidity and success. This is particularly true of the putative precursor of anal cancer, high-grade squamous intraepithelial lesions (HSIL) otherwise known as Bowen's disease, squamous cell carcinoma in situ, and anal intraepithelial neoplasia (AIN) II/III.[1] HSIL is most commonly found in the average surgeon's practice as an incidental finding noted by the pathologist upon review of a surgical specimen generally obtained during hemorrhoidectomy in an immunocompetent patient. Other patients present with complaints of pruritus and/or bleeding, and physical exam reveals a scaly, raised, erythematous patch, which, upon biopsy, is confirmed as squamous cell carcinoma in situ.

The traditional approach to these clinical scenarios entails punch biopsy mapping of the anus performed in the operating room (16–24 biopsies), with frozen section analysis and subsequent wide local excision.[2,3] This is a morbid procedure, as it often requires flap reconstruction and sometimes a diverting or permanent stoma, with some patients developing anal stenosis.[4] Despite the magnitude of the procedure, the recurrence rate varies from 12–23%. Because of the associated morbidity and uncertainty regarding the risk of progression to cancer with HSIL, some have suggested topical imiquimod[5], photodynamic

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therapy[6], or surveillance with biopsy and local excision. The results for imiquimod and photodynamic therapy are promising, but have short follow-up, and local excision has a progression to cancer rate of 11%.[7] Unfortunately, these reports either do not state the immune status of the patient or deal exclusively with the immunocompromised patient, most commonly HIV-positive men who have sex with men, leaving the practicing surgeon to extrapolate from these reports to the immunocompetent patient population.

We have advocated using high-resolution anoscopy (HRA) to directly identify and treat anal dysplasia with destruction or excision both in the office and in the operating room. This technique is analogous to colposcopy and is effective in detecting high-grade lesions[8], permitting targeted therapy[9,10] while preserving normal mucosa and skin. Ablation of lesions detected by HRA using the infrared coagulator (IRC) is an effective office-based treatment for patients with HSIL and condylomata.[11] Acceptance of HRA and targeted destruction of HSIL has been hampered by the underreporting of patients' immune status, the uncertain but low rate of progression from untreated HSIL to cancer, and whether treatment of HSIL ultimately results in cancer prevention. Further, even with low volume disease, many feel that current treatment regiments result in high recurrence rates. As a major referral center, we often see patients who would be at highest risk for local recurrence, those with either large volume disease or low volume disease not amenable to local therapy. We therefore reviewed our 10-year experience in the management of these immunocompetent patients with HRA-targeted destruction/excision in the operating room.

Materials and Methods

We reviewed patients from our prospective database who were operated on for anal dysplasia from July 1996 to July 2006 at the University of California, San Francisco after approval from the Committee on Human Research. Patients are referred to the Anal Neoplasia Clinic when they are considered at high risk for HPV-related disease secondary to sexual activity or when there is clinical evidence of HPV-related disease, such as condylomata or anal neoplasia, that is beyond the scope of the clinicians' expertise. Patients were evaluated and followed up in the Anal Neoplasia Clinic with physical examination, HRA, cytology, and biopsy (when necessary). The majority of patients are treated with HRA-directed ablation procedures such as trichloroacetic acid (TCA) destruction or IRC. Of 437 patients treated in the operating room for LSIL or HSIL with HRA-directed ablation with electrocautery or excision of the lesions, 42 were HIV-negative, did not become seropositive during follow-up, and were not immunosuppressed for other reasons. Patients were referred to surgery due to either large volume disease or low volume disease that was not amenable to office-based therapy secondary to location or coexisting anorectal pathology. Patients included in this review had at least one office visit after surgery and a minimum follow-up of 5 months. Charts were reviewed for sex, age, pathology reports, follow-up visits, and subsequent surgical and office-based procedures. A summary analysis of the data was performed.

Recurrent HSIL was defined as any cytology- or biopsy-proven HSIL in a patient who had no evidence of HSIL at the first postoperative visit. Similarly, recurrent LSIL was defined as any cytology- or biopsy-proven LSIL in a patient who had no evidence of LSIL at the first postoperative visit. Progression was defined as any increase in grade/invasion from the preoperative diagnosis during postoperative follow-up (from LSIL to HSIL, HSIL to cancer). Patients with evidence of HSIL at the first postoperative visit were considered to have persistent disease requiring staged treatment. Patients with recurrences amenable to HRA-guided office-based procedures were treated with either IRC[11,12] or TCA. Extent of disease was defined only for patients operated on for HSIL and refers to the amount of anal circumference affected by disease. Less than 25% anal circumference was considered limited, and more than 25% was considered extensive.

Surgical Technique

Surgery was performed in an outpatient setting under monitored anesthesia care as previously described.[9,10] With the patient in the prone jackknife position, a perianal block with 0.25% marcaine without epinephrine and 0.25% marcaine with epinephrine was placed in the anal sphincters submucosally and subcutaneously. A 4×4 gauze soaked in 3% acetic acid was placed in the anus for 1 min. HRA was then systematically performed examining the distal rectal mucosa, anal mucosa, and perianal skin through an operating microscope.

Tissues that became white with acetic acid (acetowhite) were scrutinized for vascular changes such as punctation and mosaicism and epithelial patterns such as honeycombing and hyperpigmentation that are consistent with HSIL.[8–10] Lugol's iodine solution was used selectively on the non-keratinized anal mucosa to assist in clarifying the clinical impression of acetowhite lesions. HSIL in the anal mucosa turns yellow due to the absence of glycogen, while normal anal mucosa turns dark mahogany brown with the application of Lugol's solution. However, Lugol's is not helpful in evaluating either the keratinized mucosa of the anal verge and perianal areas or the normal columnar rectal

mucosa. The location of all lesions visually consistent with LSIL and HSIL was documented, and then the lesions were destroyed with needle-tip cautery under direct visualization through the operating microscope, taking care to avoid injury to the surrounding normal tissues to minimize the risk of anal stenosis. Biopsies were taken when necessary to confirm disease or to rule out cancer. Often, lesions visually consistent with HSIL were not biopsied, but were destroyed with electrocautery, as the level of injury resulting from cautery is more easily controlled, thereby minimizing the impact on underlying tissues.

Planned Staged Procedures

Patients with circumferential disease were treated in a staged fashion to minimize the risk of anal stenosis. At the initial procedure, the majority of the disease was treated, but the surgeon would attempt to leave skin bridges much like when multiple hemorrhoidectomies are performed at one setting. These skin bridges were then evaluated in the Anal Neoplasia Clinic and, if persistent HSIL was not amenable to office-based therapies due to location, then patients were taken back to the operating room for a planned second procedure.

Results

Of the 42 patients reviewed, 30 (71%) were men, with age ranging from 21–63 years (mean age=39 years). Mean age for women was 50 years and ranged from 31 to 71 years. Of the 12 women, 8 (67%) had a concurrent HPV-related lesions (vulvar, vaginal, or cervical intraepithelial neoplasia). One man (3%) had a penile condyloma.

Before surgery, HSIL was present in 33 patients (79%) and LSIL in 9 (21%). Three of the nine patients with an initial diagnosis of LSIL were found to have HSIL, two at time of initial surgery and one during follow-up. Two patients with HSIL had lesions suspicious for malignancy and were taken to the operating room to rule out cancer. Extensive disease was present in 25 (67%) patients with HSIL, but only four required a planned staged procedure.

Thirty-three patients (79%) had intraoperative biopsies performed. LSIL was found in 10 (30%), HSIL in 17 (52%), and 4 (12%) had either squamous metaplasia or inflammatory changes. Biopsies confirmed the presence of SCC in two patients (6%). One had a superficially invasive SCC that was completely excised. The patient is currently undergoing treatment for surrounding HSIL. The other patient had invasive SCC, completed chemoradiation therapy, and was disease-free at 5 months follow-up. Neither patient with SCC had been previously seen or treated in the Anal Neoplasia Clinic.

Planned Staged Procedures

Of the four patients with planned staged procedures, two patients were treated in the office with IRC (±TCA) and are disease-free; one is undergoing treatment for persistent HSIL despite treatment in the operating room and one office treatment with IRC. The final patient had been previously treated with wide local excision and had anal stenosis before referral to our clinic. She had multiple recurrences at the same site, requiring five reoperations and recently progressed to invasive cancer at the site of her documented HSIL. Treatment and follow-up were compromised due to her preexisting anal stenosis.

Recurrence

Of all 42 patients, 33 had a preoperative diagnosis of HSIL, and 15 (45%) of those recurred at an average of 18 months with a range of 5 to 92 months. Of these 15 recurrences, eight were re-treated in the office with IRC, three were re-treated with IRC and TCA, two were lost to follow-up, and one had subsequent exams in which HSIL was not detected in spite of not having any specific therapy. The final patient recurred recently (55 months) and has not undergone therapy yet. Of the 11 patients that underwent IRC (±TCA) after recurrence, five (45%), five (45%), and one (1%) required one, two, and four treatments, respectively. Only 1 of the 15 patients treated with IRC (±TCA; 7%) had LSIL at their last office visit, and the rest had no evidence of dysplasia.

Of the nine patients with LSIL preoperatively, two had HSIL diagnosed at the time of surgery. One patient was re-treated in the office with IRC, but was lost to follow-up, and the other patient had no evidence of dysplasia at his last follow-up visit. Another patient progressed to HSIL 4 months after surgery, requiring a total of three re-treatments with IRC and TCA to successfully eradicate any dysplasia. At the last follow-up visit, none of the patients with LSIL had evidence of dysplasia.

At an average follow-up of 36 months (range 5–125), 36 patients (86%) had no evidence of disease, 2 (5%) had LSIL, 3 (7%) still had HSIL, and 1 (2%) had SCC.

Complications

Significant complications occurred in three patients (7%), one had a postoperative fissure, one developed cellulitis at the local anesthetic injection site, and one had worsening anal stenosis. The patient with anal stenosis had already been treated with wide local excision before referral. No patients in this series required flap reconstruction or stoma placement. There were no deaths, and one patient progressed to cancer in spite of ongoing treatment and follow-up.

Discussion

The management of HSIL (carcinoma in situ or Bowen's disease) in the immunocompetent patient is controversial due to the limited literature available to the practicing clinician. Many reports focus on the treatment of this disease in the immunocompromised patient[13], while others do not record the patients' immune status[7], making extrapolation to the immunocompetent patient difficult.

We have previously suggested that HRA with targeted destruction is an effective alternative to punch biopsy mapping and wide local excision in the management of HSIL. Those reports focused primarily on the immunosuppressed patients. Despite our local success with HRA-targeted destruction or local excision, the technique has not gained wide acceptance because of additional training requirements, high recurrence rates, reports of significant morbidity, and lack of long-term follow-up. This report is the first to define long-term follow-up in immunocompetent patients treated with a comprehensive treatment plan for anal dysplasia.

HRA is not complex and is achieved through the use of either an operative microscope or a colposcope to visualize the distal rectal mucosa, anal mucosa, and perianal skin that has been treated with acetic acid and/or Lugol's solution. Mucosa and skin containing LSIL and HSIL reveal characteristic vessel patterns when the tissues are treated with acetic acid and viewed through an operative microscope.[8–10] This approach makes largely invisible lesions apparent when the clinician has been trained to recognize the patterns associated with the various disease states. Although some have questioned the utility of HRA, a recent series notes that only 51% of patients with anal dysplasia had visible disease with standard anoscopy[7], thus, highlighting the potential benefit of HRA.[8]

Intervention with HRA and targeted destruction has been criticized for the high recurrence rates of HSIL, suggesting to some the futility of surgical intervention.[13] We have chosen to approach the management of HPV-related dysplasia of the anorectum in much the same way as the gynecologists treat HPV-related dysplasia in the cervix and vagina. Because HPV infection may persist, we will potentially encounter recurrent LSIL and HSIL. The goal of HRA and targeted destruction is that of controlling the disease, minimizing injury to uninvolved tissues, and preventing the progression to anal cancer through a comprehensive surveillance and treatment program. Through this program, we found that most recurrences occur early during follow-up (18 months; Fig. 1), with the highest recurrence rate in patients who had HSIL preoperatively (45%). Disease did recur as late as 92 months, underlining the need for continued surveillance. Although the initial recurrence rate is high, two thirds of our patients in this report had extensive disease, and we often intentionally left disease behind for subsequent office-based therapy which resulted in eradication of HSIL in 90% of the patients. This compares favorably with punch biopsies and wide local excision where recurrences have been reported in 11–23% of patients.

HRA-targeted treatment of LSIL/HSIL as an effective tool in preventing anal cancer has also been criticized for lack of follow-up. Progression described in the classic literature of Bowen's disease to anal SCC is 5.7%.[14] However, as it has not been clear when and in whom Bowen's disease will progress to invasive SCC, some have advocated surveillance with biopsies and local excision. In one series of patients managed in this fashion, 11% developed cancer[7], and the rate is even higher in immunocompromised patients.[13,15] In another series where patients

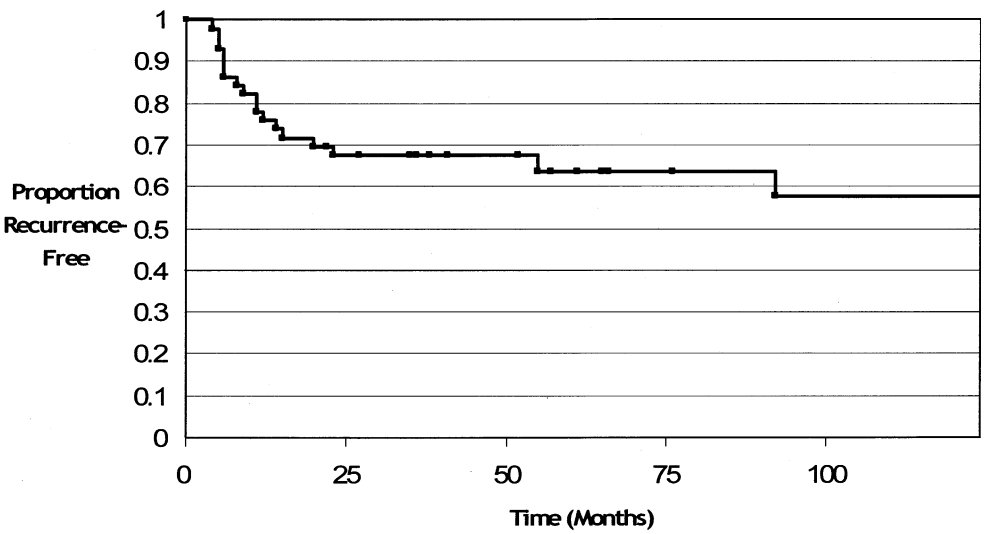

Figure 1 Kaplan–Meier analysis of proportion of recurrence-free patients after initial surgical treatment of anal high-grade squamous intraepithelial lesions.

underwent wide resection with flap reconstruction, 11% progressed to SCC.[16] In our series, one patient (2.4%) progressed to cancer. However, this patient had been treated previously with wide excision. She presented to our clinic with anal stenosis and incompletely treated disease. Her preexisting condition compromised our ability to monitor and treat her. Although it is difficult to state conclusively that our approach of treatment, surveillance, and re-treatment of HSIL prevents anal cancer, our rate of progression (2.4%) compares favorably to that of the pre-HIV era classic literature of Bowen's disease progressing to anal cancer (5.7%).

Although pathology review of intraoperative biopsies found squamous metaplasia or inflammation in four patients (12%), this most likely represents sampling error. Biopsy of mucosal lesions overlying hemorrhoidal cushions is often complicated by significant hemorrhage. Control of hemorrhage results in destruction of the lesion that the surgeon was attempting to biopsy, thereby compromising the pathologist's ability to confirm the visual impression of HSIL. These difficulties encountered while attempting to biopsy suspicious lesions led us to abandon routine biopsy of lesions, as we became more confident in the accuracy of our visual diagnosis.

It is important to note that of the three patients that had LSIL as their preoperative diagnosis, two had HSIL found at the time of surgery and one progressed to HSIL at 4 months of follow-up. This is consistent with a series where patients with cytologic and clinical evidence of LSIL also harbored HSIL and SCC[17], further underlining the need for thorough and continued evaluation.

HRA with targeted destruction of HSIL has been criticized because of the associated morbidity, principally postoperative pain.[9] Although patients with extensive disease such as those presented in this paper and in our earlier report require extensive cautery, the pain is quite similar to that associated with an hemorrhoidectomy. The morbidity that we observed with these procedures is less than that associated with traditional mapping and wide local excision, flap reconstruction, and stoma placement.[2–4]

Lastly, the equipment required to perform HRA is available in any gynecology clinic and operating room. Training in the technique is available on an ongoing basis through the American Society for Colposcopy and Cervical Pathology (http://www.asccp.org) and has been offered by the American Society for Colon and Rectum Surgeons (http://fascrs.org), and the American College of Surgeons (http://facs.org).

Conclusion

HRA-targeted therapy as the cornerstone of targeted surgical destruction is effective in the planned staged treatment of anal squamous intraepithelial lesions (HSIL and LSIL) in immunocompetent patients. Despite an initial high recurrence rate, recurrent lesions are controlled with HRA-guided office-based procedures even in patients who present with extensive disease. A planned surgical staged approach is suitable for patients with circumferential disease to minimize the risk of anal stenosis. The observed rate of HSIL progression to cancer with our approach of treatment, surveillance, and re-treatment compares favorably to that reported by others (2.4% versus 5.7–13%). This approach may be an effective means to minimize the risk of HSIL progressing to cancer.

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DISCUSSION

John H. Pemberton, M.D. (Rochester, MN): The authors must be congratulated for trying to sort out this particularly difficult neoplastic lesion. It seems like it has been confusing for just about forever. Historically, at least in the Midwest, we have seen patients with large areas of erythematous perianal skin, which, when biopsied, was positive for in situ squamous cell cancer. This was termed Bowen's disease, and these areas were widely excised. Clearly, this approach does not seem appropriate for patients with discontinuous disease such as those described by you today. This problem is so rare that few people, with the exception of these authors, have extensive experience with it. It is indeed difficult to characterize and categorize.

Perhaps we should think of factors that might influence approaches to treatment, such as HIV positive or negative; HPV positive or negative; location (perianal or anal canal); and distribution of the process (continuous or discontinuous). Therefore, I wish to ask four questions.

First, would it be useful to include distribution of disease, the location, and its distribution as an additional way of categorizing patients in order to determine an accurate and acceptable treatment plan? Second, is it reasonable to assume, for those of us who are a little older, that Bowen's disease and AIN2 and 3 are the same? Third, what is the role of HPV testing in these patients? And finally, you did not mention it, but I would be interested to know your take on the role of Aldara in the management of either discontinuous or continuous disease in order to prevent our patients from having to have those complicated flaps that you illustrated.I wish to thank you again for sending the manuscript and for a great presentation.

Carlos E. Pineda, M.D. (Stanford, CA): Regarding the distribution and categorization of disease, we think it is very important that clinicians try to specify where the lesions are located. Our group encourages the use of standardized, simple terminology in order to facilitate communication among clinicians, using intra anal, perianal and skin to define disease location. When planning therapy, it is important to note that disease can occur above the dentate line. Disease in this location is not evaluated with the standard mapping procedures for "Bowen's disease" using punch biopsies.

Anal squamous high-grade intraepithelial lesions (HSIL), anal intraepithelial neoplasia II/III (AIN), Bowen's disease, and squamous cell carcinoma in situ are different names for the same disease. Training in histopathology, cytopathology, or dermatopathology lead to the different word choices, but all refer to the same pathologic process.

The role of HPV testing at this moment is unclear. In the future, microarray technology may allow us to analyze which subsets of HPV 16 and 18 will progress to invasive disease.We have seen mixed results with the use of Aldara. Some patients respond dramatically and clear all disease. However, the majority of patients do not respond as well and require further therapy.

Dr. Pemberton: Is there anything to characterize those that don't respond? How do they differ from those that do?

Dr. Pineda: We have not had personal experience that allows us to predict treatment success. Some feel that the more keratinized lesions are slower to respond and the clinician should persist in their treatment despite apparent lack of response.

Michael J. Stamos, M.D. (Orange, CA): I really enjoyed your talk today and think this is a great addition to the literature, particularly in that group of immunocompetent patients who we are faced with on a regular basis that have this problem. A few questions.

First question is, how many of your patients had visible disease? I mean, these are not patients you are screening because they are not high risk. So if these are patients with visible disease, I think the idea that anybody recommends watchful waiting is a little bit off, because most people who recommend watchful waiting do so in patients who have no visible disease. So the first question is, how many patients had visible disease versus no apparent disease?

The second question is, do you have any information on progression in those two groups, because I think that is another separate sub categorization that is very important for us to have to know whether we need to have this kind of procedure done on patients who have no visible disease, i.e., they underwent a hemorrhoidectomy and in the specimen they found some AIN.

And then finally, you had one patient who you said progressed to squamous cell carcinoma. Are you certain that she progressed and/or was she just delayed in diagnosis

because she had this complicating factor and you didn't biopsy the correct area early on but only after subsequent staged procedures?

Thank you.

Dr. Pineda: We did not track which patients had visible disease at initial evaluation, as it predominantly represents condylomatous disease caused by HPV 6 and 11. We can say that the vast majority of HSIL were not visible without the use of an operating microscope and acetic acid.

The woman who progressed to anal squamous cell carcinoma had undergone four operations over a 53 month period for recurrent HSIL in the posterior midline. During each of these procedures she was evaluated by an experienced colorectal surgeon (senior author) with a digital rectal exam, as well as high resolution anoscopy. During the fifth procedure she was noted to have an indurated lesion in the same location, we therefore conclude that this represents progression.

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Computed Tomography in the Diagnosis of Acute Appendicitis: Definitive or Detrimental?

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Abstract
Objectives Utilization of computed tomography (CT) scans in patients with presumed appendicitis was evaluated at a single institution to determine the sensitivity of this diagnostic test and its effect on clinical outcome.
Methods Adult patients (age>17 years) with appendicitis were identified from hospital records. Findings at surgery, including the incidence of perforation, were correlated with imaging results.
Results During a 3-year period, 411 patients underwent appendectomy for presumed acute appendicitis at our institution. Of these patients, 256 (62%) underwent preoperative CT, and the remaining 155 (38%) patients did not have imaging before the surgery. The time interval between arrival in the emergency room to time in the operating room was longer for patients who had preoperative imaging (8.2±0.3 h) compared to those who did not (5.1±0.2 h, $p<0.001$). Moreover, this possible delay in intervention was associated with a higher rate of appendiceal perforation in the CT group (17 versus 8%, $p=0.017$).
Conclusions Preoperative CT scanning in patients with presumed appendicitis should be used selectively as widespread utilization may adversely affect outcomes. The potential negative impact of CT imaging includes a delay in operative intervention and a potentially higher perforation rate.

Keywords Appendicitis · Diagnosis · Perforation · Imaging · CT

Introduction

Approximately 250,000 appendectomies are done per year in the USA, making it the most common emergency procedure performed by general surgeons. Despite such a large number of cases, diagnosis is often difficult. Demonstrating this fact, at the time of operation, a normal appendix is found in approximately 15–20% of cases.[1] Much of the uncertainty in diagnosis occurs in women of childbearing age and in patients with atypical presentations.

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The consequences of a negative appendectomy include development of intraabdominal adhesions, adverse effects of anesthesia, cost, and negative effects on quality of life from unnecessary surgery.[2,3] To demonstrate the potential negative impact on these patients, the complication rate after a negative appendectomy may be as high as 6% and reoperation occurs in up to 2%.[4] On the other hand, in patients with appendicitis, delaying the time to definitive intervention may lead to negative consequences including perforation. Appendiceal perforation is associated with a threefold increase in complications, including an eightfold increase in abscess formation. There are also higher rates of reoperation, sepsis, infertility, and dehiscence associated with perforated appendicitis, compared to simple appendicitis.[1] Thus, a great deal of effort has been placed on making an early and accurate diagnosis, as multiple complications can occur, both in the setting of a false-negative and a false-positive diagnosis.

Computed tomography (CT) scan is playing a larger role in clarifying the clinical picture in patients with presumed appendicitis, particularly over the last decade. CT was popularized in the late 1990s after publication of a prospec-

tive trial that supported the routine use of CT with rectal contrast. This trial found that CT was 98% accurate in diagnosing appendicitis, although the technique employed is not commonly utilized.[5] Another prospective randomized trial in patients with atypical symptoms of appendicitis determined that noncontrast CT scan is superior to ultrasound in diagnostic accuracy and reliability.[6] Because of these studies, the use of CT for the routine diagnosis of appendicitis has markedly increased at our institution over the last decade. Therefore, we sought to evaluate the sensitivity, specificity, and positive and negative predictive value of CT, and its effect on clinical outcome at an academic teaching institution.

Materials and Methods

Four hundred and eleven adult patients (age>17 years) underwent emergency appendectomy for presumed appendicitis at the University of Wisconsin Hospital and Clinics over a 3-year period from January 2002 through December 2004. These patients were identified by ICD-9 codes. Medical records were retrospectively reviewed to assess whether CT scans were utilized for preoperative diagnosis. Patients were analyzed for demographic variables such as age and gender. In addition, each patient's medical record was reviewed to evaluate white blood cell count, time interval from emergency room to operating room, laparoscopic versus open procedure, operating room time (defined as incision to closure), and presence or absence of appendiceal perforation. Pathology results for each specimen were reviewed. Perforation was defined as either gross perforation found at the time of operation and/or microperforation discovered on histological exam. This study was approved by the University of Wisconsin Institutional Review Board.

Our policy was to utilize abdominal and pelvis CT scans with intravenous and oral contrast. However, if patients had renal insufficiency, patients either underwent prehydration or the intravenous contrast was withheld. During the time of the study, there was no institutional policy dictating which patients received CT scans. In general, patients were first evaluated by emergency room (ER) physicians followed by surgical residents. CT scans may have been ordered by the ER physician or the surgical team. Patients with negative CT scans underwent operative intervention if there was a high clinical suspicion of appendicitis. During the time of the study, patients with appendicitis underwent operation at the time of the next available operating room.

Statistical Analysis

Statistical analyses between groups were performed with analysis of variance (ANOVA) using Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., version 14.0). Data are represented as mean ± SEM. Sensitivity was defined as the number of cases of appendicitis correctly diagnosed by CT divided by the total number of cases of appendicitis. Specificity was defined as the number of cases without appendicitis divided by the number of negative tests obtained. Indeterminate CT scans were categorized as negative, as they did not assist with clinical decision-making. Positive predictive value was calculated from the number of positive cases of appendicitis cases diagnosed by CT compared to the total number of positive CT scans. Negative predictive value was calculated from the number of negative cases of appendicitis cases diagnosed by CT compared to the total number of negative CT scans. Significance was defined as a p value<0.05.

Results

Patient Demographics

Of the 411 appendectomy patients, 256 (62%) had a preoperative CT, and the remaining 155 (38%) patients did not have imaging before their operation. The median age was older for the CT group compared to the non-CT group (Table 1). The majority of the patients were male, but a higher percentage of females underwent CT imaging. The mean white blood cell (WBC) counts at presentation to the emergency room (ER) were similar between the two groups (Table 1).

Operative Results

Comparisons were made between the number of laparoscopic versus open appendectomies in each group. There was a significant difference with more laparoscopic procedures performed in the non-CT group (Table 2). The mean operating time for both CT and non-CT patients was 1.2 h.

The final pathology in the corresponding groups is found in Table 3. Overall, CT had a sensitivity of 92% (208:225) and a specificity of 68% (21:31). The positive and negative

Table 1 Patient Demographics

	Number of Patients	Mean Age	Gender		WBC (×1,000)
			Male	Female	
CT	256	37±1	127	129	13.6±0.3
No CT	155	31±1	103	52	14.4±0.3
p Value		<0.001	0.001		NS

Mean ± SEM
NS Not significant, *WBC* white blood cell

Table 2 Operative Results

	OR Time (Hours)	Percent Laparoscopic
CT	1.2±0.1	88%
No CT	1.2±0.1	96%
p Value	NS	0.003

Mean ± SEM
NS Not significant, *OR* operating room

predictive values were 91% (208:229) and 37% (10:27), respectively.

The negative appendectomy rate for patients diagnosed with appendicitis on CT was 8% (19:227). For all patients who underwent appendectomy without preoperative imaging, the negative appendectomy rate was 14% (22:155), which was not significantly different ($p=0.09$). In addition, 7 of 14 patients with negative CT scans were ultimately found to have appendicitis; thus, the negative appendectomy rate in patients with negative CT scans was 50% ($p<0.001$, compared to those with CT scans positive for appendicitis). When evaluating both negative and indeterminate scans together, the negative appendectomy rate was 37% (17:27, $p<0.001$).

Outcomes

The time interval from the patient's first contact in the emergency room to the operating room start time was significantly longer in the CT group as compared to the non-CT group (Table 4). In addition, the rate of perforation (based on final pathology and intraoperative observation) was significantly greater in the imaging group [17% (43:256) versus 8% (13:155), $p=0.017$].

Because more patients in the CT group actually had appendicitis [89% (225:254) versus 86% (134:155) in the non-CT group], we compared perforation rates in those with pathologically proven appendicitis. In this group, the perforation rate remained significantly elevated in the CT group [19% (42:225) versus 10% (13:133), $p=0.033$].

Table 3 Pathological Results

		Pathology		
		Positive	Negative	Indeterminate
CT scan				
	+	208	19	2
	−	7	7	
	+/−	10	3	
No CT		133	22	

(+) Appendicitis, (−) normal appendix, (+/−) indeterminate

Table 4 Outcomes

	Time from ER to OR (Hours)	Percent Perforation (All specimens)	Percent Perforation (Appendicitis only)
CT	8.2±0.3	17%	19%
No CT	5.1±0.2	8%	10%
p Value	<0.001	0.017	0.033

Mean ± SEM
ER Emergency room, *OR* operating room

Discussion

The diagnosis of acute appendicitis is often not straight forward. Imaging studies, including CT scans, have been employed at increasing rates over the last decade in an attempt to improve diagnostic accuracy. In this study, the use of CT scan for diagnosis of appendicitis and its effect on clinical outcome was retrospectively reviewed at our institution. The two major findings of this investigation are (1) there was no significant difference in the negative appendectomy rate between those that had preoperative imaging and those that did not and (2) there was a significantly longer time to operation in patients who had preoperative CT scan, and this was associated with an increased rate of appendiceal perforation.

Although initial reports on the use of CT scans in patients with appendicitis concluded that CT should be used routinely in all patients suspected to have appendicitis, more recent reports suggest that a selective approach is likely more beneficial.[1,5,6] As these more selective approaches to preoperative imaging have been employed, it has become clear that CT scanning is beneficial for the diagnosis of appendicitis in patients with atypical presentations and in women of childbearing age.[7] However, this is not without increased cost, radiation exposure, and a potential delay in time to definitive treatment. To demonstrate this, even in studies that utilized a selective approach to imaging with the use of an institutional pathway, CT was obtained in 529 cases but only a minority (97, 18%) actually had appendicitis.[1] It is clear that we still need to make progress in clinically assessing patients with presumed appendicitis, and, even when CT is used selectively, the cost of making an accurate diagnosis remains high. Although institution of a clinical pathway in one study, Antevil et al., led to a substantial decrease in the number of negative appendectomies (from 16 to 4%, $p<0.001$), the issue of improving patient selection for CT remains a problem.

The negative appendectomy rate in the present study was 11% (29:256), which is consistent with the national

Table 5 Summary of Recent Prospective, Randomized Trials Evaluating Use of CT for Diagnosis of Appendicitis

Study	Type of Study	Number of Patients	Type of Contrast	Sensitivity (%)	Specificity (%)	Accuracy (%)	Negative Appendectomy Rate (%)
Walker[15]	Prospective randomized	63	No CT (PE only) OR PO and/or IV contrast	100	79	89	19
		65 (CT)	Rectal	94	100	96	5
Mittal[14]	Prospective randomized	52	Triple contrast (PO, IV, rectal)	97	86	92	8.3
		39	Rectal only	88	100	92	7.7
Hong[12]	Prospective randomized	68	None	100	73	90	NA
		97(CT)	PO, IV	91	93	92	NA

CT Computed tomography group, *PO* oral contrast, *IV* intravenous contrast, *NA* not available

average. The negative appendectomy rate for patients receiving CT imaging was 8% compared to the non-CT group rate of 14%, which was not a significant difference (p=0.09). Importantly, of the 14 patients with CT scans determined to be negative, seven of these patients were found to have appendicitis at surgery, resulting in a 50% false negative rate. Thus, this reiterates the importance of relying on clinical findings even in the setting of a negative CT.

Although not examined in this study, it is clear that prolonged time from first symptoms to definitive operation increases the risk of rupture in patients with appendicitis.[8,9] In fact, the risk of rupture increases approximately 5% for each ensuing 12-h period after 36 h.[8] In addition, multiple studies, including our own, have found that utilization of preoperative CT scan leads to a delay in definitive treatment.[8,9,10–12] Some studies have found that obtaining a CT results in a delay to operative intervention as great as 6–12 h compared to patients that did not have preoperative imaging.[8,13]

One area not examined in this retrospective study is the type of contrast utilized for the CT and whether the accuracy of CT is dependent on route of contrast administration. There are conflicting opinions as to whether the use of intravenous, oral, and/or rectal contrast will result in the most accurate images (Table 5). The original prospective study evaluating the accuracy of CT for the diagnosis of appendicitis utilized rectal contrast only, and other prospective randomized trials concluded that the use of rectal contrast only compared to triple contrast (intravenous, oral, and rectal) resulted in decreased delay to definitive surgery, decreased perforation rate, and a decrease in contrast-related morbidity without any compromise in diagnosis.[5,14] In spite of this, the routine practice employed by many institutions is to utilize oral and intravenous contrast for the diagnosis of appendicitis, likely

Table 6 Summary of Recent Retrospective and Prospective Nonrandomized Trials Evaluating Use of CT for Diagnosis of Appendicitis

Study	Type of Study	Number of Patients	Type of Contrast	Sensitivity	Specificity	Accuracy	Negative Appendectomy Rate (%)
Torbati[16]	Prospective nonrandomized	250	None, PO, IV, rectal	92%	97%	96%	7.8
Hershko[17]	Prospective nonrandomized	198 (CT)	PO, IV	91%	92%	91%	16
in't Hof[18]	Prospective nonrandomized	103	None	95.4%	100%	95%	NA
Rao[5]	Prospective nonrandomized	100	Rectal	98%	98%	98%	NA
Lee[11]	Retrospective	766 (total)	NA	83	31.7	74.9	15.7
		47 (CT)	NA	83.8	40	74.5	NA
Fuchs[19]	Retrospective	42	None				11.9
		182	PO, IV	99%	96%	97%	6.3
Present study	Retrospective	155	None				14
		256 (CT)	PO, IV	92%	68%	88%	8

CT Computed tomography group, *PO* oral contrast, *IV* Intravenous contrast, *NA* not available

because of the fact that this also allows for assessment of other areas of intra-abdominal pathology. Tables 5 and 6 summarize recent studies and the sensitivity, specificity, and accuracy for CT imaging of appendicitis.

The major limitation of our study, as well as many of the cited studies, is its retrospective design. Another limitation is that only patients undergoing abdominal exploration for appendicitis were included. CT may have benefited patients with suspected acute appendicitis but who were successfully managed non-operatively after a negative CT, or who were found to have other intraabdominal explanations for their abdominal pain based on findings on CT.

In conclusion, preoperative CT scanning in patients with suspected appendicitis should be used selectively as widespread utilization may adversely affect outcomes. We believe that CT imaging does have a role in the diagnosis of acute appendicitis, particularly in patients with atypical presentation and in women of childbearing age with unusual symptoms. The routine use of CT scan to evaluate patients suspected of having acute appendicitis will result in unnecessary exposure to contrast and radiation in a large number of patients and delay in operation intervention. Therefore, it should be discouraged.

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DISCUSSION

Attila Nakeeb, M.D. (Indianapolis, IN): Thanks for a very elegant presentation and for the opportunity to review your manuscript. I think it has become clear that in many hospitals in the United States nobody goes to the operating room for an appendectomy without a CAT scan. Your study shows that a CT scan doesn't really help and it may actually be detrimental to your patients. A high index of suspicion and a good clinical exam seem to be more important in treating patients in a timely fashion and hopefully preventing perforations.

Understanding the limitations of a retrospective study, do you have any information on how many patients had CT scans in your institution to rule out appendicitis? What is your overall denominator in these patients and how many of those patients were never seen by a surgeon? Also, you have clearly shown in your study that the sensitivity is about 90%, the specificity is less than 70%, and your negative predictive value is less than 40% for CT scans in your hands. You did your scans with both oral and IV contrast. In the literature, using rectal contrast alone, you get about a 95% accuracy rate. Have you discussed changing your CT protocol to rectal contrast for patients who are specifically being evaluated to rule out appendicitis.

Finally in terms of the higher perforation rate in patients undergoing CT scans and the subsequent delay in getting to the OR, have you looked at your outcomes in those patients in regards to increases in complications, pelvic abscess, or increase in the length of stay?

I really enjoyed the paper. Thanks.

Sandeepa Musunuru, M.D. (Madison, WI): We do not have information regarding the number of patients evaluated with abdominal pain in the emergency room, or if these patients were seen by a surgical resident or attending. This is a weakness of our study due to its retrospective nature.

Regarding the second question regarding the use of rectal contrast, based on a prospective randomized study by Mittal et al., randomizing points to triple contrast vs. rectal only, there was no difference in the negative appendectomy rate.

As far as follow-up of patients for complications and length of stay, this was not included in this study.

David W. Butsch, M.D. (Barre, VT): I enjoyed your paper. I believe you said that you used the indeterminate group to be put into the negatives so that when you get your final results that might make your false negative rate higher. Did you have to take that group out and then give the rate of success of the ones that were read as positive?

Dr. Musunuru: The indeterminate scans were included in the negative scan category for statistical analysis since they did not enhance clinical decision making.

Jose M. Velasco, M.D. (Chicago, IL): I realize that it is a retrospective study. Thank you for bringing the paper and this issue to us. It is a source of frustration for all of us.

Do you have any idea as to who made the decision to obtain a CT scan? Was it before a clinical evaluation or afterwards? We are trying to encourage our residents to see the patients before a CT scan is done. Two, there are some issues as to whether a patient with a perforated appendix should be operated upon or should be treated non-operatively. Did you look at the CT scans on those patients that had perforation? Were you able to correlate whether the CT scan really was ordered because of a high suspicion for perforation and then it would be indicated? And I wouldn't include those patients. And the specificity in your study is really very low, and when you look at the series that have been published, it is much higher. Any idea why? Is it maybe technique?

Thank you. I really enjoyed it.

Dr. Musunuru: The first question was who ordered the CT scan. We do not have specific numbers of who ordered the CT scan. However at our institution, a majority of patients with acute appendicitis present to the emergency room and therefore, an emergeny medicine physician will evaluate and order the CT scan. However, if a surgical consult is requested prior to obtaining a CT scan, a surgical resident will conduct a history and physical exam and determine if imaging is necessary.

Dr. Velasco: If the person evaluated the patient clinically, did he have any idea of how frequently did the CT scan change the clinical evaluation? In other words, what is the impact of a CT scan on a patient that has clinically been evaluated?

Dr. Musunuru: The CT scan should be a tool that enhances decision making, especially in cases of atypical presentation and women of childbearing age, because of the larger differential diagnosis. Unfortunately we did not evaluate how often CT scans changed decision making. We specifically looked at patients that were operated on for presumed appendicitis, not patients with abdominal pain who were being evaluated. These are two very different patient populations, and different questions are being asked.

Dr. Velasco: The final question was, were you able to identify those patients that had a perforation and did you review the CT scan findings and how good was the CT scan in identifying those patients that had a perforation?

Dr. Musunuru: Perforations were identified based on pathology and visualization in the operating room since a majority of perforations were micro perforations not identified on CT imaging.

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Comparison of Laparoscopic vs Open Sigmoid Colectomy for Benign and Malignant Disease at Academic Medical Centers

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Abstract
Few studies have examined outcomes of laparoscopic and open sigmoid colectomy performed at US academic centers. Using ICD-9 diagnosis and procedural codes, data was obtained from the University HealthSystem Consortium (UHC) Clinical Database of 10,603 patients who underwent laparoscopic or open sigmoid colectomy for benign and malignant disease between 2003–2006. A total of 1,092 patients (10.3%) underwent laparoscopic sigmoid colectomy. Laparoscopic sigmoid colectomy was associated with a significantly shorter length of stay (5.4 vs 7.4 days), lower overall complication rate (19.7 vs 26.0%), lower 30-day readmission rate (3.4 vs 4.6), and a lower hospital cost ($13,814 vs $15,626). When a subset analysis of malignant and benign groups was performed, a significantly shorter length of stay in both the malignant laparoscopic group (6.4±6.4 vs 7.8±6.6 days) and in the benign laparoscopic groups (5.1±3.5 vs 7.2±7.6) exists. A lower wound complication rate (2.1 vs 5.5%, malignant and 4.0 vs 6.1, benign) is also evident. Laparoscopic sigmoid colectomy was associated with a shorter length of stay, less complications, and a lower 30-day readmission rate. The shorter length of stay and wound infection rate maintain significance when comparing laparoscopic vs open sigmoid resections for malignant and benign disease.

Keywords Laparoscopic sigmoid colectomy · Surgical outcomes · Laparoscopic colectomy-Open colectomy

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Introduction

In the USA, there are approximately 600,000 transabdominal colorectal procedures performed each year,[1] and it is estimated that only 10–15% of those cases are performed laparoscopically. Since the first laparoscopic cholecystectomy was performed by Muhe in 1985, laparoscopic surgery is becoming accepted as the procedure of choice for the treatment of multiple gastrointestinal procedures (e.g., antireflux, cholecystitis, and gastric bypass). Although the first reported series of laparoscopic-assisted colon resection was over 15 years ago, acceptance of laparoscopic resection for colorectal disease has been slow as a result of the technical challenge and the steep learning curve, estimated to be at least 35–50 procedures.[2] Laparoscopic resection for colorectal cancer was slowed by early reports of increased port-site recurrence when compared to the open approach.[3,4] Recent reports have shown that laparoscopic colon resection can be safe and feasible with wound recurrence that does not differ from that of open surgery.[5–10] Despite these reports, laparoscopic colorectal

surgery is still more likely performed at high-volume academic medical centers.[11] Currently both the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons have developed educational and training guidelines to aid in the increasing interest in laparoscopy.[12]

This study focuses on the in-hospital outcome of patients who underwent laparoscopic and open sigmoidectomy for both benign and malignant disease at nationwide academic centers and affiliated hospitals. We hypothesize that patients who underwent laparoscopic sigmoid colectomy for the treatment of benign or malignant disease will have better outcomes when compared to those patients who underwent open sigmoid colectomy.

Materials and Methods

Database

The University HealthSystem Consortium (UHC) Clinical Database is a source of patient-level, hospital, and discharge abstract data from affiliated academic medical centers and community hospitals in the USA. The discharge abstract data contains information regarding patient demographics, length of stay, 30-day re-admission rates, and in-hospital morbidity and mortality. The database also provides risk-adjusted data for comparison of institutions. Approval for the use of the UHC patient-level data in this study was obtained from the Institutional Review Board of the University of California, Irvine Medical Center and the UHC.

Using appropriate diagnosis and procedural codes as specified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), patients who underwent sigmoid colectomy for both benign and malignant processes between January 1, 2003 and December 31, 2006 were identified (Table 1). Using ICD-9-CM procedural codes for diagnostic laparoscopy and laparoscopic lysis of adhesions, the laparoscopic patient population was identified. Patients undergoing emergent procedures were excluded. All groups were compared with regards to patient characteristics (age, sex, race, and severity class), perioperative outcomes, and in-hospital mortality.

Patient severity class was based on the severity and complexity of the secondary diagnoses (comorbidities and complications). In-hospital mortality was defined as the percentage of patients who died before hospital discharge. Length of stay was defined as the number of days from the index procedure to hospital discharge.

Data Analysis

Statistical analysis was performed using Statistix software, version 8 (Tallahassee, FL). Analyses of differences between groups for categorical data were performed using the chi-square analysis. Differences in length of stay and cost between groups were determined by two-sample *t* tests. Data are expressed as mean±standard deviation and proportions. A *P* value of equal to or less than 0.05 was considered statistically significant.

Results

During the 4-year study period, 10,603 patients underwent either laparoscopic or open sigmoid colectomy. As shown

Table 1 ICD-9 CM Diagnostic and Procedure Codes for Laparoscopic and Open Sigmoid Colectomy

ICD-9 CM	Description
Diagnosis code	
153.0	Malignant neoplasm of colon
153.2	Malignant neoplasm of descending colon
153.3	Malignant neoplasm of sigmoid colon
153.8	Malignant neoplasm of other specified site of large intestine
153.9	Malignant neoplasm unspecified
230.3	Carcinoma in situ of the colon
211.3	Benign neoplasm of colon
562.1	Diverticula of the colon
562.10	Diverticulosis of the colon without mention of hemorrhage
562.11	Diverticulitis of the colon without mention of hemorrhage
562.12	Diverticulosis of the colon with hemorrhage
562.13	Diverticulitis of the colon with hemorrhage
Procedure codes	
457.6	Sigmoid colectomy
542.1	Diagnostic laparoscopy
545.1	Laparoscopic lysis of adhesions

Table 2 Demographics of Patients who Underwent Laparoscopic and Open Sigmoid Colectomy for Benign and Malignant Disease

	Laparoscopic (*N*=1,092)	Open (*N*=9,511)
Total no. of academic centers (N)	83	126
Age (%)		
18–30	2.6*	1.4
31–50	34.9*	26.7
51–64	39.0	37.4
>65	23.5	34.5*
Male gender (%)	52.7	50.3
Race		
White (%)	81.0*	76.9
African–American (%)	5.4	8.8*
Severity class (%)		
Minor/moderate	91.7*	82.4
Major/extreme	8.3	17.5*
Elective case (%)	94.7*	88.6
Benign disease (%)	82.6*	66.6
Malignant cases (%)	17.4	33.5*

*$p<0.05$, compared to open sigmoid colectomy chi-square analysis

in Table 2, 1,092 patients (10.3%) underwent laparoscopic sigmoid colectomy and 9,511 patients (89.7%) underwent open sigmoid colectomy at 83 and 126 academic medical centers, respectively. The proportion of men was similar in both the open and laparoscopic groups (52.7 vs 50.3%). There were a higher proportion of white patients in the laparoscopic group (81.0 vs 76.9%) and a higher proportion of African-American patients in the open group (8.8 vs 5.4%). Severity class also differed between open and laparoscopic groups. There was a higher proportion of minor/moderate severity patients in the laparoscopic groups (91.7 vs 82.4%). There was a higher proportion of major/extreme severity patients in the open groups (17.5 vs 8.3%). A higher proportion of patients underwent laparoscopic sigmoid resection for benign (82.6%) vs malignant (17.4%) disease.

During the 4-year study period, there was no difference found in in-hospital mortality or observed-to-expected in-hospital mortality ratio, which was less than one in all groups. All periopertive outcomes for benign and malignant groups are listed in Tables 3 and 4, respectively. Mean length of hospital stay was shorter, and the rate of wound infections were lower in those patients who underwent laparoscopic sigmoid colectomy when compared to those patients who underwent open sigmoid colectomy regardless of diagnosis (Tables 3 and 4). Pulmonary complications and total hospital cost were only found to be significantly lower in the benign laparoscopic group and not in the malignant groups. There were no significant differences in the rate of

Table 3 Outcomes of Laparoscopic and Open Sigmoid Colectomy for Benign Disease

	Laparoscopic (*N*=902)	Open (*N*=6,337)
Mean length of stay (days)	5.1±3.5**	7.2±7.6
Overall complications (%)	19.1*	25.4
30-day readmission (%)	3.5	4.9
In-hospital mortality (%)	0.2	0.6
Observed-to-expected mortality ratio	0.6	0.5
Total hospital cost	13,507± 8,238**	15,248± 17,373

*$p<0.05$ compared to benign open sigmoid colectomy, chi-square analysis
**$p<0.05$ compared to benign open sigmoid colectomy, two-sample *t* test

postoperative hemorrhagic complications, venous thromboembolic events, anastomotic leaks, or procedure related laceration or perforations (Figs. 1 and 2). There was no difference in 30-day readmission rate between the laparoscopic and open groups. When the benign and malignant groups were stratified by severity class, the mean length of stay difference between laparoscopic and open groups remained statistically significant in all the minor/moderate severity and in the benign major/extreme groups (Tables 5 and 6).

Discussion

Since the first reported series of laparoscopic colon resections over 15 years ago, debate over the appropriateness of open vs laparoscopic colon resection has continued. Multiple reports have shown improved perioperative out-

Table 4 Outcomes of Laparoscopic and Open Sigmoid Colectomy for Malignant Disease

	Laparoscopic malignant (*N*=190)	Open malignant (*N*=3,185)
Mean length of stay (days)	6.4±6.4*	7.8±6.6
Overall complications (%)	22.6	27.3
30-day readmission (%)	3.2	4.1
In-hospital mortality (%)	0.0	1.2
Observed-to-expected mortality ratio	0	0.9
Total hospital cost	15,154±10,644	16,371± 20,382

*p<0.05 compared to malignant open sigmoid colectomy, two-sample *t* test

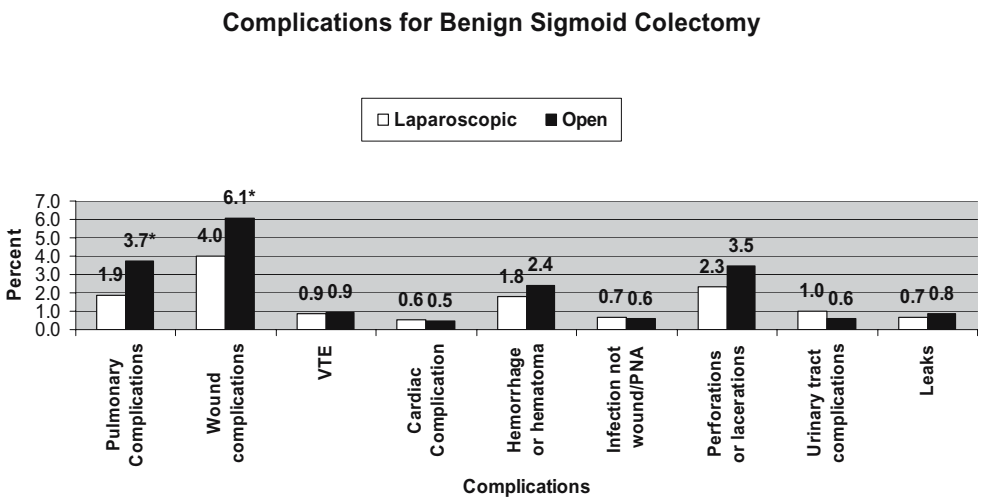

Figure 1 Complications profile for patient who underwent sigmoid colectomy for benign disease. *$p<0.05$ compared to open sigmoid colectomy, chi-square analysis. *VTE* Venous thromboembolic event.

comes in patients treated with laparoscopic colon resection when compared to open resection for diverticular disease.[13–17] Using ICD-9CM codes for laparoscopic lysis of adhesions and diagnostic laparoscopy to isolate laparoscopic sigmoid colectomy patients, Guller et al.[16] showed shorter hospital stay, fewer gastrointestinal complications, and lower overall complications for patients who underwent laparoscopy sigmoid colectomy for diverticular disease as compared to the open approach. In a retrospective review of a prospectively collected database, Schlachta et al.[15] also found no difference in outcomes among patients who underwent laparoscopic sigmoid colectomy or laparoscopic anterior resection for acute or chronic diverticulitis, substantiating claims that laparoscopic resection can be performed safely and for similar indications as open surgery. Laparoscopy colectomy for the treatment of malignant disease has been slow in gaining acceptance. Reports of a high rate of port-site recurrence in early 1994 put a moratorium on laparoscopic colectomy for malignant disease.[3,4] Recent reports have shown that laparoscopic resection for malignant disease can be performed safely, with similar outcomes and incision site recurrence rates as open technique.[5–10]

In this study of academic centers, we found that laparoscopic sigmoid colectomy is safe and has better outcomes when compared to open sigmoid colectomy performed for both benign and malignant disease. Overall mortality was low in all the study groups with an observed-to-expected in-hospital mortality ratio of less than one, which attests to the safety of laparoscopic colon resection. Mean length of hospital stay was found to be significantly shorter in all the laparoscopic groups regardless of diagnosis; these differences persisted after the groups were stratified into malignant and benign disease groups; however, when analyzed by severity of illness, there was no difference in length of hospital stay seen in the

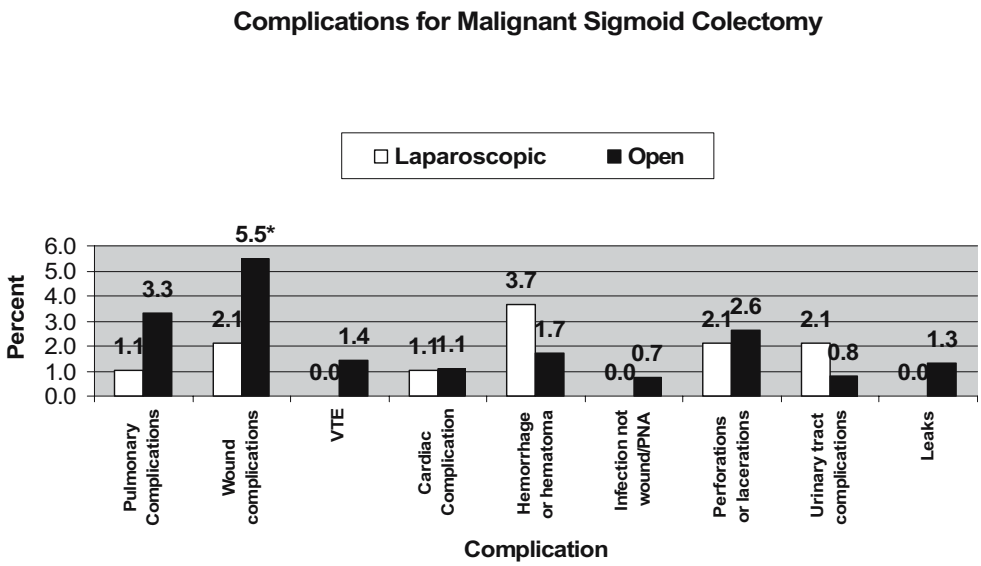

Figure 2 Complications profile for patient who underwent sigmoid colectomy for malignant disease. *$p<0.05$ compared to open sigmoid colectomy, chi-square analysis. *VTE* Venous thromboembolic event.

Table 5 Outcomes of Laparoscopic and Open Sigmoid Colectomy for Benign Disease by Severity Class

	Benign (minor/moderate)		Benign (major/extreme)	
	Laparoscopic (N=833)	Open (N=5,244)	Laparoscopic (N=69)	Open (N=1,093)
Mean length of stay (days)	4.7±2.4**	5.9±2.9	10.1±8.3**	13.8±15.6
Morbidity (%)	15.9*	19.8	58.0	52.5
Mortality (%)	0.0	0.04	2.9	5.6
Observed-to-expected mortality	0.0	0.1	0.8	0.7
30-day readmission (%)	3.3	4.7	6.1	6.0
Total hospital cost ($)	12,529±5,355	12,148±5,354	24,600±19,799	29,925±36,532

* $p<0.05$ compared to benign open sigmoid colectomy, chi-square analysis
** $p<0.05$ compared to benign open sigmoid colectomy, two-sample t test

malignant group with a severity class of major and extreme. Overall morbidity as measured by rate of complications was found to be lower among all laparoscopic groups even after stratification to benign or malignant disease groups; however, the significant difference was lost when these groups were stratified by severity of illness. The 30-day readmission rate was found to be similar between groups regardless of diagnosis. This finding was maintained even after stratification by diagnosis and severity class.

As expected, the largest proportion of patients who underwent a laparoscopic sigmoid colectomy were those treated for benign disease, of which diverticular disease represented approximately 80% of the study cohort. Mean length of hospital stay for the benign laparoscopic group was approximately 2 days shorter than that for the open group. This finding was maintained after stratification by severity class. Patients in the minor/moderate severity class had a 1-day shorter length of stay, and those in the major/extreme severity class had a 3-day shorter hospital stay when compared to the open. Overall complications, pulmonary and wound complication rates were also found to be significantly lower in the laparoscopic benign group. Overall complication rates maintained significance among the minor/moderate severity class, but significance was lost in the major/extreme severity class groups. This difference in overall complication may contribute to the shorter length of hospital stay seen in this group. Collins et al.[18] examined the risk factors to prolonged hospital stay among patients undergoing major abdominal surgery and found a correlation with the number of postoperative complications and the increased length of hospital stay in patient undergoing open colectomy. Cost was also found to be significantly lower in the benign laparoscopic group when compared to the benign open group. Reports in the literature have been conflicting with regards to the cost effectiveness of laparoscopic colon resection.[19–23] In a comparison of the cost effectiveness of laparoscopic vs open colectomy, Salloum et al. in an academic center, found that although operating room costs were higher for the laparoscopic group, total hospital cost was lower, in part due to the shorter length of stay.[23]

In the USA, there are approximately 150,000 colorectal cancer cases diagnosed per year, and surprisingly, only 10–15% of all colorectal resections are preformed laparoscopically. This was consistent with our data in which a larger proportion of patients underwent open, as compared to laparoscopic surgery for the treatment of malignant disease. This may be attributed to the hesitance among surgeons to use laparoscopic colon resection for the treatment of colon cancer.[24] In our study, laparoscopic sigmoid colectomy for

Table 6 Outcomes of Laparoscopic and Open Sigmoid Colectomy for Malignant Disease by Severity Class

	Malignant (minor/moderate)		Malignant (major/extreme)	
	Laparoscopic (N=168)	Open (N=2,610)	Laparoscopic (N=22)	Open (N=575)
Mean length of stay (days)	5.1±2.6*	6.4±2.9	15.8±14.6	14.1±12.6
Morbidity (%)	17.3	20.0	63.6	66.7
Mortality (%)	0.0	0.3	0.0	5.6
Observed-to-expected mortality	0.0	1.0	0.0	0.9
30-day readmission (%)	3.0	3.8	4.6	5.1
Total hospital costs ($)	12,955±5,125	12,807±5,710	31,597±21,815	32,452±42,810

* $p<0.05$ compared to malignant open sigmoid colectomy, two-sample t test

the treatment of malignant disease was associated with a shorter length of hospital stay and a lower rate of wound infections when compared to those patients treated with open surgery. No other differences between open and laparoscopic approach were found. After this patient group was stratified by severity of illness, length of stay remained significant only in the minor/moderate group. There was no significant difference found between laparoscopic and open outcomes in the major/extreme severity group. There was no in-hospital mortality in the malignant laparoscopic group; however, there was no significant difference found because of a low mortality rate in the open surgery malignant group. This finding may be attributed to both the safety of laparoscopic surgery and patient selection. A number of studies have found similar results. The Colon Cancer Laparoscopic or Open Resection Study group reported no difference in mortality, faster return of bowel function, shorter hospital stay, and the need for fewer analgesics compared to the open approach.[7] Similarly, the Clinical Outcomes of Surgical Therapy Study Group found that laparoscopic resection was comparable to open with regards to recurrence, incision site recurrence, postoperative complications, and 3-year survival, while having a shorter median hospital stay and needing less analgesics postoperatively.[6] Lezoche[8] also reported no difference in local recurrence or survival after 5 years of follow-up after laparoscopic colectomy.

This study has several limitations. As expected from a large retrospective administrative database, our patient populations had significant differences. There was a younger patient population and more patients with a lower severity of illness classification in the laparoscopic group, which may contribute to a selection bias. However, subanalysis by severity class after the patients were stratified to benign and malignant groups allowed us to compare a more homogenous group of patient within each diagnosis group. The data utilized in this study was obtained from a voluntary reported administrative database, which is compiled from discharge abstract data and is limited to in-hospital morbidity and mortality without follow-up data. Those complications or deaths arising after discharge are not captured in the database. The coding of certain complications may be inaccurate because postoperative adverse events are subjectively defined by the surgeon and may be coded differently (e.g., anastomotic leaks). However, objective data such as in-hospital mortality, length of stay, and 30-day readmission rates are accurate endpoints. Another limitation is that laparoscopic colectomy ICD-9CM procedural codes currently do not exist; therefore, to identify laparoscopic patients for our analysis, ICD-9CM procedural codes diagnostic laparoscopy and laparoscopic lysis of adhesions were used. This method has been used in other studies to identify laparoscopic procedures in which laparoscopic procedural codes do not exist.[16,25,26] As the codes for diagnostic laparoscopy and laparoscopic lysis of adhesions were used to obtain our laparoscopic cohort, some of the procedures may have been started laparoscopically and converted to open. In this case, the procedure would be captured as a laparoscopic procedure by the database. Estimated conversion rates in the literature are from 2 to 31% of laparoscopic colectomies.[5–10,14–16,18,20, 27] Converted laparoscopic colectomy has been found to have an increased morbidity, specifically wound complications, and a longer length of stay when compared to open or laparoscopic colectomy.[27] Therefore, conversions to open procedure in our study can lead to an overestimation of length of hospital stay and morbidity in the laparoscopic cohorts.

Conclusion

Multiple studies have shown the safety and improved perioperative outcomes of laparoscopic colectomy when compared to open procedures. Our study aims to demonstrate that laparoscopic sigmoid colectomy performed in academic centers is safe, and outcomes are better when compared to open sigmoid colectomy for the treatment of benign or malignant disease. Many of the endpoints examined in our study showed a trend toward better outcome with laparoscopic resection for the treatment of malignant and benign disease; however, not all the findings were statistically significant. Within the context of this analysis of academic centers, laparoscopic sigmoid colectomy for benign and malignant disease was associated with a significantly shorter length of stay, a lower wound infection rate, and similar morbidity, 30-day readmission rate, and mortality when compared to open sigmoid colectomy.

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Discussion

David Shibata, M.D. (Tampa, FL): Congratulations, too, on this paper. Thank you very much for submitting the manuscript to me in advance. That was much appreciated. This is a very interesting paper in that this is kind of data that supports what has been borne out by multiple prospective randomized trials done in North America as well as in Europe, and it is kind of comforting to know that the data is very similar to what we see in those trials. Some of the things that come across is that this is more of a view from 30,000 feet as this study makes use of what appears to be a mini-SEER type database for academic centers.

The limitations are quite clear, as you have pointed out. It certainly does not allow you to focus on tumor-specific factors, on previous operations, the specific nature of the patient's illnesses, and once again, it is really very difficult to tease out what is going on with the conversion rates.

First question. In terms of the codes for the procedures, I agree that there is no ICD-9 coding data, but it appears as if you have some financial data from this database. Can you actually look at the CPT codes that are associated with these billings and procedures?

Number two, in terms of the morbidity, I was a little surprised to see that in the sicker patients, even though this was just statistically non-significant, there was higher morbidity in some cases with laparoscopy than with open. This was one of your findings that I found to be a little discordant with some of the current data in the literature. And I was also wondering, did you actually stratify out parameters like pulmonary and cardiac complications when you analyzed the severity of the patients' illnesses and comorbidities?

Finally, one of the interesting things that I found, when looking at the manuscript, was that of all sigmoid colon cancers in your dataset, only 5% of these cases were actually done laparoscopically; and these were at academic centers. Was this surprising to you? And furthermore, when you were looking at some of these institutions where these procedures were done, were the volumes heavily weighted in terms of a small number of institutions or were they evenly spread across many academic centers. From your data, it appears as if one-third of the academic centers did not do any laparoscopic colon surgery whatsoever.

And finally, I think this database also includes community centers, is that correct?

Marcelo W. Hinojosa, M.D. (Orange, CA): Yes, but only those that are affiliated with academic centers are included in the database.

Dr. Shibata: As we know from the history of laparoscopic cholecystectomy, oftentimes community surgeons led the way in popularizing some of these procedures. I would be curious to see, if you separated out the community centers whether the same percentages would hold out.

Thank you very much.

Dr. Hinojosa: Thank you, Dr. Shibata for your discussion and questions. In response to your first question regarding CPT codes. The UHC database does not list CPT codes. They use ICD-9 procedure and diagnostic codes exclusively. Therefore, there would be no way for us to find the CPT codes that were associated with the billings and procedures within the database.

In response to your second question regarding the higher morbidity seen in patients with the higher severity score that underwent laparoscopic resection, we were able to stratify by individual complications. However we believe that complications can be a somewhat subjective end point and may be a limitation within the database. Also, the groups of patients with higher severity of illness who underwent laparoscopic resection were a very small group compared to patients who underwent open resections. Patient selection can also have something to do with our findings.

In response to your third question as to whether we were surprised to find that about 5% of all cancer cases were done laparoscopically? The answer is not completely. As you know, the majority of laparoscopic colon resections performed for colon cancer up until a few years ago were performed only in randomized clinical trials. Therefore, we expected the numbers of laparoscopic resection for colon cancer to be lower than that of benign disease.

In response to your final question regarding procedure volume within each institution, we did not perform a volume analysis comparison between institutions. We will attempt to do the volume analysis comparison in a future study.

Steve Sentovich, M.D. (Boston, MA): I have a question related to surgeon volume. I would argue that you cannot make the conclusions that you do without stratifying for surgeon experience. If only very experienced surgeons are doing the laparoscopic cases then that could explain all of the differences that you found in terms of length of stay and morbidity. Did you look at specific surgeon volume and experience?

Dr. Hinojosa: Unfortunately, we are not able to stratify by specific surgeon or by surgeon experience using the UHC database.

Jonathan F. Critchlow, M.D. (Boston, MA): I think the sequel to that question is the selection bias. Are you cherry-picking? Are only the most experienced surgeons doing the cases, and of the ones they are doing, are they cherry-picking the ones that are going to be easy to do laparoscopically and then leaving the hard ones to be done open? You can't tease out those specifics of each case. So it is interesting stuff, but I think we can say it is safe in selected circumstances.

Dr. Hinojosa: You are correct. Selection bias is a limitation of the study. From this database we can not tease out the specifics of each case and the experience of each surgeon. It is perceivable and even likely that the more experienced surgeons are performing laparoscopic cases. We do not know whether surgeons are "cherry picking". However, we did stratify patient by severity of illness, which factors in patient comorbidities and secondary diagnoses.

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Local Excision for ypT2 Rectal Cancer—Much Ado About Something

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Abstract
Background The role of local excision for pT2 distal rectal cancer has been challenged because of the observation of high rates of lymph node metastases and local failure. However, neoadjuvant chemoradiation therapy (CRT) has led to increased local disease control and significant tumor downstaging, possibly decreasing rates of lymph node metastases. In this setting, a possible role for local excision of ypT2 has been suggested.
Methods A total of 401 patients with distal rectal cancer underwent neoadjuvant CRT. Tumor response assessment was performed after at least 8 weeks from CRT completion. One hundred and twelve patients with complete clinical response were not immediately operated on and were excluded from the study, and 289 patients with incomplete clinical response were managed by radical surgery. Patients with final pathological stage ypT2 were analyzed to determine the risk of unfavorable pathological features that could represent unacceptable risk for local failure after local excision.
Results Eighty-eight (30%) patients had ypT2 rectal cancer. Final ypT status was not associated with pretreatment radiological staging (p=0.62). ypT status was significantly associated with the risk of lymph node metastases, risk of perineural and vascular invasion, and recurrence (p=0.001). Lymph node metastases were present in 19% of patients with ypT2 rectal cancer. The risk of lymph node metastases in ypT2 was associated with the presence of perineural invasion (47% vs 4%; p=<0.001), vascular invasion (59% vs 6%; p<0.001), and decreased mean interval CRT surgery (12 vs 18 weeks; p<0.001), but not with mean tumor size (3.2 vs 3.1 cm; p=0.8). Disease-free and overall survival rates were significantly better for patients with ypT2N0 (p=0.02 and 0.006, respectively). Fifty-five (63%) patients with ypT2 had at least one unfavorable pathological feature for local excision (lymph node metastases, vascular or perineural invasion, mucinous type or tumor size >3 cm).
Conclusion Lymph node metastases were present in 19% of patients with ypT2 and were significantly associated with poor overall and disease-free survival rates. The risk of lymph node metastases could not be predicted by radiological staging or tumor size. Radical surgery should be considered the standard treatment option for ypT2 rectal cancer after CRT.

Keywords Rectal cancer · Neoadjuvant therapy · Staging · Risk · Recurrence · Outcome

Introduction

Optimal treatment of early rectal cancer remains controversial. Although radical surgery alone leads to excellent oncological outcomes, it is associated with significant

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morbidity rates including early postoperative complications, urinary or sexual dysfunction, and requirement for temporary or definitive stomas.[1–3] For these reasons, alternative management options have been studied for the management of early rectal cancer.[4]

Local transanal excision of rectal cancer was initially considered an option for these patients. As the risk of local recurrence has a direct association with the risk of lymph node metastases in these patients, ideal candidates for local excision as a radical treatment option included patients with early rectal cancer and favorable pathological features including depth of tumor penetration, tumor differentiation, absence of vascular invasion, tumor size, and absence of ulceration.[4] However, the risk of lymph node metastases in these patients may reach rates over 13% even in pT1 rectal cancer.[5] Moreover, long-term results showed disappointing local recurrence rates of 15–30% in these patients.[6]

Introduction of neoadjuvant chemoradiation therapy (CRT) followed by radical surgery for the management of advanced rectal cancer has resulted in significant advantages in terms of toxicity, sphincter preservation, local disease control, and tumor downstaging.[7] In fact, tumor downstaging not only was observed for the primary tumor, but also for lymph node metastases, reflected by the significant decrease of stage III among these patients.[7–9] The observation of significant tumor regression in patients undergoing neoadjuvant chemoradiation has led to the utilization of alternative treatment options in patients with tumors downstaged to stage yI or even stage y0.[10] In this setting, patients with early rectal cancers (ypT1 and ypT2) after neoadjuvant CRT would be candidates for local excision, as the risk for lymph node metastases would be significantly reduced by the possible sterilization effect of CRT. Also, these tumors frequently exhibit significant downsizing after CRT, therefore facilitating the excision of a margin-negative specimen through a transanal approach. Following this rationale, a multicenter trial is now open for accrual in the United States including patients for neoadjuvant CRT followed by local excision alone in patients with ypT0-2.[11]

For this reason, we decided to review a large series of patients with distal rectal cancer managed by neoadjuvant CRT followed by radical surgery with ypT2 to determine long-term oncological results and pathological features that could possibly predict the results of local excision alone for these patients.

Patients and Methods

Four hundred and one patients with distal rectal adenocarcinoma and no radiological signs of distant metastatic disease underwent neoadjuvant CRT as described elsewhere.[12] Tumor response assessment was performed at least 8 weeks from CRT completion and included complete physical examination, DRE, rigid proctoscopy, CEA levels, abdomino/pelvic CT scans, and chest radiographs. Patients with any suspicious scar or lesion were locally excised for pathological examination. Patients with no clinical residual disease or those with negative pathological results of any excised scars were considered complete responders and were not immediately operated on.[13] Those patients who sustained complete clinical response for at least 12 months were considered Clinical Stage 0 and were excluded from this study and are reported elsewhere.[14]

Patients with incomplete clinical response detected at initial tumor response assessment or those with early tumor regrowth (within 12 months) after initial suspected complete clinical response were referred to surgery.

Radical surgery included abdominal-perineal resection, low anterior resections with coloanal or low colorectal anastomosis. All patients underwent TME and high arterial ligation of the inferior mesenteric artery (IMA). After specimen removal, 2-cm macroscopic-free distal margins were considered adequate. Final pathological examination was performed by two GI-dedicated collaborating pathologists. Patients were staged according to AJCC recommendations.[15]

Patients included in the statistical analysis were those with pathological evidence of residual cancer invading muscularis propriae after neoadjuvant chemoradiation (ypT2), irrespective of initial disease staging.

Follow-up was performed by two colorectal surgeons every 3 months for the first 2 years, every 6 months until the fourth year and yearly thereafter. Patients with pathological stage III (ypTanyN1-3M0) were referred to a medical oncologist for consideration of adjuvant chemotherapy.

Recurrences were classified into local (endorectal or pelvic), systemic or combined (local and systemic).

Statistical analysis was performed using Chi-square and Student's t tests for categorical and numeral variables between groups. Logistic and Cox's regression models were used multivariate risk factor and survival analysis. Survival analysis was performed using Kaplan–Meier curves and log-rank test. Significant differences were considered for p values <0.05.

Simulation of Recurrence After Local Excision ypT2

Considering that local recurrence rates after local excision for early rectal cancer parallels the incidence of lymph node metastases of these tumors, we simulated the expected additional local recurrence rates in the present series of ypT2 patients as if they were managed by local excision instead of radical surgery after neoadjuvant CRT. All ypT2 patients with positive lymph node metastases who did not

develop local recurrences in our series would be at a high risk for developing recurrence had local excision been performed on them instead of radical resection. We simulated disease-free survival (DFS) where only patients with N+ disease would have developed relapse had local excision been performed on them instead of radical resection. The recurrence time patterns for the current series (including N+ and N0 patients) was used to estimate survival. This simulation was performed to estimate the impact of not performing radical surgery in this subset of patients.

Results

Of the 401 patients undergoing neoadjuvant CRT, 112 were considered to have complete clinical response; they were not immediately operated on and were excluded from the study. A total of 289 patients underwent radical surgery after CRT and constitute the study population. Overall pretreatment characteristics are summarized in Table 1 and posttreatment characteristics are summarized in Table 2.

Overall recurrence rate was 33% including endorectal recurrences in 5%, pelvic recurrences in 8%, and systemic recurrences in 20%. There were 17% and 13% of overall and cancer-related deaths, respectively.

Table 1 Overall Pretreatment Characteristics of Patients with Rectal Cancer Treated with Neoadjuvant CRT Followed by Radical Surgery

Characteristics	Values
n	289
Age	
Mean years	58±13
Sex	
Female	116(40%)
Male	173(60%)
Pretreatment characteristics	
Mean tumor size	4.1±1.2 cm
Mean distance from verge	3.9±1.7 cm
Mean CEA	13.5±36.1 ng/dl
Pretreatment staging[a]	
T	
2	21(11%)
3	168(85%)
4	9(4%)
N	
0	145 (73%)
+	53(27%)
Stage	
I	20 (10%)
II	125 (63%)
III	53 (27%)
Mean CRT-surgery interval	18±10 weeks
Surgery	
APR	156 (54%)
SSO	133 (46%)

[a] Pretreatment staging available for 198 patients

Table 2 Overall Pathological Characteristics of Patients with Rectal Cancer Treated with Neoadjuvant CRT Followed by Radical Surgery

Characteristics	Values
Tumor characteristics	
Mean tumor size	3.4±1.2 cm
Recovered nodes	
Mean	9.9±9.0
AJCC/UICC Staging	
ypT	
0	24 (8%)
1	18 (6%)
2	88 (31%)
3	145 (50%)
4	14 (5%)
ypN	
N0	213 (74%)
N+	76 (26%)
Final stage	
yp0	24 (8%)
ypI	87 (30%)
ypII	102 (35%)
ypIII	76 (27%)

ypT2

A total of 88 patients were found to have ypT2 tumors after surgery. Of these patients, 51 (58%) underwent an abdominoperineal resection (APR) and 32 (42%) a low anterior resection (LAR). Mean total number of recovered lymph nodes (LN)/specimens was 10.7±12, mean tumor size was 3.2±1.5 cm, and mean distal margin was 2.6±1.8 cm. Accurate tumor size was available for 76 of these patients.

Of the 88 patients with ypT2 lesions at final pathology, 17 (19%) had positive lymph nodes, 15 (18%) had well-differentiated tumors, 11 (12%) had perineural invasion, 14 (16%) had vascular invasion, and eight (9%) were mucinous-type tumors. Overall, 55 (63%) patients with ypT2 had at least one unfavorable pathological feature (lymph node metastases, vascular or perineural invasion, mucinous type or tumor size >3 cm) (Table 3).

Even in patients with small ypT2 lesions (<3 cm in diameter), there was no decreased risk of unfavorable pathologic features including lymph node metastases (23% vs. 19%; $p=0.6$), perineural invasion (11% vs. 13%; $p=0.8$), vascular invasion (21% vs. 13%; $p=0.3$) or mucinous component (9% vs. 6%; $p=0.6$) (Table 4).

Overall, there was a significant association between the presence of lymph node metastases and perineural invasion

Table 3 Surgical and Pathological Features of Patients with ypT2 Rectal Tumors

Characteristics ypT2 (n=88)	Values
Type of surgery	
APR	51 (58%)
SSO	32 (42%)
Mean number LN/specimen	10.7±12
Mean tumor size (cm)	3.2±1.5
Lymph node metastases (ypN+)	17 (19%)
Well differentiated	15 (18%)
Perineural invasion	11 (12%)
Vascular invasion	14 (16%)
Mucinous type	8 (9%)
At least one unfavorable pathological feature	55 (63%)

(47% vs. 4%; p<0.001), vascular invasion (59% vs. 6%; p< 0.001) and shorter interval between CRT and surgery (18 vs. 12 weeks; p<0.001) (Table 5). Mean follow-up period was 57±49 months.

Recurrences and Survival

Overall, there were 21 recurrences (24%) among patients with ypT2, including eight (9%) local recurrences (two endorectal and six pelvic) and 13 systemic recurrences (15%). Among these patients, four were amenable to curative treatment, 10 died of disease-progression, and seven are alive with evidence of disease. Only nine (43%) of the patients who developed recurrence had positive LN, and of these only three developed local recurrences.

At univariate analysis, significant predictive factors for overall recurrence included presence of lymph node metastases (ypN+) and perineural invasion (p=0.002 and 0.01, respectively). After multivariate analysis, only the presence of lymph node metastases remained a significant predictor of recurrence (p=0.003; OR=5.5, 95% CI 1.7–17.2).

Interestingly, the presence of perineural invasion was the only significant predictive factor for local recurrence at univariate analysis (36% vs. 5%; p=0.001).

Five-year overall and disease-free survival was 86% and 66%, respectively. Patients with N+ disease had significantly worse OS and DFS rates (OS: 89% vs. 49%; p=0.02 and DFS: 75% vs 30%; p=0.0006; Figs. 1 and 2) At univariate analysis, the presence of lymph node metastases was the only significant predictor of poor outcome among patients with ypT2 tumors (p=0.003).

After simulation in which patients with ypT2N+ developed recurrences, as it would be expected after local excision instead of radical surgery, 5-year local recurrence rates were significantly worse than in patients managed by radical surgery after neoadjuvant CRT (5-year LR 33% vs 14%; p=0.009; Fig. 3).

Table 4 Surgical and Pathological Features in ypT2 Rectal Cancer According to Final Tumor Size

	Size < 3 cm	Size > 3 cm	p
n	44 (58%)	32 (42%)	
ypN			
ypN0	34 (77%)	26 (81%)	
ypN+	10 (23%)	6 (19%)	0.6
Differentiation			
Moderate	37 (84%)	24 (77%)	
Well	7 (16%)	7 (23%)	0.4
Invasion			
Lympho-Vascular	5(11%)	4(13%)	0.8
Perineural	9(21%)	4(13%)	0.3
Mucinous type	4(9%)	2(6%)	0.6

Accurate tumor size was available for 76 of the 88 ypT2 patients

Table 5 Association Between Lymph Node Metastases and Other Clinico-pathological Features in ypT2 Rectal Tumors

	ypN+	ypN0	p
N	17 (19%)	71(81%)	
Mean age (years)	58.4±17.0	5.7±13.7	0.77
Gender			
Male	7 (41%)	47 (66%)	0.051
Female	10 (59%)	24 (34%)	
Prereatment characteristics			
Tumor size(mm)	40.6±12.7	43.2±12.2	0.49
Distance from anal verge(cm)	3.2±1.2	3.6±2.0	0.41
Clinico-Radiological Stage			
I	3 (21%)	3 (6%)	0.08
II	7 (50%)	39 (78%)	
III	4 (29%)	8 (16%)	
Type of Surgery			
APR	11 (65%)	40 (56%)	0.53
SSO	6 (35%)	31 (44%)	
CRT-Surgery Interval (weeks)	12.2±4.3	18.4±12.4	<0.001
Mean tumor size (cm)	31.8±14.9	32.5±15.2	0.87
Differentiation			
Well	14 (83%)	55 (82%)	0.98
Moderate	3 (18%)	12 (18%)	
Invasion			
Perineural	8 (47%)	3 (4%)	<0.001
Vascular	10 (59%)	4 (6%)	<0.001
Mucinous type	2 (12%)	6 (9%)	0.66

Discussion

Radical surgery has resulted in excellent oncological outcomes of patients with early rectal cancer (stage I disease).[1,16–18] However, these results were not at low cost. In fact, overall morbidity and mortality rates are significant after radical

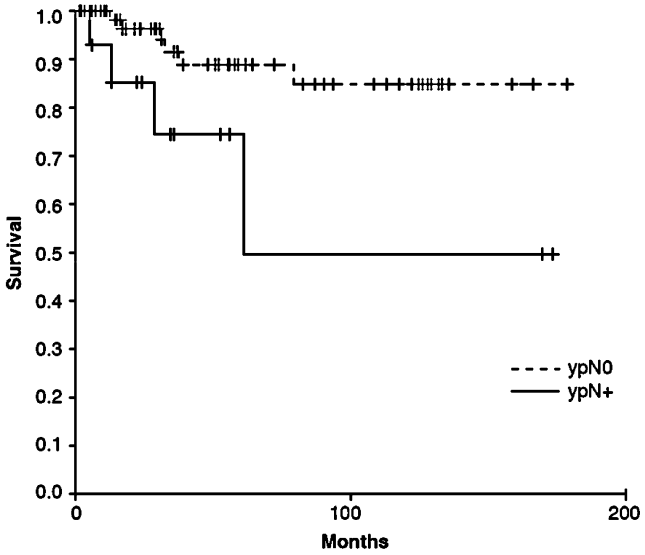

Figure 1 Overall survival according to ypN status in patients with ypT2 rectal tumors. Five-year overall survival was 89% for ypN0 and 49% for ypN+ patients, which was significantly different (p=0.02).

surgery for rectal cancer including total mesorectal excision varying from 7% to 68% and 0% to 6%, respectively.[4,7,19] Moreover, these operations are frequently followed by readmissions to the hospital because of postoperative complications, significant rates of permanent and temporary stomas, and sexual or urinary dysfunction.[3,20,21] Finally, adequate total mesorectal excision (TME) demands specific training, and incomplete rates of TME may reach up to 40% of operations performed and positive circumferential margins in over 10% of patients, specially in distally located tumors.[22,23]

In this setting, an alternative radical treatment strategy was warranted. Transanal full-thickness local excision with

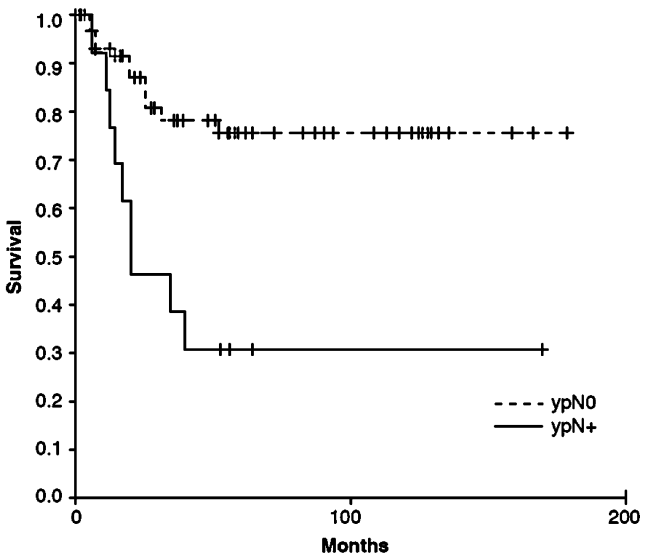

Figure 2 Disease-free survival according to ypN status in patients with ypT2 rectal tumors. Five-year disease-free survival was 75% for ypN0 and 30% for ypN+ patients, which was significantly different (p=0.006).

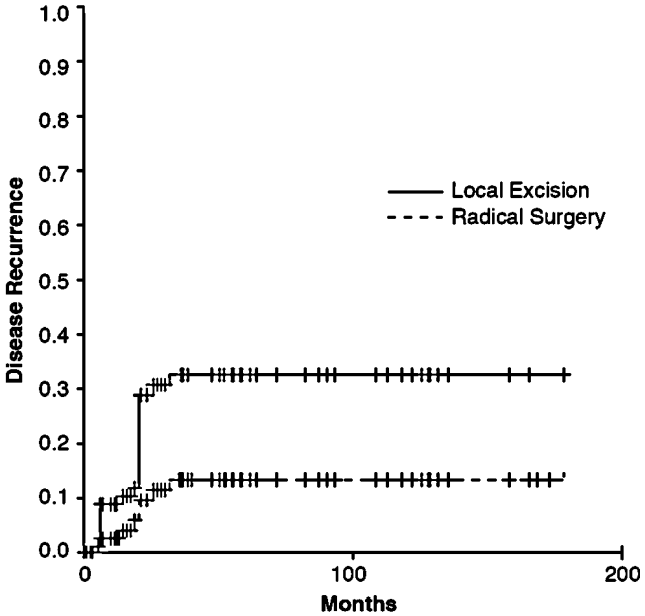

Figure 3 Local recurrence rates simulation comparing patients with ypT2 after radical surgery to local excision (LE) alone, considering patients with ypN+ would have recurred if LE was performed instead of radical surgery. LE estimated disease-free survival (DFS [local relapse]) were significantly worse to those observed after radical surgery (86% vs 67%; p=0.009).

free margins was initially considered an ideal treatment option for these patients with early rectal cancer (pT1-2) as a result of its low associated morbidity, no requirement for stomas, absent mortality, excellent functional and oncological outcomes.[4] However, as there is neither lymph node nor mesorectal excision with this approach, selection of patients included identification of favorable features that could predict minimal risk for lymph node metastases in these patients. In a large retrospective study of patients with pT1 colorectal cancer, the overall risk for lymph node metastases was 13%. After multivariate analysis, this same study identified depth of submucosal invasion and presence of lymphovascular invasion as significant predictors of lymph node metastases.[5] Interestingly, in their series, distal rectal location, which is considered the ideal location for local excision, was also a significant risk factor for lymph node metastases.[5] In a similar study of patients with pT1 colorectal cancer, predictive pathological features for lymph node metastases, observed in 11% of this series, included poor tumor differentiation, lymphovascular invasion, peritumoral inflammation and budding at the invasive front of the tumor.[24]

Therefore, local excision was considered as an alternative radical treatment option by many in selected patients with well-differentiated pT1-2, radiological evidence of N0 and M0, accessible (low) and small tumors (<3–4 cm).[4] However, results were disappointing. In a review of 22 studies including more than 900 patients after local excision

alone for rectal cancer, local relapse for pT2 was 25%, ranging from 0% to 50%.[25] Besides differences in patient selection, other variables such as surgical technique, assessment of resection adequacy, and salvage procedures may have contributed to the wide range of results. In another study of patients with pT2 undergoing local excision alone, it was shown that 37% had local relapse after 54 months of follow-up.[26] Moreover, these authors compared patients with pT2 after LE alone to patients with pT2 after radical surgery in a retrospective study and demonstrated significantly higher overall and local recurrence rates and decreased disease-free survival associated with LE. Apparently, these differences remained significant even after exclusion of patients with unfavorable pathology.[17]

In this setting, there was room for improvement, and radiation therapy alone or combined with chemotherapy was considered either pre- or postoperatively.[4] Although adjuvant CRT after LE has resulted in lower local and overall recurrence rates in small retrospective studies, the neoadjuvant approach seems to be better tolerated, less toxic, and more effective.[7, 27] In fact, neoadjuvant CRT may lead to significant tumor downstaging and downsizing. These advantages may not only facilitate surgical resection caused by decrease in tumor size, but also decrease the risk of lymph node metastases and micrometastases.[7–9,28]

In a retrospective series of patients undergoing neoadjuvant CRT followed by radical surgery after 6–8 weeks, the rate of lymph node metastases was significantly affected by ypT stage. The rate of LN metastases in patients with ypT2 was 16.9% in this series of patients.[29] In another reported series of patients with distal rectal cancer after CRT and radical surgery, ypT2 had 21% risk of lymph node metastases.[30] In our study, ypT stage was also a significant predictor of lymph node metastases, and ypT2 had a 19% of positive lymph nodes. Although there seems to be less number of patients with stage III disease after neoadjuvant CRT, the rates of lymph node metastases in ypT2 seem considerably high, especially when considering local excision. One argument could be raised, stating that these metastatic nodes would be clinically irrelevant after CRT in terms of recurrence and survival. In a previous report, we found final pathological stage to remain a significant prognostic factor after neoadjuvant CRT.[31] In fact, in an interesting retrospective study of patients after CRT and radical surgery, final pathological features including final pathological disease stage, presence of lymph node metastases and lymphovascular invasion were all shown to be significant predictors of disease-free and overall survival.[30] Therefore, these so-called unfavorable pathological features seem to be clinically relevant even after CRT and probably should be considered before embarking on alternative treatment strategies for distal rectal cancer, a location that by itself constitutes a significant predictor of disease recurrence.[5] In our study, the rate of positive lymph nodes among patients with ypT2 was 19%, lymphovascular invasion was 15%, perineural invasion was 12% and mucinous type tumors were observed in 10%. In addition, the presence of at least one unfavorable pathological feature was found in over 60% of these patients. The presence of lymph node metastases was a significant predictor for overall recurrence, whereas perineural invasion was a significant predictor of local recurrence, further emphasizing the clinical relevance of these unfavorable features. Interestingly, 53% of patients with ypN+ disease developed recurrences. Therefore, there would a potential significant increase in overall and local recurrence rates had these (metastatic) lymph nodes not been removed. Considering lymph node metastases was not a significant predictor of local failure in our series, these results suggest that radical resection in the setting of N+ disease may have a significant role in optimizing results, especially in terms of local disease control.

Although there was a significant downsizing of tumors after CRT (4.2 vs 3.2 cm), the risk of lymph node metastases remained unchanged in patients with small tumors (<3 cm). In fact, small tumors (<3 cm) had similar risks of lymph node metastases, perineural invasion, lymphovascular invasion, and mucinous type tumors when compared to larger lesions (>3 cm). Small tumors were significantly associated with sphincter-preserving operations and there was no difference in overall or disease-free survival. Although size has been considered a selection criterion for local excision, our data support that this feature may be related only to technical issues. Larger lesions may have more difficulty undergoing complete negative-margin resection and therefore are associated with increased risk of recurrence, rather than a higher risk of harboring lymph node metastases, lymphovascular or perineural invasion, and mucinous type tumors.

In fact, the addition of neoadjuvant CRT to the management of rectal cancer has raised significant issues in terms of the choice of type of operation, benefit of additional adjuvant therapy, and the usefulness of final pathological features in prognosis estimation. Randomized controlled trials have demonstrated a benefit in sphincter preservation favoring the neoadjuvant therapy group.[7,32] This is related to the observation that tumors that exhibited downsizing and downstaging were more amenable to sphincter-preserving operations and therefore indicates that surgeons decided on the type of operation after neoadjuvant therapy. The interval between CRT and surgery may actually further impact the rate of sphincter preservation.[32] Also, it has been shown that the final pathological features, even after neoadjuvant CRT, remain significant prognostic factors.[30,31] On the other hand, final pathology staging of ypT2 may include tumors with different biological behav-

iors as reflected by their initial disease staging. ypT2 that was already a cT2 showing no response to CRT may be indistinguishable from a cT4 that showed significant response to CRT. Still, in our current series pretreatment staging (including cT and cN) was not a predictor of recurrence or survival, albeit pretreatment staging was not available for all patients. In the subset of patients with complete clinical response managed by non-operative management reported elsewhere, there were 13% of patients with initial cT2N0 disease.[14] Again, pretreatment staging was not a predictor of recurrence among this subset of patients. Therefore, in a setting where accurate staging for rectal cancer is lacking, especially after neoadjuvant CRT, it seems reasonable to make management decisions, such as type of surgery to be performed and prognostic information, based on posttreatment (CRT) status.

The ACOSOG 6041 is based on uT2N0 rectal cancers undergoing neoadjuvant CRT followed by local excision. In this study, patients with final pathological ypT2 will be considered for observation without immediate radical surgery.[11] In fact, this subpopulation of the study will represent a subset of patients with no downstaging after CRT and therefore represent a different and rather worse (in terms of biological behavior) population when compared to our study.

Reviewing the results of local excision after neoadjuvant CRT in small retrospective series, reported recurrence rates may reach up to 25% and may closely relate to observed rates of lymph node metastases in these patients.[4,33] Interestingly, salvage surgery for recurrent rectal cancer after local excision seems to be associated with more advanced disease than the original primary and may not provide the same chance for cure as a radical resection performed as the initial treatment.[18,34] On the other hand, immediate radical surgery (not salvage radical surgery) after local excision for selected patients did not compromise outcome, especially when performed within 30 days.[18,35]

In our study, neoadjuvant CRT and radical surgery for ypT2 rectal cancer resulted in a 5-year overall recurrence rate of 34% and local recurrence rate of 14%. However, considering that this series of patients would have been treated by local excision for ypT2, additional recurrences could be expected for those patients who did not recur after radical surgery, but would have recurred as a result of positive lymph nodes left behind. In this hypothetical setting, local recurrence rates at 5-year follow-up would have reached an unacceptable rate of 33%, instead of 14%, after radical surgery.

In conclusion, ypT2 tumors after neoadjuvant CRT and radical surgery exhibit considerably high rates of lymph node metastases, lymphovascular invasion, perineural invasion, and mucinous type tumors. These pathological findings are considered unfavorable pathological features and were not associated with tumor size. At least one unfavorable pathological feature is present in over 60% of the patients. The presence of lymph node metastases and perineural invasion are clinically relevant features in predicting overall and local recurrence even after radical resection and would certainly play a role in recurrence after local excision. An additional recurrence rate would be expected after local excision as a result of leaving behind a significant proportion of patients with positive lymph node metastases. This expected increase in local failure after local excision of ypT2 might be considered unacceptable in a setting where salvage resection has been demonstrated to be associated with worse results than would be radical surgery as the initial treatment. In the setting where residual rectal cancer after neoadjuvant CRT leads to a ypT2 lesion, radical surgery should be strongly recommended and local excision regarded as a diagnostic, staging, or palliative procedure.

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DISCUSSION

Robert W. Beart, Jr., M.D. (Los Angeles, CA): We appreciate the opportunity to review this manuscript and I appreciated personally the opportunity to see it ahead of time. Your group has championed efforts nationally and internationally to tailor the extent of treatment to the extent of the disease. You are bringing your work repetitively to this forum for review, which we all appreciate at the SSAT.

The literature in this area is confusing. You confirm data that suggest that substantial downstaging is associated with improved survival and that in fact patients tend to behave as their pathologic stage after surgery rather than their clinical stage before surgery. But there's equally impressive data that suggest in large retrospective pathologic reviews that even a complete response to neoadjuvant therapy is not associated with a change in the incidence or patterns of recurrence. So I think at this stage this is a very confusing area, and I think your effort to shed some light on the issue is important.

I had a little trouble with the manuscript in that you focus on survival, but I think the real issue here is local control, and I am not sure that a radical operation will necessarily improve or change the incidence of liver metastases. I understand lymph node positivity is associated with long-term survival. In your manuscript, lymph node positivity was not associated with local occurrence, and so I think local control should be the focus.

I have just a few questions. First of all, you noticed a significant difference in the patients who had delayed surgery, out to 18 weeks, I believe, and I wondered if that long delay had an impact and if that is something to which we should be attentive.

Can you tell us what happened to the eight local recurrences? Were they controlled, were they manageable?

What about ongoing chemotherapy? You used chemotherapy selectively in your patient population. Do you think that either local control or survival would have been improved with a more consistent use of postsurgical chemotherapy?

And then finally, do you have any data on the relationship of these patients to their pretreatment T stage?

Thank you.

Rodrigo O. Perez, M.D. (São Paulo, Brazil): Dr. Beart, thank you for those kind words and for those excellent questions. I will try to address each one of them.

The first one, our 5-year local recurrence rate was about 14%. It is true that local recurrences did not significantly correlate with the presence of lymph node metastases in our series. Actually, the only risk factor for local recurrence in our study was the presence of perineural invasion, which was quite surprising. What we think is that this is an effect of radical surgery. Removing lymph nodes by total mesorectal excision leads to some lymph node positivity. However, excision of such lymph nodes probably prevents local recurrences in a subset of these patients, and this is why we believe that lymph node metastasis was not correlated with local recurrence after radical surgery. Now, our main concern was that if we had left those positive lymph nodes behind, a subset of these patients would probably develop local recurrences, and in this setting, the presence of lymph node metastasis would possibly become a significant prognostic factor and a significant predictor for local recurrence.

The second question, which is very interesting, regards the interval period between chemoradiation therapy and surgery. We were very much concerned if delayed surgery did have any impact on survival. Actually, we did present a paper at the SSO annual meeting this year, also in Washington, which looked into that. We found that the patients that had delayed surgery, for whatever reason, between chemoradiation therapy and surgery, final survival rates, either overall or disease-free survival, were similar, and this delayed surgery was not harming them.

The third question is about the management of local recurrences. I can say that three out of eight patients in this series with local recurrences were salvaged. Of these three, all were after anterior resections and two of them were endoluminal recurrences and only one was with an extra-rectal recurrence.

About chemotherapy, I do agree with you that we did selectively use chemotherapy in these patients, as it is currently recommended that patients with stage III disease, that is, with the presence of lymph node metastasis, require, or there are some data indicating that these patients benefit from chemotherapy, and this is our current recommendation. So patients with positive lymph nodes did get some adjuvant therapy as opposed to those with no lymph node metastasis who did not get any adjuvant therapy. I am not sure if giving all these patients chemotherapy would have helped any in terms of local recurrence rates, even though some benefit could be expected for systemic recurrences. Still, I am not sure there are enough data to support that giving all of these patients with ypT2N0 rectal cancer might be of any benefit. We might have to look for other risk factors, and probably some molecular markers might help us in that way.

Finally, to answer the question of pretreatment staging, I do agree with you, that downstaging might reflect tumor behavior in a way that patients that were T4s or T3 before chemoradiation therapy and became ypT2 may be better than the ones that were T2 and remained T2 after chemoradiation therapy. And it is not easy to accurately document that. Some colorectal surgeons still feel that they do better with the finger than with other radiological studies such as endorectal ultrasound for T staging. Still, we do think that the main question here, if we are going to consider local excision, is the lymph node status, and staging of lymph nodes either pre-chemoradiation or post-chemoradiation is quite difficult. In our study, we did not have the data on endorectal ultrasound of all patients. We did have the data on CT scans as pretreatment staging, and I can say that did not correlate with the presence of lymph node metastasis or with survival. However, we should look into that more carefully prospectively.

Thank you once again.

Alessandro Fichera, M.D. (Chicago, IL): I enjoyed your presentation, as I often do with work presented by your group. If I have understood your data correctly, the incidence of positive lymph nodes was lower if the patient had a longer interval between the treatment and the surgery, and this is a very interesting point. Julio Garcia-Aguilar is conducting a trial at UCSF and we have now started enrolling patients in the longer interval arm. Based on this information, these data, and these assumptions, I am not sure that your conclusion that if you do a local excision in these patients you would have had higher recurrence rates is valid. Indeed

we don't know what happens to these lymph nodes if you do wait longer or if you don't touch them by doing just a local excision. So it would be interesting to look at that, and hopefully Julio will help us find the answer, but I am afraid your conclusion may not be in the future completely on target.

I have truly enjoyed your presentation.

Dr. Perez: I do agree with you. We have tried to set up a trial to study that as well. We have an ongoing trial, which is open for accrual in Brazil, and is recruiting patients with distal rectal cancer undergoing neoadjuvant chemoradiation therapy. We are performing PET-CT in a sequential fashion. Patients undergo a baseline PET-CT before chemoradiation, a second PET-CT after 6 weeks and an additional PETCT after 12 weeks. I can say that we do have additional downstaging with waiting a little longer. However, I am not sure how long is enough. Probably, after some point we might not get any benefit from waiting anymore. In our series, the mean interval between chemoradiation therapy and surgery is a little over 10 weeks for the whole group. Maybe, we will get to 12 weeks, but I am not sure we are going to get much longer than that. But I do agree with you, there might be a bias after a retrospective analysis.

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Surgery for Rectal Cancer Performed at Teaching Hospitals Improves Survival and Preserves Continence

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Abstract We sought to compare the outcomes of teaching and community hospitals on long-term outcomes for patients with rectal cancer. All rectal adenocarcinomas treated in Florida from 1994 to 2000 were examined. Overall, 5,925 operative cases were identified. Teaching hospitals treated 12.5% of patients with a larger proportion of regionally advanced, metastatic disease, as well as high-grade tumors. Five- and 10-year overall survival rates at teaching hospitals were 64.8 and 53.9%, compared to 59.1 and 50.5% at community hospitals (P=0.002). The greatest impact on survival was observed for the highest stage tumors: patients with metastatic rectal adenocarcinoma experienced 5- and 10-year survival rates of 30.5 and 26.6% at teaching hospitals compared to 19.6 and 17.4% at community hospitals (P=0.009). Multimodality therapy was most frequently administered in teaching hospitals as was low anterior resection. On multivariate analysis, treatment at a teaching hospital was a significant independent predictor of improved survival (hazard ratio=0.834, P=0.005). Rectal cancer patients treated at teaching hospitals have significantly better survival than those treated at community-based hospitals. Patients with high-grade tumors or advanced disease should be provided the opportunity to be treated at a teaching hospital.

Keywords Survival · Institution · Outcomes · FCDS · Teaching hospital · Colon cancer · Disparities

Introduction

Colorectal cancer is the third most common malignancy occurring in both men and women in the USA and the second leading cause of cancer-related death. In 2007, an estimated 41,420 Americans will be diagnosed with rectal cancer.[1] Despite advances in surgical and endoscopic treatments in addition to the use of adjuvant and neo-adjuvant treatment for rectal adenocarcinoma, this malignancy remains a major cause of morbidity and mortality in this country, with a 5-year survival rate of approximately 50% for all stages of disease.[2]

The evaluation and treatment of the rectal cancer patient is a multifaceted process that may involve gastroenterologists, surgeons, medical oncologists, and radiation oncologists. Central to providing high-quality care for these patients is the seamless interaction of all of these elements. Large university-based or university-affiliated teaching hospitals are poised to deliver this multidisciplinary care, whereas smaller community-based hospitals often lack this forum.

We postulate that treatment of rectal cancer at teaching hospitals results in superior outcomes and improvement in overall survival. This hypothesis was addressed in a retrospective analysis of operative cases of rectal adenocarcinoma from a large, population-based state cancer registry.

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Methods

Florida is the fourth most populous state in the country. Since 1981, the Florida Cancer Data System (FCDS) has collected information on all cancer cases in the state of Florida, which comprises approximately 6% of the US population. This cancer registry currently includes over 2.7 million records. In 1994, the FCDS became part of the National Program of Cancer Registries (NPCR), which is administered by the Centers for Disease Control and Prevention (CDC). Over 96,000 reportable invasive cancer cases are abstracted annually, following the North American Association of Central Cancer Registries (NAACCR) procedure guidelines. The FCDS is wholly supported by the State of Florida Department of Health, the NPCR of the CDC, and the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine.

The study was approved by the Institutional Review Board of the University of Miami Miller School of Medicine. The most current 2006 FCDS data was used to identify all operative cases of rectal adenocarcinoma diagnosed in the state of Florida between 1994 and 2000 (Fig. 1). Operative cases were defined as those patients receiving a cancer-directed operation during their treatment course. Greater than 95% of the patients in our cohort received all or a portion of their therapy at the reporting hospital (i.e., the same hospital that reported the case to the FCDS). In almost all cases, the reporting hospital was the same hospital where the case was diagnosed.

Patient demographics and treatment data were extracted from the FCDS database. Tumor stage was determined using standardized codes from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. These codes are used to represent localized, regional (both by direct extension and nodal involvement), and distant, or metastatic, disease groups. Tumors were characterized as low grade or high grade. Low-grade tumors included well-differentiated and moderately-differentiated lesions, while high-grade tumors comprised poorly-differentiated, undifferentiated, and anaplastic lesions.

Medical facilities were defined as either teaching hospitals or community hospitals based on recognition as a teaching institution by the American Association of Medical Colleges (AAMC). The AAMC is a nonprofit organization representing the nation's 125 accredited degree-granting medical schools and approximately 400 major hospital-based teaching programs.

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 14.0 (SPSS, Chicago, IL). Correlations between categorical variables and type of institution were made using the chi-square test. Five- and 10-year overall survival rates were calculated by the Kaplan–Meier method. Survival data is passively reported by the Department of Vital Statistics to the FCDS. Survival was calculated from the time of the initial rectal cancer diagnosis to the date of death or last follow-up. The date of the last FCDS update was used as the date of last follow-up for those patients that were not reported as deceased. The effect of the type of institution on survival in various subgroups was examined using the log-rank test for categorical values. A multivariate analysis using the Cox proportional hazards model was used to further test the significance of both demographic and treatment variables on survival. Statistical significance was defined as a P value of <0.05.

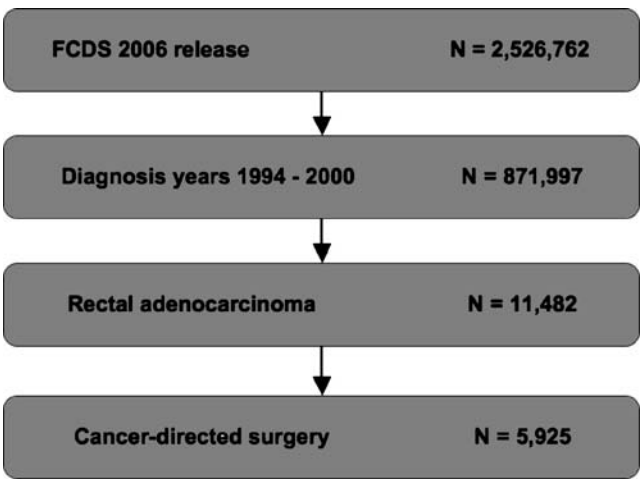

Figure 1 Selection of study sample (*FCDS* Florida Cancer Data System).

Results

A total of 5,925 surgical cases of rectal adenocarcinoma diagnosed in the state of Florida between 1994 and 2000 were extracted from the database for analysis. Eight hospitals in the state are recognized by the AAMC as teaching hospitals and are referred to as such in this paper—the remaining 288 are classified as community hospitals. A total of 742 patients (12.5%) were treated at teaching hospitals, and 5,183 patients (87.5%) were treated at community hospitals.

The median age of the entire cohort was 69 years with 552 (9.3%) of patients under the age of 50. The study population was predominantly white (92.7%). Regionally advanced disease was present in 3,177 (53.6%) cases, whereas 568 patients (9.6%) had evidence of distant metastases. The median follow-up was 68 months for the entire cohort and 93 months for survivors only.

Demographic and clinical variables by type of treatment facility are provided in Table 1. Patients at teaching

Table 1 Association of Type of Facility with Demographic and Clinical Variables

	Teaching Hospital (%)	Community Hospital (%)	*P* value*
Age (year)			
<50	14.7	8.5	<0.001
≥50	85.3	91.5	
Median	64	70	
Race			
White	91.1	92.9	0.152
Black	6.7	5.7	
Other	2.2	1.4	
Stage of Disease			
Localized	34.5	37.1	0.097
Regional	53.8	53.6	
Distant	11.6	9.3	
Tumor Grade			
Low-grade	83.9	84.8	0.546
High-grade	16.1	15.2	
Tumor Size (cm)			
<4.0	45.7	43.2	0.165
≥4.0	54.3	56.8	
Mean	4.17	4.32	

*P value by chi-square test for association between variables

hospitals were generally younger than at community hospitals (median age 64 years vs 70 years, $P<0.001$). There was no significant difference in average tumor size between the two types of institutions (mean size 4.17 cm at teaching hospitals vs 4.32 cm at community hospitals, $P=0.165$). There was a trend toward a larger percentage of distant staged disease at teaching hospitals when compared to community hospitals (11.6 vs 9.3%, $P=0.097$) Furthermore, there were no differences in either tumor grade or patient race between the two treatment groups.

Information regarding principal payer at the time of diagnosis is provided in Table 2. A larger percentage of both uninsured patients (4.8%) and Medicaid subscribers (3.6%) were seen at teaching hospitals in comparison to community hospitals (2.3% and 1.7%, respectively, $P<0.001$). Community hospitals treated a larger fraction of Medicare patients than did teaching hospitals (45.7 vs 38%, respectively, $P<0.001$). The percentage of managed care, health maintenance organization (HMO), and preferred provider organization (PPO) subscribers was similar at all facilities.

Differences in both surgical and adjuvant treatment were observed between the two groups (Table 3). Teaching hospitals performed a greater percentage of sphincter-preserving surgeries (low anterior resection, LAR) than did community hospitals (78.7 vs 71.9%, $P<0.001$), and community hospitals performed a greater percentage of abdominoperineal resections (APR; 28.1 vs 21.3%, $P<0.001$). A greater proportion of patients treated at teaching hospitals received radiation therapy (58.1 vs 40.4%, $P<0.001$) and chemotherapy (60.8 vs 40.2%, $P<0.001$) than did those patients who were treated at community hospitals. These results are broken down further by stage of disease in Table 4. The mean number of lymph nodes examined in each group was similar and the results shown in Fig. 2.

Treatment times for both patient groups were calculated as either median time from diagnosis to surgery or median time from diagnosis to first treatment (surgery, chemotherapy, or radiation). These results are shown in Fig. 3. Time from diagnosis to surgery was longer at teaching hospitals when compared to community hospitals (30 vs 11 days, respectively). Similarly, the time from diagnosis to first treatment was also longer at teaching hospitals in comparison with community hospitals (19 vs 8 days, respectively).

Five- and 10-year survival rates are summarized in Table 5. Overall, 5- and 10-year survival was significantly higher in teaching hospitals as compared to community hospitals (64.8 and 53.9% at teaching hospitals vs 59.1 and 50.5% at

Table 2 Primary Payor at Time of Diagnosis

	Teaching Hospital $n=742$ (%)	Community Hospital $n=5183$ (%)
Medicare	38.0	45.7
Managed care, HMO, PPO	20.6	23.5
Insurance, NOS	15.0	11.1
Medicaid	3.6	1.7
Uninsured, self pay	2.2	1.7
Uninsured	2.6	0.6
Military	2.8	0.5
Indian Health Service	0.1	0.1
Unknown	15.1	15.1

NOS not otherwise specified

Table 3 Association of Type of Facility with Treatment Variables

	Teaching Hospital $n=742$ (%)	Community Hospital $n=5183$ (%)	*P* value*
Type of Surgery			
LAR	78.7	71.9	<0.001
APR	21.3	28.1	
Radiation Therapy			
Yes	58.1	40.4	<0.001
No	41.9	59.6	
Chemotherapy			
Yes	60.8	40.2	<0.001
No	39.2	59.8	

*P value by chi-square test for association between variables
LAR Low anterior resection, *APR* abdominoperineal resection

Table 4 Association of Type of Facility with Treatment Variables According to Tumor Stage

	Teaching Hospital				Community Hospital			
	All	Loc	Reg	Dis	All	Loc	Reg	Dis
Type of Surgery								
LAR	*78.7*	86.0	79.2	61.0	71.9	74.8	69.7	71.7
APR	*21.3*	14.0	20.8	39.0	28.1	25.2	30.3	28.3
Radiation Therapy								
Yes	*58.1*	40.1	74.7	35.8	*40.4*	27.4	50.0	27.4
No	*41.9*	59.9	25.3	64.2	*59.6*	72.6	50.0	72.6
Chemotherapy								
Yes	*60.8*	34.3	75.5	77.5	*40.2*	20.5	51.4	49.8
No	*39.2*	65.7	24.5	22.5	*59.8*	79.5	48.6	50.2

Values indicate percent of patients within each particular subgroup at each type of treatment facility; numbers in italics indicate a P value <0.05 by chi-square test for association between variables

LAR Low anterior resection, *APR* abdominoperineal resection, *All* All patients, *Loc* localized, *Reg* regional, *Dis* distant disease

community hospitals, respectively, P=0.002). Patients with metastatic disease had better outcomes at teaching hospitals than at community hospitals (5- and 10-year survival, 30.5 and 26.6% vs 19.6 and 17.4%, respectively, P=0.009), as did individuals with high-grade tumors. Patients over the age of 50 had improved 5- and 10-year survival in teaching hospitals as compared to community hospitals (64.8 and 53.8% vs 58.4 and 49.5%, P=0.002). Kaplan–Meier survival curves comparing survival between teaching hospitals and community hospitals are shown for all patients as well as select subgroups in Fig. 4.

Stepwise multivariate analysis of all demographic, clinical, and treatment variables was undertaken using the Cox regression model (Table 6). Age greater than 50 years and regionally advanced or metastatic disease were all independent predictors of lower overall survival. Radiation therapy, chemotherapy, and utilization of an LAR vs APR procedure were all independently associated with improved outcomes. Finally, treatment at a teaching hospital was an independent predictor of improved survival (hazard ratio= 0.834, P=0.005).

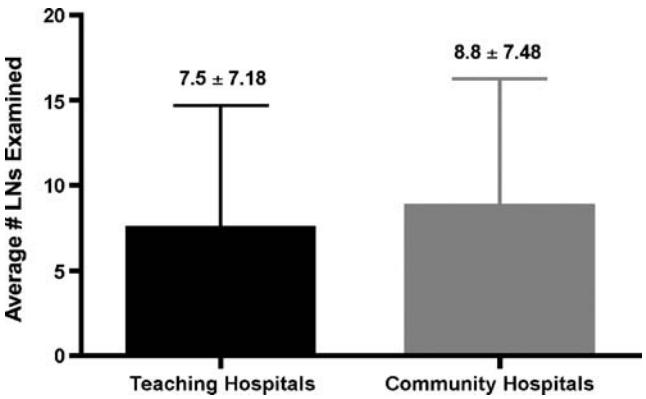

Figure 2 Comparison of the average number of lymph nodes examined per patient in each treatment group (mean values shown, with *error bars* representing±1 standard deviation).

Discussion

In recent years, both institutional or surgeon case volume and a hospital's status as a teaching/specialty center have been compared with outcomes for a number of surgical diseases, including colorectal cancer.[3–9] In the current study, using a large population-based state cancer registry, we found a significant association between a facility's status as an AAMC-recognized teaching hospital and improved patient outcomes, including overall survival and sphincter preservation.

Our review of 5,925 patients with rectal adenocarcinoma revealed that only a small fraction (12.5%) of these patients were cared for at teaching hospitals. LAR and sphincter preservation was more frequently utilized at teaching hospitals (78.7%) than at community hospitals (71.9%, P< 0.001) despite there being no differences in tumor size or grade between the two groups. Patients with either localized or regionally-advanced disease received a greater percentage of LAR at teaching hospitals than at community hospitals (86.0 vs 74.8% for localized tumors and 79.2 vs 69.7% for regionally advanced disease, P<0.05) as seen in Table 4.

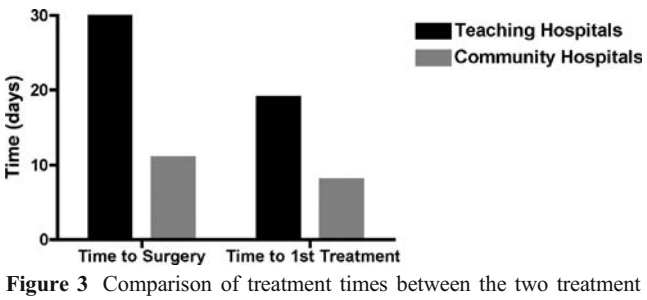

Figure 3 Comparison of treatment times between the two treatment groups. *Columns* represent either median time from diagnosis to surgery or median time from diagnosis to first treatment (surgery, chemotherapy, or radiation).

Table 5 Comparison of 5- and 10-year Overall Survival According to Type of Facility

	Teaching Hospital		Community Hospital		*P* value*
	5-year survival (%)	10-year survival (%)	5-year survival (%)	10-year survival (%)	
All patients	64.8	53.9	59.1	50.5	0.002
Age (year)					
<50	65.1	54.5	65.9	60.9	0.629
≥50	64.8	53.8	58.4	49.5	0.002
Stage					
Localized	78.2	68.3	72.5	63.2	0.071
Regional	65.2	53.1	56.9	49.3	0.004
Distant	30.5	26.6	19.6	17.4	0.009
Tumor Grade					
Low-grade	64.7	55.1	61.7	53.4	0.085
High-grade	61.3	52.5	46.5	40.5	0.007
Tumor Size (cm)					
<4.0	70.5	63.2	65.3	57.2	0.084
≥4.0	61.0	49.2	54.2	47.3	0.062

*P value for log-rank test for association between overall survival and categorical variables

Previous studies have documented differences in patient care related to either hospital teaching status or volume. Several studies, both prospective[10,11] and retrospective,[12,13] each noted significantly improved overall survival of rectal cancer patients in university hospitals compared with community hospitals. Wibe et al.[10] prospectively examined outcomes in 3,388 patients and noted improved survival in university hospitals compared with local community hospitals. In a separate evaluation of 637 patients, Schroen and Cress[14] revealed that treatment at a teaching hospital was associated with higher compliance with National Institute of Health (NIH) treatment recommendations.

The data presented here highlight a striking difference in the use of adjuvant treatments for rectal cancer among teaching and community hospitals. A greater proportion of patients treated at teaching hospitals received either radiation therapy (58.1 vs 40.4%, $P<0.001$) and/or chemotherapy (60.8 vs 40.2%, $P<0.001$) than did those patients treated at community hospitals (Tables 3 and 4). A focused analysis of those patients with regionally advanced disease or localized disease showed a significantly greater use of radiation therapy at teaching hospitals than at community hospitals (74.7 vs 50.0% for regionally advanced disease, $P<0.05$). For those individuals with localized disease, radiation therapy was utilized more frequently at teaching hospitals than at community hospitals (40.1 vs 27.4% for localized tumors, $P<0.05$).

We report a significant improvement in both 5- and ten-year overall survival for those patients treated at teaching hospitals compared to community hospitals (Table 5). These differences in outcome are even greater in those subsets of patients with higher-grade tumors or those individuals with advanced-stage disease. After correcting for all significant demographic and clinical variables, multivariate analysis supports our conclusion that treatment at a teaching hospital is associated with a lesser risk of death (hazard ratio 0.834, $P<0.05$).

Teaching hospitals have the advantage of being able to provide an optimum level of protocol-based care, as well as having the infrastructure and resources in place to provide palliative care when necessary. This concept is highlighted in a study by Schroen and Cress,[14] which found higher rates of patients receiving the recommended therapy in teaching hospitals compared to a nonteaching hospital. Furthermore, there were a greater proportion of patients that underwent sphincter-sparing surgery at teaching hospitals. Several large randomized trials have demonstrated decreased local recurrence rates and an increase in disease-free survival rates if patients are treated with adjuvant radiotherapy and chemotherapy,[15–19] which are utilized more frequently in teaching hospitals according to our data.

Detailed analysis of the subgroup of patients with advanced, metastatic disease suggests that these patients benefited most from regionalized care. Individuals treated at teaching hospitals had 5- and 10-year survival rates of 30.5 and 26.6%, respectively, compared to 19.6 and 17.4% for those treated at community hospitals. In addition, those with regionalized disease treated at teaching hospitals demonstrated significant survival benefit with both increased 5- and 10-year survival rates (65.2 and 53.1% in teaching hospitals vs 56.9 and 49.3% in community hospitals, $P=0.004$).

Using the clinical data available to us from the FCDS registry, we attempted to identify any differences in the

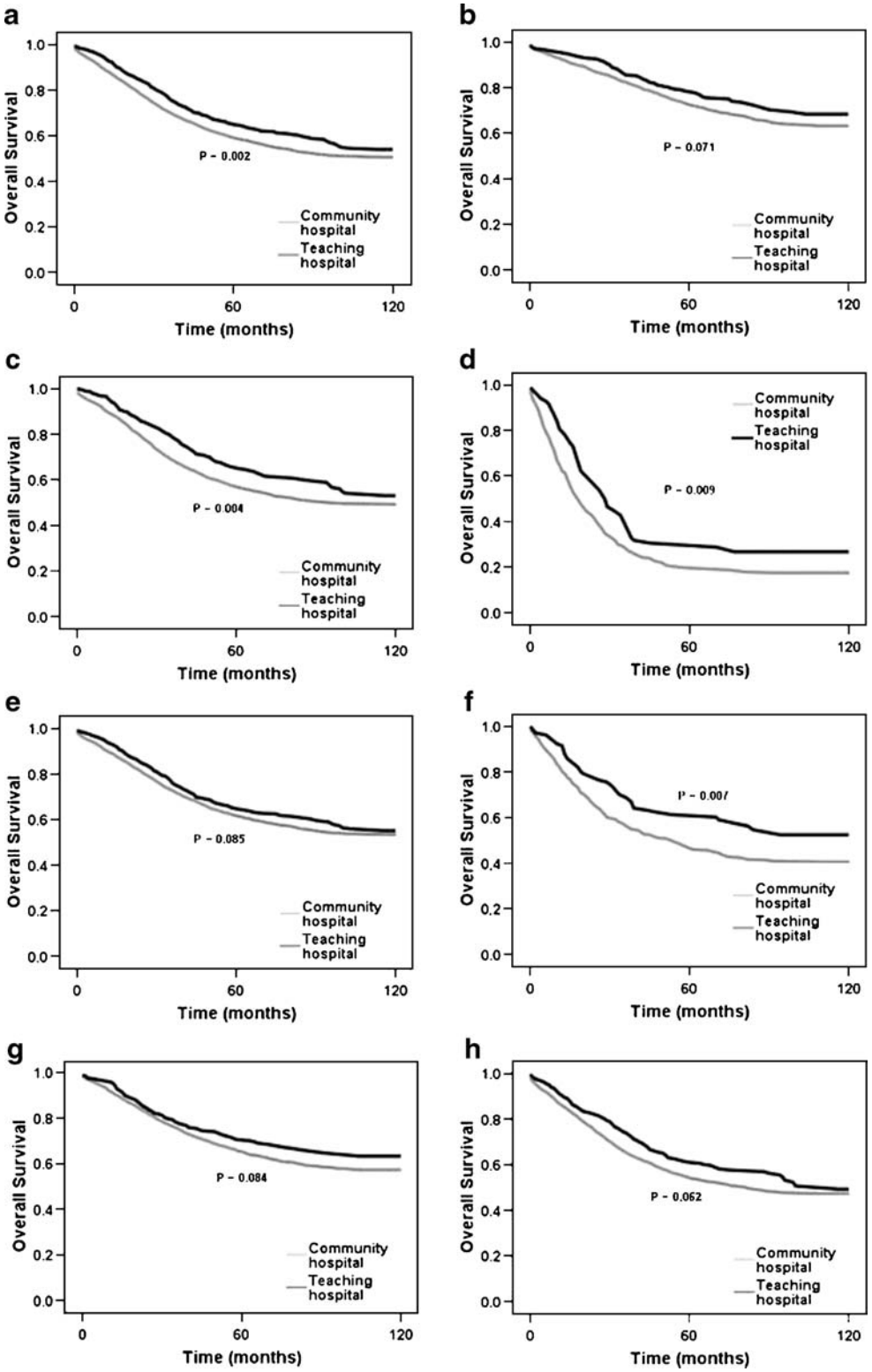

Figure 4 Overall survival comparison between teaching hospitals and community hospitals for **a** all patients, as well as those subgroups with **b** localized disease, **c** regionally advanced disease, **d** metastatic disease, **e** low-grade tumors, **f** high-grade tumors, **g** tumors <4 cm, and **h** tumors ≥4 cm (*P* value for log-rank test for association between median survival and each categorical variable).

quality of care between the two types of institutions that may explain these survival differences. Using the number of lymph nodes examined per patient as a surrogate for the adequacy of surgical resection, we find no difference between patients treated at teaching hospitals vs community hospitals. An analysis of treatment times revealed that teaching hospital patients waited twice as long from diagnosis to any form of treatment in comparison to

Table 6 Cox Proportional Hazards Model for Risk of Death from Rectal Adenocarcinoma

	n	Hazard Ratio	95% CI	*P* value
Type of Facility				
Community hospital	4,546	Reference group	Reference group	Reference group
Teaching hospital	689	0.834	0.735–0.947	0.005
Age				
<50	484	Reference group	Reference group	Reference group
≥50	4,751	1.352	1.158–1.578	<0.001
Gender				
Male	3,176	Reference group	Reference group	Reference group
Female	2,059	0.946	0.871–1.028	0.190
Race				
White	4,856	Reference group	Reference group	Reference group
Black	312	0.995	0.837–1.184	0.959
Other	67	0.877	0.607–1.266	0.483
Ethnicity				
Non-Hispanic	4,774	Reference group	Reference group	Reference group
Hispanic	461	0.992	0.859–1.145	0.914
Stage				
Localized	1,957	Reference group	Reference group	Reference group
Regional	2,785	1.881	1.705–2.074	<0.001
Distant	493	5.316	4.661–6.063	<0.001
Type of Surgery				
LAR	3,799	Reference group	Reference group	Reference group
APR	1,436	1.156	1.059–1.262	0.001
Radiation Therapy				
Yes	2,224	Reference group	Reference group	Reference group
No	3,011	1.306	1.166–1.462	<0.001
Chemotherapy				
Yes	2,228	Reference group	Reference group	Reference group
No	3,007	1.236	1.102–1.386	<0.001

CI Confidence interval; *LAR* low anterior resection, *APR* abdominoperineal resection

community hospital patients. Whereas one may speculate that these differences are due to referral-related delays in the teaching hospital group, we are not able to determine this from the available data.

The limitations in this study are similar in type and scope to those based on other large cancer registries. Although such databases are excellent for population-based incidence and outcomes studies, they often lack clinically important information specific to the disease. For example, data on patient comorbidities, carcinoembryonic antigen levels, and specific anatomic location in the rectum were not included in the FCDS registry and thus was not included in our analysis. The FCDS provides only passive follow-up for registered patients. Because of this problem, the FCDS estimates that survival data may be overestimated by as much as 5–10%. Further, as the database does not record detailed information on cause of death, we were unable to include disease-specific survival in our examination.

Potential pitfalls in analysis of institutional type and volume–outcome relationships are well characterized.[20] Despite these disadvantages, this registry provides critical information regarding treatment of patients with invasive rectal cancer. Thus, although the FCDS dataset is not perfect, it provides an excellent source of data for assessment of institution–outcome relationship in the management of patients with rectal adenocarcinoma.

In conclusion, our study demonstrated a significant improvement in survival for all patients when treated at a teaching hospital. It would be impractical to propose that all rectal cancer patients should be referred to a teaching hospital for treatment. Any number of financial, logistical, and geographic barriers would exist in recommending a complete regionalization of rectal cancer treatment. These results do suggest, however, that certain disparities in patient care do exist, especially for those patients presenting with advanced disease. Our study suggests that these subsets of individuals would greatly benefit from regionalized care. Furthermore, quality improvement studies should be implemented at community hospitals to improve multidisciplinary care for those patients with less advanced disease.

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DISCUSSION

Attila Nakeeb, M.D. (Indianapolis, IN): I would like to congratulate Dr. Gutierrez on an excellent presentation and a very well-written manuscript. I think this is a very important topic and it raises several questions. We are all well aware of the fact that people with pancreatic cancers, esophageal cancers, and even liver cancers have benefited by having surgeries at high volume centers and or university hospitals. Your study confirms several other author's findings that the same applies to rectal cancer.

I think what is really concerning is the disparity in the use of adjuvant therapies when you look at the community hospitals vs the teaching hospitals, and I think that is really where the meat is in this analysis. Do you have any idea what proportion of these patients were treated with neoadjuvant therapies vs just adjuvant therapies? Can you speculate on why there is a difference in the community hospitals vs the teaching hospitals for us?

In the manuscript, you point out that there is a higher incidence of low anterior resections being done at teaching hospitals as opposed to APRs in the community hospitals. In your database, is there any way to drill down as to who is actually doing the operations? Are there more operations being done in the teaching hospitals by either colorectal surgeons or surgical oncologists as opposed to the general surgeon who does the occasional rectal operation in the community?

And finally, have you looked at your database in terms of colon cancer treatment to see if there are differences in the use of adjuvant therapies?

Juan C. Gutierrez, M.D. (Miami, FL): Thank you, Dr. Nakeeb, for those questions. I will start with your last question first. We have not looked at colon cancer in this database yet, but that is something that we are looking to explore in the future.

As far as your second question goes, unfortunately, the information contained in this database does not allow us to pick apart which patients were treated by which particular surgeons, although that would be something interesting to analyze. I know others have looked at surgeon volume as compared to institutional volume. Unfortunately, our data doesn't allow us to do that at this point.

In response to your first question, I am sorry your first question again?

Dr. Nakeeb: Can you speculate on why there is a difference in chemotherapy and radiation therapy in the community vs teaching hospitals?

Dr. Gutierrez: One reason that we are looking at is the large proportion of patients in Florida living in rural communities and whether or not these patients have access to localized facilities for either radiation or chemotherapy treatment. Actually, recently we have gotten this database linked to the American Health Care Association (AHCA) database, which will give us some more in-hospital information as well as geographic information to see where they are living in relationship to a high-volume or a teaching-type institution in order to see if distance to a treating facility is one of the barriers to these patients receiving care.

As to your other question regarding type of surgery between the two different hospitals, unfortunately one of the drawbacks of administrative databases is that the coding for these types of surgeries doesn't really catch up to the surgeries that are being performed at this date. So that is one reason we couldn't tease apart those patients that actually had certain surgeries compared to others or operations by one type of surgeon compared to another.

Luca Stocchi, M.D. (Cleveland, OH): I have two questions. One is that I was surprised by the high survival rate in the metastatic disease groups, both in teaching hospitals and in community hospitals, and I would ask you if you could comment and elaborate on that? The other question regards the pattern of adjuvant treatment. It is not infrequent that in referral centers the patient receives surgery but then the patient who might live several miles away from that center ends up receiving adjuvant treatment in a local hospital, and I was wondering if there is any way you could extrapolate that pattern from your database because that would potentially change the data and show that, for example, one patient could receive surgery in a teaching hospital but adjuvant treatment in a community hospital.

Dr. Gutierrez: Thank you for your questions. As far as your first question goes, I am sorry, your first question again?

Dr. Stocchi: Just in general, I don't remember the exact data, but I was struck by the high survival rate in your metastatic disease. I would have expected a 5-year survival rate would be less than 10%.

Dr. Gutierrez: We actually took the data from Florida and compared it to the national SEER data and found very similar numbers. One of the caveats to these types of database-related studies is that there is a large amount of patient selection that takes place to get those patients that have all their variables listed, and that might be one reason that you are selecting for a certain group of patients.

And as far as your question regarding access to treatment, that is not really something that we can pick up as far as those patients that are lost to follow-up or undergo treatment elsewhere at another hospital.

Dr. Stocchi: So your database doesn't allow to show that one single patient had surgery, let's say, in Miami but had other treatment somewhere else?

Dr. Gutierrez: If it was in the State of Florida it would show up as yes, that they had two different types of treatment. If they go outside the state, we lose those patients to follow-up.

Frank Makowiec, M.D. (Freiburg, Germany): Did you have patients who were treated first for the primary tumor at a community hospital and then for metastatic or recurrent disease and the curative intention in a teaching hospital, and did this influence your results?

Dr. Gutierrez: No, we didn't include those patients in the study.

Sven Erik Karlsson, M.D. (Copenhagen, Norway): Have you tried to correlate the results with body mass index (BMI) with and without adjuvant therapy?

Dr. Gutierrez: At this time we didn't have that information in our data set. This is something that we are getting access to right now. But that would be a great point, to include BMIs as well as other comorbidities in this analysis.

Dr. Karlsson: And what about local recurrence?

Dr. Gutierrez: There were no data for recurrence in these patients.

Dr. Karlsson: How can you then explain the difference in survival?

Dr. Gutierrez: I am sorry, between the two?

Dr. Karlsson: Between the local hospitals and teaching hospitals. If there is no difference between local recurrence, how can you then explain the difference in survival between the two groups of patients? Do you understand my question?

Dr. Gutierrez: I assume that they die from their disease.

Dr. Karlsson: Yes, okay.

Dr. Gutierrez: No, we didn't have any data on the type of recurrence.

Robert W. Beart, Jr., M.D. (Los Angeles, CA): That is sort of my question as well. If I understood right, there was almost a decade difference in the age of the community- vs the university-treated patients, and doesn't that introduce a bias that 5- and 10-year survivals, of all causes, not just cancer, are going to be less good in the community than at the university hospital?

Dr. Gutierrez: That is correct, there was a 6-year difference in the median age between the two groups, but in multivariate analysis it did not appear to be a factor between the two groups, although that may introduce some bias, you are right.

Ibrahim Suliman, M.D. (Riyadh, Sudan): Thank you for the data. My question is, did you compare those who had

low anterior resection in a university hospital with those who had abdominoperineal in the community hospital regarding long-term survival?

And my comment is you said only eight University hospitals are there in Florida and they are doing only 12% of the patients you presented. So is it better to take all the patients to the university hospital or to improve what is already there (i.e., community hospitals), especially that the number of lymph nodes retrieved was pretty good in the community hospitals (better than University hospitals)?

Dr. Gutierrez: We did not perform an analysis of patients receiving low anterior resection at one type of institution vs those receiving APR at another institution because there was not enough information about the type of disease in each group to make that comparison. One very important piece of information which we do not know is the level of the tumor in regards to where in the rectum it is occurring.

Bryan M. Clary, M.D. (Durham, NC): Can I just make one comment? I think you do need to include a disclosure, and your disclosure is that you are from an academic teaching institution. Although I agree in general with your assessment and what has been demonstrated in other fields such as an hepatobiliary and pancreatic (HPB) surgery, I think we have to be honest and include that as a disclosure.

A question for you as well. How does AAMC define a teaching institution because it appears that it is less than 10% of your hospitals in Florida. Is it that they don't have residencies?

Dr. Gutierrez: It is a combination of having residencies and being associated with a medical school. Both factor into it.

Susan Galandiuk, M.D. (Louisville, KY): One last question. Although the lymph node yields were equal, was that corrected for whether or not the patient received preoperative radiation?

Dr. Gutierrez: Yes, that was corrected for in the multivariate analysis.

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Pancreatic Anastomotic Leakage After Pancreaticoduodenectomy in 1,507 Patients: A Report from the Pancreatic Anastomotic Leak Study Group

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Abstract
Several definitions for pancreatic leakage after pancreaticodoudenectomy exist, and the reported range of 2–50% underscores this variation. The goal was to determine if drain data alone was predictive of a leak and validate International Study Group on Pancreatic Fistula (ISGPF) leak criteria. Participating surgeons entered de-identified data into a web-based database designed to collect Whipple-related data. Definitions used were the ISGPF definition, ≥3 days, amylase 3× normal; and Sarr's definition, ≥5 days, amylase 5× normal, >30 ml. We compared how well these two definitions were at detecting a leak and its complications. There were 1,507 cases submitted from 16 international institutions. A pancreaticoduodenectomy (PPPD) was performed in 76.2%. Drain placement occurred in 98.0%. Using the ISGPF definition, the pancreatic leak rate was 26.7 and 14.3% with the Sarr definition. There were more grades A and B leaks detected by the ISGPF definition. Both determined grade C leaks equally. Both definitions correlated with an increased length of stay (LOS), need for percutaneous drains, reoperation, and delayed gastric emptying (DGE). Neither was associated with an increased risk of intensive care unit (ICU) stay or 30-day mortality. The ISGPF was able to capture more patients with clinically relevant leaks than Sarr's criteria; however, the ability to detect a leak by drain data alone is imperfect.

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Keywords Pancreas · Surgery · Pancreaticoduodenectomy · Anastomotic leak · Fistula

Introduction

Pancreaticoduodenectomy (PD) is a complex surgical procedure, considered to be one of the most challenging.[1–4] Whereas, in the last two decades, the rate of mortality associated with PD has dramatically decreased

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and is approaching zero at high volume centers, the morbidity rate remains high (30 to 50%), resulting in both prolonged in-hospital stays and increased costs.[2–8] Pancreatic anastomotic leakage is the most important technique-related complication after PD. Leakage after PD significantly contributes to the development of other major abdominal complications[5–8] and is among the most common causes of perioperative morbidity and mortality, along with patient related co-morbidities.

The reported rate of anastomotic leak is highly variable, ranging from 2 to 51%.[1–19] This wide range has been the result of the lack of a universally accepted definition of leak, which has historically included various ranges of drain fluid amylase concentration and volume.[18] In a recent study, four different definitions of leak were applied to a group of 242 patients who underwent proximal or central pancreatectomy with a pancreatic–enteric anastomosis. In the study, the incidence of leak ranged from 10 to 29%, depending upon the definition selected.[12] Moreover, the lack of a standardized and universally accepted definition of leak makes it difficult to compare surgical techniques, rates of complication, and the usefulness of prophylactic drugs in pancreatic surgery.[9–17]

To address these issues and to attempt to standardize drain fluid parameters that accurately predict clinically significant anastomotic leakage, an international working group of 37 pancreatic surgeons from high-volume centers formed the International Study Group on Pancreatic Fistula (ISGPF). They reviewed their experience and that of the literature.[12] The ISGPF developed consensus regarding drain fluid characteristics indicative of anastomotic leak. Moreover, in recognition that drain fluid characteristics alone were unlikely to predict outcome, a grading system was proposed to characterize clinical impact.[12] The ISGPF consensus definition was based on data obtained from surgical drain fluid (amylase concentration and drainage volumes) and was designed to have a low threshold to maximize leak identification. The ISGPF definition achieving consensus was defined as *any* volume of drainage on or after the third postoperative day (≥POD 3) that had an amylase content >3 times the normal value for serum. It should be noted that the ISGPF definition of leak was derived from expert opinion and a limited number of actual cases and surgical drain data from one institution.[5]

Once the ISGPF study group agreed on amylase concentration, which was deemed abnormal, clinical correlation was possible. The study panel proposed a three-tier grading system for anastomotic leak based upon clinical severity. The ISGPF grade A comprised those cases with no clinical impact related to a leak, and grade C were those with major complications resulting in sepsis, reoperation, or other interventions (including percutaneous drainage) or death. Grade B leaks were more difficult to define but could be generally described as non-A and non-C. Whereas the study group was able to agree upon a standardized drain fluid amylase concentration indicative of leak and a clinical severity scheme, consensus was based upon expert opinion rather than data.

Therefore, to test the hypothesis that the ISGPF definition was a valid predictor of outcome, accrual of a large number of cases was required for clinical correlation. A web-based pancreatic leak database was designed to serve as a repository for clinical information and drain fluid characteristics in patients undergoing a pancreaticoduodenectomy. International participation allowed for a rapid accrual of cases. The ultimate goals of the database included (1) to validate the ISGPF definition of leak and its clinical severity; (2) to better understand the practice patterns and outcomes of participating high volume centers; (3) to allow surgeons to compare personal leak rates in a blinded fashion with a goal of continuous improvement (available 24/7 from the website); (4) to establish a set of definitions for subsequent multicenter, randomized-controlled trials; (5) to provide an analysis that would allow guidelines for interpreting drain data and generate logical methods for drain management; and (6) to identify practice patterns that might be useful to lower leak rates, e.g., the use of anastomotic stents or the stomach as the reconstruction organ. This report is preliminary and is an attempt to address the first two aforementioned goals.

Methods

Database and Data Form Elements

The pancreatic leak database was developed in 2004 to collect both retrospective and prospective data after PD. An independent software contractor was tasked with writing the framework for the data set provided by the data set committee (representatives from the Pancreatic Anastomotic Leak Study Group). This contractor had prior experience with a national surgical database and was cognizant of Health Insurance Portability and Accountability Act (HIPAA) guidelines. The database entry form consisted of 57 unique variables that covered patient demographics, preoperative data, operative data, postoperative course, death, and a drain data table to record drain amylase, drain volume/day, and upper limit of "normal serum amylase". The database entry form was structured to avoid using the 17 HIPAA identifiers including the day of operation (month and year was recorded). Data were submitted electronically through an encrypted https web site (http://www.pancreaticdata.org/), and the data were then stored in a "secure" server. Each hospital and their surgeon's cases were de-identified, encrypted, and remained anonymous. Participating surgeons used their own password and

username to allow individual access to their own data for editing and comparison. None of the participating surgeons, including those analyzing the data, had access to surgeon or hospital identity. Quality data checks were performed within each institution and at the depository level. Additional quality control was performed face–face by the data-use committee, initially, by analyzing the summary report of all data points from the data set. Data distributions and cross-tabulations were examined to identify nonsensical data resulting from data entry errors. During this process, the computer codes that allowed entry of nonsensical values were identified and upgraded. Ambiguous questions that led to missing data points were modified and the database updated.

Patient Population

Twenty-four surgeons from 16 institutions submitted cases to the database. Data were collected from Canada, Germany, Italy, Japan, and the USA. Patients were eligible if they underwent a pancreaticoduodenectomy for either benign or malignant disease. Of 1,537 total cases submitted, 30 from two institutions were excluded because normal amylase upper limits were unavailable from the two sites at the time of data analysis. The remaining 1,507 were included in the data analysis and constitute the cases analyzed in this report.

Definitions Used

Operating room (OR) time was defined as the time from skin incision to skin closure. The number of postoperative days (POD) did not include day of surgery. Delayed gastric emptying (DGE) was defined as oral intake ad libitum occurring on or after POD 10.

Drain Fluid Analysis

Drain data definition: Two definitions were compared for the purposes of defining a leak. The ISGPF definition: at ≥3 days, amylase 3× normal, any volume, and the definition used by Sarr et al. in prior studies[15]: at ≥5 days, amylase >5× normal, >30 ml in 24 h.

Modification of clinical grading scale: After polling the participants who were using the ISGPF criteria, we modified the ISGPF's clinical severity grading scale of leak to make it more discriminant in the following manner. Grade A leaks were defined as those that met drain criteria but were not associated with any adverse clinical outcomes. Grade C leaks were defined as leaks associated with death or reoperation. Grade B leaks were those that were associated with postoperative placement of a percutaneous drain, delayed gastric emptying, intraabdominal abscess, or readmission. Note that the original ISGPF grading scale included the percutaneous drainage as category C and sepsis, but data on this variable was not collected.

Statistical Analysis

Data analysis was done utilizing the SAS 9.1 software program (SAS Institute Inc., Cary, NC, USA). Standard descriptive statistics were used to describe patient characteristics, operative data, and postoperative data. Odds ratios and 95% confidence intervals were calculated to assess the associations between pancreatic anastomotic leaks and adverse clinical outcomes of interest. Patients who had missing data for adverse outcomes (<1–9%) or insufficient drain data to determine leak status (20 and 35% for ISGPF and Sarr, respectively) were excluded from analyses involving the variables for which data were missing.

Results

Database Statistics

The majority of cases were from PD done from 2000 to 2006 (89%), whereas the remaining 11% of patients underwent PD during 1995–1999.

Patient Characteristics

As listed in Table 1, the gender ratio was approximately 1:1 with men at 54% (n=795). The median age was 64 years [15–91 years]. Co-morbidities are also listed in Table 1. Pancreatitis was reported in 18% of the patients (n=263). Patient presentations often included abdominal pain (46%) and jaundice (52%). A common bile duct stent was present preoperatively in 43% of the patients, whereas a main pancreatic duct stent was present in 7% of the patients. Over 90% had an ASA severity of ≥2 (ASA 2=50%, ASA 3=41%). The most common indication for PD was for pancreatic adenocarcinoma (43.6%).

Operative Data

Surgeons reported performing a pylorus preserving pancreaticoduodenectomy (PPPD) in 76% of reported cases (Table 2). Median operating time was 374 min (189–1,020 min), whereas the median estimated blood loss was 350 cc (0–5,000 cc). Details about the pancreatic remnant and the anastomosis are presented in Table 2. One surgeon reported using a microscope in fashioning the anastomosis, whereas others reported using no magnification or magnification in the form of surgical loupes. Surgical drains were placed at operation in 98% of the patients.

Table 1 Patient Characteristics

		Number of Patients (Median Age, 64 [15–91])	Percent
Gender			
Male		795	53.8
Female		682	46.2
Smoking history		556	38.2
Alcohol history		275	18.9
Co-morbidities			
Cardiac		298	19.9
Pulmonary		180	12.0
Diabetes		312	20.9
Hypertension		564	37.7
Obesity (BMI>30)		188	18.2
Pancreatitis		263	17.5
Preoperative data			
Jaundice		784	52.3
Abdominal pain		656	45.9
CBD stent		651	43.6
MPD stent		101	6.7
ASA			
I		116	7.7
II		744	49.6
III		617	41.1
III		23	1.5
Final pathology (n=1,484)			
Pancreas	Ductal adenocarcinoma	647	43.6
	IPMT	197	13.3
	Islet cell	49	3.3
	Other	92	6.2
	Chronic pancreatitis	162	10.9
Bile duct	Adenocarcinoma	65	4.4
	Adenoma	5	0.3
	Other	5	0.3
Duodenal	Adenocarcinoma	33	2.2
	Adenoma	13	0.9
	Other	23	1.5
Ampullary	Adenocarcinoma	161	10.8
	Adenoma	21	1.4
	Other	10	0.1

Postoperative Data

Postoperatively, the median length of stay was 10 days (1–80 days); median ICU stay was 1 day (0–79 days). Median time to resume unlimited oral intake was at the sixth POD [0–71 days], and median day of nasogastric tube removal was POD day 4 (range 0–56). Drain removal occurred at median day 7 [range of 0–219].

The 30-day mortality rate was 1.3%, and the most frequent complication was DGE at 12.5% (Table 3). Percutaneous drainage was required in 7.9% (n=119) of all patients and was first placed on day 3.7 (SD±7.9). Other complications are further listed in Table 3.

Drain Fluid Analysis

We classified patients in two groups based upon drain characteristics according to the ISGPF and Sarr definitions. Only cases with complete drain data were included (ISGPF group, n=1,200; Sarr group, n=983). We found the following number of leaks (as defined by drain fluid amylase only): 320 by ISGPF versus 141 by Sarr definition, translating into a leak rate based on drain data of 26.7 and 14.3%, respectively. Next, we divided each group into categories of clinical severity using our modified ISGPF severity grading (Table 4). Only patients with complete data relative to complications were included (ISGPF group,

Table 2 Operative Data

		Number of Patients	Percent	Median (range)
Operative procedure[a]	PD	336	23.8	
	PPPD	1,075	76.2	
OR time (minutes)[b]				374.0 (189–1,020)
EBL[c]				350.0 (0–5,000)
Transfusion of RBC[d]	Yes	277	19.7	
	No	1,130	80.3	
Details of anastomosis				
Pancreatic duct size (mm)[e]				3.0 (0–50)
Firmness of gland[f]	Soft	410	32.4	
	Firm	691	54.7	
	Very firm	163	12.9	
Reconstruct organ[g]	Jejunum	1258	87.6	
Anastomosis[h]	Duct-to-mucosa	995	66.4	
	Dunking	494	33.0	
	None	9	0.6	
Internal stent[i]		745	49.9	
Inside suture[j]	Vicryl	360	25.7	
	PDS	749	53.5	
	Non-absorbable	278	19.8	
	None	14	1.0	
Surgical loupes[k]	Yes	574	44.9	
	No	704	55.1	

[a] Procedure unknown, $n=96$
[b] OR time unknown, $n=6$
[c] EBL unknown, $n=770$
[d] Transfusion of RBC unknown, $n=100$
[e] Duct size unknown, $n=257$
[f] Firmness unknown, $n=243$
[g] Jejunum unknown, $n=71$
[h] Anastomosis unknown, $n=9$
[i] Internal stent unknown, $n=14$
[j] Internal suture unknown, $n=106$
[k] Surgical loupes unknown, $n=229$

$n=1092$; Sarr group, $n=901\%$). There were more leaks type A (48%, $n=134$) than B (43%, $n=119$) or C (9%,=26) leaks in the ISGPF group. The more exclusive Sarr criteria resulted in the majority of leaks being classified as type B leaks (65%, $n=80$) and classified only 27% ($n=33$) as type A leaks. Type C leaks were proportionally similar to those in the ISGPF group at 9%. Utilizing the Sarr definition, then 101 grade A leaks and 39 grade B and 15 grade C leaks were missed.

To assess how well drain fluid characteristics predicted poor clinical outcomes, we compared the rates of complications in patients with both normal and abnormal drain fluid values using the criteria set by both definitions (Table 5). The ISGPF criteria were better at detecting patients who had a postoperative complication, such as intraabdominal abscess, DGE, percutaneous drainage, intraabdominal bleeding, readmission, reoperation, and 30-day mortality. However, it should be noted that, even with normal drain fluid characteristics, there were cases with the aforementioned complications not classified as having a "leak." For example, 31 of the 79 patients with an intraabdominal abscess and 30 of the 89 patients that required percutaneous drainage (most likely as a result of anastomotic leakage) met neither ISGPF nor Sarr criteria. There were patients with DGE, intraabdominal bleeding, readmission, reoperation, and 30-day mortality that did not meet the criteria of leak; however, the etiology of these complications may have occurred in the absence of anastomotic leakage or if the drains were nonfunctional.

To determine if either the ISGPF or Sarr criteria were better at predicting outcomes, we calculated the odds ratio (OR) for each of the aforementioned complications. Both definitions were associated with increased risk of prolonged length of stay (LOS>10 days), requiring a percutaneous drain, reoperation, and delayed gastric emptying. Neither definition could predict ICU LOS longer than the median (1 day) or 30-day mortality (Table 6).

Discussion

The Pancreatic Leak Database was established in an effort to further refine the original ISGPF definition and to determine the incidence of clinically significant leaks. International participation allowed for rapid accrual of cases with many participating institutions. Feasibility of such a "community effort" was achieved and an element of surgical pride was palpable.

Initially, we planned to analyze the data after the first 1,000 cases were accumulated; however, this report presents data on over 1,500 cases mostly because of the rapid entry of patient data by enthusiastic participants. The goal is to accrue 5,000 cases or a sufficient number required to ultimately achieve the six goals posed in the introduc-

Table 3 Postoperative Complications—Entire Cohort

		Number of Patients	Percent
30-Day mortality[a]	Yes	18	1.3
	No	1,353	98.7
Bile leak[b]	Yes	53	3.5
	No	1,448	96.5
Intraabdominal abscess[c]	Yes	97	6.5
	No	1,401	92.6
Delayed gastric emptying[d]	Yes	187	12.5
	No	1,310	92.9
Percutaneous drainage[e]	Yes	119	7.9
	No	1,379	92.1
Reoperation[f]	Yes	53	3.5
	No	1,443	96.5
Intraabdominal bleeding[g]	Yes	54	3.6
	No	1,441	96.4
Readmission[h]	Yes	96	6.4
	No	1,393	93.6

[a] Mortality unknown, $n=136$
[b] Bile leak unknown, $n=6$
[c] Intraabdominal abscess unknown, $n=9$
[d] Delayed gastric emptying unknown, $n=10$
[e] Percutaneous drainage unknown, $n=9$
[f] Reoperation unknown, $n=11$
[g] Intraabdominal bleeding, $n=12$
[h] Reoperation unknown, $n=18$

tion. Leak-related questions cannot be definitively answered by analyzing small administrative databases but might be answered by an international collaborative effort such as the Pancreatic Leak Database reported herein, which provides a large sample size for study. Upon its completion of accrual, this database will potentially be the largest prospectively acquired data repository using a standard set of definitions for characterizing patients that have undergone a PD.

Many lessons were learned throughout the process from design to data collection. Most importantly, we learned that selecting the "right" variables is critical in providing correct information for analysis. For example "date of death" was originally excluded. Coding difficulties made it difficult to interpret the responses to a few of the variables, and this led to modifications in the database to meet these challenges (for example, in the initial effort to capture patient diagnosis, one could choose between "neoplasm," malignant," "ca in situ," or "benign" and could select one or all of the above, a confusing set of parameters for the statistician). As is the case with many large databases, the volume of missing data often hampered the analysis; however, in spite of this shortcoming, there remained a large sample size to compensate for this limitation.

Table 4 Comparison of Leaks Detected on Analysis of Drain Fluid Amylase Concentration Using the ISGPF and Sarr Definitions

	ISGPF, *N* (%)	Sarr, *N* (%)
Total no. leaks[a]	320/1,200 (26.7)	141/983 (14.3)
Cases available for severity grading[b]	279/1,092	124/901
Type A	134 (48)	33 (27)
Type B	119 (43)	80 (65)
Type C	26 (9)	11 (9)

Leaks defined as *Type A* no complications related to leaks; *Type B* required percutaneous drain, had delayed gastric emptying, readmission, or intraabdominal abscess; *Type C* death or reoperation.
[a] Of the 1,507 in the cohort, 307 are excluded from the ISGPF column due to missing amylase on and after POD 3 (i.e., ISGPF leak status could not be determined). Similarly, 524 are excluded from the Sarr column because of the missing amylase or volume on and after POD 5.
[b] Also excluded are an additional 108 and 82 (ISGPF and Sarr, respectively) for whom leak severity classification (type A/B/C) is unknown because of missing data. Thus, 1,092 are available for ISGPF and 901 for Sarr analysis of leak severity

The leak database has revealed a number of interesting practice patterns. The most noteworthy is the low mortality rate of 1.3%, which underscores the fact that, in experienced hands, PD is a safe operation. Future follow-up will provide information on long-term survival. The achievement in improved surgical mortality has allowed for a shift in focus toward decreasing surgical morbidity such as pancreatic anastomotic leakage, the focus of this paper.

In the present study, the pancreatic anastomotic leak rate, based on drain data alone, was well over 15% regardless of the definition applied (ISGPF versus Sarr). The ISGPF definition was more discriminant, detecting 279 cases of leak compared to the 124 detected by the Sarr definition. However, almost half (47%) of the leaks were not clinically significant (grade A), using our modified ISGPF clinical grading scale. The minority of leaks were grade C, 9% of the total number of leaks, utilizing either definition. Most leaks do not lead to operative intervention or death (grade C leaks), an observation that has been reported by others.[15] This observation may be because of the effectiveness of surgically placed drains "controlling" a leak when present. One might surmise that a number of complications caused by a leak in the presence of a surgically placed drain might be the result of a malfunctioning or misplaced drain. This

Table 5 Postoperative Complications by Sarr and ISGPF Status Excluding Patients with Missing Drain Data

		Total	Normal Drain Fluid Analysis	Abnormal Drain Fluid Analysis	
				Sarr	ISGPF
Intraabdominal abscess	Yes	79 (8.1)	31 (3.5)	34 (24.1)	56 (17.5)
	No	902 (91.9)	845 (96.5)	107 (75.9)	264 (82.5)
Delayed gastric emptying	Yes	133 (13.6)	94 (10.7)	37 (26.4)	55 (17.3)
	No	846 (86.4)	783(89.3)	103 (73.6)	263 (82.7)
Percutaneous drainage	Yes	89 (9.1)	30 (3.4)	46 (32.6)	69 (21.6)
	No	892 (90.9)	847(96.6)	95 (67.4)	250 (78.4)
Intraabdominal bleeding	Yes	37 (3.8)	25 (2.9)	10 (7.2)	19 (6.0)
	No	942 (96.2)	851 (97.1)	129 (92.8)	299 (94.0)
Readmission	Yes	61 (6.2)	47 (5.4)	16 (11.4)	25 (7.9)
	No	916 (93.8)	829 (94.6)	124 (88.6)	292 (92.1)
30-Day mortality	Yes	12 (1.3)	8 (1.0)	1 (0.8)	6 (2.1)
	No	899 (98.7)	801 (99.0)	132 (99.2)	285 (97.9)
Reoperation	Yes	35 (3.6)	20 (2.3)	11 (7.9)	23 (7.3)
	No	944 (96.4)	857 (97.7)	128 (92.1)	294 (92.7)

Of the 1,507 in the cohort, 307 are excluded from the table because of missing amylase on and after POD 3 (i.e., ISGPF leak status could not be determined), leaving 1,200 for analysis (note that where *N* for individual complication variables do not sum to 1,507, the difference is because of the missing data for the associated complication).

may explain why a number of patients in the B or C category had normal drain fluid analysis (Table 5).

Grade B leaks were more frequent than grade C and accounted for a large percentage of the patients. A modest improvement in leak detection was made with the application of the ISGPF drain criteria when compared to the Sarr drain criteria. Group B patients along with those in grade C are clearly the group of patients that will require the most scrutiny in our future studies, as these patients can suffer from poor clinical outcomes and increased cost for patient care.[20]

Our overall actual leak rate as determined by drain fluid analysis was very similar to that seen by Pratt et al. whose study is the first to apply the ISGPF criteria and severity grading scheme to their institutional data.[20] Their overall leak rate was 30.1% with the majority being type A leaks (49%). Type B and C leaks occurred at about the same rate observed in our study (40 and 11%, respectively).

When drain data were used to determine a leak, both the ISGPF definition and the Sarr definition, were equally good at predicting postoperative complications, with the Sarr definition being better at predicting prolonged LOS associated with a leak. However, both missed identifying 31 patients with intraabdominal abscess, 30 requiring percutaneous drainage, and 20 requiring reoperation. Clearly, there are inherent weaknesses in utilizing drain fluid characteristics alone in predicting outcome. We do not know of a way to predict if a drain will malfunction and exacerbate complications associated with a leak. The surgeon must take into consideration the clinical course of the individual patient and not rely solely on drain data alone. At best, drain data can serve as a guide to warn the surgeon of potential danger and serve as a conduit to eliminate pancreatic or biliary juices from the abdominal cavity. Even when drain fluid characteristics are normal, an aberrant clinical course should suggest occult anastomotic leakage and prompt appropriate imaging. These data suggest our drain techniques could be improved.

There has been published criticism of the original classification scheme set forth by the ISGPF[21] and, perhaps, rightly so. The two major criticisms are that grade A leaks should not be included in the grading scale, as they are not associated with any complication and that grade C should be more refined, as the implications of percutaneous drain placement is so dissimilar from reoperation or even death. These criticisms are valid, and for the purposes of this study, the ISGPF definition was modified such that patients

Table 6 Comparison of ISGPF and Sarr Definition Prediction of Outcomes

Outcome of Interest	ISGPF OR (CI)	Sarr OR (CI)
LOS[a]	2.2 (1.7, 2.9)	4.3 (2.8, 6.6)
ICU LOS[b]	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)
Percutaneous drainage	8.4 (5.3, 3.2)	9.0 (5.6, 14.4)
Reoperation	3.3 (1.7, 6.1)	2.5 (1.2, 5.5)
Delayed gastric emptying	1.7 (1.2, 2.5)	2.7 (1.8, 4.3)
30-Day mortality	2.1 (0.7, 6.1)	0.5 (0.1, 4.1)

[a] LOS>10-day median
[b] ICU LOS>1-day median

who required percutaneous drains were classified as grade B, whereas those classified as grade C were associated with death or reoperation.

A lesson learned in our database design is that we did not record the clinicians' opinion of whether reoperation, abscess, or death was a direct result of anastomotic leakage. While this was assumed, it is possible that some complications and deaths were not a direct result of anastomotic complications. Complete patient information is the strength of a single institutional study, and in an effort to have our database embody, this strength we will modify the database entry form to capture this important piece of information.

The findings of this study are preliminary. In the future, we will use the pancreatic leak database data to further explore predictive factors (patient factors, surgical technique, post-operative complications) associated with an anastomotic leak and clinical outcomes.

Conclusion

Mortality after PD at these high-volume centers is low (1.3%). Despite an improvement in mortality, clinically relevant pancreatic leak remains common after PD at 13.2%. While the ISGPF criteria allows for a larger detection of patients with pancreatic leaks, this study suggests that utilization of drain data alone to predict clinical outcome is imperfect. Even with inclusive criteria, cases of leak may be missed because of drain failure. In spite of these shortcomings, this study confirmed that international collaboration via a web-based method is feasible and could be used in the future to study and improve our rate of pancreatic leakage.

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DISCUSSION

Craig P. Fischer, M.D. (Houston, TX): I would like to congratulate you and your co-authors for carrying out a large multi institutional study which seeks to determine if drain data are predictive of leak following pancreaticoduodenectomy. This study also intends to validate the International Study Group on Pancreatic Fistula(ISGPF)criteria for pancreatic fistula. Participating surgeons in this Web based program, entered de identified data into the database relevant to the Whipple operation. The two definitions that were looked at were the ISGPF definition versus the Sarr definition (described in the manuscript). The definitions have different thresholds for amylase content and drain output. One of the issues here is the wide range of reported pancreatic fistula following the Whipple operation – this has led to various proposals to standardize the reporting of this complication. Most prominently, the International Study Group on Pancreatic Fistula met and proposed a system of classification.

In this study there were more grade A and B leaks that were detected by the international study group definition, than by the Sarr definition. Both definitions, however, determined grade C leaks equally. The ISGPF definition was able to capture more patients with clinically relevant leaks than Sarr's classification, however, both definitions missed some cases of clinically significant leaks (grade B and C).

I have two specific questions for you. The first, in the manuscript you modified the international study group's definition. The original definition, placed percutaneous drainage placed into class C, yet you moved it to class B. This does seem to be some disagreement about the validity of the international study group's definition, and I would like your comment about other definitions. We do need to settle on a single definition, validate it, and then report our data according to the same definition. Does your group plan to use the ISGPF definition, a modification, or a different definition as the project moves forward? There is a recent publication in Surgery in January by Steve Strasberg and Pierre Clavien, which is the most recent contribution to this effort. I would appreciate your comments.

Of course, the real power of this database is to compare techniques, and clinical risk factors that contribute to the development of pancreatic fistula. This database will eventually have over 5,000 patients for examination. So what future data points will you be examining? Will you examine the correlation between various techniques of the pancreatic/enteric anastomosis and fistula as well as patient and pancreas specific risk factors.

Again, I would like to thank the authors for providing me the manuscript in advance and to congratulate you all on an outstanding effort that is a real advance in moving towards a unified definition, used by all authors in this field, so we may accurately compare our work. Thanks very much.

Michael B. Farnell, M.D. (Rochester MN): Dr. Fischer, thank you very much for your comments and your questions. I would like to emphasize that while this is a beginning, it does demonstrate the feasibility of a group to utilize both technology and collaboration to attempt to improve outcome.

Drain data are a harbinger of complications but alone are insufficient to define a pancreatic leak. Perhaps the drain data would be best at directing drain management. Clinical information is essential in the definition of a pancreatic leak.

You asked about recently published grading systems for complications following pancreaticoduodenectomy. I would agree with Dr. Strasberg, and I am sorry that he can't be here to participate in that discussion. A grading system based upon the need for an intervention for a leak is perhaps more relevant than a grading system based upon biochemical analysis of drain fluid and outcome. So the answer to your question is yes, I think there should be refinements in the ISGPF grading system for pancreatic fistula.

Your second question addressed what the future holds. As we refine the web-based tool, I would like to see a quality committee constituted to help ensure the quality and accuracy of the data. Data entry personnel need to be trained to ensure data accuracy and consistent definitions. Once accomplished, we can begin to examine issues such as stent versus no stent, technique of anastomosis, use of loupe magnification, use of an operating microscope, and the question of whether a drain should even be used at all. There is support in the literature for Whipple resection without placing a drain and responding to a change in clinical course with appropriate intervention.

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Clinicopathologic Features and Treatment Trends of Pancreatic Neuroendocrine Tumors: Analysis of 9,821 Patients

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Abstract The natural history of pancreatic neuroendocrine tumors (PNET) remains poorly defined. Our objectives were to examine the clinicopathologic features of PNETs, to assess treatment trends over time, and to identify factors associated with undergoing resection. From the National Cancer Data Base (1985–2004), 9,821 patients were identified with PNETs. Clinicopathologic features and treatment trends were examined. Multivariable logistic regression was used to assess factors associated with undergoing resection. Of 9,821 patients with PNETs, 85% were nonfunctional, 7.1% were functional, and 7.9% were carcinoid tumors. Of the 3,851 (39.0%) patients who underwent pancreatectomy, 449 (11.7%) received adjuvant chemotherapy, and 254 (6.6%) received adjuvant radiation. From 1985 to 2004, utilization of pancreatectomy increased from 39.4 to 44.3% ($P<0.0001$). Patients were less likely to undergo resection if they were >55 years old, had tumors in the head of the pancreas, tumors ≥4 cm, or had distant metastases ($P<0.0001$). Patients treated at NCCN/NCI, academic, or high-volume hospitals were more likely to undergo resection. There are disparities in the utilization of pancreatectomy for PNETs. As PNETs have a better prognosis than adenocarcinoma, concerns regarding the morbidity and mortality of pancreatic surgery and neoplasms should not preclude resection.

Keywords Pancreatic neuroendocrine tumors · Surgery · Pancreatectomy · National Cancer Data Base

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Introduction

Pancreatic neuroendocrine tumors (PNET) are rare malignancies of the endocrine pancreas with a poorly defined natural history. Annual incidence estimates of PNETs range from 4 to 5 cases per million persons in the USA.[1] PNETs account for approximately 3% of all pancreatic neoplasms.[2] However, the incidence of PNETs has increased 2–3 fold in the past 16 years whereas the incidence of pancreatic adenocarcinoma has remained stable.[3]

A PNET pathologic classification scheme was adopted by the World Health Organization (WHO) in 2000.[4] This classification system recognizes clinical, molecular, and histopathologic characteristics of PNETs and is reflected by the change in nomenclature to "neuroendocrine carcinoma" with an increased emphasis on the degree of tumor differentiation.

Over the past 20 years, significant advances in preoperative evaluation, surgical techniques, and postoperative care have reduced the perioperative morbidity and mortality associated with pancreatectomy.[5–8] Mortality after pancreaticoduodenectomy has dropped from ~25% in the 1960s to less than

3% in some specialized centers.[7–11] PNETs, in general, have a more indolent tumor biology with better long-term survival rates than tumors of the exocrine pancreas.[2,12,13]

Thus, PNETs are poorly understood tumors, and despite decreased morbidity associated with pancreatic surgery, pessimistic attitudes toward resection persist and may result in underutilization of pancreatectomy for PNETs. We utilized the National Cancer Data Base (NCDB) to identify a large population of patients with PNETs. The objectives of this study were (1) to characterize the clinicopathologic features of PNETs, (2) to assess treatment trends in the management of PNETs over the last 20 years in the USA, and (3) to assess factors associated with utilization of pancreatectomy for PNETs.

Materials and Methods

Data Acquisition and Patient Selection

The NCDB is a program of the American College of Surgeons and the Commission on Cancer (CoC).[14] The NCDB has been collecting data on newly diagnosed cancers since 1985 and now contains information on more than 20 million patients from more than 1,440 hospitals. The NCDB collects information regarding patient demographics, diagnosis, treatment, recurrence, survival, and health systems information. Based on national incidence estimates from the American Cancer Society, the NCDB currently captures ~76% of all new pancreatic cancers diagnoses in the USA each year.[15]

Using the NCDB (1985–2004), patients were identified based on *International Classification of Diseases for Oncology*, Second and Third Edition (ICD-O-2/3) site codes for tumors of the pancreas: C25.0 to C25.9. Histology ICD-O-2/3 codes were used to select patients with PNETs (8150, 8151, 8152, 8153, 8155, 8156, 8150, 8240–8246), resulting in 9,821 cases. Malignancies reported as "islet cell tumors" and "neuroendocrine carcinomas" were combined for the analysis as "neuroendocrine carcinoma" is the current nomenclature adopted by WHO in 2000.[4]

Patients who underwent pancreatectomy were identified based on the CoC's *Registry Operations and Data Standards* and the *Facility Oncology Registry Data Standards* site-specific procedure coding.[16,17] Pancreatectomy is classified as enucleation/local excision, pancreaticoduodenectomy (with or without pylorus preservation), distal pancreatectomy, total pancreatectomy, and pancreatectomy not otherwise specified. Palliative procedures and exploratory surgery without a cancer-directed resection cannot be differentiated in the NCDB and are not included in our analysis.

Procedure volume quartiles were calculated based on average annual procedure volume of surgery for all pancreatic tumors with approximately equal numbers of patients distributed within the quartiles. Hospitals in the NCDB are classified into "academic" and "community" cancer centers based on case volume and services offered.[18] Academic hospitals must be primarily affiliated with teaching and research institutions, meet annual case-volume requirements, and fulfill criteria regarding the scope of cancer-specific resources and services. Hospitals reporting to the NCDB include 17 National Comprehensive Cancer Network (NCCN) hospitals and 31 National Cancer Institute (NCI)-designated cancer centers.

Statistical Analysis

Descriptive statistics were calculated for all variables. Trends in patient, tumor, and treatment characteristics were assessed over time using the χ^2 test for trend. Continuous variables were assessed for normality and examined with independent sample t tests, whereas categorical variables were evaluated with χ^2 tests with Bonferroni correction. Multiple logistic regression was used to identify factors predicting pancreatectomy for PNETs. Factors examined in the model included gender, age (<55, 55–75, >75 years), race (white, black, Asian, Hispanic, other), median household income (< \$36,000 vs≥\$36,000), tumor size (0–2, 2.1–4.0, 4.1–6.0, 6.0–10.0, > 10.0 cm), nodal status, distant metastases (none, liver, other), year of diagnosis (1985–1993, 1994–1999, 2000–2004), and hospital type (academic vs community hospitals; NCCN/NCI vs non-NCCN/NCI cancer centers). Before analysis, all independent variables in the model were examined for collinearity. The hospital type variables were inserted separately into the model because of the degree of collinearity. Odds ratios with 95% confidence intervals were generated. Odds ratios less than 1.0 indicate that patients are less likely to undergo pancreatectomy. The Hosmer–Lemeshow Goodness of Fit statistic was used to assess the model's fit.[19]

Because patient-level socioeconomic data is not collected by the NCDB, median household income was assessed at the zip-code level based on the patient's residence at the time of diagnosis through linkage with 2000 United States Census Bureau data.[20] The level of statistical significance was set to $P<0.05$. All P values reported are two tailed. Statistical analyses were performed using SPSS, version 14 (SPSS Inc., Chicago, IL). This study was reviewed by the Northwestern University Institutional Review Board.

Results

Clinicopathologic Features

From the NCDB, 9,821 patients were identified with PNETs (Table 1). The median age of patients presenting

with PNETs was 60.0 years (inter-quartile range: 48–70 years). Tumors were located in the head of the pancreas (34.0%), body (7.9%), tail (21.0%), or the tumor location was diffused/not specified (37.1%). Grade was reported for 1,211 patients (31.4% of resected patients); 22.1% of reported patients had poorly differentiated tumors. The median tumor diameter was 4.5 cm (inter-quartile range: 3.0–7.0 cm.). Examination of the extent of disease at presentation revealed 43.6% of patients had nodal metastases, and 56.3% presented with distant metastases (26.6% liver metastases and 73.4% other distant metastases).

The histologic subtypes included 4,261 (43.4%) neuroendocrine carcinomas, 4,083 (41.6%) islet cell tumors, 229 (2.3%) insulinomas, 131 (1.3%) glucagonomas, 301 (3.1%) gastrinomas, 80 (0.8%) VIPomas, 3 (0.03%) somatostatinomas, and 773 (7.9%) carcinoid tumors (Table 1). Patient and tumor characteristics by histologic subtype are shown in Table 2. There were significant differences by histology in patient age at diagnosis, race, tumor location within the pancreas, tumor size, distant metastases, and degree of differentiation. Patients with nonfunctional tumors, insulinomas, and carcinoid tumors presented at an older median age ($P<0.0001$). Blacks were frequently diagnosed with gastrinomas, VIPomas, and carcinoid tumors compared to other histologies ($P=0.001$). Nonfunctional tumors, gastrinomas, and carcinoid tumors more frequently presented in the head of the pancreas compared to other histologic subtypes ($P<0.0001$). Insulinomas and gastrinomas were diagnosed at smaller tumor sizes compared to nonfunctional tumors, glucagonomas, and carcinoid tumors ($P<0.0001$). Distant metastases were more frequently observed with nonfunctional and carcinoid tumors ($P<0.0001$).

From 1985 to 2004, the proportion of patients reported as having a "neuroendocrine carcinoma" per the WHO terminology increased from 1.5 to 70.4% ($P<0.0001$), whereas the proportion of patients reported with an "islet cell tumor" correspondingly decreased from 74.5 to 20.2% ($P<0.0001$; Fig. 1). The proportion of patients with a reported tumor grade increased from 17.9% in 1985 to 54.4% in 2004 ($P<0.0001$), correlating with the increase in the use of the "neuroendocrine carcinoma" nomenclature. In 2004, 64.7% of neuroendocrine carcinomas were reported with an associated tumor grade; whereas, only 30.5% of the other histologic subtypes had a reported tumor grade ($P<0.0001$).

Table 1 Patient Characteristics

Characteristics	
Number of patients	9,821
Patient	
Gender	
Male	5173 (52.7%)
Female	4638 (47.3%)
Age	
Median (interquartile range)	60 years (48–70)
Race	
White	7914 (80.6%)
Black	1029 (10.5%)
Asian	152 (1.5%)
Hispanic	437 (4.4%)
Other	289 (2.9%)
Tumor	
Histology	
Neuroendocrine carcinoma	4261(43.4%)
Islet cell tumor	4043 (41.2%)
Insulinoma	229 (2.3%)
Glucagonoma	131 (1.3%)
Gastrinoma	301 (3.1%)
VIPoma	80 (0.8%)
Somatostatinoma	3 (0.03%)
Carcinoid	773 (7.9%)
Location within pancreas	
Head	3336 (34.0%)
Body	774 (7.9%)
Tail	2066 (21.0%)
Diffuse or NOS	3645 (37.1%)
Tumor size	
Median (interquartile range)	4.5 (3.0–7.0)
Nodal status	
Node negative	1928 (56.4%)
Node positive	1492 (43.6%)
Distant metastases	
None	3426 (43.7%)
Liver	1173 (15.0%)
Other (+/− liver)	3239 (41.3%)
Grade	
Well/moderately differentiated	943 (77.9%)
Poorly differentiated	268 (22.1%)
Hospital	
NCCN/NCI cancer center	1941 (19.8%)
Academic institution	2902 (29.5%)
Community hospital	4978 (50.7%)

Treatment Utilization

Of the 9,821 diagnosed with a PNET, 3,851 (39.2%) patients underwent pancreatectomy, and thus the majority, 5,960 (60.8%), did not undergo resection (27.3% localized and 72.7% metastatic). Of those who underwent pancreatectomy, 2,061 (72.8%) had localized or locally advanced disease, and 771 (27.2%) had distant metastases. Surgical procedures included 13.5% enucleation, 31.6% pancreaticoduodenectomy, 19.8% distal pancreatectomy, 9.2% total pancreatectomy, and 25.9% other pancreatectomy not otherwise specified. Of those who underwent pancreatectomy, 449 (11.7%) received adjuvant chemotherapy, 254 (6.6%) received adjuvant radiation therapy, and 92 (2.4%) received some form of systemic therapy which was not specified. Of

Table 2 Patient and Tumor Characteristics by Histology

	Nonfunctional	Insulinoma	Glucagonoma	Gastrinoma	VIPoma	Somato-statinoma	Carcinoid	Significance
Number of Patients	8,344	229	131	301	80	3	773	
Gender (% female)	46.8	52.8	49.6	51.5	54.4	66.7	47.4	P=0.24
Median age (interquartile range)	60 (49–70)	61 (45–73)	56 (48–69)	53 (41 –65)	57 (45– 68)	43 (33–44)	63 (51–73)	P<0.0001
Race								
White (%)	80.8	82.5	79.4	75.4	81.3	66.7	79.4	P=0.001
Black (%)	9.9	7.4	9.9	18.3	12.5	33.3	14.2	
Asian (%)	1.6	1.7	2.3	1.0	2.5	0.0	1.2	
Hispanic (%)	4.5	7.0	4.6	3.0	2.5	0.0	3.5	
Other (%)	3.1	1.3	3.8	2.3	1.3	0.0	1.6	
Anatomic location								
Head (%)	34.6	16.2	16.0	31.2	21.3	100.0	37.8	P<0.0001
Body (%)	7.9	9.2	6.1	6.6	11.3	0.0	7.2	
Tail (%)	21.4	30.6	29.8	14.3	28.8	0.0	14.3	
Diffuse/NOS (%)	36.0	44.1	48.1	47.8	38.8	0.0	40.7	
Median tumor size (cm)	4.5	2.5	5.0	3.0	5.0	3.1	4.5	P<0.0001
(interquartile range)	(3.0–7.0)	(1.6–5.0)	(3.5–8.0)	(1.8–5.0)	(3.0–6.5)	(2.6–3.5)		
Distant metastases								
None (%)	42.7	31.8	30.5	28.1	47.0	0.0	36.4	P<0.0001
Liver (%)	43.0	53.4	44.8	56.2	43.9	50.0	43.3	
Other distant (%)	14.4	14.8	24.8	15.8	9.1	50.0	20.2	
Grade(% poorly differentiated)	39.5	16.7	33.3	18.6	45.5	0.0	45.0	P=0.01

the 5,960 patients who did not undergo pancreatectomy, 32.9% underwent chemotherapy alone, 30.3% did not undergo any treatment, and 17.3% underwent a nonoperative treatment that was not otherwise specified.

Treatment utilization over time is shown in Fig. 2. From 1985 to 2004, there was a modest increase in the proportion of patients undergoing pancreatectomy (with or without adjuvant therapy): 39.4 to 44.3% ($P<0.0001$). The proportion of patients receiving adjuvant chemotherapy did not change significantly (12.7 vs 11.2%, P=0.44).

Factors Predicting Pancreatectomy

Factors predicting whether a patient underwent resection were examined. First we examined all patients, specifically to assess whether distant metastases affected resection rates (Table 3). On multivariate analysis adjusting for patient, tumor, and hospital characteristics, patients with liver metastases and other distant metastases were significantly less likely to undergo pancreatectomy compared to patients without metastatic disease (P<0.0001). However, patients with liver metastases were as likely to undergo resection as patients with other distant metastases (P=0.71). Patients who were >55 years of age or had pancreatic head or body lesions were also less likely to undergo resection (P< 0.0001). Furthermore, patients treated at NCCN/NCI, academic, or highest volume hospitals were more likely to undergo resection than patients at non-NCCN/NCI, community, or lowest volume hospitals (P<0.0001). Gender, race, median income, tumor size, and nodal status were not significant predictors of undergoing pancreatectomy.

Patients who had localized disease (no distant metastases) were examined separately to identify factors predicting the likelihood of undergoing pancreatectomy (Table 4). Advanced age (>55 years) and tumor location within pancreas (head/body of the pancreas) were again associated with a lower likelihood of undergoing pancreatectomy (P< 0.0001). When the patients with metastatic disease were excluded, tumor size (≥4.0 cm) was independently associated with a lower likelihood of undergoing pancreatectomy. Patients treated at NCCN/NCI centers, high-volume hospitals, or academic centers were more likely to undergo cancer-directed surgery for localized PNETs. Gender, race, median income, and nodal status were still not significant predictors of undergoing pancreatectomy.

Discussion

PNETs are relatively rare tumors which are being identified more frequently, likely because of increased detection of incidental disease on abdominal imaging for other reasons.[3] However, the poorly understood natural history has led to uncertainty regarding treatment. PNETs generally have a better prognosis than pancreatic adenocarcinoma; however, skepticism regarding pancreatic surgery may affect resec-

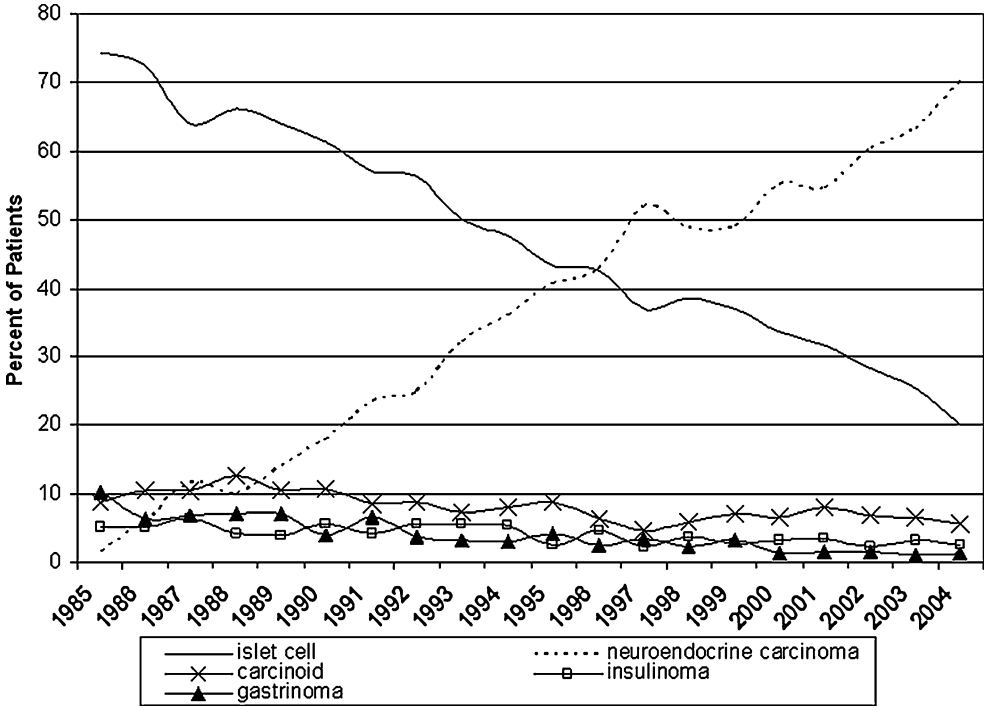

Figure 1 Distribution of reported histologic subtypes in the NCDB from 1985 to 2004.

tion rates of PNETs although surgery remains the only curative treatment for PNETs. Our objectives were to examine clinicopathologic features of PNETs using a large national cancer registry, to assess trends in the treatment of PNETs over the last two decades, and to examine factors associated with undergoing pancreatectomy.

Clinicopathologic Features

A PNET pathologic classification scheme proposed by Capella et al.[4] in 1995 was adopted by WHO in 2000. This classification system recognizes clinical, molecular, and histopathologic characteristics of PNETs. It distinguishes highly differentiated, mostly benign endocrine tumors with an excellent prognosis; well-differentiated neuroendocrine carcinomas with a low malignant potential and a favorable prognosis; and poorly differentiated, mostly small-cell, malignant neuroendocrine carcinomas with a poor prognosis. Accordingly, we observed an increase in the proportion of patients being reported with "neuroendocrine carcinomas" over time. The emphasis on tumor differentiation in the WHO classification is likely also responsible for the

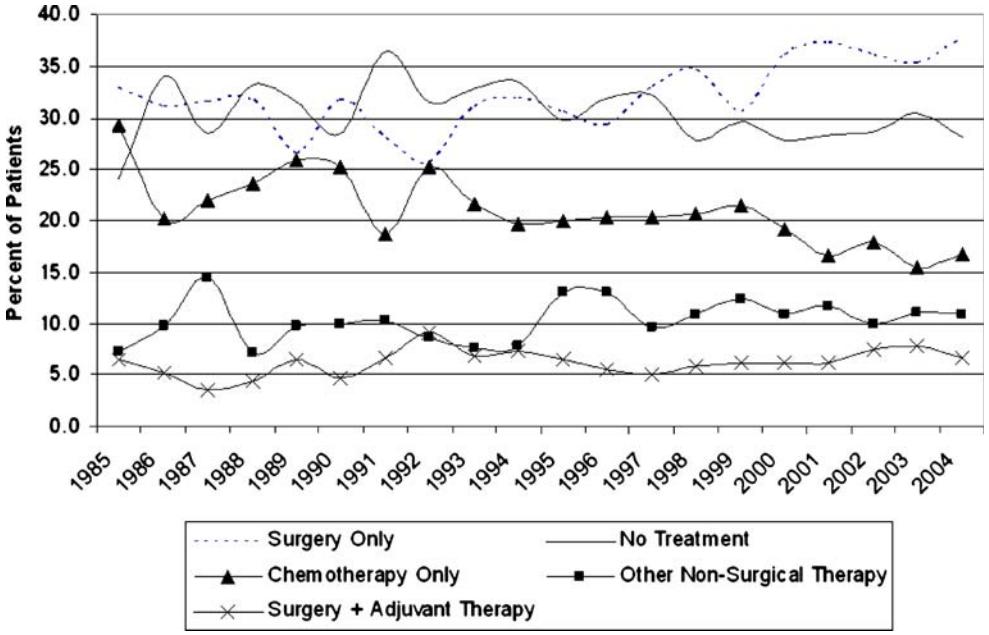

Figure 2 Treatment trends for patients with PNETs from 1985 to 2004.

Table 3 Evaluation of Factors Predicting whether Patients Undergo Pancreatectomy for PNETs

	All Patients	
	Odds Ratio (95% CI)	Significance
Patient		
Age		
<55 years	1.0 (Referent)	
55–75 years	0.63 (0.52–0 .73)	*P*<0.0001
>75 years	0.27 (0.21–0.34)	*P*<0.0001
Tumor		
Location within pancreas		
Head	0.40 (0.33–0.49)	*P*<0.0001
Body	0.59 (0.45–0.79)	*P*<0.0001
Tail	1.0 (Referent)	
Diffuse/NOS	0.48 (0.39–0.59)	*P*<0.0001
Size		
0–1.9 cm	1.0 (Referent)	
2.0–3.9 cm	1.10 (0.87–1.39)	*P*=0.37
4.0–6.0 cm	0.83 (0.67–1.03)	*P*=0.13
≥6 cm	1.03 (0.81–1.32)	*P*=0.79
Nodal Status		
Node negative	1.0 (Referent)	
Node positive	0.89 (0.35–2.26)	*P*=0.80
Distant Metastases		
None	1.0 (Referent)	
Liver	0.11 (0.10–0.13)	*P<0.0001*
Other	0.11 (0.09–0.15)	*P<0.0001*
Hospital Type[a]		
NCCN	1.0 (Referent)	
Non-NCCN	0.66 (0.52–0.83)	*P<0.0001*
Academic	1.0 (Referent)	
Community	0.63 (0.54–0.74)	*P<0.0001*
Hospital Volume Quartiles		
Highest volume	1.0 (Referent)	
High volume	0.88 (0.71–1.08)	*P=0.21*
Moderate volume	0.64 (0.52–0.80)	*P<0.0001*
Low volume	0.61 (0.49–0.75)	*P<0.0001*

Gender, race, median income, tumor size, and nodal status were not significant predictors of undergoing pancreatectomy.
CI: confidence interval; *NOS*: Not otherwise specified
[a] Hospital type and volume variables were inserted separately into the model

significant increase in reported tumor grade in recent years. Nonetheless, in our examination of NCDB data, grade is still significantly underreported for PNETs in comparison to pancreatic adenocarcinoma (22.8 vs 56.2%). Additional emphasis should be placed on improving reporting of tumor grade for PNETs because numerous studies have suggested its prognostic significance.[21–24]

Treatment Trends

No previous study has examined national treatment trends over time for PNETs. Surgical resection is the only curative treatment for localized PNETs.[25] Patients often present with liver metastases, and if feasible, resection improves outcome and may serve as a palliative treatment in patients with functional tumors.[26,27] Little data are available to support adjuvant therapy, and most clinical trials thus far have focused on locally advanced or metastatic, unresectable disease.[25] We found that from 1985 to 2004, there has been little change in the treatment of PNETs, likely a reflection of the poor understanding of this disease. Utilization of pancreatectomy increased modestly over the past two decades. Clinical trials are warranted to assess the impact of emerging adjuvant therapy regimens on outcomes.

Table 4 Evaluation of Factors Predicting whether Patients with *Localized Disease* Undergo Pancreatectomy for PNETs

	No Distant Metastases	
	Odds Ratio (95% CI)	Significance
Patient		
Age		
<55 years	1.0 (Referent)	
55–75 years	0.55 (0.44–0.68)	*P*<0.0001
>75 years	0.25 (0.18–0.35)	*P<0.*0001
Tumor		
Location within pancreas		
Head	0.29 (0.21–0.39)	*P*<0.0001
Body	0.40 (0.26–0.62)	*P*<0.0001
Tail	1.0 (Referent)	
Diffuse/NOS	0.32 (0.23–0.44)	*P*<0.0001
Size		
0–1.9 cm	1.0 (Referent)	
2.0–3.9 cm	1.02 (0.75–1.38)	*P*=0.91
4.0–6.0 cm	0.67 (0.49–0.92)	*P*=0.01
≥6 cm	0.68 (0.49–0.94)	*P*=0.02
Nodal status		
Node negative	1.0 (Referent)	
Node positive	1.89 (0.36–9.79)	*P*=0.45
Hospital Type[a]		
NCCN	1.0 (Referent)	
Non-NCCN	0.53 (0.37–0.77)	*P*<0.0001
Academic	1.0 (Referent)	
Community	0.65 (0.53–0.80)	*P*<0.0001
Hospital Volume Quartiles		
Highest volume	1.0 (Referent)	
High volume	0.88 (0.66–1.19)	*P*=0.41
Moderate volume	0.69 (0.51–0.93)	*P*=0.02
Low volume	0.58 (0.43–0.77)	*P*<0.0001

Gender, race, median income, and nodal status were not significant predictors of undergoing pancreatectomy.
CI: confidence interval, *NOS*: Not otherwise specified
[a] Hospital type and volume variables were inserted separately into the model

Factors Predicting Resection

Prior studies of underutilization of pancreatectomy for adenocarcinoma have suggested that age, socioeconomic factors, and hospital type and volume are associated with undergoing surgery.[28,29] However, no prior study has examined factors predicting whether patients undergo pancreatectomy for PNETs. Multiple studies have suggested that liver metastases may not be a contraindication to resection for PNETs.[26,27] In this study, we found that distant metastases were a strong predictor of not undergoing pancreatectomy; but this was not associated with the location of the metastases (liver vs other metastases). We also found that patients with advanced age were less likely to undergo surgery. However, recent reports have demonstrated that pancreatectomy can be undertaken in the elderly with reasonable morbidity and perioperative mortality rates at high-volume centers.[30] Furthermore, tumor location within the pancreas was also a strong predictor of whether patients underwent pancreatectomy as patients with lesions in the head of the pancreas were less likely to undergo pancreatectomy. A previous study of surgery for pancreatic adenocarcinoma demonstrated similar findings, and these results may reflect outdated views regarding the safety and efficacy of surgery for pancreatic head lesions.[31] Numerous studies have demonstrated decreased postoperative morbidity and mortality rates after pancreaticoduodenectomy, especially at high-volume centers.[7,10,11,32,33] Correspondingly, we found that patients were more likely to undergo pancreatectomy for PNETs at academic, high-volume, or NCCN/NCI-designated cancer centers. As our multivariate models adjusted for case mix between hospital types, these findings likely represent higher rates of referrals from physicians to surgeons and/or the increased willingness of surgeons to operate on pancreatic tumors at specialized centers.

When we focused on patients with localized disease by excluding those with distant metastases, tumor size ≥4.0 cm was associated with decreased utilization of cancer-directed surgery. Numerous studies of PNET prognostic factors have failed to show an association between tumor size and survival.[12,22–24,34–38] Therefore, excluding patients from surgery based on tumor size alone may not be warranted.

Our study has some potential limitations. First, data regarding the functionality of islet cell tumors is not explicitly available in cancer registries. The majority of cases are reported as neuroendocrine carcinomas or islet cell tumors, but some are reported by the associated clinical syndrome (i.e., insulinoma, gastrinoma). It is likely that those reported by their clinical syndromes are functional tumors, but it is also likely that there is underreporting of tumor functional status. For carcinoid tumors, there is not a separate category by which functional status can be denoted. A second limitation is that the NCDB only collects data on "malignant" tumors. Patients with PNETs classified as "benign" by the pathologist are not included in cancer registries in the USA. To develop a better understanding of these tumors, consideration should be given to requiring reporting of all PNETs to cancer registries as the distinction between "benign" and "malignant" is unclear and seems arbitrary.

The rarity of PNETs has limited large-scale investigation. Our study is the largest report on PNETs. National cancer registries offer a unique opportunity to study rare tumors. Treatment over time has remained relatively unchanged, with only a modest increase in resection rates over the past 20 years. Utilization of pancreatectomy for PNETs is associated with patient age, tumor location, tumor size, and hospital type and volume. However, age, tumor location, and size should not preclude resection in otherwise well-suited, resectable patients. PNETs generally have a better prognosis than pancreatic adenocarcinoma; however, pessimistic attitudes toward pancreatic surgery and neoplasms may affect resection rates of PNETs. There may be an opportunity to improve care by increasing utilization of surgery for patients with PNETs.

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Discussion

C. Max Schmidt, M.D. (Indianapolis, IN): Congratulations, Karl, on an excellent study. I have enjoyed watching you continue to succeed as a clinician scientist.

Dr. Bilimoria and his group presented the largest study that I know of pancreatic neuroendocrine tumors, defining their clinical and pathological characteristics and outcomes, finding that age, grade, as well as distant metastases, and not size predict survival after resection. I have a few questions for you and your co-authors.

Pancreatic neuroendocrine tumors, as you noted in your talk and in your paper, in the National Cancer Center Data Base are included only when they are determined to be malignant as opposed to benign by the pathologist. This is rather intriguing because I am not sure how this would be determined. Did you talk to any pathologists at your institution or others to try to get an idea of maybe the proportion of tumors that have been categorized as benign and what characteristics they might have?

Secondly, you have done extensive analysis with this data, and you have looked at factors that predict whether or not patients with pancreatic neuroendocrine tumors will undergo surgical resection. Interestingly, size and location are predictive factors, i.e., larger size and location in the head of the pancreas, which are not associated with resection. In the last 20 years, despite the fact that surgical resection is the only effective treatment, we have only increased the number of resections for this cancer by 5%. So my question to you is, how are we going to get this message to the community? Fifty percent of these tumors are resected in academic centers or National Cancer Institute centers, and 50% are resected in the community.

The third question is about your prognostic score in resected patients. Interestingly, age, grade and distant metastases were utilized in your score and all significant on multivariate analysis. I would like you to speculate why age in resected patients is associated with survival? Eventually all of us must die, but there have been some nice studies to suggest that pancreatic surgery in the elderly is safe, and perhaps you can comment if it is different in terms of age predicting survival in the community versus the academic setting?

And finally, you mentioned some ways in which you are going to validate your prognostic score, but I have not worked with the National Cancer Data Base. I wonder if there is a way to prospectively use the database to validate from here onwards?

Thank you for the privilege of the floor.

Dr. Bilimoria: Thank you for those insightful questions. First, it was a source of irritation when realized that only the malignant tumors are reported to cancer registries. This is partly due to the WHO classification of 2000 where they try to make the distinction between benign and malignant, and our pathologists give this no credence and don't understand the WHO's distinction between benign and malignant. They don't think it is a useful system. Other people have classified benign versus malignant in the literature by patients who have metastases vs. no metastases or nodal involvement vs. no nodal involvement to classify the tumor as benign or malignant, and so it is sort of a confounded definition. I think that it is very unclear, and I think it shouldn't be used, and I hope that we can have all of these tumors reported to the National Cancer Data Base regardless of whether they are deemed benign or malignant.

As far as utilization goes, it is similar to our work with pancreatic adenocarcinoma where we found that nearly 40% of patients were not undergoing surgery for resectable disease. We saw the same thing here, and age, size and tumor location really affected utilization of surgery. Certainly the issue of location of the tumor is probably based on historical concerns with the Whipple procedure, such as high perioperative mortality and complications. Thus, those views are based on outdated data. It probably goes to the point of trying to influence our community hospitals and surrounding hospitals to utilize surgery for this disease.

And that goes to the next question of how are we going to get the message out. It is not the people in this room who won't operate on pancreatic cancer. So it is the people in this room who can spread the message and take it to other surrounding hospitals and state medical societies and continue to educate and update the medical community on the improving data for pancreatic cancer resection.

Your third question was regarding the importance of age on utilization of surgery. A study by Dr. Makary and colleagues from Hopkins looked at age for the Whipple procedure and found that old patients did pretty well, and I think Dr. Cameron's review of 1,000 Whipples actually had a 103-year-old patient who underwent a Whipple procedure. I agree that we need to think about pushing the limit, but that may speak directly to what we were talking about next door yesterday. It's the system and the team that are really involved in being able to take care of the elderly patient. It is the ICU care, the anesthesia care, and so forth. If that turns out to be the case, then maybe referral for those older patients is important. We are going to submit some data to that effect looking at 15 different cancers very soon. Also age is an important prognostic factor no matter what cancer you look at. In a multivariate model, age was the most powerful predictor of outcome. Simply having age in the model doesn't completely account for it, but it does to some extent, and it is a powerful predictor of survival. Older people die, old people have more comorbidities, and so it is also a proxy for the severity of comorbidities. There were no differences between academic and community hospitals in the multivariate models by age, but community hospitals on univariate analysis typically, as we saw in the rectal cancer paper, have older patients and actually they have sicker patients than at the academic hospitals by Charlson score.

Finally, to validate the model using a prospective system is exactly something that we would like to look into. SEER in the Detroit and LA regions allow investigators to get the names of patients and follow them once they have been diagnosed, and this happens relatively quickly after diagnosis so you can actually do a study early on. The National Cancer Data Base isn't set up that way and there are some limitations because we have so much sensitive data on the hospital and the patient that we cannot to give out freely at this point. We are looking at developing a public use data set. But to do this prospectively where we can identify patients quickly after diagnosis and include them in clinical trials would be fantastic, and I think that we need to take a lesson from SEER on how to do that and move in that direction. That is a great idea.

Dr. K. Lillemoe (Indianapolis, IN): Karl, another nice bit of work from you and your group. I do quibble a little bit with this study, though, because I really think you are mixing apples with oranges. All these tumors are rare, but I think clinicians have got an idea of the natural history of gastrinomas, they have an idea of the natural history of carcinoids, insulomas, as we have talked before, the rare one that is malignant, falls into your group. The big unknown is the nonfunctional neuroendocrine or islet cell

tumors which make up the vast majority of your cases. So I guess my question for you is, if you just threw out all the functional tumors and just focused on the nonfunctional islet tumors, is this a valid tool, because that is where we need help in telling patients what to do. Obviously we don't have a lot of options in terms of adjuvant therapies, but clearly those are the big unknown and that is where I really question if you could mine your database to answer the real prognosis with those tumors.

Another nice bit of work from your group.

Dr. Bilimoria: We did exactly that. We excluded the carcinoid tumors and the functional tumors separately and then we excluded both groups, the carcinoid and the functional tumors. When we just looked at the nonfunctional tumors, the remaining 83% of tumors that underwent resection, the prognostic score held up in exactly the same way. The magnitude and direction of the hazard ratios in the Cox model were almost identical to when we included the functional and/or carcinoid tumors.

Dr. Lillemoe: And lymph nodes didn't have any prognosis with the nonfunctional?

Dr. Bilimoria: No, they did not.

Dr. H. Chen (Madison, WI): Fantastic study. Congratulations. I just had a quick question for clarification. In your carcinoids, were all those pancreatic carcinoids or did you throw in gastrointestinal carcinoids in your study?

Dr. Bilimoria: They were purely pancreatic carcinoids. These did not include peripancreatic or other gastrointestinal tumors. They had to be coded as a primary pancreatic neoplasm to be included in our study.

Dr. B. Clary (Durham, NC): One last question. For your multivariate analysis, that was done on the entire population. If you limited it to your resected patients, do nodal status and margin become important and should you create your prognostic scoring system from that population?

Dr. Bilimoria: Sorry if I didn't make that clear. The score and the prognostic factors are based entirely on resected patients. We did the analyses on all patients as well, but what I have shown you here is only on the resected patients.

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Prospective Evaluation and 7-Year Follow-up of Swedish Adjustable Gastric Banding in Adults with Extreme Obesity

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Abstract
Background Swedish adjustable gastric banding (SAGB) is a widespread laparoscopic procedure in bariatric surgery. Few long-term data is available.
Aim To determine long-term outcome after SAGB in 196 patients studied prospectively.
Patients and Methods 196 patients, 40 men, and 156 women have been operated from 1996 to 2005. Age was 38±1 (mean± sem) years. Mean follow-up was 63±2 months.
Results Hospital morbidity was 3% (0.5% early reoperation); mortality was 0. Late complications were band migration (1%), leakage (5%), slipping (4%), or pouch dilatation (8%). Minor reoperations (tube replacement, port-related, and hernias) were needed in 7.5%. Cumulative major reoperation rate reached 32%. Eighteen percent had a band replacement; 14% had removal of band anatomy. Late mortality was 0.5%. Exactly 7 years after SAGB, BMI decreased from 45±1 kg/m^2 to 33±1 kg/m^2, and excess weight loss (EWL) was 61±4%. Sixty-eight percent of the patients reached ≥50% EWL.
Conclusion In 14% of the patients, the band anatomy had to be removed. Seven years of intact band anatomy leads to a successful EWL of 61±4% and to EWL of ≥50% in 68%. However, cumulative major reoperation rate of 32% in 7 years makes it mandatory to offer and discuss other bariatric procedures to the respective patients.

Keywords Extreme obesity · Morbid obesity · Bariatric surgery · Laparoscopic · Swedish adjustable gastric banding

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Introduction

Obesity has become a major problem in our health care system. In the USA, in 2003/2004, 32.2% (approximately 66 million) of adults were obese (BMI >30 kg/m^2). Almost 5% of adults were extremely obese (BMI >40 kg/m^2).[1] WHO's latest world-wide estimate indicates that in 2005, at least 400 million adults (age 15+) were obese. By 2015, approximately more than 700 million will be obese.[2] According to the NHANES studies,[3] the age-adjusted prevalence of obesity increased from 15% in 1976–1980 (NHANES II) to 31% in the examination period 1999–2002 (NHANES).

Hospital Stay of obese patients increased by 112% between 1996 and 2004, rising from 797.000 to 1.7 million hospital days. Average cost for each patient was $11.700 per stay (Agency for Healthcare Research and Quality [AHRQ], 2007). Already in the 1985 National Institute of Health (NIH) Consensus conference, elevated BMI is mentioned as a risk factor and correlation with markedly increased mortality and morbidity, i.e., as a result of diabetes, cardiovascular and pulmonary disease, carcino-

mas, etc.[4] In the context of the obesity epidemic, WHO predicts that death by diabetes will increase by more than 50% worldwide in the next 10 years.[2]

The European section of the WHO reports 2–8% of all health expenses because of obesity (lack of productivity, decrease of income). In Spain, this accounts to more than 3 billions $ per year spent for direct and indirect costs for the treatment of obesity (7% of all health expenses; WHO, Faktenblatt EURO/13/05, Kopenhagen, Bukarest, 12, September 2005). Meanwhile many authors have proved that obesity-related morbidity and mortality is markedly reduced by weight reduction induced by bariatric surgery.[5–10]

Two mainly restrictive procedures have been accepted by the NIH[4] as valuable approaches: the Roux-en-Y Gastric bypass (RYGB)[11] and the Vertical banded Gastroplasty (VBG).[12] Whereas in the early 1990s, many groups in Europe considered the Gastric bypass to be "too mutilating," and the VBG results seemed not to be satisfactory in terms of weight loss and reoperation rate,[13,14] the development of adjustable gastric bands, omitting gastrointestinal dissections, and staple lines was welcome and promising. Belachew[15] and Cadière[16] were among the first to place the band laparoscopically.

In Europe, laparoscopic adjustable gastric banding has been established since the mid-1990s.[17] Meanwhile, laparoscopic gastric banding is widespread in the surgical community, and mainly two systems have been used: The *LAP-BAND®* (*BioEnterics®*, Carpinteria, CA) and the *Swedish Adjustable Gastric Band* (SAGB, Obtech Medical, 6310 Zug, Switzerland). In our group, we started laparoscopic implantation of the SAGB in early 1996.

The aim of this study was to prospectively evaluate this surgical approach, and this report summarizes our long-term experience.

Patients and Methods

From February 1996 through March 2005, 196 patients with extreme obesity (40 men and 156 women; median age was 38 years, range 18 to 63 years) underwent bariatric laparoscopic SAGB. One hundred and ninety five were done laparoscopically; one had a primary celiotomy.

The median preoperative weight was 120 kg (range 84–175 kg), the median BMI was 44 kg/m^2 (range 31–65), and the median excess body weight (EBW) was 52% (range 16–95%) above the ideal body weight. Almost all patients had one or more weight-related comorbidities including 28% hypertension, 18% diabetes, 32% hyperuricemia, and 39% dyslipidemia.

All patients were preoperatively managed by a multidisciplinary team. All patients had multiple unsuccessful conservative attempts of weight reduction of at least 2 years duration. Preoperatively, the operation and its rational, expected results, necessary changes of eating habits, and life style have been outlined in depth. Patients were seen, and the first band filling was performed 4 weeks after the procedure. Three to four milliliters of a radiology contrast medium (Iopamiro® 200 Iopamidol; Bracco, Milan, Italy) was injected. Further clinical controls and fillings were performed every 4–6 weeks until band filling resulted in satiety induction by a small food serving or until food regurgitation was more frequent than one to two times a week. During the first year, a patient was therefore seen at least three to four times, and after 3 months and 1 year, a contrast swallow was performed. Clinical and contrast swallow controls were repeated yearly thereafter. Patients seen 84 months after operation were encouraged to participate in the evaluation according the BAROS (Bariatric analysis and reporting outcome system),[18–20] which combines subjective quality of life parameters with weight reduction, need for reoperation, improved or resolved comorbidities.

Preoperative, operative, and all follow up data during the observation time until January 2005 was recorded prospectively in a computerized data base. All patients have been seen by at least one of the authors on an outpatient basis. Mean follow up was 63±2 months, with a mean postoperative period of 71±1 months. Longest follow up was 108 months, 12 patients had a follow up >84 months. All but 22 patients (11%) have been seen within the last 12 months period before the end of the observation time. Seven of them belong to one extended tribal family, who regularly failed appointments for follow up. Two patients died, one because of a bike accident. Another polyallergic patient with longstanding coronary heart disease died at the age of 66 years. He initially developed secondary band intolerance 5 years postoperatively after excess weight loss (EWL) of 40% (30 kg) but still with a BMI of 40 kg/m^2 and was reoperated for RYGB. One year later, his BMI was 41 kg/m^2, and he therefore was reoperated for a biliopancreatic diversion. He developed sepsis and anaphylactic shock in presence of an anastomotic leak despite two reoperations.

During the observation period, 28 patients underwent reoperation with band removal alone (n=4), band removal and RYGB (n=22), and band left in situ but additional RYGB (n=2). Because these patients do not have an intact "band anatomy" anymore, they will be considered a failure for the method of gastric banding. We included all patients but concentrated our weight data analysis during at the time of intact "SAGB anatomy."

Operative Procedure

The patients were given a single shot antibiotic (1.5 g cefuroxime) at the induction of anaesthesia. Weight-adjusted low molecular weight heparin was started at the day of surgery and was continued for 4 weeks. We

performed the laparoscopic implantation of the SAGB with the pars flaccida technique as described previously.[21]

In brief, five trocars were used with a 30° angled optic. The SAGB was placed in the pars flaccida technique using the "goldfinger" (Obtech Medical), which is very convenient for blunt dissection of the avascular part of the gastrophrenic ligament, the retrogastric tunnel, and to pull the attached SAGB around the back of the stomach to the lesser curvature. The band system was not filled at the end of the operation.

Weight Loss Data

We analyzed weight and weight loss in kilograms; BMI and excess weight loss in percent. The general preoperative goal in bariatric surgery is a ≥50% excess weight loss (EWL). We expressed this data not only representing the whole group but also the percentage of patients who reached that goal.

In addition, we chose two ways of presentation of weight parameters. First, we show all available data at each time period, and second, we present the data of the 47 patients with available follow up at 0, 12, 48, and 84 months. With this approach, we try to present the data from different angles and with less bias.

The data is presented as actual weight values, BMI, and excess weight loss as median (range) or mean±sem.

Results

SAGB was implanted in 196 patients. Additional procedures were cholecystectomies in 25 (13%) and hiatal hernia repair (crurorraphy) in 24 (12%) patients. Median time for surgery was 85 (30–190) min, and hospital stay was 6 (2–19) days. Fifteen patients (8%) required intensive care treatment, 12 (6%) for 1 day. Maximum was 3 days.

Perioperative Complications

All but one operation was started laparoscopically. Bleeding occurred in seven patients (five epigastric artery, one ligamentum teres hepatis, one lesion of the spleen). Therefore, in five cases, a conversion was needed (3%).

Early Complications

One day postoperatively intraabdominal bleeding occurred in one patient (0.5%). She was successfully reoperated laparoscopically. One patient (0.5%) had dysphagia, which resolved within 2 weeks.

Two patients (1%) had a wound infection.

Systemic complications comprised of two cardiac problems (one tachycardia, one stenocardia), two patients with respiratory distress and one with an undefined allergic reaction. All five (3%) resolved without further complications.

Long-term Complications

Two patients died during the follow-up period. One died of an unrelated cause (a bike accident), the other because of septic shock after the second remedial bariatric procedure 5 years after SAGB and 1 year after RYGB. The RYGB was indicated because of unsatisfactory weight loss after SAGB (EWL 34%, BMI 40), and the operation 1 year after RYGB—biliopancreatic diversion—was performed because the BMI has still been 41. With this patient, we have a long-term mortality of 0.5%.

One patient (0.5%) underwent ERCP for recurrent biliar colic 12 months after SAGB, and one patient (0.5%) underwent laparoscopic cholecystectomy 9 months after SAGB.

Port-related Complications and Local Reoperation

Ten patients had port related complications, nine (4.5%) needed reoperation. We did not experience any port infections. Five patients (2.5%) developed ventral hernias. All of them needed hernia repair surgery 38 months (20–80 months) after SAGB implantation (Table 1).

Band-related Complications and Major Reoperation

During the 7-year follow up, 63 reoperations were necessary (32%). Median intervals from implantation of SAGB to reoperation and complications leading to reoperation are shown in (Table 2). Thirty six (18%) had a reimplantation of the SAGB. Four patients (2%) had the band totally removed without further procedure.

Twenty two (11%) had a band removal and a remedial RYGB 56 (20–102) months after SAGB. Sixteen of these

Table 1 Port-related Complications and Local Reoperation

Type of complication	Number	Percent (%)	Time to reoperation (months)
Port dislocation	1	0.5	No operation
Pain inside the port bed	3	1.5	11 (3–18)
Disconnection (tube → port)	4	2	27 (18–38)
Combined disconnection/dislocation	2	1	28 (4–52)
Hernia	5	2.5	38 (20–80)
Trocar site	3		
Laparotomy scar	2		
Total	15	7.5	21 (3–80)

Numbers represent median (range).

Table 2 Directly Band-related Complications and Major Reoperation

Description of reoperation	Number	Percent (%)	Time to reoperation (months)[a]
Complete band removal	4	2	51 (27–89)
Slippage	1		27
Band migration	2		32 (38–33)
Band infection	1		89
Reimplantation of SAGB	36	18	28 (6–77)
Pouch dilatation	16		32 (11–51)
Band leakage	10		35 (6–77)
Slippage	8		29 (8–68)
Esophageal dilatation	1		9
Reflux due to hiatal hernia	1		39
Band removal and RYGB	22	11	56 (20–102)
Secondary band intolerance	16		55 (20–90)
Combined SAGB and RYGB	2	1	19 (15–23)
Total	63	32	39 (6–102)

[a] Numbers represent median and (range) months.

patients (8%) suffered of secondary band intolerance with either discomfort or daily food regurgitation not responding to deflating the band system. These patients presented with or without satisfactory weight loss (mean EWL 39%±4; median 42% [12–68%]). The six other patients had unsatisfactory weight loss with a mean EWL of 38±9%.

Two (1%) of our first patients had a very good induction of satiety but no satisfactory weight loss. In these patents, we left the band in place and added RYGB anatomy. These two operations and one band replacement were done with open surgery; all the others were laparoscopic reoperations. In total, we had to break down the "SAGB anatomy" in 28 patients (14%; Table 2).

Weight Loss and Maintenance

When including all patients available at each time period, most of the weight loss was observed in the first 12 months. EWL was 47±2% and further improved to 61±2% after 4 years. At 7 years, EWL decreased to 56±3%. The percentage of patients reaching at least 50% of EWL decreased from 68% after 4 years to 58% after 7 years (Table 3).

There were 62 patients that could have had a follow up of ≥7 years. Twelve (20%) were reoperated, and three (1.5%) had a follow up at 7 years but had only one follow up in between. Therefore, we analyzed 47 patients with a band in place, who were seen exactly after 7 years and who had at least two follow-up consultations in between. Their EWL was 61±4% at 84 months. Percentage of patients reaching an EWL of ≥50% after 12, 48, and 84 months was 55, 74, and 68% (Table 4).

This excellent weight loss in this select group with intact band anatomy after exact 7 years and the difference between the whole cohort could be explained by the fact that patients with insufficient weight loss have been more likely to be reoperated prior to reaching the 7-year follow up than patients who tolerated the band well and who had a successful course (Fig. 1).

Table 3 Weight Loss of all Available Patients at each Follow-up Period

Months	0	12 (11±0.2)[a]	24 (23±0.2)[a]	48 (47±0.6)[a]	84 (79±0.7)[a]
BMI (kg/m^2)					
Median (range)	44 (31–65)	35 (21–58)	33 (20–56)	32 (21–52)	34 (20–49)
Mean±sem	44±0	35±0	33±0	33±1	34±1
Weight (kg)					
Median (range)	120 (84–175)	97 (60–154)	91 (59–139)	88 (60–142)	92 (60–169)
Mean±sem	122±1	99±1	93±1	92±2	94±2
Weight loss (kg)					
Median (range)		23 (21–24)	29 (26–36)	32 (25–33)	28 (24–6)
Mean±sem		23±1	29±1	30±1	28±2
EWL (%)					
Median (range)		44 (−2 to 145)	58 (3–152)	63 (6–139)	56 (−6 to 135)
Mean±sem		47±2	58±2	61±2	56±3
Success[b]		38% (70)	63% (101)	68% (92)	58% (53)
n	196	182	160	136	92

n Number of patients available at this follow-up period
[a] Mean±sem months
[b] Percentage and absolute number in parentheses of patients with weight loss ≥50%

Table 4 Weight Loss of all Patients Seen Exactly after 7 years and with Data of Two other Consultations in Between

Months	0	12 (12±0.2)[a]	48 (51±2)[a]	84
BMI (kg/m^2)				
Median (range)	44 (35–58)	34 (21–48)	31 (21–47)	32 (22–49)
Mean±sem	45±1	35±1	32±1	33±1
Weight (kg)				
Median (range)	122 (92–175)	94 (60–148)	88 (60–133)	85 (64–169)
Mean±sem	124±3	96±3	88±3	91±3
Weight loss (kg)				
Median (range)		28 (27–32)	35 (33–42)	37 (6–28)
Mean±sem		28±3	36±3	33±3
EWL (%)				
Median (range)		52 (7–145)	69 (0.0–139)	64 (−6 to 135)
Mean±sem		54±4	68±4	61±4
Success[b]		55% (26)	74% (35)	68% (32)
n	47	47	47	47

n Number of patients
[a] Mean±sem months
[b] Percentage and absolute numbers (in parentheses) of patients with weight loss ≥50%

BAROS after 84 months

We received quality of life data (self-esteem, physical activity, social contacts, job satisfaction, and sexual activity) from 31 patients (62%) to complete the BAROS score. Median points were 4.75 (0.75–8.55), which represents a good result. Ninety seven percent scored with a satisfactory score (>1), 67.7% (21 of 31) scored ≥4 points, which represents a good result. Therefore, according to BAROS, 97% were successfully treated.

Discussion

The aim of our study was to prospectively evaluate the long-term outcome of all patients operated for extreme obesity with an SAGB and personally seen yearly by one of the authors. Our focus was on long-term complications and on weight loss and maintenance.

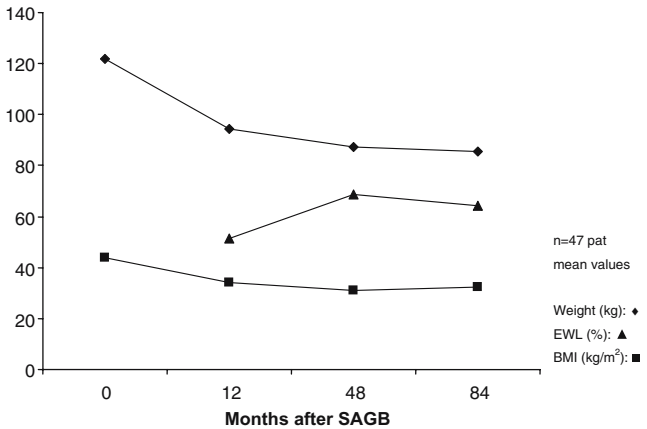

Figure 1 Weight loss of 47 patients seen at exactly 7 years after SAGB with an intact "band anatomy."

Our main findings are that the SAGB implantation is a safe procedure and that the outcome according to weight loss and maintenance and BAROS score is good up until 7 years after initial surgery. However, failure because of SAGB removal was 14 and 42% because of EWL <50%. In addition, cumulative band-related reoperation rate after 7 years was slightly more than 30%.

We had no perioperative mortality, and morbidity was minimal and comparable to other series with laparoscopic band implantations.[22–24]

Our long-term mortality of 0.5% is not really because of the SAGB procedure; however, in an intention to treat analysis, it represents the small but eminent mortality risk of bariatric surgery in general.[8] We should always be aware of this risk, albeit the benefit of surgical therapy with regard of treating obesity-related comorbidity, i.e., the metabolic syndrome[5–10] and most importantly reducing mortality.[9,10,25]

Our long-term morbidity was 3.5% for general reinterventions (one ERCP and one lap cholecystectomy, five ventral hernia repairs) and 4.5% for port-related local reoperations. Directly band-related complications accounted for 32% over 7 years. Most of which led to band

Table 5 Reoperations in 2-Year Intervals after SAGB

Months after SABG	0–24	24–48	48–72	>72	Total
Number of reoperations	19 (9.5%)	23 (12%)	11 (5.5%)	10 (5%)	63
Cumulative reoperation rate (%)	9.5	21.5	27	32	32

replacement (18%) or band removal and remedial operation with RYGB (11%).

When not focussing on operations itself but on individual patients who needed one or more reoperation, band-related reoperations remain at 28%. Considering the band leakages (5%) in the first generation of SAGB—this technical problem has been solved—as not being relevant for today's estimate of future SAGB-associated complications, an individual patient undergoing SAGB has still a risk of developing band-related problems mandating major reoperation of 23%. Thus, if we add the risk for minor reoperations, we should inform a prospective "band patient" about a total long-term risk of any kind of reoperation of 31%.

When comparing to the literature, our reoperation rate is at the upper end of the reported values.[8,22–24] Compared to other series, the surgical technique was comparable, and the best explanation of the differences in complication rates may be their shorter follow up (between 13 and 39 months) compared to our 63±1 months.[22,23,26,27] Regarding the distribution of reoperations in our series over the years (Table 5), it is conceivable that these series will accumulate a similar reoperation rate in future years. However, we have a higher reoperation rate in our SAGB cohort than the reported 9% by Miller et al.[24] after a mean 93 months follow up in a mixed group of SAGB and LapBand patients. It is unlikely that the choice of the band system plays a role, as Miller et al.[24] and others have not shown a great difference in band system specific complications.[23,29]

Our 14% of band removal after 63±1 months seems realistic in comparison to the large range of band removal rates (0.6–70%) outlined in an excellent review of 18 articles reporting adjustable gastric banding results.[28]

In general, our long-term complications and reoperation rate after adjustable gastric banding seems to reflect the experience of other centers as well. The high reoperation rate is the reason that at our institution, since about 2001, the tendency to favor RYGB instead of gastric banding is apparent. The same seems to be true for other groups.[23]

Weight loss of our patients, EWL between 63 and 56% after 4–7 years, has been very well and is in accordance to the literature.[7,29] Interestingly, success is even more impressive with a mean EWL of 61%, 68% of patients maintaining EWL ≥50% and 97% good BAROS results in patients who remained with the Band anatomy until 7 years. This is a difference to patients with VBG anatomy still intact 10 years after operation compared to the Mayo Clinic results,[14] however comparable to VBG weight loss results after 10 years in another report.[24]

SAGB is, in terms of weight loss, comparable to other more invasive procedures and seems to provide a good quality of life also after 7 years.[7] As mentioned above, efficacy of bariatric surgery in reducing obesity-related comorbidities is very good,[5–10] and also, the effect of SAGB on morbidity is well documented.[22] However, comparative studies suggest that RYGB has a higher metabolic impact and reduces the metabolic syndrome more than a purely restrictive procedure.[7] This aspect should also be thought of when choosing the gastric banding procedure.

In addition, our own long-term results suggest that the risk of band-related complications over time, requiring major reoperation, seems to be higher than in other procedures such as RYGB or duodenal switch.[7,28] Because it seems relatively simple to implant the adjustable band, we see a risk that surgeons and patients might be tempted too easily to decide upon implantation. We recommend that other procedures, mainly RYGB, are offered and discussed with the patient. Equally, as recommended for more invasive bariatric procedures, adjustable bands should only be implanted in centers of excellence[30] and within a multidisciplinary group.[31]

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DISCUSSION

Bruce D. Schirmer, M.D. (Charlottesville, VA): Since Dr. Murr isn't here, I will take the liberty of making a few comments, if you don't mind.

I want to congratulate you on a very nice paper, and it seems pretty clear that most of your patients fall into a specific category after 7 years. Approximately 70% of them that have good weight loss, over 50% of excess weight, and they seem pretty satisfied. Now, some of these, almost 35 or 38%, required two bands. But then you have another 20% that obviously have decided this is not the operation for them, and they have either had the band removed or they have had a subsequent different weight reduction operation. My first question to you is, what is the time frame of that? How long did people take before they decided? What was the average time until they lost their band anatomy in the group?

My second question to you is, of the satisfied group, about 35% of them needed a second band. Long-term, do you think they are going to need additional bands? Were most of the bands replaced early on and now they have been very stable, or is this a cumulative thing in which you see about 5 or 10% need the band replaced every few years for various reasons, which would imply if they are going to keep the band for 20 years they might need multiple bands?

Bruno M. Balsiger, M.D. (Bern, Switzerland): Thank you very much for your questions. To take the last question first, we had ten patients who had to be re-banded because the band leaked. That was the first generation of the bands. We didn't have any leaks after 1999 or so. So, this is one group. And then the median time of re-banding was somewhere around 28 months. And actually some of these patients had already their third band.

It is hard to tell how long these bands really stay in place. The group of these 47 patients include not only the ones with the band leakage, but it includes also the ones in the learning curve. So, this is really difficult to say, and we are looking forward to see the other patients that are now 4 or 5 years out to see how they do in future years.

Haggi Mazeh, M.D. (Jerusalem, Israel): You have a pretty high reopration rate. I have two questions for you: First, you presented cases from 1996 and on; do you have a learning curve? Did you have less cases that needed re-operation later on? My second question is, did you routinely use sutures to fix the band in place?

Dr. Balsiger: We did three to four sutures to fix the band. I didn't really look into the learning curve, but as expected, this has to be a factor as well. One thing is that the technique developed quite a bit. In the beginning, around 1998, 1999,

the Swiss and Swedish group around Klaiber and Forsell developed the pars flaccida technique, which is usually performed now, and there seems to be less slippage and pouch dilatation.

Eric S. Hungness, M.D. (Chicago, IL): Do you have any demographic or comorbidity data for patients who were successful or those who failed, or are you going to be looking at that in the future to help us determine, which patients may not be good for the band?

Dr. Balsiger: Thanks for that question. That is actually exactly what we would like to find out, which patients really do well with the band. We think that we need a really compliant patient for the band. We think that it is more difficult for the patient to deal with the band than with a Roux-en-Y gastric bypass. It is not thinking of being consistent in taking supplements, that is a different story, but of eating well, not eating too much at the time, chewing well. That is the one thing I can tell you, that we think it needs a more compliant patient. But otherwise we really don't have any data.

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Incidence of Finding Residual Disease for Incidental Gallbladder Carcinoma: Implications for Re-resection

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Abstract Re-resection for gallbladder carcinoma incidentally discovered after cholecystectomy is routinely advocated. However, the incidence of finding additional disease at the time of re-resection remains poorly defined. Between 1984 and 2006, 115 patients underwent re-resection at six major hepatobiliary centers for gallbladder carcinoma incidentally discovered during cholecystectomy. Data on clinicopathologic factors, operative details, TNM tumor stage, and outcome were collected and analyzed. Data on the incidence and location of residual/additional carcinoma discovered at the time of re-resection were also recorded. On pathologic analysis, T stage was T1 7.8%, T2 67.0%, and T3 25.2%. The median time from cholecystectomy to re-resection was 52 days. At the time of re-resection, hepatic surgery most often consisted of formal segmentectomy (64.9%). Patients underwent lymphadenectomy (LND) (50.5%) or LND + common bile duct resection (43.3%). The median number of lymph nodes harvested was 3 and did not differ between LND alone (n=3) vs LND + common duct resection (n=3) (P=0.35). Pathology from the re-resection specimen noted residual/additional disease in 46.4% of patients. Of those patients staged as T1, T2, or T3, 0, 10.4, and 36.4%, respectively, had residual disease within the liver (P=0.01). T stage was also associated with the risk of metastasis to locoregional lymph nodes (lymph node metastasis: T1 12.5%; T2 31.3%, T3 45.5%; P=0.04). Cystic duct margin status predicted residual disease in the common bile duct (negative cystic duct, 4.3% vs positive cystic duct, 42.1%) (P=0.01). Aggressive re-resection for incidental gallbladder carcinoma is warranted as the majority of patients have residual disease. Although common duct resection does not yield a greater lymph node count, it should be performed at the time of re-resection for patients with positive cystic duct margins because over one-third will have residual disease in the common bile duct.

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Keywords Gallbladder carcinoma · Incidental · Resection · Residual disease · Common bile duct

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Introduction

Approximately 8,500 new cases of gallbladder carcinoma are diagnosed annually, making it the sixth most common gastrointestinal malignancy in the United States.[1] Identification of gallbladder carcinoma can occur either late after symptomatic presentation or incidentally after routine cholecystectomy. In fact, approximately 1 gallbladder cancer is diagnosed per 100 cholecystectomies performed.[2,3] Gallbladder adenocarcinoma has traditionally been associated with a poor prognosis, with overall survival ranging from 5 to 10%.[4,5] More recently, extended operations that combine hepatic resection, lymph node dissection, and even common bile duct resection with reconstructive hepaticojejunostomy, have been advocated to improve long-term survival.[6–8] Prognosis after surgery, however, can vary dramatically with 5-year survival rates ranging from 10 to 90%,[2] depending on both the extent of the curative resection, and perhaps more importantly, the stage of disease.[9,10]

The selection of the subset of patients who might benefit most from aggressive repeat surgery and the actual extent of the repeat surgery, remain somewhat controversial.[11,12] Specifically, several investigators have stated that patients with nodal metastasis should not be considered for curative resection,[7] as 1-year survival after radical resection in this group of patients is rare.[13] In contrast, proponents of radical resection argue that all T2 and T3 lesions should be treated with radical resection, regardless of eventual nodal status, because these patients may derive a survival benefit, and liver surgery can now be performed with minimal mortality and acceptable morbidity.[14,15] To assess the potential benefit of repeat surgery, accurate identification of those patients who most likely harbor additional disease at the time of re-resection is necessary. However, the incidence of finding additional disease at the time of re-resection remains poorly defined. Data on the incidence of residual disease and the identification of factors that may be associated with specific patterns of residual disease (e.g. gallbladder fossa, regional lymph nodes, common bile duct) are important. Such data may help determine not only whether repeat surgery is warranted, but also clarify the extent of the surgical extirpation (e.g., whether routine resection of common bile duct is necessary or not). Therefore, the objective of the current study was to determine the incidence and location of residual/additional carcinoma discovered at the time of re-resection for incidentally discovered gallbladder adenocarcinoma. In addition, we sought to identify and evaluate those factors associated with specific patterns of residual disease. The current study also aimed to examine factors influencing postoperative survival after resection of gallbladder adenocarcinoma.

Patients and Methods

Between September 1984 and November 2006, 225 patients with gallbladder adenocarcinoma underwent surgical treatment at six major hepatobiliary centers in the United States (Johns Hopkins School of Medicine, Baltimore, MD; Emory University School of Medicine, Atlanta, GA; University of Virginia Medical Center, Charlottesville, VA), Brazil (Universidade Federal do Rio Grande do Sul), and Europe (Institute for Research and the Cure of Cancer, Candiolo, Italy; University Hospital Essen, Essen, Germany). The study was approved by the Institutional Review Boards of the respective institutions. Only patients with histologically confirmed gallbladder adenocarcinoma were included in the current study. Routine frozen section analysis of the gallbladder was not performed at the time of initial cholecystecomy; frozen section analysis was performed, however, if the patient was noted to have a previously unsuspected suspicious mass/lesion. Of the 225 patients included in the study, 148 (65.8%) had incidental gallbladder carcinoma; 77 (34.2%) patients had non-incidental gallbladder carcinoma that was suspected before surgery.

Standard demographic, clinicopathologic, and tumor-specific data were collected on each patient. Specifically, data on presentation (incidental vs non-incidental) and details from both the initial surgery and any re-resection were collected. Where applicable, hepatic resection was classified as wedge, segmentectomy of 4b + 5, or hemi-hepatectomy. Additional information on the extent of the surgical approach (e.g., lymphadenectomy, resection of bile duct with hepaticojejunostomy, etc.) was also collected. Pathological data including cystic duct margin status, residual disease in the common bile duct or liver, and primary tumor American Joint Commission on Cancer (AJCC) stage (T, N, M) were recorded.[16] After surgery, all patients were regularly followed and prospectively monitored.

Summary statistics were obtained using established methods and presented as percentages or median values with the interquartile (IQ) range. Time to recurrence and survival were estimated using the nonparametric product limit method (Kaplan and Meier).[17] Differences in survival were examined using the log-rank test. Factors associated with recurrence and survival were examined using univariate and multivariate Cox regression analyses. The hazard ratio and the 95% confidence intervals (CI) were estimated, and a P value less than 0.05 was considered significant. All statistical analyses were performed using SPSS Version 11.5 (Chicago, Illinois).

Results

Table 1 shows the clinicopathologic features of the 148 patients with incidental gallbladder adenocarcinoma. There

Table 1 Clinicopathologic Characteristics of Patients with Incidental Gallbladder Carcinoma (n=148) Stratified Whether Treated with Single- or Two-Stage Operation

Variable	Single Operation [n=33; n (%)]	Two-Stage Operation [n=115; n (%)]	P Value
Age			
Median (years)	64.4	70.0	0.02
Gender			
Female	8 (24.2)	79 (68.7)	0.52
Male	25 (75.8)	36 (31.3)	
Cholelithiasis on presentation	31 (93.9)	97 (84.3)	0.26
Initial laparoscopic cholecystectomy	N/A	92 (80.0)	
T Stage			
T1	9 (27.3)	9 (7.8)	<0.001
T2	8 (24.2)	77 (67.0)	
T3	12 (36.4)	29 (25.2)	
T4	4 (12.1)	0	
Lymph node status after cholecystectomy			
No node in cholecystectomy specimen (Nx)	32 (97.0)	93 (80.9)	0.04
Negative	1 (3.0)	6 (5.2)	
Positive	0	16 (13.9)	
Positive cystic duct margin	9 (27.3)	34 (29.6)	0.97
Time to re-resection			
Median (days)	N/A	52	

N/A Not applicable

were 44 (29.7%) men and 104 (70.3%) women. The median patient age was 64 years old (range, 22 to 87 years). Most patients (n=128; 86.5%) presented with cholelithiasis. In 33 (22.3%) patients, incidental gallbladder cancer was discovered intraoperatively and treated at the time of cholecystectomy. In these 33 patients, the diagnosis of gallbladder carcinoma was made based on frozen section analysis of a previously unsuspected mass/lesion. Of the 33 patients in whom the gallbladder cancer was discovered at the time of operation, four patients had advanced locoregional disease (T4), and no additional surgical intervention was undertaken. The extent of disease varied among the other 29 patients (T1, n=9; T2, n=8; T3, n=12). A liver resection with a hepatoduodenal portal lymphadenectomy was performed in the 12 patients with T3 disease, while the other 17 patients underwent simple cholecystectomy. In addition, 3 of the 11 patients with T3 disease underwent a concomitant common bile resection in conjunction with their lymphadenectomy.

The remaining 115 patients who had incidental gallbladder cancer underwent a second staged surgical intervention. The overwhelming majority of patients (n=92; 80.0%) had initially undergone a laparoscopic cholecystectomy. On final pathology from the initial cholecystectomy, the stage of the gallbladder cancer was T1 in 9 (7.8%) patients, T2 in 77 (67.0%) patients, and T3 in 29 (25.2%) patients (Table 1). Of the 24 (20.9%) patients who had at least one cystic node evaluated in the initial cholecystectomy specimen, 16 had a positive cystic duct node. Thirty-four (29.6%) patients had a positive cystic duct margin.

The median time from cholecystectomy to re-resection was 52 days (IQR, 33 to 72 days). Of the 115 patients with incidental gallbladder carcinoma who underwent a second surgical therapy, 18 patients were explored and found to have unresectable disease. In those patients who did undergo re-resection (n=97), surgery consisted of hepatic resection (n=97), portal lymphadenectomy without bile duct excision (n=49), portal lymphadenectomy plus common bile duct excision with hepaticojejunostomy (n=42), and resection of laparoscopic trocar sites (n=48) (Table 2). Hepatic resection consisted of wedge resection (n=28; 28.9%), formal segmentectomy of 4b + 5 (n=63; 64.9%), or hemi-hepatectomy (n=6; 6.2%). The extent/type of liver resection was associated with T stage of disease; as expected, patients with T2 or T3 disease tended to be more likely to have undergone a major liver resection (e.g., formal segmentectomy of 4b + 5 or hemi-hepatectomy) (T1, 44.4% vs T2/T3, 73.9%; P=0.11). In those patients undergoing lymphadenectomy, the median number of lymph nodes harvested was the same regardless of whether the common bile duct was or was not resected concomitantly with the lymphadenectomy: lymphadenectomy alone, median 3 lymph nodes (range, 1 to 5) vs lymphadenectomy plus common bile duct resection, median 3 lymph nodes (range, 1 to 6) (P=0.35) (Table 2).

On repeat exploration, residual/additional disease was noted in 70 (60.8%) patients. Specifically, 28 (24.3%)

Table 2 Details of Patients with Incidental Gallbladder Carcinoma (n=115) who Underwent a Repeat Surgical Procedure

Variable	Number of Patients (%)
Second surgery (n=115)	
Exploratory Laparotomy only	18 (15.7)
Re-Resection	97 (84.3)
Hepatic resection (n=97)	
Wedge	28 (28.9)
Segmentectomy 4b + 5	63 (64.9)
Hemi-hepatectomy	6 (6.2)
Excision of Laparoscopic Trocar Sites	48 (41.7)
Lymphadenectomy	
Without common bile duct resection	49 (50.5)
With common bile duct resection	42 (43.3)
No lymphadenectomy reported	6 (6.2)

patients were found to have evidence of metastatic disease (peritoneal metastasis, n=21, hepatic metastasis, n=5, peritoneal + hepatic metastasis, n=2). In addition, three patients were found to have locally advanced disease that precluded further surgical therapy. Of the 97 patients who did undergo re-resection, pathology demonstrated residual/additional gallbladder carcinoma in 45 (46.4%)—including in the liver bed (n=15), lymph nodes (n=32), cystic stump/common bile duct (n=19), and trocar sites (n=3). T stage was strongly associated with risk of finding *any* residual disease (T1, 37.5%; T2, 56.7%; T3, 77.3%) (P=0.01) (Table 3). T stage was also strongly associated with the presence of both residual liver disease and the risk of locoregional lymph node metastasis (Table 3). Of those patients initially staged as T1, T2, or T3, 0, 10.4, 36.4%, respectively, had residual disease within the liver after hepatic resection (P=0.006). T stage was similarly associated with the risk of metastasis to locoregional lymph nodes (lymph node metastasis: T1, 12.5%, T2, 31.2%, T3, 45.5%; P=0.04)

Residual disease in the common bile duct was found in 9 out of 42 (21.4%) patients who underwent common bile duct resection. Cystic duct margin status predicted residual disease in the common bile duct. Patients who had microscopic disease of the cystic duct margin (either on the pathologic review of the initial cholecystectomy specimen or biopsy of the cystic duct stump at the time of the second surgery) were significantly more likely to have residual/additional disease in the common bile duct. Patients with microscopically positive disease at the cystic duct margin had a 42.1% incidence of residual disease in the resected common bile duct compared with only 4.3% for those patients with a microscopically negative cystic duct margin (P=0.01) (Table 3).

On final pathologic analysis of the 97 patients who underwent re-resection, the overwhelming majority of patients (n=93; 95.9%) had microscopically negative surgical margins. Of the remaining four patients, two had macroscopically positive margins (R2), and two had microscopically positive margins (R1).

The median overall survival for the 225 patients with gallbladder adenocarcinoma was 18.0 months and 1-, 3-, 5-year overall survival rates were 63.0, 42.2, 38.4%, respectively. Patients who had incidental gallbladder carcinoma (n=148) were noted to have a better prognosis compared with patients who underwent surgery for non-incidental gallbladder carcinoma (n=77) (P<0.001) (Fig. 1). Looking specifically at the 115 patients who had incidental gallbladder cancer and who underwent a second staged surgical intervention, the finding of metastatic disease at the time of the second procedure was associated with a median survival of only 11.8 months compared with 52.5 months for patients with no metastatic disease (P<0.001). On univariate analysis, several factors were associated with outcome in those patients (n=97) who underwent re-resection at the time of the second surgery (Table 4). T stage was associated with overall 5-year survival (T2, 67.3% vs T3, 26.1%; P=0.03). Final AJCC tumor stage was also strongly correlated with long-term survival. The actuarial 5-year survival rate was 84.0% for stage I patients, 42.5% for stage II, and 0% for stage IV (P<0.001) (Fig. 2). No stage III patients underwent re-resection given that stage III patients are defined as having T4 disease, which invades the main portal vein or hepatic artery.[16]

In addition, prognosis was associated with the finding of residual disease at the time of the re-resection. Patients who had no additional detectable disease after the second surgery had a better 5-year survival (84.8%) than patients who were found to have residual disease (36.9%) (P=0.01). Of note, the finding of residual disease in the hepatic parenchyma adversely impacted prognosis (HR=3.07, 95% CI 1.37–6.89; P=0.006). The actuarial 5-year survival of patients with no residual liver disease was 61.5 vs 26.2% for patients who had residual disease in the hepatic parenchyma (P=0.004) (Fig. 3). Lymph node status also affected survival. Patients with metastatic nodal disease had a 5-year survival rate of 26.5 vs 72.9% for patients with no nodal metastasis (P=0.007) (Fig. 4). In contrast, the extent of hepatectomy was not associated with prognosis. Specifically, patients who underwent a major hepat-

Table 3 Incidence of Residual/Additional Disease of Incidental Gallbladder Adenocarcinoma in those Patients Undergoing Re-Resection (n=97)

Site of Disease After 2nd Surgery	Number of Patients (%)					*P* Value
	T1 (n=8)	T2 (n=67)	T3 (n=22)	Positive Cystic Duct (n=19)	Negative Cystic Duct (n=23)	
Disease any site	3 (37.5)	38 (56.7)	17 (77.3)			0.01
Residual cancer in liver bed	0 (0)	7 (10.4)	8 (36.4)			0.006
Metastatic disease in lymph nodes	1 (12.5)	21 (31.3)	10 (45.5)			0.04
Common bile duct				8 (42.1)	1 (4.3)	0.01

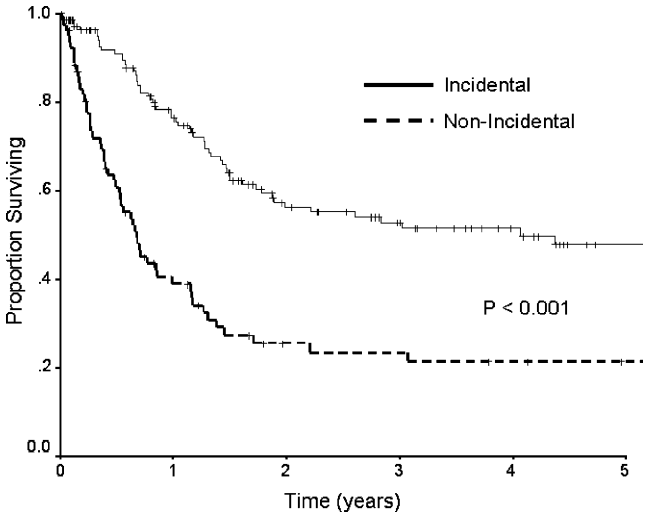

Figure 1 Patients who had incidental gallbladder carcinoma (n=148) were noted to have a better prognosis compared with patients who underwent surgery for non-incidental gallbladder carcinoma (n=77) (P<0.001).

ic resection (e.g., formal segmentectomy of 4b + 5 or hemi-hepatectomy) had a similar risk of disease-specific death compared with patients who underwent a hepatic wedge resection (HR=1.44, 95% CI 0.71–2.94; P=0.31). Whether a common bile duct resection was performed concomitantly with the lymphadenectomy also did not affect survival. Both the median and actuarial 5-year survival for patients undergoing lymphadenectomy with or without bile duct resection was the same (P=0.56) (Fig. 5). Finally, surgical margin status was strongly correlated with long-term outcome, as R1/R2 margin status was associated with no long-term survivors (P<0.001) (Fig. 6).

On multivariate analysis both the presence of residual/additional disease in the liver bed and AJCC stage remained important predictors of survival (Table 4). After controlling for other competing risk factors, after the second surgery, patients who had residual/additional disease in the liver bed had a higher risk of disease-specific death compared with patients in whom no carcinoma was found in the liver resection specimen (HR=4.79, 95% CI 1.95–11.8; P=0.001). Similarly, AJCC stage II patients (HR=2.60, 95% CI 1.07–6.35; P=0.03) and AJCC stage IV patients (HR=16.41, 95% CI 4.73–56.9; P=0.001) both had an increase risk of disease-specific death vs AJCC stage I patients. In contrast, on multivariate analysis, neither extent of the liver resection (HR=1.25, 95% CI 0.54–2.92; P=0.60) nor history of common bile duct resection (HR=0.91, 95% CI 0.41–1.96; P=0.80) were associated with survival.

Discussion

Most gallbladder carcinomas are diagnosed incidentally after laparoscopic cholecystectomy for gallstone disease. Although simple cholecystectomy appears to be an adequate treatment for patients with carcinoma infiltrating only the lamina propria (p T1a), radical re-resection has been advocated for most patients.[18] The selection of patients—and the degree to which residual/additional disease is found at the time of the second operation—has been the subject of some debate. Specifically, how to manage T2 and T3 lesions that are identified during surgery or pathologically after cholecystectomy has been somewhat controversial. Some groups contend that T2 lesions require only a simple

Table 4 Clinicopathologic Factors Influencing Prognosis After Re-Resection of Gallbladder Adenocarcinoma

Prognostic Factor	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
AJCC Tumor Stage						
Stage I	1.00	–	–	–	–	–
Stage II	2.67	1.12–6.34	0.02	2.60	1.07–6.35	0.03
Stage IV	9.22	3.50–24.29	<0.001	16.41	4.73–56.88	<0.001
Any residual/additional disease	3.77	1.63–8.71	0.002	[a]		
Residual carcinoma in liver bed	3.07	1.37–6.89	0.006	4.79	1.95–11.77	0.001
Metastatic Disease in lymph nodes	2.34	1.18–4.66	0.01	[a]		
R1/R2 surgical resection	10.22	3.43–30.47	<0.001	2.43	0.58–10.04	0.22
Major hepatic resection	1.44	0.71–2.94	0.31	1.25	0.54–2.92	0.60
Resection of common bile duct	0.83	0.41–1.66	0.59	0.91	0.41–1.96	0.80

AJCC American Joint Commission on Cancer, *R1* microscopic positive surgical resection margin, *R2* macroscopically positive surgical resection margin

[a] These prognostic factors were not entered into the multivariate model because they were colinear with other covariates in the model.

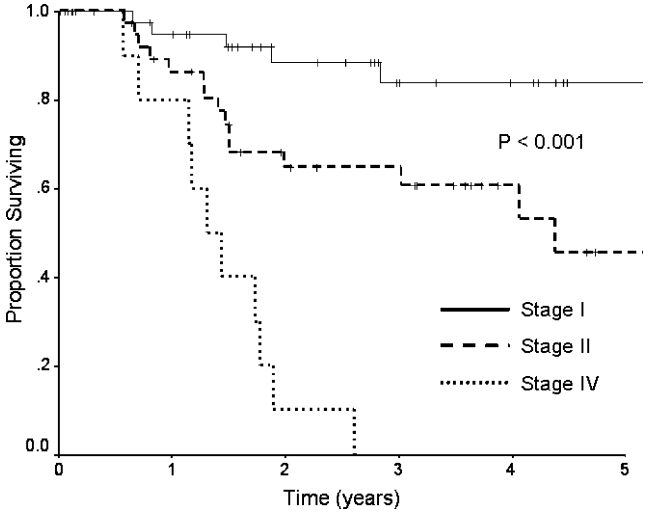

Figure 2 Final AJCC tumor stage was also strongly correlated with long-term survival. The actuarial 5-year survival rate was 84.0% for stage I patients, 42.5% for stage II, and 0% for stage IV ($P<0.001$).

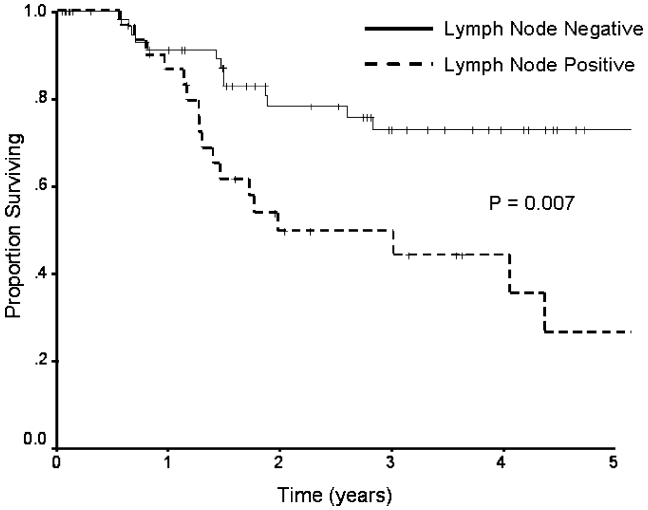

Figure 4 Lymph node status affected survival. Patients with metastatic nodal disease had a 5-year survival rate of 26.5 vs 72.9% for patients with no nodal metastasis ($P=0.007$).

cholecystectomy, asserting that most T2 patients will not have residual/additional disease found at the time of re-resection.[4,19] Most groups agree that re-resection for T3 lesions is warranted,[8,11] but the incidence and site of residual/additional disease even in this subset of patients remains ill-defined. The current study is important because it specifically sought to define the incidence of residual/additional disease in a large cohort of patients with incidental gallbladder adenocarcinoma. In addition, we were able to identify factors associated not only with prognosis, but also the risk of site-specific (e.g., liver bed, lymph nodes, common bile duct) residual disease.

Of the 115 patients with incidental gallbladder carcinoma, a substantial number (60.8%) was found to have evidence of additional disease at the time of re-resection—including some patients who had metastatic or locally advanced disease. When we looked specifically at the 97 patients who underwent re-resection, 46.4% were noted to have residual disease. While residual/additional disease was relatively infrequent at the trocar sites (6.3%), carcinoma was found more frequently in the liver bed (15.5%), bile duct (19.6%), and lymph nodes (35.2%). Perhaps, more importantly, we identified a direct correlation between T stage and the rate of finding residual disease in the liver and/or lymph nodes. In fact, T3 lesions were associated with residual liver or lymph node disease in 36.4 and 45.5% of cases, respectively. Of note, however, was that even patients with T2 disease had residual/additional carcinoma between 10 and 30% of the time in either the liver

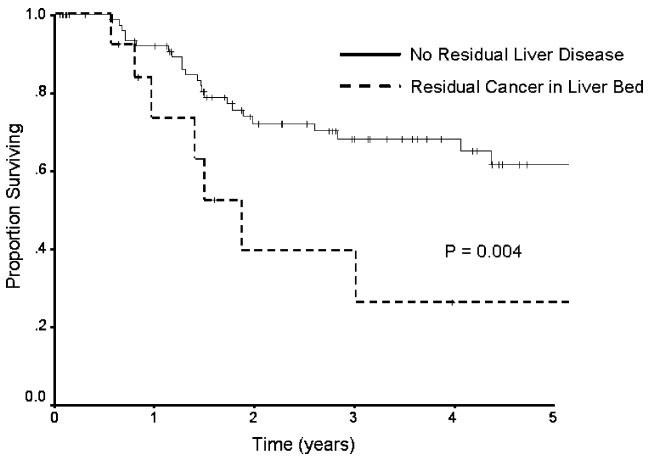

Figure 3 The finding of residual disease in the hepatic parenchyma adversely impacted prognosis. The actuarial 5-year survival of patients with no residual liver disease was 61.5 vs 26.2% for patients who had residual disease in the hepatic parenchyma ($P=0.004$).

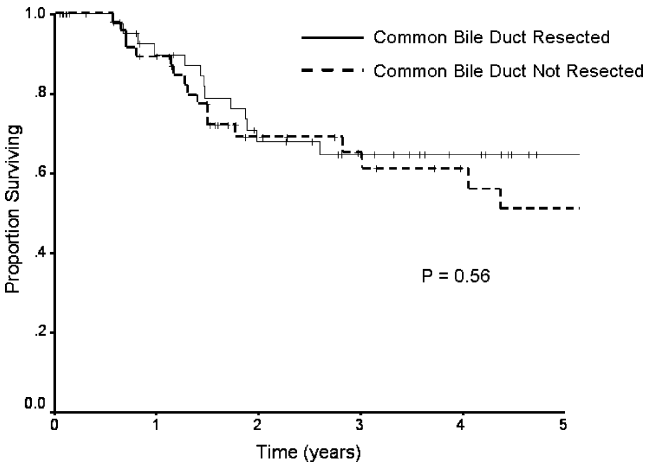

Figure 5 Whether a common bile duct resection was performed concomitantly with the lymphadenectomy also did not affect survival. Both the median and actuarial 5-year survival for patients undergoing lymphadenectomy with or without bile duct resection was the same ($P=0.56$).

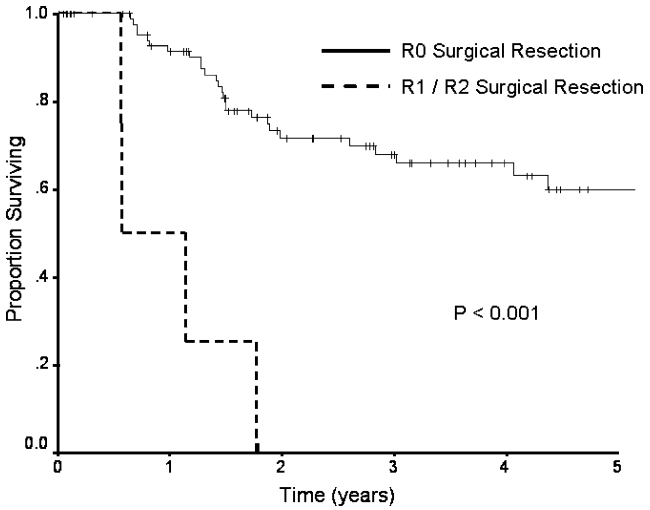

Figure 6 Surgical margin status was strongly correlated with long-term outcome, as R1/R2 margin status was associated with no long-term survivors ($P<0.001$).

or regional lymph nodes (Table 3). In aggregate, these data strongly suggest that aggressive re-resection for incidental T2 or T3 gallbladder carcinoma is warranted as the majority of patients have residual disease.

Most data regarding the extent of surgery for gallbladder carcinoma has compared simple cholecystectomy vs "radical" re-resection.[8,11,12] In the current study, of the 115 patients who underwent a repeat operation for incidental gallbladder carcinoma, 97 had a hepatic resection as part of their radical re-section. As such, we were able to compare the extent of the hepatic resection (e.g., wedge, formal segmentectomy of 4b + 5, hemi-hepatectomy) with regard to prognosis. Whether to perform a nonanatomical resection or an anatomical resection for other primary or secondary malignancies of the liver has been controversial.[20,21] Although some studies[20] have reported that the performance of an anatomical resection improves tumor clearance and outcome, other reports[22] have not demonstrated a benefit for anatomic re-section. While there has been little—if any—data on this subject with regard to hepatic resection for gallbladder carcinoma, we found that the extent of hepatectomy was not associated with prognosis. Patients who underwent a major hepatic resection (e.g., formal segmentectomy of 4b + 5 or hemi-hepatectomy) had a similar risk of disease-specific death compared with patients who underwent a hepatic wedge resection both on univariate and multivariate analyses. Rather than type of hepatic resection, surgical margin status was one of the key determinants of outcome. Specifically, R1/R2 margin status was associated with no long-term survivors ($P<0.001$) (Fig. 6). Chijiwa et al. has similarly reported that margin positive surgery yielded no 5-year survivors.[23] As such, rather than dogmatically adhering to an anatomical vs non-anatomical approach, the surgeon's goal should be to resect all disease with negative histologic margins.

Many surgeons, especially in Japan, advocate for the routine resection of the common bile duct at the time of curative resection and portal lymphadenectomy.[6,24–26] Shimizu et al.[26] reported that resection of the common bile duct facilitates lymphadenectomy. In addition, Shimizu et al.[26] noted that gallbladder carcinoma may often extend into the subserosa or beyond and can invade the hepatoduodenal ligament. As such, this group recommends routine resection of the extrahepatic bile ducts with lymphadenectomy. However, other investigators, including Makuuchi's group from Japan,[27] have questioned this approach. Citing data showing no improvement in long-term survival,[27,28] and the possible increased risk of complications after a bilioenteric anastomosis, the Makuuchi group recommends preservation of the extrahepatic bile duct in radical surgery for gallbladder cancer.[27] In the current study, the median number of lymph nodes harvested at the time of lymphadenectomy was the same ($n=3$) regardless of whether the common bile duct was or was not resected concomitantly with the lymph node dissection. These data suggest that resection of the common bile duct did not facilitate a more "thorough" lymphadenectomy, as reflected in the identical lymph node counts. In addition, similar to previous reports,[27,28] resection of the lymphadenectomy plus common bile duct resection was not associated with an improvement in survival (Fig. 5). We did note, however, that a positive cystic duct margin was strongly associated with residual disease in the common bile duct (Table 3). As such, to obtain an R0 resection, patients with a positive cystic duct margin—based either on the initial cholecystectomy specimen or intraoperative biopsy of the cystic duct stump—should undergo a common bile duct resection in conjunction with lymphadenectomy.

Similar to previous studies,[8,11,12] a number of prognostic factors were identified that stratified patients with regard to prognosis after re-resection for incidental gallbladder carcinoma. Factors associated with poor prognosis included advanced T- and AJCC stage and metastatic nodal disease, as well as positive surgical margin status (Table 4). Some surgeons[7,13,29] have suggested that lymph node metastasis should be a relative contraindication to proceeding with radical re-resection because short-term survival is the rule. It should be noted, however, that in the current study, the overall 5-year survival for patients with lymph node metastasis was 26.5%. Our findings indicate that surgical re-resection of gallbladder carcinoma with lymph node metastasis can lead to long-term survival in a subset of patients. Another interesting finding of the current study was that residual disease in the liver at the time of re-resection was strongly associated with outcome. In fact, after adjusting for competing risk factors on multivariate

analysis, the presence of residual/additional disease in the liver was one of the strongest predictors of survival (HR= 4.79; P=0.001). These data corroborate previous findings that suggested perforation or invasion of the gallbladder carcinoma into the adjacent liver (formerly designated T4 disease in the fifth edition of the AJCC staging manual) was associated with a particularly dismal prognosis.[30,31]

The current study had several limitations. Despite combining the experience of six major hepatobiliary institutions on three different continents, the overall number of patients in the series (n=115) was relatively small. The relative small sample size limited the study's power and increased the chance of a type II statistical error. Specifically, as evidenced in Table 3, the resultant statistical analyses and point estimates were subject to increased degrees of variance, and consequently, wide confidence intervals. Another limitation of the dataset was that the location of the gallbladder carcinoma (e.g., whether it was on the "liver" or "peritoneal" side of the gallbladder) could not be ascertained. As such, the potential association of tumor location and residual/additional disease in the gallbladder fossa/liver bed could not be assessed. Finally, although it was not the aim of this study, whether a second re-resection had a direct effect on survival was not investigated. Given the high rate of residual/additional disease, re-resection would clearly seem to have a therapeutic effect (e.g., extirpation of residual carcinoma) in T2 and T3 patients. It must also be kept in mind that repeat surgery also provides a "staging effect" by identifying patients who otherwise would have been understaged with a single operation. Whether re-resection is warranted in T1 patients remains unclear. Our data cannot provide an evidence-based recommendation as only eight T1 patients had re-resection. However, the finding that 37.5% of patients with stage I disease had any residual/additional disease clearly warrants further study.

Conclusion

The incidence of finding residual/additional disease at the time of repeat surgery for incidental gallbladder cancer was high (60.8%). Specifically, in patients who underwent a re-resection, residual/additional disease was found in over 40% of cases. Lymph node metastasis was the most frequent site of additional disease. Residual/additional disease in the liver was strongly correlated with T stage and was found in 36.4% of patients with T3 lesions. As such, aggressive re-resection for incidental gallbladder carcinoma is warranted as the majority of T2 and T3 patients have residual disease. Although lymph node status and the presence of residual/additional disease were associated with outcome, long-term survival can be achieved in a subset of these patients. Therefore, when feasible, radical re-resection—which offers the only potential of cure—should be strongly considered. While the type of hepatic resection does not appear to affect outcome, it is critical that negative surgical margins be achieved. Finally, although common duct resection does not yield a greater lymph node count, it should be performed at the time of re-resection for patients with positive cystic duct margins because over one-third will have residual disease in the common bile duct.

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Discussion

Bryan M. Clary, M.D. (Durham, NC): That was a very nice presentation. This paper is important, I think, for a couple of reasons. Number one, I think it does help to cast a pall over the concept that you need to do a bile duct excision just to get a better lymph node clearance in patients who do not clearly have cystic duct involvement. The second important concept is that it does help, I think, to better define those patients who have residual disease and the likely sites of their residual disease. With its design, it does not help, in my mind, to define whether these interventions are necessarily the reason why these patients demonstrate long-term survival. So the value of the intervention is a little less clear, again, given the retrospective nature of this design. I have some questions for Tim.

Number one, you made conclusions about the extent of the hepatic resection. Now, unless you are very clearly taking hepatic segment 4B and 5, in general, a segment 4B/5 resection as most people practice, is just a big glorified wedge excision. Can you comment on whether this was truly a formal segmental resection?

You did not really comment on adjuvant therapy, and I hope that you would, especially in light of your 5-year survival in your node positive patients, which is better than most nihilistic individuals tend to expect.

In reading through the manuscript, you had 28 patients who had peritoneal and liver metastasis, yet, you only had 18 patients who did not undergo a radical re-excision during that exploration. Were you resecting metastatic disease in the other ten patients?

Lastly you do have a population of patients who underwent simple cholecystectomy alone, actually 17 of those 33 patients. Did you actually look at their survival compared to your radical re-excision staged patients?

Thanks again Tim for a great presentation.

Timothy M. Pawlik, M.D. (Baltimore, MD): Thank you Bryan for your questions. I would like to address your last question first. The objective of this study was not to look at long-term survival and the survival "value" of the actual second operation. Whether cholecystectomy alone vs radical re-resection yields improved overall survival is difficult to address. As we stated in the paper, the second operation not only has a therapeutic effect, it also has a staging effect. So, it is hard to know if someone who had a simple cholecystectomy and was T2 Nx is truly similar to someone who had a radical re-resection and is T2 with known lymph node status. In other words, are these two patient cohorts truly the same stage or is one better staged due to the difference in lymph node evaluation? As you can see from our work, in T2 patients, a fair number of T2 patients will have lymph node metastases. So, when comparing T2 patients after simple cholecystectomy vs those who underwent re-resection, it is hard to know if you are comparing apple to apples or apples to oranges. As such, we wanted to avoid the question of whether the second operation provided a direct survival benefit. Rather, we tried to indirectly address the relative benefit of the re-resection by the notion of how much residual disease is being left behind by performing only a simple cholecystectomy.

I have to say it was my bias that these re-resections for patients with gallbladder cancer were not going to yield

much residual disease. However, as we showed, over 40% of patients did indeed have additional disease discovered at the time of the second operation. These data again suggest that a staging migration phenomena can occur based on the findings of the second operation. They also suggest that re-resection of patients with T2 or T3 disease should continue to be recommended.

As far as the extent of hepatic resection, I completely agree with you. This was self-reported, so I cannot tell you for sure that these segmentectomies of 4B and 5 were truly anatomic resections. As you know, there are data in the literature on colorectal hepatic metastasis and hepatocellular carcinoma regarding the topic of anatomic vs nonanatomic resection. We have previously published on hepatic resection of colorectal metastasis and reported that an anatomic resection was not necessary. As long as the margins were negative, the results were the same. Similarly, in our current study on hepatic resection for gallbladder cancer, an anatomic vs nonanatomic resection did not affect outcome. However, what did matter was whether the surgeon was able to obtain an R0 resection. Whether the R0 resection could be accomplished by an anatomic vs nonanatomic resection did not seem to matter.

Unfortunately I cannot comment on adjuvant therapy. We were not able to collect these data because, as you can imagine, it was difficult to obtain adjuvant data from six centers that spanned the United States, Europe, and South America.

Finally, you are correct. There were ten patients who underwent a re-resection who had metastatic disease. Some of the centers in Brazil and in Italy did resect a couple of patients who had limited metastatic disease.

Charles M. Vollmer, Jr., M.D. (Boston, MA): Great talk again. I have got two questions about this. The first is that group of 33 patients which you did not seem to focus here, and if I heard Bryan right, he said that there were 17 that got a simple cholecystectomy alone; what happened to the other group in that 33? What kind of operations were they getting? Is this a scenario where they were getting a resection of the gallbladder, there is an obvious tumor found, and then someone decides to convert to a bigger operation? I would be curious to know what kind of results in survival came from that operation.

The second thing is in your cohort that did get the re-resection; do you have any data on the interval period between the original cholecystectomy and then the operation? Because some feel that you can wait these things out and restage many months later to get a better staging effect, others will go directly to the operation within a week or two of the finding. So do you know anything about that?

Thanks.

Dr. Pawlik: Charles, thanks so much for your comments. The median time between cholecystectomy and radical re-resection was 52 days. The range was fairly wide, but the median was 52 days.

Your other question was about those 33 patients who were treated "definitively" at the time of the initial operation. These patients underwent a myriad of operations. Some had a simple cholecystectomy, while others had a more extensive resection. It was largely based on T stage, with some T2 and the T3 patients actually undergoing hepatic resection. I believe 3 of the 33 patients had a common bile duct resection and lymphadenectomy. So, indeed, there was really a mix of the type of operations performed—even when the surgeon chose to definitively treat the gallbladder cancer at the time of the initial cholecystectomy.

What we did not do, and perhaps we should have, is investigate how patients who had the "definitive" surgical procedure done at the time of the initial cholecystectomy compared with those patients who had a staged operation.

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Trends in Survival after Surgery for Cholangiocarcinoma: A 30-Year Population-Based SEER Database Analysis

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Abstract The prognosis of patients with cholangiocarcinoma historically has been poor, even after surgical resection. Although data from some single-institution series indicate improvement over historical results, survival after surgical therapy for cholangiocarcinoma has not been investigated in a population-based study. We used the Surveillance, Epidemiology, and End Results database to identify patients who underwent surgery for cholangiocarcinoma from 1973 through 2002. Multivariate modeling of survival after surgery for intrahepatic cholangiocarcinoma showed an improvement in survival only within the last decade studied, resulting in a cumulative 34.4% improvement in survival from 1992 through 2002. In contrast, multivariate modeling of survival after surgery for extrahepatic cholangiocarcinoma revealed a 23.3% increase in adjusted survival per each decade studied, resulting in a cumulative 53.7% improvement from 1973 through 2002. We conclude that survival after surgery for extrahepatic cholangiocarcinoma has dramatically improved since 1973. Patients with intrahepatic cholangiocarcinoma, however, have achieved an improvement in survival largely confined to more recent years. We suggest that these trends are largely caused by developments in imaging technology, improvements in patient selection, and advances in surgical techniques.

Keywords Cholangiocarcinoma · Biliary tract neoplasms · SEER

Introduction

Cholangiocarcinoma is a malignancy arising from the ductal epithelium of the biliary tree. It is relatively uncommon, accounting for approximately 3% of all gastrointestinal cancers,[1] but historically it has carried a very poor prognosis. Cholangiocarcinomas are classified by location as either intrahepatic or extrahepatic, and extrahepatic cholangiocarcinomas are often subclassified into those involving the hepatic duct bifurcation versus more distal lesions.[2] Temporal trends in the population-based survival of patients diagnosed with cholangiocarcinoma have been studied, but in limited detail. For intrahepatic cholangiocarcinoma (ICC), the 5-year survival has not changed significantly and has remained below 5% from 1975 to 1999.[3] In contrast, the 5-year survival of patients with extrahepatic cholangiocarcinoma (ECC) increased from 11.7% in 1973–1977 to 15.1% in 1983–1987.[4] These figures represent the aggregate prognosis of all patients with cholangiocarcinoma, most of whom are unresectable at presentation.[5] Importantly, they may not accurately describe the outcomes of those patients who receive surgical therapy. Trends in survival after surgical therapy for cholangiocarcinoma have not been investigated in a population-based study.

Data on long-term survival of patients after surgical resection are limited to single-institution case series. Reported 5-year survival rates in recent surgical series (irrespective of margin status) vary widely, from 17 to 40% for ICC[6–14] and from 9 to 41% for ECC.[10,14–27] These

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single-institution data may not offer generalizable information and may not reflect outcomes in the general population. To determine whether there have been improvements in survival after surgery for cholangiocarcinoma on a population level, we investigated trends in the survival of patients undergoing cancer-directed surgery for both ECC and ICC over the last 30 years using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

This study was a retrospective analysis of prospectively collected data from the SEER database maintained by the National Cancer Institute.[28] The SEER database began in 1973 with data from seven cancer registries and today includes data from 17 cancer registries, representing 26.2% of the United States population. Compared to the general U.S. population, the SEER population is slightly more urban and has a slightly higher percentage of foreign-born individuals. Available data include patient demographics (e.g., age, gender, race), tumor data (histology, grade), SEER stage of disease, use of cancer-directed surgery, use of radiation therapy, and attributes of the patient's county of residence (e.g., urban-rural continuum code). Other data elements (e.g., American Joint Committee on Cancer staging, details of surgical therapy, tumor size, lymph node involvement) are consistently available only in more recent time periods.

Patients with cholangiocarcinoma were identified by the International Classification of Diseases for Oncology (ICD-O-3)[29] topography and histology codes that were chosen to minimize the possibility of inadvertently including metastatic lesions or non-cholangiocarcinoma hepatobiliary malignancies in the analysis (Table 1). Klatskin tumors that were coded as intrahepatic tumors were reclassified as extrahepatic, accounting for a known problem that erroneously cross-references Klatskin tumors to the topography code for intrahepatic tumors.[30] The ICD-O-3 coding system does not allow perihilar tumors to be reliably distinguished from other tumors of the extrahepatic biliary tree, so all extrahepatic tumors were analyzed as one category. Only patients who were actively followed were included, and all patients diagnosed at autopsy or by death certificate were excluded. Those patients who underwent cancer-directed surgical procedures were identified using site-specific surgery codes 10–90 or surgery of primary site codes 10–90.

Table 1 ICD-O-3 Codes for Cholangiocarcinoma Identification

Site	Topography	Histology
Intrahepatic	220	8160, 8161
	221	8000, 8001, 8010, 8012, 8020, 8031, 8032, 8140, 8160, 8161, 8260, 8310, 8440, 8470, 8480, 8481, 8490, 8500, 8560
Extrahepatic	240	8000, 8001, 8010, 8012, 8020-8022, 8033, 8041, 8045, 8046, 8050, 8070, 8140, 8141, 8144, 8145, 8160, 8161, 8211, 8255, 8260, 8161, 8262, 8263, 8310, 8323, 8430, 8440, 8450, 8470, 8480, 8481, 8490, 8500, 8503, 8521, 8560, 8570, 8572
	241	8160
	Any	8162

For descriptive analyses, crude survival statistics for ECC and ICC were generated using the Kaplan–Meier method[31] and were then adjusted for expected death rates in SEER*Stat version 6.2.4 (Surveillance Research Program, National Cancer Institute, Silver Spring, MD). The resulting relative survival curves were compared using log-likelihood statistics.[32] Differences in patient and tumor characteristics between decades were evaluated by Pearson's chi-squared test or Cuzick's nonparametric test for trend,[33] as appropriate. Trends in survival were then further explored using Cox proportional hazards models.[34] The SEER database codes cases with less than 1-month survival time as having zero survival time, an apparent truncation that would bias the survival analysis. To avoid this potential bias, we redefined survival times for these cases (81/2,107 for ECC and 15/591 for ICC), as 0.1 months. The variables considered in our analysis were age, gender, race, marital status at diagnosis, rural versus urban area of residence, SEER historic tumor stage, tumor grade, receipt of radiation therapy, SEER registry, and year of diagnosis.

Univariate and multivariate modeling of survival were performed using Cox proportional hazards models using the Efron method for ties. The appropriate functional forms of covariates were determined during exploratory data analysis using Martingale residuals. Entry of covariates into the multivariate models was generally determined by statistical significance in the univariate Cox models (using the likelihood ratio test). An exception was the variable for rural area of residence, which was force-entered in the model for ICC because of its significance in the multivariate model for ECC. Extensive sensitivity analyses of the final models were performed using likelihood ratio tests, Akaike information criteria, and stratified analyses to ensure that important variables or interaction terms had not been erroneously excluded. Adherence to the proportional hazards assumption was confirmed by Schoenfeld residuals and log–log plots.

The multivariate analyses were performed both by using complete records only and by including missing categories for covariates with missing data > 5%. For ICC, these two approaches did not agree, so missing data were dealt with using multiple imputation.[35–37] For ECC, these two approaches produced the same significant variables with

<10% difference in the hazard ratios, so the results of the simpler model are reported. The final models included 591 of 591 ICC cases (with multiple imputation) and 1,529 of 2,107 ECC cases (using complete records only).

All tests of statistical significance were two-sided, and statistical significance was established at $\alpha=0.05$. Statistical analysis was performed using Stata/SE 9.2 for Windows (StataCorp, College Station, TX), and multiple imputation was performed using the ICE module for Stata.[38] This study was approved by the Johns Hopkins University School of Medicine Institutional Review Boards.

Results

Our selection criteria identified 591 patients with ICC and 2,107 patients with ECC who were diagnosed from 1973 through 2002 and underwent a cancer-directed surgical procedure. The range of follow-up times was 0–323 months for ICC and 0–321 months for ECC. Five-year relative survival (RS) over the entire period of study was 20.6% (crude survival 17.7%) for ICC and 20.5% (crude survival 17.1%) for ECC. There was no significant difference in overall relative survival (RS) between ECC and ICC ($P=0.221$) (Fig. 1).

Intrahepatic Cholangiocarcinoma

The only statistically significant trend in ICC patient and tumor characteristics (Table 2) was an increase in the proportion of male patients over this period ($P=0.046$). Because the type of cancer-directed surgery was not specified for a high proportion of patients (122 of 591), we were not able to analyze trends in the type of surgical procedure performed. Comparison of ICC survival between decades (Fig. 2) showed no significant difference between 1973–1982 and 1983–1992 ($P=0.547$), but survival improved between 1983–1992 and 1993–2002 ($P=0.015$). Because there was no difference in survival between the first two decades, and because there were only 42 patients in the first decade, we combined the first two decades in further analysis. Comparison of ICC survival in 1973–1992 compared against 1993–2002 showed a significant improvement ($P=0.003$), with 5-year RS rising from 16.5% to 22.9%. Comparisons of survival curves by stage at diagnosis (Fig. 3) were all highly significant ($P<0.001$). As expected, more advanced disease conferred a worse prognosis, with 5-year RS of 37.4% for localized disease, 14.7% for regional disease, and 5.3% for distant disease.

Although our exploratory univariate analysis revealed better survival for patients undergoing surgery for ICC in the last decade versus previous decades, this benefit did not persist in initial multivariate models that adjusted for

Table 2 ICC Patient and Tumor Characteristics

	1973–1982	1983–1992	1993–2002	Total
Number of patients	42	129	420	591
Percent of total	7.1	21.8	71.1	100
Mean age at diagnosis (years)	62.5	62.5	63.2	63.0
Male (%)*	40.5	42.6	51.4	48.7
White (%)	81.0	81.4	84.7	83.7
Married (%)	60.6	64.5	67.1	66.1
Rural (%)	9.5	15.5	11.7	12.4
Stage (%)				
Localized	29.0	35.1	43.9	41.0
Regional	42.1	40.4	30.5	33.3
Distant	29.0	24.6	25.6	25.6
Grade (%)				
Well differentiated	35.3	16.4	18.4	18.8
Moderately differentiated	17.7	53.7	42.4	43.3
Poorly differentiated	47.1	26.9	36.8	35.6
Undifferentiated	0	3.0	2.3	2.3
Radiation therapy (%)	21.4	35.7	22.9	25.6
Survival <1 month (%)	2.4	4.7	1.9	2.5
Median survival (months)				
Crude	11	12	22	19
Relative	11	12	24	21
Five-year survival (%)				
Crude	11.9	15.0	19.7	17.7
Relative	14.0	17.2	22.9	20.6

Percentages exclude missing values.
*Significant test for trend ($P<0.05$). Tests for trend not performed for median and five-year survival.

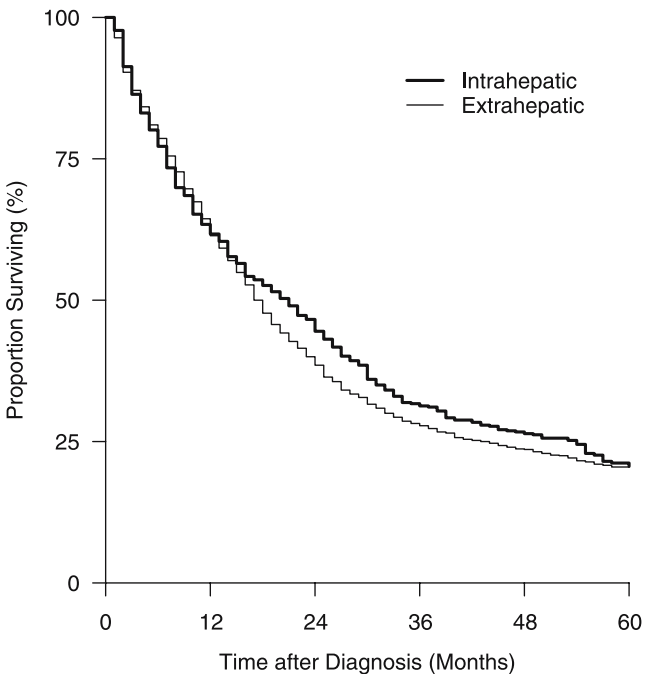

Figure 1 Relative Kaplan–Meier survival after surgery for cholangiocarcinoma, 1973–2002. ICC vs. ECC: $P=0.221$.

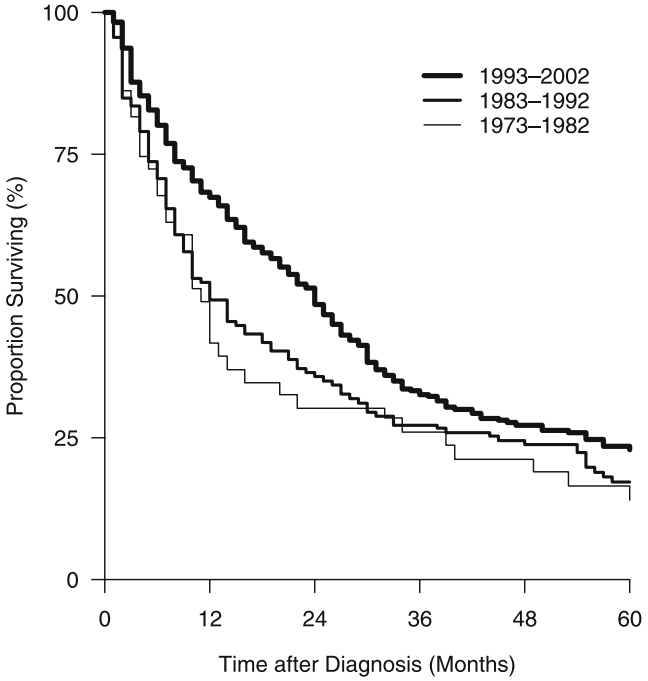

Figure 2 Relative Kaplan–Meier survival after surgery for ICC, by decade. 1973–1982 vs. 1983–1992: P=0.547. 1983–1992 vs. 1993–2002: P=0.015.

demographics, tumor characteristics, and receipt of radiation therapy. Having found no improvement in the aggregate survival of patients diagnosed in 1993–2002 versus 1973–1992, we explored the possibility that there has nevertheless been more recent incremental improvement by focusing on the year-to-year changes after 1992. Univariate Cox proportional hazards analysis for ICC (Table 3) showed the following variables to be significantly associated with decreased survival (P value for likelihood ratio test, percent of data missing): age per year over 80 years (P=0.001, 0%), tumor stage (P<0.001, 7.6%), tumor grade (P=0.017, 34.4%), and year of diagnosis per year after 1992 (P<0.001, 0%). These variables, together with rural area of residence (0.2% missing), were entered into the multivariate model for ICC. This approach revealed a year-to-year improvement in ICC survival over the years 1992–2002 that remained significant in multivariate analysis. In the final model of ICC survival (Table 3), age per year over 80 years and stage at diagnosis were strong predictors of worse survival, but the effect of tumor grade was not statistically significant. This analysis demonstrated a significant year-to-year improvement in ICC survival after 1992, corresponding to a cumulative 34.4% increase in adjusted survival from 1992 through 2002.

Extrahepatic Cholangiocarcinoma

Several ECC patient and tumor characteristics changed significantly over the period of this study (Table 4). On average, patients in later decades tended to be older (P=0.021), and fewer came from rural areas (P<0.001). They also had higher stages of disease (P=0.008) and more aggressive tumor histology (P<0.001). There was no significant association between stage of disease and rural area of residence. The proportion of patients surviving less than 1 month after diagnosis (a surrogate marker of perioperative mortality) decreased over the three decades studied from 6.7% to 2.7% (P<0.001). Because the type of cancer-directed surgery was not specified for a high proportion of patients (771 of 2,107), we were not able to analyze trends in the type of surgical procedure performed.

Higher proportions of patients in later decades received radiation therapy (P<0.001). Receipt of radiation therapy was not significantly associated with tumor grade, but it was associated with tumor stage. Overall, 31.1% of patients with regional disease received radiation therapy, significantly more than those with localized (21.8%) or distant (22.0%) disease (P<0.001). Stratification by decade consistently demonstrated that patients with regional disease had the highest rate of radiation therapy, but this difference was statistically significant only in 1993–2002, when 39.2% of patients with regional disease received radiation therapy versus 23.6% of those with localized and 27.9% of those with distant disease (P<0.001). Stratification by stage showed that patients with every stage of disease were more likely to receive radiation therapy in later decades.

Comparison of ECC survival between decades (Fig. 4) showed significant improvements between 1973–1982 and

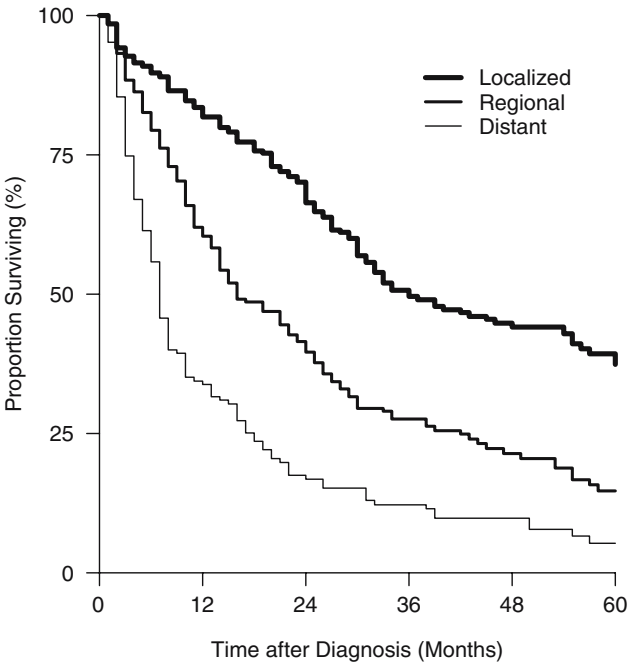

Figure 3 Relative Kaplan–Meier survival after surgery for ICC, by stage. All comparisons: P<0.001.

Table 3 Predictors of Survival after Surgery for ICC

	Univariate			Multivariate		
Variable	HR	95% CI	*P* Value*	HR	95% CI	*P* Value
Age at diagnosis†	1.80	1.33–2.45	<0.001	2.19	1.56–3.10	<0.001
Male	1.09	0.91–1.31	0.354	NE	–	
White	1.06	0.82–1.37	0.676	NE	–	
Married	0.85	0.70–1.04	0.112	NE	–	
Rural area of residence	0.82	0.62–1.08	0.163	0.76	0.56–1.02	0.067
Stage						
Localized	1.00	–	Ref.	1.00	–	Ref.
Regional	1.77	1.42–2.20	<0.001	1.71	1.36–2.15	<0.001
Distant	3.05	2.40–3.88	<0.001	2.98	2.31–3.85	<0.001
Grade						
Well differentiated	1.00	–	Ref.	1.00	–	Ref.
Moderately differentiated	1.07	0.80–1.43	0.641	1.07	0.79–1.44	0.679
Poorly differentiated	1.34	0.97–1.83	0.073	1.18	0.86–1.61	0.305
Undifferentiated	1.58	0.78–3.21	0.204	1.61	0.73–3.52	0.236
Radiation therapy	1.06	0.86–1.30	0.592	NE	–	
Year of diagnosis‡	0.58	0.45–0.76	<0.001	0.66	0.50–0.86	0.003

Results for SEER registry site are omitted for brevity but were not statistically significant.
*See text for *P* values for likelihood ratio tests, used to determine entry into multivariate model.
† Modeled continuously per year over 80 years; HR shown is per 5-year increment over 80 years.
‡ Modeled continuously per year after 1992; HR shown is for the decade 1992–2002.
HR = hazard ratio, CI = confidence interval, Ref. = reference, NE = not entered into final model

1983–1992 (P=0.004) and again between 1983–1992 and 1993–2002 (P=0.001). These improvements corresponded to 5-year RS of 14.4%, 19.1%, and 24.5% in the three decades studied. Comparisons of survival curves by stage at diagnosis (Fig. 5) were all highly significant (P<0.001). As with ICC, more advanced disease conferred a worse prognosis, with 5-year RS of 33.7% for localized disease, 17.7% for regional disease, and 16.6% for distant disease.

Univariate Cox proportional hazards analysis for ECC (Table 5) showed the following variables to be significantly associated with decreased survival (P value for likelihood ratio test, percent of data missing): age per year over 60 years (P<0.001, 0%), male gender (P=0.007, 0%), marital status (P=0.006, 5.7%), rural area of residence (P< 0.001, 1.4%), tumor stage (P<0.001, 3.2%), tumor grade (P<0.001, 22.7%), radiation therapy (P=0.003, 0%), and year of diagnosis per year after 1973 (P<0.001, 0%). These variables were entered into the multivariate model for ECC. In the final model of ECC survival (Table 5), age over 60 years and rural area of residence were strong predictors of worse survival. Advanced stage of disease and histological de-differentiation also conferred a worse prognosis. Gender, marital status, and radiation therapy did not show statistically significant effects on survival in the multivariate model. In sharp contrast to ICC, there was a dramatic improvement in adjusted ECC survival over the entire 30-year period studied, corresponding to a 23.3% increase in adjusted survival per decade and a cumulative 53.7% improvement from 1973 through 2002. A sensitivity analysis that restricted the cohort to those patients surviving at least 1 month did not yield qualitatively different conclusions, suggesting that the observed improvement was not solely a result of decreasing perioperative mortality.

Discussion

Historically, analyses of patient survival after surgery for cholangiocarcinoma have been restricted to single-institution series. Although such institutional data may offer great depth of clinical information, they may be limited by poor generalizability and potential selection bias. In this population-based study, we analyzed long-term survival after cancer-directed surgery for cholangiocarcinoma using data derived from a national cancer registry. We found 5-year crude survival rates of 17.7% for ICC and 17.1% for ECC over the period 1973–2002. For ICC, recent single-institution surgical series have reported 5-year crude survival rates of 17–40%.[6–14] Even the highest 5-year crude survival rate for ICC in our analysis, 19.7% in the decade 1993–2002, falls below all except one of these single-institution rates.[6] For ECC (including perihilar tumors), recent single-institution surgical series have reported 5-year crude survival rates of 9–41%.[10,14–27] Again, our analysis found 5-year crude survival rates for ECC that were at the lower end of this spectrum. These results are not surprising, as the results we

Table 4 ECC Patient and Tumor Characteristics

	1973–1982	1983–1992	1993–2002	Total
Number of patients	434	623	1,050	2,107
Percent of total	20.6	29.6	49.8	100
Mean age at diagnosis (years)*	67.4	66.7	65.6	66.3
Male (%)	55.5	55.4	58.1	56.8
White (%)	85.5	81.1	81.2	82.1
Married (%)	62.7	66.6	67.9	66.6
Rural (%)*	16.8	14.5	8.7	12.1
Stage (%)*				
Localized	31.4	30.2	22.1	26.4
Regional	60.4	57.4	71.3	65.0
Distant	8.2	12.4	6.7	8.7
Grade (%)*				
Well differentiated	37.9	30.7	18.4	24.9
Moderately differentiated	37.9	42.8	49.6	45.9
Poorly differentiated	22.6	24.3	30.7	27.6
Undifferentiated	1.7	2.3	1.3	1.7
Radiation therapy (%)*	10.8	27.6	34.7	27.7
Survival <1 month (%)*	6.7	3.9	2.7	3.8
Median survival (months)				
Crude	12	16	19	17
Relative	14	16	20	18
Five-year survival (%)				
Crude	11.8	15.9	20.8	17.1
Relative	14.4	19.1	24.5	20.5

Percentages exclude missing values.
*Significant test for trend ($P<0.05$). Tests for trend not performed for median and five-year survival.

report are not restricted to specialized centers, and single-institution series are susceptible to publication bias.

Our analysis offers a more generalizable assessment of the progress made in the surgical therapy of cholangiocarcinoma. In particular, we defined cancer-directed surgery as it is defined in the SEER database, including a range of procedures from cryoablation and enucleation to hepatectomy and pancreaticoduodenectomy. Some of these less aggressive practices might not be considered oncologically adequate at specialized centers, which may also explain the poorer survival seen in this analysis as compared to single-institution series. Importantly, however, our analysis reflects the full range of practice patterns in the treatment of cholangiocarcinoma in the United States, not just the results of specialized centers employing more aggressive surgical approaches.

We did not find an improvement in ICC survival until the last decade studied. During the period from 1992 through 2002, there was a cumulative 34.4% increase in adjusted survival after surgery. Unfortunately, the SEER data do not allow us to specifically identify the factors responsible for this improvement, but based on the

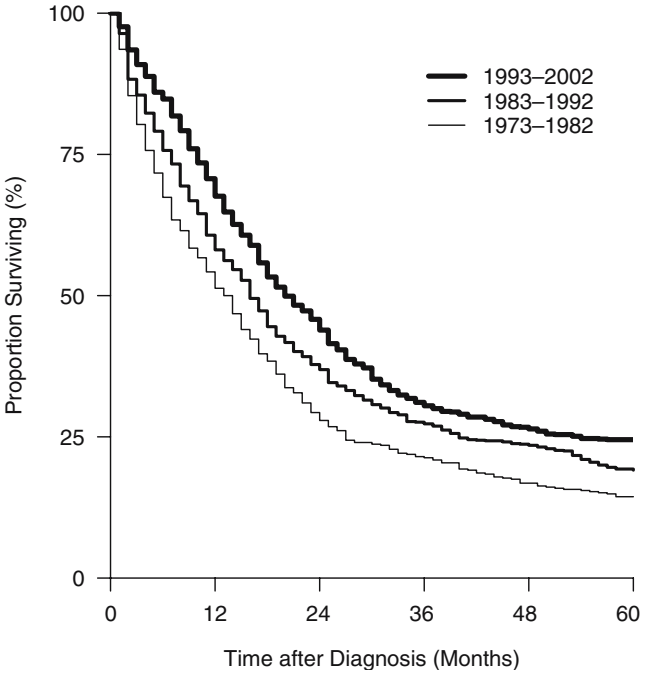

Figure 4 Relative Kaplan–Meier survival after surgery for ECC, by decade. 1973–1982 vs. 1983–1992: $P=0.004$. 1983–1992 vs. 1993–2002: $P=0.001$.

substantial collective experience with cholangiocarcinoma at our institution there are several factors that we believe have likely played an important role. The improvement in ICC survival may reflect improving patient selection over time, likely as the result of improvements in imaging technology, such as multidetector computed tomography,

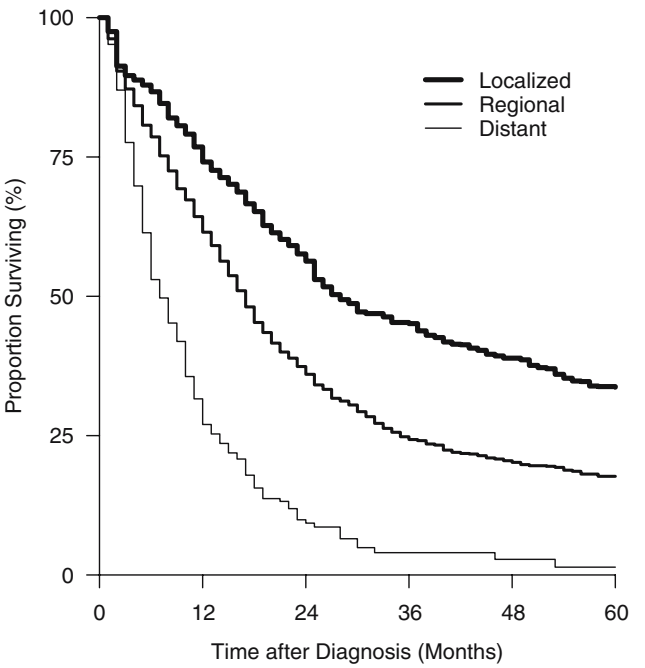

Figure 5 Relative Kaplan–Meier survival after surgery for ECC, by stage. All comparisons: $P<0.001$.

Table 5 Predictors of Survival after Surgery for ECC

	Univariate			Multivariate		
Variable	HR	95% CI	*P* value*	HR	95% CI	*P* value
Age at diagnosis†	1.16	1.12–1.19	<0.001	1.14	1.10–1.19	<0.001
Male	0.88	0.80–0.97	0.007	0.98	0.87–1.10	0.724
White	0.99	0.88–1.12	0.884	NE	–	
Married	0.87	0.78–0.96	0.005	0.93	0.82-1.05	0.257
Rural area of residence	1.31	1.14–1.51	<0.001	1.43	1.21–1.69	<0.001
Stage						
Localized	1.00	–	Ref.	1.00	–	Ref.
Regional	1.50	1.34–1.68	<0.001	1.61	1.40–1.84	<0.001
Distant	3.34	2.78–4.00	<0.001	3.57	2.84–4.49	<0.001
Grade						
Well differentiated	1.00	–	Ref.	1.00	–	Ref.
Moderately differentiated	1.17	1.02–1.34	0.024	1.19	1.04–1.38	0.015
Poorly differentiated	1.57	1.36–1.82	<0.001	1.67	1.43–1.95	<0.001
Undifferentiated	1.66	1.11–2.48	0.013	1.38	0.91–2.09	0.124
Radiation therapy	0.85	0.77–0.95	0.003	0.93	0.82–1.05	0.258
Year of diagnosis‡	0.82	0.78–0.87	<0.001	0.77	0.71–0.83	<0.001

Results for SEER registry site are omitted for brevity but were not statistically significant.
*See text for *P* values for likelihood ratio tests, used to determine entry into multivariate model.
† Modeled continuously per year over 60 years; HR shown is per each 5-year increment over 60 years.
‡ Modeled continuously per year after 1973; HR shown is per each decade after 1973
HR = hazard ratio, CI = confidence interval, Ref. = reference, NE = not entered into final model

that allow better preoperative assessments of resectability. Also, improvements in the safety of hepatic resection[39] have likely led to the increased utilization of aggressive hepatic resection for ICC, contributing to improved oncologic results and increased long-term survival. Unfortunately, details of the type of surgical resection in the SEER database are inconsistently available, and margin status information is absent, preventing us from further investigating these hypotheses.

We noted improvements in ECC survival over the entire 30-year time period studied, corresponding to a 23.3% increase in adjusted survival per decade and a cumulative 53.7% improvement from 1973 through 2002. As with ICC, the improvement in ECC survival may reflect improvements in preoperative imaging and patient selection, as well advances in surgical techniques. Decreases in the morbidity and mortality of complex hepatobiliary procedures may have expanded the use of such operations in ECC patients. For example, advances in the safety of pancreaticoduodenectomy are well documented.[40] Technical advances may also have resulted in a higher proportion of margin-negative resections, resulting in fewer patients undergoing inadequate resections. For example, concomitant hepatic resection for hilar cholangiocarcinoma has recently gained popularity as a strategy to achieve adequate margins.[14,19,22,27] It is possible that the increased use of hepatic resection in hilar cholangiocarcinoma has resulted in better oncologic results. Again, the SEER data do not permit the identification of such specific reasons for the observed trends.

The proportion of surgical patients surviving less than 1 month after diagnosis of ECC has decreased from 6.7% in the first decade to 2.7% in the last. Although these figures are not, strictly speaking, measures of 30-day surgical mortality, this decrease in 1-month survival likely indicates decreasing perioperative mortality. This interpretation assumes that the interval from diagnosis to surgery has not lengthened over the last three decades. More likely, this interval has either not changed or has shortened, which would underestimate perioperative mortality in the early years and overestimate it in the later years, resulting in a bias toward the null. Furthermore, our analysis demonstrates that an improvement in long-term ECC survival persists even when the effect of decreasing perioperative mortality is removed.

Despite these overall improvements, patients from rural areas who undergo surgery for ECC experience a 43% decrease in adjusted survival compared with those who live in more metropolitan areas. Rural patients did not, in fact, present with more advanced disease, suggesting that differences in survival were not related to delayed diagnosis. Instead, such differences may be related to discrepancies in access to specialized care or adequate follow-up, although we note that a rural area of residence does not necessarily imply treatment at a rural hospital. Another possible explanation is that the effect of rural area of residence

was confounded by socioeconomic status. Socioeconomic data are only available in later years of the SEER database, so we were unable to test this hypothesis.

The use of radiation therapy in ECC patients increased from 10.8% in the first decade to 34.7% in the last. Patients with regional disease were especially likely to receive radiation therapy. Most prior studies show that adjuvant radiation does not confer a survival benefit in cholangiocarcinoma,[41–43] although some evidence suggests that higher doses of radiation and concurrent chemotherapy may be of benefit.[44,45] In the present study, the increasing use of adjuvant radiation therapy demonstrated no independent survival benefit, underscoring the need for rigorous prospective evaluation of its efficacy in resected patients.

This study is limited primarily by the depth of surgical data in the SEER database. In addition to the lack of margin status data, the level of detail and completeness of data on tumor size, lymph node involvement, and details of resection have varied since 1973, such that comparisons that account for these factors over all 30 years are not possible. Although we did have some data on radiation therapy, we did not have any information on the use of chemotherapy. Finally, the ICD-O-3 coding scheme used in the SEER database did not allow us to separate perihilar tumors from other ECC, limiting comparisons with other studies.

Alternative explanations for the improvements we describe include the possibilities of lead time bias and stage migration. Even today, just as 30 years ago, patients with cholangiocarcinoma are typically diagnosed only after they develop symptoms of obstructive jaundice. Lead time bias is therefore unlikely to play a role in explaining these findings. Stage migration may have also played a role, but because we focused on a surgical population we would expect that patients would be appropriately upstaged at the time of surgery, even if their preoperative workups did not reveal the full extent of their disease. This would have resulted in more uniform coding of stage than in a nonsurgical population, for whom stage migration would be a more important issue.

In conclusion, this population-based analysis demonstrates that survival after surgery for extrahepatic cholangiocarcinoma has dramatically improved since 1973. Patients with intrahepatic cholangiocarcinoma, however, have achieved an improvement in survival largely confined to more recent years. We suggest that improvements in imaging technology, patient selection, and surgical techniques are largely responsible for these improvements. The discrepancies between the survival rates we report and those reported in single-institution series deserve further investigation to determine whether they are the result of publication bias, patient selection, disease characteristics, or disparities in access to adequate care. Finally, these population-based survival statistics demonstrate that extrahepatic and intrahepatic cholangiocarcinoma continue to carry very poor prognoses. Despite incremental advances in the surgical therapy of these biliary tract malignancies over the last three decades, there remains much opportunity for improvement.

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DISCUSSION

Bryan M. Clary, M.D. (Durham, NC): This is another very nice paper. I must admit when I read reports of this nature, I am not always sure what to do with them. Number one, I would like to commend you on your manuscript. This type of a study is all about the statistics, and in your manuscript's methods section you very eloquently state the methods that you use, and you also include a number of very relevant references to help guide individuals such as myself as to what the statistics mean.

Again, the problem is what you gain from this. You in general get a look at how we are doing in certain eras, and trying to come up with the explanations as to why that is, is really pure speculation. One of the main concerns I have with the intrahepatic cholangio population is just the definition as to what is an intrahepatic cholangiocarcinoma during different eras. In eras past, including the '70s and '80s, this was essentially adenocarcinoma of unknown primary in the liver, and really it was a diagnosis of exclusion for cytokeratin staining was not as sophisticated as it is now. And so I would venture to guess that one of the problems that you have in this series is that a large proportion of your intrahepatic cholangiocarcinomas were adenocarcinomas metastatic from other sites such as occult pancreatic cancers which were very common with poor imaging back then, and possibly even gastric cancers and lung cancers, et cetera. I wonder if you might make some comment to that specific issue.

The thing that clearly isn't brought out in this, which you already mentioned, is that of chemotherapy and the issue about rural populations not doing as well. Again, that explanation may not be a surgical issue but it instead that in their follow-up they don't have

medical oncologists who were offering chemotherapy, et cetera. But again, those types of things are pure speculation.

Hari Nathan, M.D. (Baltimore, MD): Dr. Clary, thank you very much for your review of our manuscript and your insightful questions. Your first question was whether the intrahepatic cholangiocarcinomas are truly cholangiocarcinomas. We specifically designed our selection criteria with that issue in mind. The SEER data allow the identification of tumors based on two codes: one is a topography code indicating the location of the tumor and the other is a histology code indicating the pathological diagnosis. For tumors that were located in the liver, the intrahepatic cholangiocarcinomas, we specifically excluded adenocarcinomas that were not otherwise specified and other lesions that we could not specifically identify as being cholangiocarcinomas. We were less stringent, for example, in the extrahepatic biliary tree, where we might accept a histological diagnosis of adenocarcinoma, not otherwise specified. But in the liver or at the ampulla we were much more strict about requiring a specific histological diagnosis of cholangiocarcinoma. So we feel very comfortable that we have excluded metastatic malignancies and other adenocarcinomas not arising from the bile ducts.

With regard to chemotherapy and rural patients, you are correct in pointing out that one of the weaknesses of the study is that we just don't have the depth of data in this database that would be required to specifically identify what the reasons for the improvements are. But I think this study provides two important pieces of information.

One, it gives us a sense as to the generalizability of the results that we see reported from single institutions. In terms of prognostication for patients and to get a general sense of how we are doing in the country as a whole, it is important to have that reality check of not exclusively relying on reports from specialized centers to guide our impression of how we are doing across the entire country.

And the other contribution is that it points to a direction for future research. There are other data that are available that may help us to identify why exactly, for example, rural patients with ECC have worse survival. The SEER-Medicare data, for example, which we are currently trying to acquire, do include information on chemotherapy receipt. So as we investigate further why these disparities do exist in patient outcomes, not just with cholangiocarcinoma but with a variety of malignancies, I think that this study and others like it give us a starting point. In future work, we hope to move from describing the differences to identifying the reasons for these disparities and actually trying to do something about them.

Thanks again for your comments and questions.

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Systemic Chemotherapy and Two-Stage Hepatectomy for Extensive Bilateral Colorectal Liver Metastases: Perioperative Safety and Survival

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Abstract

Background Two-stage hepatectomy has been proposed for patients with bilateral colorectal liver metastases (CLM). The aim of this study was to compare the outcome of patients with CLM treated with preoperative chemotherapy followed by one- or two-stage hepatectomy.

Methods From a prospective database, 214 consecutive patients who received preoperative systemic chemotherapy (fluoropyrimidine with irinotecan or oxaliplatin) followed by planned one- or two-stage hepatectomy were retrospectively analyzed (1998–2006). In patients undergoing two-stage procedures, minor hepatectomy (wedge or segmental resection[s]) was systematically performed before major (more than three segments), second-stage hepatectomy. Preoperative portal vein embolization (PVE) was performed if indicated.

Results One- (group I) and two-stage(group II) hepatectomies were performed in 184 and 21 patients, respectively. Median number of metastases in groups I and II were two (range 1–20) and seven (range 2–20). All patients in group II had bilateral disease vs 39% in group I. Major hepatectomy was performed in all patients in group II and 79% in group I. PVE was performed in 18 group I and 12 group II patients without increase in morbidity. For group I, group II first stage, and group II second stage, respectively, morbidity (24%, 24%, 43%), median hospital stay (7 days, 6 days, 6.5 days) and 30 days postoperative mortality (2%, 0%, 0%) were not significantly different (P=NS). Median follow-up was 25 months; median survival has not been reached. One- and 3-year overall and disease-free survival rates from the time of hepatic resection were 95% and 75%, 63% and 39%, respectively in group I; 95% and 86%, 70% and 51%, respectively in group II (P=NS).

Conclusions Two-stage hepatectomy with preoperative chemotherapy results in comparable morbidity and survival rates as one-stage hepatectomy. This approach enables selection and treatment of patients with multiple, bilateral CLM who will benefit from aggressive surgery with good outcomes.

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Keywords Two-stage hepatectomy · Colorectal cancer · Liver metastases

Introduction

Hepatic resection is the only potentially curative treatment for patients with colorectal liver metastases (CLM) and results in 5-year survival rates of up to 58%.[1–3] Patients with extensive, bilateral disease present a challenge in the goal of achieving margin-negative resection while preserving sufficient functional liver parenchyma to support normal postoperative hepatic function. Two-stage hepatectomy, with or without preoperative portal vein embolization (PVE), has been advocated for patients with extensive bilateral CLM that cannot be resected in a single procedure.[4–7] This strategy was first reported by Adam et al.,[5] who proposed resecting the highest possible number of tumors at the first stage, followed by chemotherapy (±PVE), and a second-stage minor resection of remaining tumors in the future liver remnant. Using this strategy, 13 patients who completed two-stage resection had a 3-year survival rate of 35%. This approach raised concerns regarding accelerated growth of metastases in the future liver remnant during the period of regeneration between the two stages, particularly after PVE. To avoid this problem, Jaeck and colleagues presented a two-stage program in which all metastases from the future liver remnant were resected at a first-stage minor resection; followed by a period of liver regeneration, with PVE when indicated; and subsequently, a second-stage major hepatectomy.[4] In their series, 25 patients completed two-stage hepatectomy with low perioperative morbidity and mortality rates and achieved 3-year overall and disease-free survival rates of 54% and 14%.

Modern chemotherapy using oxaliplatin and irinotecan have more than doubled median survival and tripled response rates in patients with stage IV colon cancer.[8] Moreover, neoadjuvant chemotherapy can downsize tumors that would otherwise be unresectable, treat systemic disease to lower the risk of distant failure, and allow the identification of patients with biologically aggressive tumors that progress on chemotherapy, who would not benefit from surgery.[9,10] Resection after chemotherapy may also be associated with a higher complete resection rate.[11] The purpose of this study was to assess the feasibility, morbidity and mortality, and oncologic outcomes of two-stage hepatectomy in the era of modern chemotherapy. In addition, outcomes of patients who underwent one- vs. two-stage hepatectomy after preoperative oxaliplatin or irinotecan-based chemotherapy were compared.

Material and Methods

Patient Selection and Preoperative Assessment

Nine hundred sixteen consecutive patients were identified in the prospective hepatobiliary surgery database at the University of Texas M. D. Anderson Cancer Center who underwent hepatic resection for CLM between May 1998 and May 2006. Patients treated with prehepatectomy chemotherapy *not* including irinotecan or oxaliplatin and those treated at any time with hepatic arterial infusion chemotherapy or radiofrequency ablation were excluded. Clinical data on patients who received preoperative systemic chemotherapy for hepatic metastases using fluoropyrimidine with irinotecan or oxaliplatin, followed by planned one- or two-stage hepatectomy, were retrospectively analyzed (214 patients). All patients underwent complete resection of hepatic metastastic disease.

All patients underwent preoperative abdominopelvic imaging with computed tomography (CT) or magnetic resonance imaging (MRI), as well as chest radiograph or chest CT when indicated. Patients were deemed candidates for hepatic resection if a negative-margin resection of all tumors ever present could be achieved with sparing of two adjacent liver segments with preserved vascular inflow and outflow, while preserving sufficient liver remnant volume.[12] Synchronous presentation was defined as diagnosis of liver metastasis within 6 months of the colorectal primary.

Perioperative Factors

First-stage hepatectomy was performed as soon as tumor downsizing with chemotherapy was sufficient to permit complete resection. In patients undergoing two-stage resection, minor hepatectomy (wedge or segmental resection[s]) was systematically performed before major (three or more segments), second-stage hepatectomy. The timing of the second-stage procedure was determined by the adequacy of liver regeneration, tumor response to chemotherapy, and the probability that second-stage major resection would be curative. Preoperative PVE was performed if the FLR volume was 20% or less of the estimated total liver volume, as previously described.[13]

All metastases identified on preoperative imaging were addressed at hepatectomy. All patients underwent intraoperative ultrasound to assess the presence of lesions not seen on preoperative imaging, association between metastases and intrahepatic vascular structures, and the appropriate plane for parenchymal transection. All patients had pathologic confirmation of CLM. Hepatic parenchyma remote from the resected tumor was examined for pathologic findings of hepatic injury, as previously described.[14]

Postoperative complications were graded according to a published classification scheme.[15] Patients who sustained multiple complications were assigned a complication grade with the highest severity.

Follow-up, Outcome, and Analysis

Postoperatively, patients were followed with physical examination, CT scans, and serum carcinoembryonic antigen (CEA) levels at 3- to 6-month intervals for the first 2–3 years after resection and at more extended intervals thereafter. Recurrence was identified by new or growing lesions on radiographic studies.

Comparisons between groups were performed using the Chi-square test for categorical variables and the Student's *t* test for continuous variables (SPSS software version 12.0, SPSS Inc., Chicago, IL). Overall and disease-free survival rates were estimated from the time of hepatectomy in the one-stage group and first hepatectomy in the two-stage group using Kaplan–Meier analysis; differences in survival were analyzed using the log-rank test. Differences were considered to be statistically significant when the *P* value was <0.05.

Results

Patient Characteristics

The clinicopathological characteristics of the 214 studied patients are presented in Table 1. Median age was 57 years (range 22–85) for the entire cohort, and 129 (60%) of the patients were male. Median number of metastases in groups I and II were two (range 1–20) and seven (range 2–20), respectively ($P<0.001$). All patients in group II had bilateral disease vs. 39% in group I ($P<0.001$). Patients in group II were more likely to undergo simultaneous colorectal and first-stage hepatic resections ($P<0.001$). Group II patients were more likely to have higher preoperative serum levels of CEA ($P=0.016$).

Figure 1 depicts the sequential multimodality strategy used to treat 184 and 21 patients who completed one- (group I) and two-stage (group II) hepatectomies, respectively.

Feasibility

Of 30 patients intended to undergo two-stage hepatectomy, 21 patients completed the second-stage resection, yielding a feasibility rate of 70%. Nine patients underwent first-stage but not the second-stage procedure because of disease progression ($n=5$; 2 extrahepatic and 3 intrahepatic), poor performance status ($n=3$), and inadequate liver regeneration ($n=1$).

Table 1 Clinicopathological Features of 214 Patients Treated with Preoperative Oxaliplatin- or Irinotecan-based Systemic Chemotherapy Followed by One- or Intended Two-stage Hepatectomy

Variable[a]	Group I	Group II	*P* value
	One-stage ($n=184$)	Two-stage ($n=30$)	
Age in years	57 (22–85)	51 (35–68)	NS
Gender			
Male	107 (58%)	22 (73%)	NS
Female	77 (42%)	8 (26%)	
Primary tumor site			
Right colon	40 (22%)	4 (13%)	NS
Transverse	6 (3%)	0	
Left colon	73 (40%)	17 (57%)	
Rectum	59 (32%)	9 (30%)	
Unknown	6 (3%)	0	
Stage of primary (M excluded)			
I	17 (9%)	0	NS
II	46 (25%)	8 (26%)	
III	117 (64%)	22 (73%)	
Unknown	4 (2%)	0	
No. of hepatic metastases	2 (1–20)	7 (2–20)	< 0.001
Patients with bilateral disease	72 (39%)	30 (100%)	< 0.001
Size of largest metastasis in cm	3.2 (0.5–11.1)	3 (1.3–9.9)	NS
Patients with largest tumor > 5 cm	47 (26%)	6 (20%)	NS
Presentation			
Synchronous[b]	85 (46%)	17 (57%)	NS
Metachronous	99 (54%)	13 (42%)	
Simultaneous colon and liver resection	11 (6%)	9 (30%)	< 0.001
Preoperative CEA (ng/ml)	6 (0.5–1265)	8.6 (0.5–135.1)	0.016

NS, not significant

[a] Median (range) or (%) as indicated

[b] Synchronous = diagnosis of liver metastasis within 6 months of primary colorectal cancer

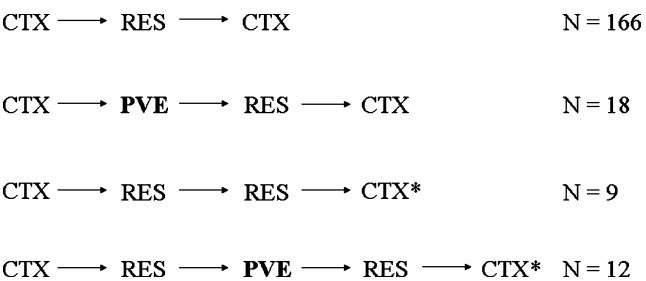

Figure 1 Treatment scheme in 205 patients who underwent perioperative oxaliplatin- or irinotecan-based chemotherapy (CTX) with one-stage ($n=184$) or two-stage ($n=21$) hepatic resection (RES), ± preoperative PVE. *Four patients in the two-stage group did not receive chemotherapy after the second-stage resection.

Table 2 Summary of Postoperative Complications in Patients Who Underwent One- or Two-stage Hepatectomy

	Group I	Group II First-stage	Group II Second-stage
Overall morbidity	45/184 (24%)	5/21 (24%)	9/21 (43%)
Grades I–II[a]	24/45 (53%)	5/5 (100%)	1/9 (11%)
Grades III–IV[a]	21/45 (47%)	0	8/9 (89%)

[a] Complications graded by previously published classification scheme[15]

Perioperative Chemotherapy and Hepatic Injury

All patients in this study received preoperative irinotecan- or oxaliplatin-based chemotherapy for a median of five cycles (range 2–23). In group II, patients underwent first-stage resection a median of 7 weeks after completing chemotherapy. Among the 21 patients who completed two-stage resection, chemotherapy regimens consisted of infusional 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX, n=12), infusional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI, n=8), and capecitabine and oxaliplatin (XELOX, n=1). Eleven patients were treated concurrently with bevacizumab. Chemotherapy was administered to five patients between the first- and second-stage procedures, and 17 patients after second-stage resection. In the nontumorous liver parenchyma, mild to moderate steatosis was found in 12 of the 21 patients. Chemotherapy neither induced steatohepatitis nor prevented any patients from undergoing second-stage hepatectomy.

Surgical Procedures

R0 resection was performed in 176 of 184 (96%) group I patients and in all group II patients (P=NS). In group I, 79% of patients underwent major hepatectomy vs. 100% in group II (P=0.03). In group II, 30 patients underwent first-stage minor hepatectomy, and of these patients, 21 went on to second-stage major hepatectomy. Among these 21 patients, 10 underwent extended right hepatectomy at the second-stage resection, including four who required caudate resection. In group II, the median interval between first- and second-stage resections was 8 weeks (range 5–64 weeks). PVE was performed in 18 (10%) patients in group I and before the second-stage hepatectomy in 12 (57%) patients in group II (P<0.001). PVE resulted in one complication—portal vein thrombosis, which was treated with anticoagulation and did not preclude second-stage resection. The second-stage hepatectomy was aborted in only one patient because of extensive adhesions. He received chemotherapy for 2 months, and second-stage resection was performed uneventfully 3 months after aborted hepatectomy.

Postoperative Complications

For group I, group II first stage, and group II second stage, respectively, morbidity (24%, 24%, 43%), median hospital stay (7 days, 6 days, 6.5 days) and 30-day postoperative mortality (2%, 0%, 0%) were not significantly different (P=NS). Postoperative complications are summarized in Table 2. The most common grades I–II complications were wound infection, urinary tract infection, and ileus. The most common grades III–IV complications were bile leak and perihepatic abscess.

Recurrence and Outcome

Median follow-up was 25 months; median survival has not been reached. One- and 3-year overall survival rates after the first hepatic resection were 95% and 75% in group I; and 95% and 86% in the 21 patients in group II who completed the two-stage program (P=NS, Fig. 2). Recurrent disease occurred in 99 patients (54%) in group I and nine patients (43%) in group II, and their characteristics are shown in Table 3. One- and 3-year disease-free survival rates after the first hepatic resection were 63% and 39% in group I; and 70% and 51% in group II (Fig. 3). Median

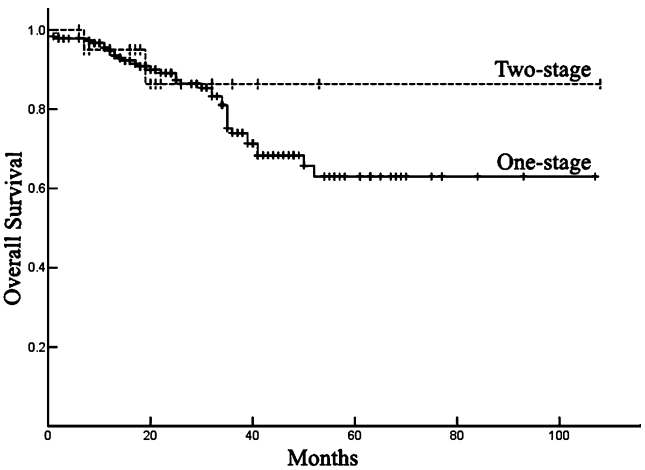

Figure 2 Overall survival in 205 patients after one- and two-stage hepatectomy.

Table 3 Sites of First Disease Progression in Patients Who Underwent One- or Two-stage Hepatectomy

Sites	One-stage $n=184$	Two-stage $n=21$
Total	99 (54%)	9 (43%)
Overall liver recurrence	51 (28%)	7 (33%)
Overall pulmonary recurrence	45 (24%)	4 (19%)
Liver only	33 (18%)	1 (5%)
Lung only	30 (16%)	0
Peritoneum/nodes only	15 (8%)	2 (10%)
Liver and lung	9 (5%)	3 (14%)
Liver and peritoneum/nodes	6 (3%)	2 (10%)
Lung and peritoneum/nodes	3 (2%)	0
Lung, liver, peritoneum/nodes	3 (2%)	1 (5%)

disease-free survival was 15 months in group I and has not been reached in group II.

The median follow-up among the nine patients who did not achieve two-stage hepatectomy was 8 months. Three patients died of disease 4, 8, and 34 months after first-stage resection. Six patients are receiving chemotherapy and remain alive with the disease.

Discussion

The current study demonstrates that a step-wise approach to patients with multiple, bilateral CLM using preoperative systemic chemotherapy and two-stage hepatectomy results in comparable morbidity and mortality rates and similarly favorable patient outcomes as one-stage hepatectomy in patients with less advanced disease. Building on previously described two-stage approaches,[4,6] we utilized sequentially more aggressive treatments (chemotherapy first, then minor hepatectomy, then portal vein embolization if indicated, and finally major hepatectomy) as a strategy to optimize patient selection for aggressive treatment and to minimize morbidity. The minor resection involved extirpation of low-volume disease in the planned future liver remnant before regeneration was stimulated. Performing the minor hepatectomy first enabled protection of the future liver remnant by avoiding manipulation and resection in a small, friable, hypertrophic remnant, which would be required if minor resection was performed second. Further, repeat dissection of the remnant and associated adhesions at the time of planned second-stage major resection were avoided using this approach. Finally, if disease progressed between stages, the patient was spared the morbidity of a major hepatectomy.

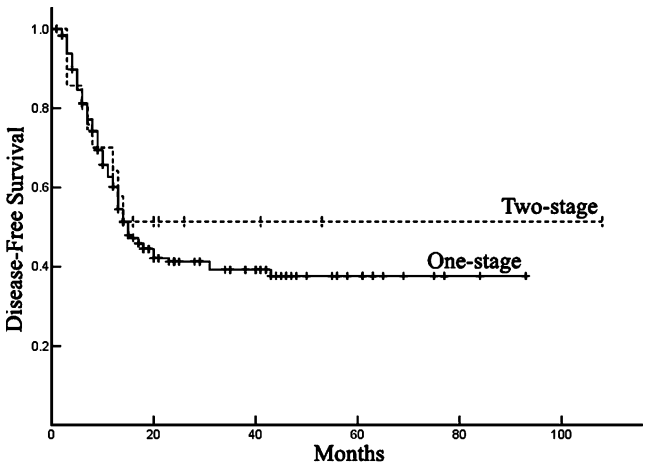

Figure 3 Disease-free survival in 205 patients after one- and two-stage hepatectomy.

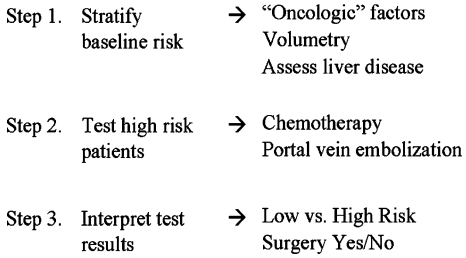

Figure 4 Individualized patient care in two-stage strategy.

All of our patients underwent one- or two-stage hepatectomy after irinotecan- or oxaliplatin-based chemotherapy regimens. In patients with four or more CLM, tumor control before hepatectomy is critical to provide patients a chance of prolonged survival.[9] Adam and colleagues showed that in patients with multinodular CLM, tumor progression on chemotherapy is associated with a poor outcome.[10] Most patients in the two-stage group had four or more metastases, and all patients who proceeded to second-stage resection had tumor response to chemotherapy. Despite this initial response, five patients did not complete the second-stage resection because of subsequent tumor progression and were never subjected to the risk of major hepatectomy.

Despite a significantly higher number of metastases, preoperative serum CEA level, and proportion of patients with bilateral disease in the two-stage cohort, we demonstrated comparable survival rates among patients who underwent one- and two-stage resections, with 3-year overall survival rate of 86% in the two-stage group. This favorable outcome likely reflects the individualized patient selection and treatment enabled by this two-stage surgical strategy, which includes three components (Fig. 4). The first component focuses on baseline risk assessment, which depends on oncologic factors including number, size, and distribution of metastases, and upon liver factors such as volumetry of the planned remnant. The second component includes assessment of the tumor response to chemotherapy, and when indicated, the hypertrophy response of the liver to PVE (which has been shown to predict outcome after major resection[16]). First-stage resection may be

considered part of the first and second components, as it allows assessment of underlying or chemotherapy-induced liver disease and determination of recovery and liver regeneration before proceeding with the second-stage resection. Finally, the third component requires interpretation of all of these findings before major resection is performed. If tumor progression occurs despite chemotherapy, liver regeneration is inadequate, or severe liver disease is found, then resection is considered to be high risk. Integration of these data helps to determine whether the second-stage major resection should or should not be performed in the individual patient after careful assessment of the risks.

Of 30 patients intended to undergo two-stage hepatectomy, 70% successfully completed two-stage resection, reflecting the determination that risk for second-stage resection was not appropriate in all patients selected for first-stage surgery. This result is similar to the findings of other authors who reported feasibility rates of 76–81% to complete both planned stages.[4,5] In our study, nine patients did not complete two-stage resection because of disease progression, poor performance status, or impaired liver regeneration. As in other studies, we found that patients who do not complete the second-stage resection have a poor prognosis.[5]

This two-stage strategy is suited for patients presenting with synchronous primary colorectal tumors and hepatic metastases, which cannot be resected at the time of colectomy with a single curative hepatectomy. In the current study, more patients in the two-stage group had simultaneous resection of their colorectal primaries with liver resection than patients in the one-stage group. This result is similar to a report by Tanaka et al.,[7] in which 86% of patients in the two-stage group had synchronous disease, compared to 67% of patients who underwent single hepatectomy after PVE. A planned strategy in which minor hepatic resection is performed at the time of colectomy and major hepatectomy is reserved for the second stage agrees with the current consensus to avoid major hepatectomy at the time of colectomy to minimize morbidity.[5,17]

The morbidity and mortality rates of each stage of two-stage hepatectomy were not significantly different from those of one-stage resection. As expected, second-stage major hepatic resection resulted in a higher number and severity of complications than first-stage minor resection. In prior studies of resection of multiple, bilateral CLM without preoperative PVE, high mortality rates of 9–15% were reported as a result of insufficient remnant liver volume and resultant hepatic failure.[5,18] However, systematic liver volumetry and PVE in patients with FLR volume ≤20% of the total estimated liver volume have reduced mortality rates after extended hepatic resection to less than 1%.[19] This study confirms the safety of this approach.

Conclusion

Two-stage hepatectomy with perioperative chemotherapy is a safe and effective strategy to treat patients with extensive, bilateral CLM, who may otherwise not be eligible for surgery. We demonstrated 3-year overall and disease-free survival rates of 86% and 51% in patients who completed two-stage hepatectomy, which were similar to survival rates of patients treated with one-stage hepatectomy. The morbidity and mortality rates were comparable between the one- and two-stage groups. Two-stage hepatectomy is part of a multidisciplinary approach that includes modern systemic chemotherapy, portal vein embolization, and careful patient selection to offer a chance of prolonged survival in patients who would otherwise not be candidates for resection.

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Discussion

Timothy M. Pawlik, M.D. (Baltimore, MD): I would like to congratulate Dr. Chun and the group from M.D. Anderson for another outstanding study regarding the evolving strategies of expanding the criteria of resectability for patients with colorectal liver metastasis. And I want to thank them for providing me a copy of the manuscript beforehand. I do have a number of questions.

If we go through the numbers, you start off with more than 900 patients and you end up with 21 or roughly 2% of patients who actually underwent a two-stage hepatectomy. So clearly this is a highly select subgroup of patients. Could you shed some additional light on exactly how to best select patients who might benefit from this aggressive surgical therapy, as a full one-third of the patients who initially were planned on having a two-stage hepatectomy dropped out and only 21 out of the 30 were able to go on to have both stages of the operation.

Related to this, another manner of treating patients with extensive bilobar disease is to combine resection with contralateral hepatic ablation, and in fact, several investigators from your own institution have reported on both the safety and efficacy of combining resection with ablation. Could you help us understand which patients may benefit from resection plus ablation versus those patients who may benefit more from a two-stage hepatectomy? Also in the current study, there was no mention of portal vein ligation, and hypertrophy was induced exclusively with portal vein embolization. Is it your group's current recommendation not to ligate the portal vein at the time of the first operation, but rather to embolize between surgeries and to rely exclusively on this modality of hypertrophying the future liver remnant?

Also, I was a little suspicious that the majority of patients who underwent a two-stage procedure had a synchronous colorectal primary in place. Did the patients who underwent a staged procedure truly undergo two operations because of purely anatomic liver-related factors, or do you think some patients were staged because of the surgeon's reluctance to combine a major colon surgery with a major hepatic resection?

I would also like to comment just briefly on your data regarding the morbidity and mortality. You state in one of your conclusions that the overall morbidity of a two-stage operation is comparable to that of a one-stage and note that there was no statistical difference. However, given that there were only 21 patients in the two-stage arm, the study is clearly underpowered and susceptible to a type II statistical error, and we wouldn't even expect a p value of less than 0.5. But if you look at the cumulative morbidity, it was over 65% for the two-stage operation compared to only 24% for the single-stage. So could you clarify a little bit your comments about the morbidity?

And then finally, could you comment a little bit on the 3-year survival rate of greater than 85%. The data published by Rene Adam in Paris with regards to his two-stage procedure noted a 5-year survival rate of 35%. So can you help us understand this truly almost unbelievable 3-year survival rate of greater than 80% in patients who clearly have a number of poor prognostic factors?

Again, I would like to thank you for an outstanding presentation and a worthwhile contribution to the literature. Thank you.

Yun Shin Chun, M.D. (Houston, TX): Thank you, Dr. Pawlik, for your questions.

The crux of our approach integrates steps to optimize patient selection. Several components are integrated stepwise, namely, systemic chemotherapy (and assessment of response), first-stage resection (and assessment of recovery), and portal vein embolization (and assessment of hypertrophy), all before second-stage major hepatectomy. This approach is designed to select patients with extensive hepatic disease who are likely to

benefit from complete resection of bilateral tumors. It is likely that the outcome reported here at early follow-up is good because of the effect of the selection process.

Regarding survival, it is clear from recent studies that survival following hepatic resection is improving, probably because of many factors including better chemotherapy and patient selection.

To answer your question about portal vein ligation, our policy is to embolize all tumor-bearing liver, which has been shown not only to improve the degree of hypertrophy of the liver remnant, but also to avoid the problem of tumor progression in the nonembolized liver. It is well known that portal vein ligation can lead to recanalization from collateral flow and incomplete portal flow diversion.

With regard to morbidity, there is little difference in the morbidity rates for each stage, but naturally, the additive morbidity of the two operations is greater in the two-stage group, although 100% of patients in the two-stage group underwent major resection and many underwent concomitant colon resection, far more than in the one-stage group.

Regarding RFA, we have shown that ablation results in higher local recurrence rates than complete surgical resection, and our preferred approach is to treat patients with bilateral disease with one- or two-stage hepatectomy rather than combining resection with RFA. Further, if all patients with bilateral lesions undergo major resection on one side and RFA on the other side, one would not expect the results we have shown because the effect of careful, stepwise patient selection is lost. Using this approach, we excluded 1/3 of the initial patient pool who might have been treated with resection plus RFA. We have shown that survival with combined resection/ablation is similar to current best chemotherapy and does not enable survival comparable to complete resection.

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Clarithromycin Resistance, Tumor Necrosis Factor Alpha Gene Polymorphism and Mucosal Inflammation Affect *H. pylori* Eradication Success

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Abstract Several bacterial and host-related factors concur in causing *Helicobacter pylori* eradication failure. We ascertained the role of bacterial virulence genes (*cagA*, *vacA*), clarithromycin resistance [Cla^R, 23S ribosomal RNA (rRNA) mutations], host polymorphism of CYP2C19 (polyphosphoinositide, PPI, metabolism) and of the cytokines IL-1B-31C>T, IL-1RN VNTR, IFN-γ+874A>T, TNF-α-1031T>C, TNF-α-857C>T, TNF-α-376G>A, TNF-α-308G>A, TNF-α-238G>A, IL-10-1082A>G, IL-10-819C>T, IL-10-592C>A, IL-12A+6686G>A, IL-12B+15485A>C. Two groups of *H. pylori*-infected and *H. pylori*-treated patients were retrospectively identified: 45 not eradicated and 57 eradicated. Treatment failure was significantly correlated with Cla^R (all resistant strains in non-eradicated patients); with TNF-α-238, IL10-819, IL10-592, IL-12B+15485 single nucleotide polymorphism (SNP); with IL10 ATA/ATA haplotype; and with antral inflammatory grade. On considering Cla^S-infected patients only, logistic regression analysis (eradication = dependent; TNF-α-238, IL12B+15485 genotypes, IL10 ATA/ATA as present or absent, antral gastritis grade = covariates) confirmed as significantly correlated with eradication antral gastritis grade only (Exp(B) = 6.48; 95% CI, 1.2–35.01). In conclusion, the bacterial determinant causing triple therapy failure is clarithromycin resistant, being virulence genes not involved. The host related factors that favor eradication are those linked to inflammation: a higher inflammatory infiltrate in the mucosa, possibly favored by genotypes able to down regulate the anti-inflammatory cytokine response, enhance the chance of eradication success.

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Keywords *H. pylori* · Triple therapy · Pharmacogenetics · Cytokines · Gene polymorphisms

Abbreviations

Cla^R	Clarithromycin resistant
Cla^S	Clarithromycin sensitive
EM	extensive metabolizer
IM	intermediate metabolizer
MGB	DNA minor groove binder
PAI	pathogenicity island
PCR	polymerase chain reaction
PM	poor metabolizer
PPI	proton pump inhibitor
RFLP	restriction fragment length polymorphism
rRNA	ribosomal RNA
SNP	single nucleotide polymorphism

UBT	urea breath test
UM	ultrarapid metabolizer
VNTR	variable number of tandem repeats
6-FAM	6-carboxyfluorescin

Introduction

The prevalence of the Gram-negative S-shaped *Helicobacter pylori* varies according to geographic area, age, race, and socio-economic status.[1,2] In general, *H. pylori* is not spontaneously cleared from the infected stomach, and it can survive for decades in this ecologic niche, causing gastric damage and disease.[3] All *H. pylori* infected individuals have mild to severe gastric mucosal inflammation,[4] but only a subset develops peptic ulcer (10–20%) or gastric adenocarcinoma or MALToma (1–2%).[3,5]

Many factors are involved in favoring the severe *H. pylori*-associated clinical outcomes, including the duration of the infection,[6] the virulence of the infecting strain[3,7–11] and the different host response to the infection.[4] The main *H. pylori* virulence determinants are the pathogenicity island (*cag PAI*) and the vacuolating cytotoxin A (Vac A). *cag PAI*, *a*≅ 40 kb DNA fragment present in a fraction of *H. pylori* strains comprises at least 31 genes with a strong homology with type IV secretion system (TFSS).[12] All *H. pylori* strains bear the *vacA* gene and almost all secrete a VacA product. The vacuolating toxin activity, however, varies significantly among strains, and this may depend on differences in *vacA* transcription, correlated to sequence variations in *vacA* gene, located mainly in the signal (s) and in the mid region (m). Two main s and m alleles have been identified: s1, s2, m1, and m2. The *H. pylori* strains bearing the s1m1 *vacA* alleles exert the highest cytotoxicity toward HeLa cells "in vitro"; an intermediate toxicity is recorded for s1m2 *vacA* and a low toxicity for s2m2 *vacA* alleles, indicating geno-phenotype associations.[13]

Gastric mucosal inflammation in response to *H. pylori* infection is triggered and maintained by the release of inflammatory cytokines. High mucosal levels of mononuclear- (IL-8, IL-6, IL-1α, TNF-α, and IFN-γ) and lymphocytic-derived (IL-2, IL-2RA) cytokines have been described in *H. pylori*-infected patients.[14–16] Some cytokines, IL-1α and TNF-α in particular, may also inhibit gastric acid secretion.[17,18] Functional gene polymorphisms have been demonstrated to influence the amount of newly synthesized cytokines and, consequently, the pattern and severity of inflammation, the extent of gastric acid inhibition, and finally, the risks for severe outcomes of *H. pylori* infection.[19–30]

The best and cost-effective approach to cure both gastric and duodenal ulcer and to prevent their recurrence is *H. pylori* eradication therapy,[31] which can cure also early stage gastric MALTomas in about two thirds of the cases.[32]

According to the Maastricht 2-2000 Consensus Report[33] and the Revised Maastricht Guidelines,[5] the first-line *H. pylori* eradication regimen should be a 7-day triple therapy made of a proton pump inhibitor (PPI) combined with Clarithromycin and Amoxycillin or Metronidazole. Triple therapy failure, registered in about 20% of the cases,[34,35] is mainly consequent to (1) poor patient compliance, (2) *H. pylori* infection caused by antibiotic resistant or virulent bacteria, and (3) inter-individual variability of host genes involved in PPI pharmacokinetics and in modulating the immune response.[36] Clarithromycin resistance is essentially because of point mutations in the 23S rRNA gene, which abrogate clarithromycin activity/binding to bacterial ribosomes.[37,38] Molecular-based diagnostic assays aimed to detect these mutations are preferable to culture-based methods in clinical laboratory settings, as they are more accurate and rapid. PPI are metabolized in the liver mainly by cytochrome P450 2C19, being CYP3A4 less relevant. Different genotypes derived from the combination of the three main CYP2C19 alleles (CYP2C19*1, functional; and CYP2C19*2/CYP2C19*3, defective) result in different phenotypes: extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM).[39] Recently Sim et al.[40] have identified a novel allele (CYP2C19*17) associated with an increased enzyme activity.

The aim of the present study was to evaluate, in a group of *H. pylori*-infected and previously untreated patients, whether there was any association between triple therapy efficacy and (1) clarithromycin resistance, (2) the bacterial virulence determinants *cagA* and *vacA*, and (3) host CYP2C19 and cytokines gene polymorphisms.

Matherial and Methods

The cohort consisted of 102 *H. pylori*-infected, previously untreated, and unrelated Italian patients (55 males, 47 females; age range 5–77 years; median age, 54 years).

This cohort was selected from a series of 800 individuals consecutively subjected to upper gastrointestinal endoscopy (esophagogastroduodenoscopies, EGD) for dyspeptic symptoms from 1995 to 2005. The inclusion criteria for patients' selection were (1) diagnosis of *H. pylori* infection without any previous eradication treatment, (2) 7-day triple therapy (1 g amoxicillin twice daily, 500 mg clarithromycin twice daily and 20 mg omeprazole twice daily) followed after 2 months by ^{13}C-UBT. To study bacterial and host factors causing triple therapy failure, we identified a first group of patients with a positive ^{13}C-UBT (55 cases) and a second group of patients, matched for age, sex, and number of cases, with a negative ^{13}C-UBT (47 cases).

Endoscopic findings were antral predominant gastritis (n=37), diffuse gastritis (n=26), oesophagitis (n=5), duodenal ulcer (n=15), gastric ulcer (n=4), and duodenitis (n=15). One antral and one body biopsy were taken for *H. pylori* culture, whereas two antral and two body biopsies were obtained for histology. A K_3 ethylenediaminetetraacetic acid (EDTA) blood sample was also obtained and immediately frozen at −20°C until laboratory processing. *H. pylori* culture was performed as previously described.[22] Gastric mucosal biopsies were evaluated after H&E to assess chronic inflammation, polymorphonuclear cell infiltration, atrophy and intestinal metaplasia, and after Giemsa and/or Wartin Starry staining, to assess *H. pylori* colonization density.[22]

The ^{13}C-UBT assay was performed by means of the breath-quality UBT (AB Analitica, Padova, Italy).

ureA, *vacA*, and *cagA* genes were studied by means of PCR using genomic *H. pylori* DNA as template following the procedure previously described by us elsewhere.[22]

Clarithromycin resistance was assayed by "RHA kit *H. pylori* clari" (Labo Bio-medical Products BV, The Netherlands), which allows the identification of five-point mutations of the 23S rRNA.

Genomic DNA, extracted from 5-ml peripheral blood by the Qiamp DNA blood maxi kit (QIAGEN S.p.A., Milan, Italy), was used to study the variable number tandem repeat of intron 2 of IL-1 RN and the cytokines single nucleotide polymorphisms (SNP). IL-1B-31 C>T, IFN-γ+874 A>T, TNF-α-1031 T>C, TNF-α-857 C>T, TNF-α-376 G>A, TNF-α-308 G>A, TNF-α-238 G>A, IL-10-1082 A>G, IL-10-819 C>T, and IL-10-592 C>A were assayed as described by us elsewhere.[24] Genotype discrimination of IL-12A+6686 G>A and IL-12B+15485 A>C were performed by means of TaqMan dual probes allelic discrimination assays on the real-time PCR instrumentation ABI Prism 7900 HT (Applied Biosystems, Foster City, CA, USA), carried out starting with 50 ng DNA in a final volume of 30 μl containing 1× TaqMan Universal PCR Master Mix (Applied Biosystems). Primers and probes sequences and concentrations are reported in Table 1. The thermocycling conditions were 50°C for 2 min, 95°C for 10 min, then 40 cycles at 95°C for 15 s, and 60°C for 60 s.

The CYP2C19-3402 C>T polymorphism was studied by a custom-made restriction fragment length polymorphism (RFLP) analysis. PCR was performed in a 25-μl final reaction volume containing 100 ng DNA, 1× PCR Gold Buffer (Applied Biosystems), 1.5 mM MgCl2, 200 μM each deoxyribonucleotide triphosphate (dNTP), 500 nM each primer (2C19-3402 F: 5′ AAT AAA GAT GAC CTT GAT CTG G 3′; 2C19-3402 R : 5′ GTC TCC TGA AGT GTC TGT AC 3′), 1.5 U AmpliTaq Gold (Applied Biosystems). The thermocycling conditions were: 95°C for 10 min, then 35 cycles at 94°C for 30 s, 52°C for 30 s, 72°C for 30 s, then 72°C for 7 min. To discriminate between the different alleles, RFLP analysis was performed by incubating 10 μl of PCR products at 37°C for 5 h in a final restriction digestion volume of 25 μl including 1× NEBuffer 2 (New England Biolabs, Beverly, MA, USA), 5 U Mnl I (New England Biolabs) and 100 μg/ml BSA. The restriction fragments (287+217 bp for allele C, 504 bp for allele T) were separated by electrophoresis on 3% NuSieve agarose gel (BMA, Rockland, ME, USA) and stained with ethidium bromide (0.5 μg/ml).

CYP2C19+681 G>A and CYP2C19-806 C>T polymorphisms were performed by means of TaqMan dual probes allelic discrimination assays on the real-time PCR instrumentation ABI Prism 7900 HT (Applied Biosystems). The former SNP was analyzed by using primers and probes provided by Applied Biosystems. CYP2C19-806 C>T was carried out starting with 100 ng DNA in a final volume of 25 μl containing 1× TaqMan Universal PCR Master Mix (Applied Biosystems), primers (900 nM each; F: 5′ GTT TGG AAG TTG TTT TGT TTT GCT AA 3′; R: 5′ TGG CGC ATT ATC TCT TAC ATC AG 3′), and probes (200 nM each; 5′ 6-FAM-TTC TGT TCT CAA AGC AT-MGB 3′ and 5′ 6-VIC-CTT CTG TTC TCA AAG TAT-MGB 3′). The thermocycling conditions were 50°C for 2 min, 95°C for 10 min, then 40 cycles at 95°C for 15 s, 60°C for 60 s.

Haplotype analysis and linkage calculation were made using Arlequin ver 2.000 software for population genetics data analysis.[41] Genotype frequencies were tested for Hardy–Weinberg equilibrium (HWE) proportions using a chi-square test. For each SNP, the allele frequencies were first calculated

Table 1 Primers and Probes Sequences and Concentrations Used to Analyze IL-12A+6686 G>A and IL-12B+15485 A>C SNP

Name	Sequence	Target
P35 UTR-A (probe A, 100 nM)	5′ 6-VIC-TTG ATC AGA GGT ATT ATG TG-MGB 3′	IL-12A 3′ UTR
P35 UTR-G (probe G, 100 nM)	5′ 6-FAM-TGA TCA GAG GTA TCA TGT G -MGB 3′	
P35 UTR-FP (primer F, 300 nM)	5′ AAC TTT GAT AGG ATG TGG ATT AAG AAC TAG 3′	
P35 UTR-RP (primer R, 900 nM)	5′ TGG ATA TTT TCC CTT CTT AGC AAT TC 3′	
P40NF3A-A (probe A, 100 nM)	5′ 6-FAM-CTT CTT AAC AGC CAT GTG A-MGB 3′	IL-12B 3′ UTR
P40NF3A-C (probe C, 100 nM)	5′ 6-VIC-CTT CTT AAC AGC CCT GTG A-MGB 3′	
P40NF3A-FP (primer F, 900 nM)	5′ CAA GTA GTT ATG GCT AAG GAC ATG AAA 3′	
P40NF3A-RP (primer R, 900 nM)	5′ CTA ATG AGA AAG GGA TTC CAG ATT TT 3′	

on the basis of the observed genotypes. The expected genotypes frequencies were then calculated on the basis of the following formula:

$$p^2 + 2pq + q^2 = 1 \ ,$$

p and q being the observed allele frequencies. The chi-square test, Fisher's exact test, and binary logistic regression analysis were performed using the Statistical Package for the Social Sciences (SPSS) 9.0 for Windows software.

Results

Forty-seven *H. pylori* eradicated and 55 not eradicated patients were chosen for this study.

Point mutations of the 23S rRNA were investigated in the clinical isolates from 18:47 eradicated and from the whole 55 non-eradicated patients. In the remaining 29 eradicated cases, clinical isolates of the infecting bacteria were not available for this analysis. In a subset of three cases, both pre- and post-treatment isolates were available for the analysis. In these cases, both samples showed the same 23S rRNA mutation.

Twenty-three out of the 73 *H. pylori* clinical isolates had mutations in the 23S rRNA: 7 (30.4%) isolates had the A2142G, 2 (8.7%) had the A2142C, and 14 (60.9%) had the A2143G mutation; the A2115G and the G2141A mutations were never found. Hereon Cla^R will be used to identify clinical isolates with any 23S rRNA mutation, whereas Cla^S to identify clinical isolates with no 23S rRNA mutation.

Figure 1 shows the association between Cla^R and eradication failure. Cla^R was never found in clinical isolates from eradicated patients, whereas it was recorded in 41.5% of not eradicated patients, the association being statistically significant (Fisher's exact test, $p<0.001$; odds ratio, 1.71; 95% CI, 1.36–2.14). Cla^R was also correlated with the female gender ($\chi^2=7.38$, $p<0.01$, odds ratio, 1.91; 95% CI, 1.24–2.96), but not with *cagA* ($\chi^2=1.20$, *p*/ns) or with s ($\chi^2=0.38$, *p*/ns) and m ($\chi^2=1.82$, *p*/ns) *vacA* alleles.

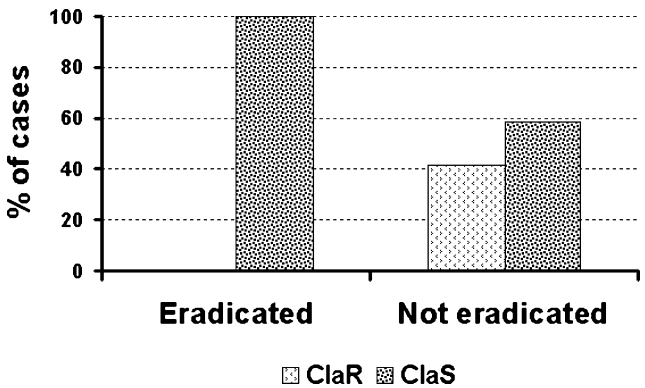

Figure 1 Frequencies of Clarithromycin resistant (Cla^R) and sensitive (Cla^S) clinical isolates among *H. pylori* eradicated and not eradicated patients.

cagA or *vacA* s and m polymorphisms were not associated with triple therapy success, both considering all ($\chi^2=0.22$, *p*/ns; $\chi^2=0.97$, *p*/ns; $\chi^2=0.92$, *p*/ns, respectively) or only Cla^S strains ($\chi^2=0.10$, *p*/ns; $\chi^2=0.98$, *p*/ns; $\chi^2=0.30$, *p*/ns respectively).

Table 2 reports the overall genotype and allele frequencies of the three CYP2C19 SNP considered in the study. All the polymorphisms were in Hardy–Weinberg equilibrium.

There was a complete linkage disequilibrium between the −3402C>T and −806C>T SNP ($\chi^2=180.68$; $p<0.0001$). These two SNP were in linkage, although not absolute, with the +681G>A polymorphism ($\chi^2=9.09$; $p<0.01$).

No statistically significant association was found between *H. pylori* eradication after triple therapy and CYP2C19 −3402, −806, +681 genotypes both considering all patients ($\chi^2=2.40$, *p*/ns; $\chi^2=2.40$, *p*/ns; $\chi^2=0.01$, *p*/ns, respectively) or only those infected by Cla^S strains ($\chi^2=1.91$, *p*/ns, $\chi^2=1.91$, *p*:ns; $\chi^2=0.09$, *p*/ns, respectively).

Since CYP2C19 alleles are defined by haplotypes (http://www.imm.ki.se/CYPalleles/) resulting from the combination of multiple CYP2C19 SNP, we performed on −3402, −806, and +681 SNP the haplotype analysis by means of the Arlequin software. Table 3 reports the possible haplotypes, their estimated frequencies and the corresponding CYP2C19 alleles. CYP2C19 genotype frequencies were inferred from the CYP2C19 *1, *2, and *17 classification. No statistically significant association was found between *H. pylori* eradication efficacy and CYP2C19 genotypes, considering patients overall ($\chi^2=2.39$, *p*/ns) or only those infected by Cla^S strains ($\chi^2=2.12$, *p*/ns).

All studied cytokine gene polymorphisms were in Hardy–Weinberg equilibrium. IL-1B −31 C>T, IL-1RN VNTR, IFN-γ+874 A>T, TNF-α −1031 T>C, TNF-α −857 C>T, TNF-α −376 G>A, TNF-α −308 G>A and IL-12A+6686 G>A were not correlated with triple therapy failure or success, both considering whole patients or only those infected by Cla^S strains.

Table 4 reports the overall genotype and allele frequencies of the IL-10 −1082 A>G, −819 C>T, and −592 C>A SNP. There was a complete linkage disequilibrium between the −819 and −592 SNP ($\chi^2=165.47$; $p<0.01$). These two SNP were in linkage, although not absolute, with the −1082 polymorphism ($\chi^2=37.76$; $p<0.01$). A significant association was found between IL-10 −819 or IL-10 −592 SNP and eradication success considering patients overall ($\chi^2=8.98$; $p<0.05$): the IL-10 −819 T/T or IL-10-592 AA homozygotes were more frequently found among eradicated (13.3%) than among not eradicated subjects (1.8%). Considering Cla^S *H. pylori*-infected subjects only, this association was weaker and not statistically significant ($\chi^2=0.74$, *p*/ns).

Table 2 Genotype and Allele Frequencies of the Three CYP2C19 SNP Studied

CYP2C19 SNP	Genotypes (Frequency)			Alleles (Frequency)		HW Equilibrium
−3402	C/C (0.515)	C/T (0.426)	T/T (0.059)	C (0.728)	T (0.272)	χ^2=0.22; *p*/ns
−806	C/C (0.515)	C/T (0.426)	T/T (0.059)	C (0.728)	T (0.272)	χ^2=0.22; *p*/ns
+681	G/G (0.748)	G/A (0.233)	A/A (0.019)	G (0.864)	A (0.136)	χ^2=0.01; *p*/ns

Patients were Considered Overall (*HW* Hardy–Weinberg)

Table 5 reports the possible IL10 haplotypes and their estimated frequency in the overall studied population. Estimated haplotypes were used to infer the extended genotypes (combination of two haplotypes) for IL-10. A significant positive association was found between the homozygosity for the ATA haplotype (ATA/ATA genotype) and triple therapy success (Fisher's exact test $p<0.05$, odds ratio=7.33, 95% CI, 0.92–58.70), being ATA/ATA genotype more frequent in eradicated than in not eradicated patients (Fig. 2).

A significant association was found among patients infected by Cla^S strains and the IL-12B+15485 SNP (χ^2=6.35; $p<0.05$): The C/C homozygotes were absent in eradicated patients while recorded with a prevalence of 13.3% in not eradicated subjects.

A significant association was found between TNF-α −238 genotypes and *H. pylori* eradication outcome considering patients overall (χ^2=3.90; $p<0.05$; odds ratio=3.26, 95% CI=0.92–11.57) or only Cla^S *H. pylori*-infected subjects (χ^2=3.72; p=0.05).

Severe antral inflammatory grade was correlated with a higher rate of successful triple therapy (χ^2=10.43, $p<0.001$; odds ratio=4.31; 95% CI, 1.75–10.62; Fig. 3).

To verify whether cytokines' SNP exert an independent role over inflammation in conditioning eradication, we performed logistic regression analysis. Only Cla^S-infected patients were considered in the analysis; predictor variables were TNF-α −238 and IL12B+15485 genotypes, IL10 ATA/ATA as present or absent, and antral gastritis grade. Table 6 reports the results of the analysis. Only gastritis grade was confirmed to be significantly correlated with the response to therapy, cytokines genes polymorphisms playing a less relevant role.

Table 3 CYP2C19 Haplotypes Derived from the −3402C>T, −806C>T, and +681G>A SNP

Haplotype[a]	Frequency	SD	Allele
CCG	0.59	0.05	CYP2C19 *1
TTG	0.27	0.03	CYP2C19 *17
CCA	0.14	0.03	CYP2C19 *2

Frequencies were estimated by means of the Arlequin statistical software. Each of the estimated haplotyes corresponded to a specific CYP2C19 allele whose nomenclature is reported in the Web site http://www.imm.ki.se/CYPalleles/.

[a] For example, CCG stands for −3402C −806C +681G and defines CYP2C19 allele *1.

Discussion

Triple therapy allows *H. pylori* to be eradicated in about 75–80% of the cases.[42] Among the causes of the unsuccessful rate, bacterial as well as host determinants are involved.

In this study, we verified whether there was any association between the efficacy of triple therapy and (1) *H. pylori* clarithromycin resistance or virulence determinants; (2) CYP2C19 polymorphism, as this might affect omeprazole metabolism and, consequently, its effects on gastric acid secretion; (3) cytokines genes polymorphisms, as they might affect host response to the infection.

Bacterial resistance to Amoxycillin, one of the two antibiotics used in triple therapy, was not considered in this study, as its prevalence among Italian patients was demonstrated to be very low.[43,44] By contrast, clarithromycin resistance is much more prevalent and suggested to be mainly involved in causing eradication failure. This antibiotic resistance is due in 95% of the cases to five different point mutations in the 23S rRNA gene of *H. pylori*. We tested these five mutations in bacterial strains from 18 eradicated and 55 not eradicated patients. Positive findings were obtained in 23 clinical isolates. Among the five studied point mutations, the A2143G, the A2142G, and the A2142C were detected in 60.9, 30.4, and 8.7% of the cases respectively, whereas the A2115G and the G2141A substitutions were never found. The frequency 23S rRNA mutations found by us in the present series of cases is in agreement with that described by De Francesco et al.[45] in Italian patients and by Megraud[46] in other European series.

The successful rate of *H. pylori* eradication therapy was significantly lower in patient infected by Cla^R strains, which were recorded only in non-eradicated subjects (41.8%). We estimated that patients infected by Cla^R strains had a risk of triple therapy failure, 1.7 times higher than that of patients infected by Cla^S strains. Our data are in agreement with findings from Megraud[46] who reviewed data from 20 different recent studies (1,975 patients),

Table 4 Genotype and Allele Frequencies of the IL-10 −1082 A>G, −819 C>T, and −592 C>A SNP

IL-10 SNP	Genotypes (Frequency)			Alleles (Frequency)		HW Equilibrium[a]
−1082	A/A (0.29)	A/G (0.51)	G/G (0.20)	A (0.545)	G (0.455)	*p*/ns
−819	C/C (0.66)	C/T (0.27)	T/T (0.07)	C (0.795)	T (0.205)	*p*/ns
−592	C/C (0.66)	C/A (0.27)	A/A (0.07)	C (0.795)	A (0.205)	*p*/ns

The three polymorphisms were all in Hardy–Weinberg equilibrium.
[a] Exact test using a Markov chain

determining an overall 70% decrease in the eradication rate (18.3 vs 87.8%) in Cla^R-infected patients.

Cla^R strains were more frequently encountered among females (47.2%) than males (13.9%), in agreement with previous data of the literature.[44] These findings might be consequent to a higher incidence of genital tract infections among females and a consequent larger use of clarithromycin before *H. pylori* triple therapy, causing a selection of 23S rRNA mutants.

Among the bacterial-related factors causing eradication failure, the virulence determinants CagA and VacA have also been investigated. Some authors found an association between a lower eradication efficacy and *H. pylori* strains missing the *cagA* gene or bearing the s2 and m2 *vacA* alleles,[47,48] whereas other authors did not.[49,50] Our findings did not provide any evidence for an association between eradication failure and *cagA* or s and m *vacA* alleles, not between these virulence determinants and 23S rRNA mutations, in agreement with previous data in the literature.[47]

Triple therapy combines two antibiotics and a proton pump inhibitor, and these drugs have been demonstrated to synergize in the eradication of the infection. Inter-individual variations in CYP2C19 gene, which encodes cytochrome P450 2C19, the most relevant liver enzyme for PPI metabolism, were shown to affect omeprazole metabolism and the response to triple therapy.[39] Beside the wild type CYP2C19 *1 allele, several CYP2C19 alleles have been described so far, but only two are significantly represented in white populations: the *2 allele defective of any cytochrome P450 2C19 activity and the *17 allele associated with increased enzymatic activity.[40] The existence and distribution of the CYP2C19 *17 allele has not jet been described in the Italian population.

We studied three CYP2C19 SNP (CYP2C19-3402 C>T, CYP2C19-806 C>T, CYP2C19+681 G>A), the combination of which defines the CYP2C19 *1, *2, *17 alleles. As described by Sim et al.,[40] we found a complete linkage disequilibrium between CYP2C19-3402 and CYP2C19-806 SNP. On the basis of the observed genotypes distributions of the three SNP, we estimated the possible CYP2C19 haplotypes and their frequency in our population by means of Arlequin 2.000 software. Three different haplotypes (CCG, CCA, TTG) corresponding to the CYP2C19 *1, *2 and *17 alleles were found. The CYP2C19 *17 allele frequency was 27%; this was similar to that of Polish (27%),[51] but higher that that reported in Swedish and Ethiopians (18%).[40] We did not find any significant association between CYP2C19 polymorphism and eradication success. This finding, although made in a limited number of cases, suggests that CYP2C19 genetic polymorphism play a minor role in affecting triple therapy success, in agreement with findings from Polish patients.[51]

Table 5 Possible IL10 Haplotypes and Their Estimated Frequency in the Overall Studied Population

Haplotype[a]	Frequency	SD
GCC	0.46	0.04
ACC	0.34	0.03
ATA	0.20	0.03

[a] For example, ATA stands for −1082A −819T −592A

H. pylori infection if not treated causes invariably chronic inflammation. The type and grade of gastric mucosal inflammation, as well as the clinical outcomes of *H. pylori* infection, depend on both *H. pylori* virulence determinants and on the genetic background of the host, particularly in cytokines genes.[19–21,23,24]

In the course of triple therapy, the host–*H. pylori* equilibrium is deeply perturbed, and some authors have postulated that, in such phase, the host immune system might interplay with the pharmacological treatment in determining the eradication success.[52] We have evaluated the possible association between triple therapy efficacy and

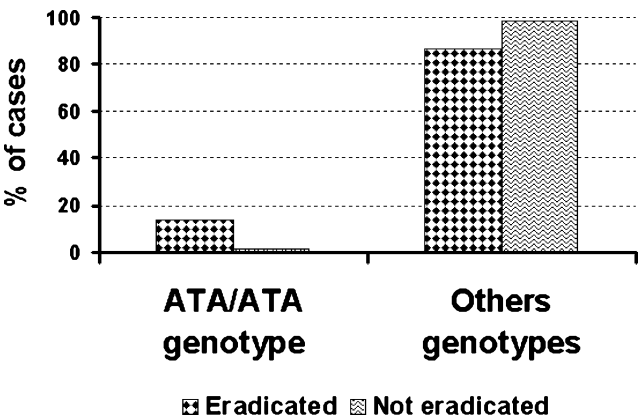

Figure 2 IL-10 ATA/ATA homozygous frequency in *H. pylori* eradicated and not eradicated patients.

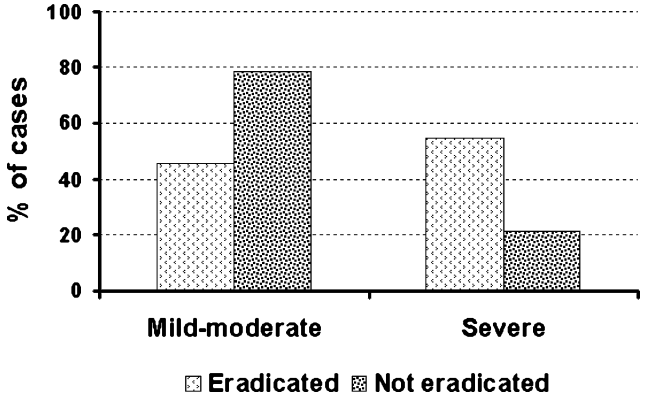

Figure 3 Antral gastritis grade among *H. pylori* eradicated and not eradicated subjects. Cases with mild or moderate gastritis were grouped together because of the low number (n=2) of cases of mild gastritis.

polymorphisms of a series of genes coding for cytokines (IL-1β, IL-1RN, Il-10, IL-12, IFNγ, and TNFα) known to be involved in the gastric mucosal inflammatory response to *H. pylori* infection. Triple therapy success correlated only with IL-10, IL-12B, and TNFα, being the other polymorphisms studied of no relevance.

Of particular interest are the polymorphisms of IL10 at −1082, −819, and −592 positions, as the derived haplotypes seem to affect IL10 production on the one hand and *H. pylori* infection outcome on the other. Patients bearing the ATA/ATA genotype are IL-10 low producers, develops more severe inflammation, and they are at higher risk of cancer development.[29] In agreement with the assumption that a reduced IL-10 production might favor eradication, we found a higher frequency of patients with ATA/ATA genotype in eradicated (13.3%) than in not eradicated patients (1.8%).

TNF-α and IL-12 might enhance the inflammatory infiltrate in infected gastric mucosa. We studied five TNF-α polymorphisms of the promoter region that might affect transcription and, consequently, the amount of the translated protein. Only the SNP at −238 position was associated with the eradication success, which was reached in a higher percentage of cases among those bearing the A allele. The role of this allele in affecting transcription remains unclear, and unclear remains also the role of IL-12B+15485 A>C SNP, found to be correlated with eradication in our series. IL-10, TNF-α, and IL-12 gene polymorphisms may affect eradication because they might influence the mucosal inflammatory grade, which was clearly demonstrated to be correlated with eradication: The worse was the inflammatory grade, the higher was the probability of eradication success.

Our data provide evidence that gastric mucosal inflammation and some host genetic polymorphisms are involved in determining the eradication success. At the univariate statistical analysis, besides antral inflammatory grade, IL-10 genotype, TNF-α −238, and IL12B+15485 SNP were found to significantly correlate with *H. pylori* eradication. At the multivariate statistical analysis, only inflammatory grade was confirmed to significantly affect eradication success. Any single SNP, conditioning the amount of the encoded cytokine, has probably its own significant but limited role in the overall eradication process, as it represents a portion of the whole genetic inter-individual variability modulating the inflammatory response to *H. pylori* infection.

In conclusion, the bacterial determinant causing triple therapy failure is clarithromycin resistance, being virulence genes not involved. The host-related factors that favor eradication are those linked to inflammation: a higher inflammatory infiltrate in the mucosa, possibly favored by genotypes able to down regulate the anti-inflammatory cytokine response, enhance the chance of eradication success.

Table 6 Logistic Regression Analysis

Parameter	EXP (B)	95% CI	p Value
IL12B+15485 ref	1		
IL12B+15485 A/A	0.0003	0.00–4.06E+36	p/ns
TNF-α-238 ref	1		
TNF-α −238 G/A	0.53	0.015–18.45	p/ns
IL10 ref	1		
IL-10 ATA/ATA	0.30	0.016–5.63	p/ns
Antral gastritis severe	1		
Antral gastritis mild/ moderate	6.48	1.20–35.01	$p<0.05$

Dependent variable: response to *H. pylori* eradication triple therapy
Exp(B) is referred to as the probability of eradication failure

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DISCUSSION

Kimberly M. Dalal, M.D. (Travis AFB, CA): I would like to commend Dr. Zambon and Dr. Pedrazzoli and their colleagues for their work and thank them for submitting their manuscript to me for comment.

They examined the issue of H. pylori eradication failure, which is clinically important as this may lead to not only peptic ulcers but also gastric adenocarcinoma or MALToma in a subset of patients. They ascertained the association between triple therapy efficacy and various methods of failure, including clarithromycin–resistance genes, bacterial virulence genes, and host polymorphisms of PPI metabolism as well as various cytokines. Treatment failure was noted to be significantly correlated with clarithromycin resistance and antral gastritis grade. Moreover, inflammation seemed to favor eradication. I have two questions.

You demonstrated that severe antral inflammatory grade is correlated with a higher rate of successful therapy, and you also showed that patients bearing the ATA/ATA genotype who are low IL–10 producers and develop more severe inflammation were found to be at a higher frequency in the eradicated than the non–eradicated group. How do you reconcile this role of inflammation with eradication in some patients but also a higher risk of cancer development in others?

Sergio Pedrazzoli, M.D. (Padova, Italy): We found that more inflammation was better and was due to the onset of cytokines locally. Now, there are enough patient studies to tell you what happens with cancers in these patients. On the other hand, the ATA haplotype is significantly associated with lower production of interleukin 10, and this may explain why the result was different in this kind of patient.

Dr. Dalal: My second question is: you mentioned that bacterial resistance to amoxicillin among Italian patients is low while clarithromycin resistance is more prevalent. How will your data that you have shown today change your approach to patient management in Italy?

Dr. Pedrazzoli: The findings from the Maastricht III Consensus Report indicated that you have to change therapy when you have a prevalence higher than 20%. You need to know if the patient is resistant and then change therapy. We in Italy are in the range lower than 20%. But when you have a prevalence that is higher, you need to look for resistance. Otherwise you treat the patient, observe the patient, and if the patient does not recover, you can change therapy.

Jonathan F. Critchlow, M.D. (Boston, MA): You had a high level of resistant patients. You had a 45% resistance rate.

Dr. Pedrazzoli: Sorry, this was a mistake. I am not the specialist on the matter because he was not able to come here. When preparing the discussion, I posed the same question. Allow me to explain why.

It is a selection bias because we selected from among 800 patients a group of patients who responded and a group of patients who did not respond and compared the pattern of patient characteristics and H. pylori characteristics that would influence the response. But our response rate to triple therapy is about 80–85%, as is usually observed.

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Suberoyl Bishydroxamic Acid Inhibits Cellular Proliferation by Inducing Cell Cycle Arrest in Carcinoid Cancer Cells

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Abstract Carcinoid cancers arise from the neuroendocrine cell system of the gastrointestinal tract, lungs, and other organs. Hepatic metastases are common, and patients often suffer from endocrinopathies secondary to tumor secretion of various hormones and peptides. As complete surgical resection is often not possible because of widespread disease, new therapeutic and palliative treatments are needed. In this study, we characterized the effects of suberoyl bishydroxamic acid (SBHA), a histone deacetylase inhibitor, on the growth and neuroendocrine phenotype of carcinoid cancer cells. SBHA treatment of human gastrointestinal and pulmonary carcinoid cancer cells resulted in a dose-dependent inhibition of cell proliferation. Western blot analysis showed a decrease in cyclin D1 and an increase in p21 and p27, indicating that the mechanism of this growth inhibition is cell cycle arrest. Furthermore, SBHA treatment suppressed two neuroendocrine tumor markers, chromogranin A and achaete-scute complex-like 1. These changes in the growth and neuroendocrine phenotype of carcinoid cells were associated with activation of the Notch1 signaling cascade. We conclude that SBHA shows promise as a potential anticancer agent for the treatment of patients with advanced carcinoid tumor disease.

Keywords Suberoyl bishydroxamic acid (SBHA) · Suberoylanilide hydroxamic acid (SAHA) · Carcinoid tumors · Neuroendocrine tumors · Notch1 · Achaete-scute complex-like 1 (ASCL1)

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Introduction

Carcinoid cancers arise from the disseminated neuroendocrine cell system of the gastrointestinal (GI) tract, lungs, and other organs. Carcinoid tumors are uncommon, with an incidence of 1.5 cases per 100,000 people in the United States.[1,2] Carcinoids frequently metastasize to the liver, and many patients have debilitating symptoms related to tumor secretion of various bioactive amines and peptides. Complete surgical resection is often not possible because of widespread disease, and other anticancer treatments such as radiation and chemotherapy are largely ineffective in carcinoids.[3,4] Therefore, new curative and palliative treatments for patients with advanced carcinoid cancer disease are needed.

Several signal transduction pathways have been shown to regulate the growth and phenotype of carcinoids and other neuroendocrine tumors. These include the Raf-1 pathway,[5] GSK3β pathway,[6] and Notch1 pathway.[7] Activating or suppressing these signaling pathways can have antitumor effects in carcinoid cancer cells. We have previously shown that ectopic expression of Notch1 in carcinoid cells resulted in suppression of cell growth and

hormone production,[7–10] suggesting that Notch1 is a potential therapeutic target for the treatment of carcinoid tumor disease. Until recently, however, no small molecules capable of activating Notch1 signaling in carcinoids have been identified.

Histone deacetylase (HDAC) inhibitors are a class of molecules that modulate gene transcription by increasing histone acetylation, thereby altering chromatin structure.[11] Numerous HDAC inhibitors have shown promising anti-neoplastic effects in preclinical and clinical studies in a variety of cancers.[12] Recently, Stockhausen and colleagues reported that HDAC inhibition resulted in increased Notch1 expression in neuroblastoma cells.[13] The aim of the current study was to determine the effects of suberoyl bishydroxamic acid (SBHA), an HDAC closely related to suberoylanilide hydroxamic acid (SAHA),[14] on Notch1 signaling, cell growth, and neuroendocrine tumor marker expression in human carcinoid cancer cells.

Materials and Methods

Cell Culture

BON human GI carcinoid cancer cells, kindly provided by Drs. B. Mark Evers and Courtney M. Townsend, Jr. (University of Texas Medical Branch, Galveston, TX, USA), and H727 human lung carcinoid cancer cells (American Type Culture Collection, Manassas, VA, USA) were maintained as previously described.[15,16]

Western Blot Analysis

Carcinoid cancer cells were treated with SBHA (Biomol, Plymouth Meeting, PA, USA) for 48 hours and whole-cell lysates were prepared as previously described.[15] Total protein concentrations were quantified with a bicinchoninic acid assay kit (Pierce Biotechnology, Rockford, IL, USA). Denatured cellular extracts were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), transferred onto nitrocellulose membranes (Schleicher and Schuell, Keene, NH, USA), blocked in milk, and incubated with appropriate antibodies. The antibody dilutions were: 1:1,000 for Notch1 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), mammalian achaete-scute homolog 1 (ASCL1; BD Biosciences, San Diego, CA, USA), chromogranin A (Zymed Laboratories, San Francisco, CA, USA), and cyclin D1 (Cell Signaling Technology, Danvers, MA, USA); 1:2,000 for p21 (Cell Signaling Technology) and p27 (Santa Cruz Biotechnology); and 1:10,000 for glyceraldehyde-3-phosphate dehydrogenase (G3PDH; Trevigen, Gaithersburg, MD, USA). Horseradish-peroxidase-conjugated goat antirabbit or goat antimouse secondary antibodies (Pierce Biotechnology) were used depending on the source of the primary antibody. For visualization of the protein signal, Immunstar (Bio-Rad Laboratories, Hercules, CA, USA) or SuperSignal West Femto (Pierce Biotechnology) kits were used according to the manufacturer's instructions.

Cell Proliferation Assay

Carcinoid cancer cell proliferation was measured by the MTT (methylthiazolyldiphenyl-tetrazolium bromide; Sigma-Aldrich, St. Louis, MO, USA) rapid colorimetric assay as previously described.[16] Briefly, cells were seeded in quadruplicate on 24-well plates and incubated for 24 h to allow cell attachment. The cells were then treated with SBHA in concentrations of 0 to 50 μM and incubated for up to 6 days. The MTT assay was performed by replacing the standard medium with 250 μL of serum-free medium containing MTT (0.5 mg/mL) and incubated at 37°C for 3 h. After incubation, 750 μL of dimethyl sulfoxide (Sigma-Aldrich) was added to each well and mixed thoroughly. The plates were then measured at 540 nm using a spectrophotometer (μQuant; Bio-Tek Instruments, Winooski, VT, USA).

Statistical Analysis

Analysis of variance (ANOVA) with Bonferroni post hoc testing was performed using a statistical analysis software package (SPSS version 10.0, SPSS, Chicago, IL). A P value of <0.05 was considered significant.

Results

SBHA Activates Notch1 Signaling in Carcinoid Cells

We have previously reported that active Notch1 protein is absent in GI carcinoid cancer cells, and that ectopic Notch1 expression leads to inhibition of tumor cell growth and hormone production.[7,9] Based on a recent report describing an increase in Notch1 protein levels in neuroblastoma cells after HDAC inhibition,[13] we hypothesized that the HDAC inhibitor SBHA might activate Notch1 signaling in carcinoid cells, with effects on cell proliferation and the neuroendocrine phenotype.

To assess the ability of SBHA to induce Notch1 expression in carcinoids, we performed Western blot analysis. At baseline, Notch1 protein signal was either absent or minimal in untreated GI and pulmonary carcinoid cancer cells, respectively (Fig. 1). SBHA treatment of GI carcinoid cells in concentrations as low as 5 μM resulted in induction of both full-length Notch1 and the Notch1 intracellular domain

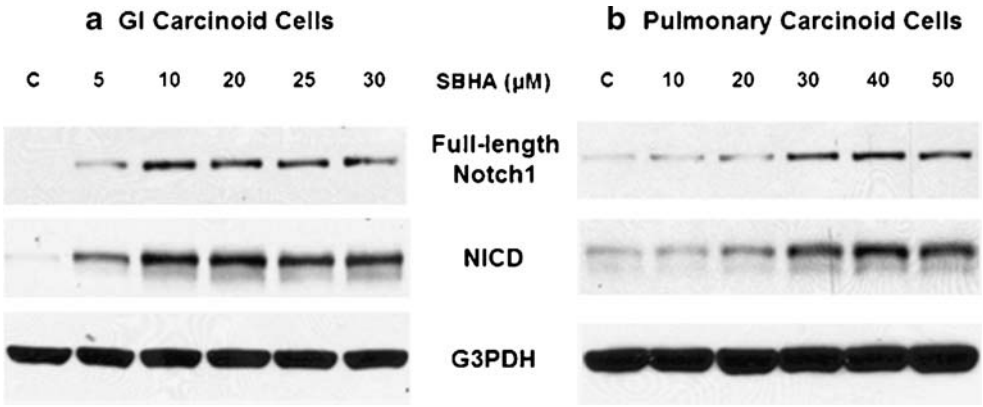

Figure 1 SBHA activates Notch1 in carcinoid cells. GI (**a**) and pulmonary (**b**) carcinoid cancer cells were treated with SBHA in the indicated concentrations for 48 h and whole cell lysates were immunoblotted for Notch1. At baseline, Notch1 protein was absent or barely detectable in both cell lines. VPA treatment resulted in an increase in full-length Notch1 and the active Notch1 intracellular domain (NICD). G3PDH was used as a protein loading control.

(NICD), the active form of the protein (Fig. 1a). Significant Notch1 induction was seen in pulmonary carcinoid cells at SBHA concentrations above 20 μM (Fig. 1b).

SBHA-Mediated Notch1 Activation Results in Suppression of Neuroendocrine Tumor Markers

We have previously shown that overexpression of active Notch1 in GI carcinoid cells results in suppression of achaete-scute complex-like 1 (ASCL1), a basic helix loop–helix transcription factor that regulates the neuroendocrine phenotype.[7,9] Based on these data, we expected to find a decrease in ASCL1 after Notch1 activation with SBHA. Indeed, SBHA treatment of GI and pulmonary carcinoid cells resulted in a decrease in ASCL1 protein (Fig. 2). Treatment of GI carcinoid cells with 30 μM of the drug for 2 days suppressed ASLC1 to an undetectable level (Fig. 2a).

We next examined the impact of SAHA on expression of another neuroendocrine tumor marker, chromogranin A. Chromogranin A is an acidic glycoprotein that is cosecreted with amines and peptides by carcinoids and other neuroendocrine tumors. Clinically, the presence of chromogranin A by immunohistochemistry can help confirm the histopathologic diagnosis of a neuroendocrine neoplasm, and serum chromogranin A levels are often monitored in patients as a metric of disease burden. As with ASCL1, SBHA treatment of carcinoid cancer cells suppressed levels of chromogranin A (Fig. 2). A dramatic decrease was seen in pulmonary carcinoid cells (Fig. 2b), with complete suppression after a 2-day treatment with 50 μM of SBHA. Compared to pulmonary carcinoid cells, the GI carcinoid cell line produces a greater amount of chromogranin A at baseline, and only modest inhibition of chromogranin A was seen after 48 h of treatment (Fig. 2a). Taken together, the observed changes in ASCL1 and chromogranin A expression indicate that SBHA alters the neuroendocrine phenotype of carcinoid cancer cells.

SBHA Inhibits Carcinoid Cancer Cell Proliferation

After confirming that SBHA activates Notch1 signaling and modifies the neuroendocrine phenotype in carcinoid cells, we were interested in measuring its effect on tumor cell growth. GI carcinoid cells treated with SBHA exhibited a profound dose-dependent inhibition of cell proliferation (Fig. 3a). Significant growth inhibition was seen after 4 days of exposure to 5 μM of SBHA. SBHA treatment of pulmonary carcinoid cells also resulted in dose-dependent growth suppression, although higher concentrations of the

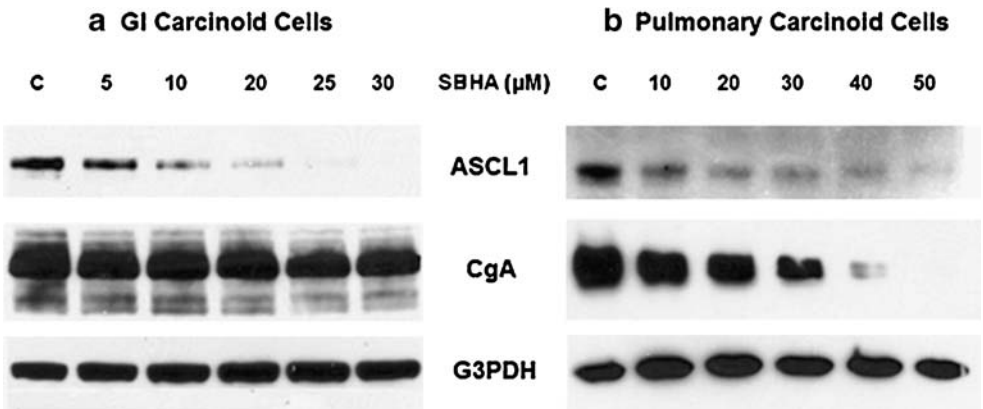

Figure 2 SBHA decreases levels of ASCL1 and chromogranin A in carcinoid cells. Treatment of GI (**a**) and pulmonary (**b**) carcinoid cells with SBHA for 48 h resulted in a decrease in protein levels of the neuroendocrine tumor markers ASCL1 and chromogranin A (CgA). Antibodies against G3PDH confirmed equal loading of the gel.

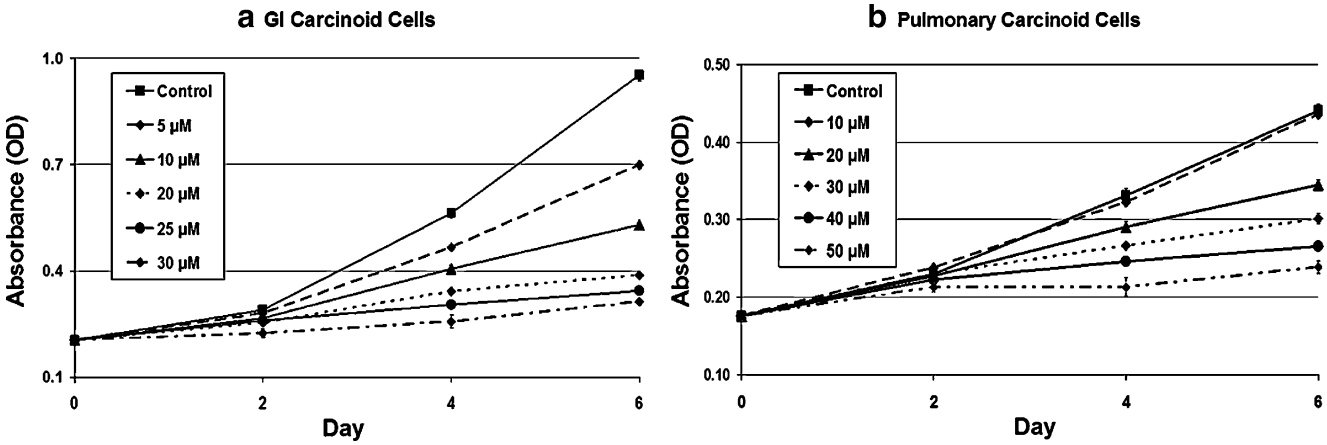

Figure 3 SBHA suppresses growth of carcinoid cancer cells *in vitro*. GI and pulmonary carcinoid tumor cells were treated with SBHA at the indicated concentrations for up to 6 days and cell viability was measured every 2 days with the MTT assay. SBHA inhibited cell proliferation in both GI (**a**) and pulmonary (**b**) carcinoid cell lines in a dose-dependent manner.

drug were required (Fig. 3b). Interestingly, the concentrations of SBHA that produced growth inhibition, 20–50 μM, were the same concentrations that yielded Notch1 induction as observed by Western blot (Fig. 1b).

The Mechanism of SBHA-Induced Carcinoid Growth Suppression is Cell Cycle Arrest

After establishing that SBHA inhibits cell proliferation in carcinoids *in vitro*, we were interested in determining the mechanism of action for this effect. Previous research has shown that activation of Notch1 in neuroendocrine tumor cell lines such as small cell lung cancer[17] and medullary thyroid cancer[18] leads to cell cycle arrest. To assess whether Notch1 activation with SBHA also results in decreased cell cycle transit, we performed Western blot analysis for various markers of cell cycle arrest. Progression through the cell cycle is controlled by cyclin-dependent kinases (CDKs), which are regulated by cyclins and CDK-inhibitors.[19] G1- phase cell cycle arrest is associated with increases in the Cip/Kip family CDK-inhibitors p21 and p27, and degradation of cyclin D1, which results in downregulation of CDK4. As shown in Fig. 4, SBHA treatment of GI and pulmonary carcinoid cells increased p21 and p27, and suppressed cyclin D1. These findings suggest that the growth inhibition induced by SBHA is mediated by cell cycle arrest at the G1 phase.

Discussion

Notch1 signaling is minimal or absent in neuroendocrine tumors such as small cell lung cancer,[17,20] medullary thyroid cancer,[18] and carcinoid tumors.[7–9] Notch1 overexpression in carcinoid and medullary thyroid cancer cell lines resulted in inhibition of cell growth and suppression of neuroendocrine tumor markers and hormones,[7,18] suggesting that in neuroendocrine malignancies Notch1 acts as a tumor suppressor.[10] However, pharmacologic methods to activate Notch1 signaling in carcinoid tumors *in vivo* have, until recently, not been available.

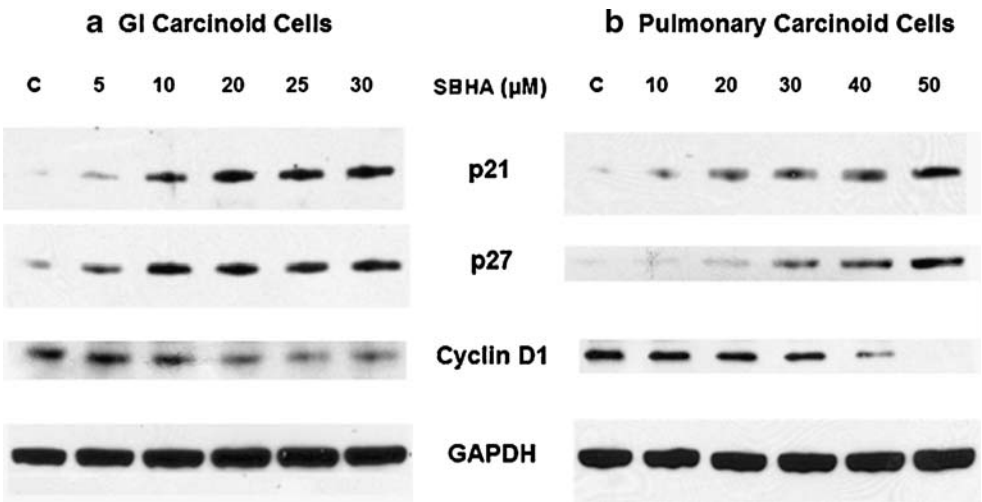

Figure 4 SBHA-mediated carcinoid growth inhibition is caused by cell cycle arrest. GI (**a**) and pulmonary (**b**) carcinoid cells were treated with SBHA for 48 h and Western blot analysis was performed to measure levels of cell cycle proteins. SBHA induced expression of cyclin-dependent kinases p21 and p27, and downregulated cyclin D1, indicating G1-phase cell cycle arrest.

In the current study, we report the novel finding that the HDAC inhibitor SBHA activates Notch1 signaling in human GI and pulmonary carcinoid cells. At baseline, Notch1 signaling is suppressed in these cells. However, with SBHA treatment, a dose-dependent induction of both full-length Notch1 and the active, cleaved form, NICD, is seen. The consequences of Notch1 induction with SBHA include suppression of the neuroendocrine tumor markers ASCL1 and chromogranin A. Furthermore, SBHA significantly inhibits cell proliferation in both carcinoid cancer cell lines. Western blot analysis indicated that the mechanism of this growth inhibition is cell cycle arrest. This is consistent with earlier studies, which demonstrated that overexpression of Notch1 in medullary thyroid cancer cells and small-cell lung cancer cells resulted in an increase in p21 and induction of cell cycle arrest.[17,18] Similar to our current results, Baradari et al.[21] also recently reported that treatment of carcinoid tumor cells with other HDAC inhibitors, including sodium butyrate and trichostatin A, led to an increase in p21 and p27, and a concomitant downregulation of cyclin D1, indicating the induction of G1-phase cell cycle arrest. SBHA is a close analogue of suberoylanilide hydroxamic acid (SAHA).

Of all the HDAC inhibitors, SAHA has undergone the most extensive clinical development as an antineoplastic agent. SAHA causes growth arrest and death in numerous malignant cell lines at concentrations that have minimal toxic effects in normal cells.[22] Currently, several clinical trials are underway, evaluating the efficacy of SAHA alone or in combination with other agents in the treatment of a variety of hematologic and solid tumors, including carcinoma of the colon and rectum, breast, lung, kidney, and prostate gland.[23] In October of 2006, the United States Food and Drug Administration approved the use of SAHA, which has the generic drug name of vorinostat, for the treatment of cutaneous T-cell lymphoma.[24] As phase I clinical trials have established the safety profile of the drug, our data suggest that SAHA may represent a promising new potential therapy for patients with advanced carcinoid cancer, a disease for which few effective treatments currently exist.

In summary, the HDAC inhibitor SBHA activates Notch1 signaling, suppresses the neuroendocrine tumor markers ASCL1 and chromogranin A, and inhibits cell proliferation in GI and pulmonary carcinoid cancer cells by inducing cell cycle arrest. We conclude that Notch1 activation with SBHA and other HDAC inhibitors is a promising target for the treatment of carcinoid tumor disease, warranting further research.

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Discussion

Kevin Staveley-O'Carroll, M.D. (Hershey, PA): Thanks very much, Dr. Greenblatt, for a very well-executed study and an excellent presentation. In your study you describe the consequences of treating two carcinoid tumor cell lines with SBHA, and you found that SBHA suppressed the growth in a dose-dependent manner, and you further showed with Western blot analysis that this was associated with cell cycle arrest. In addition to this, SBHA upregulated protein expression of Notch1, and from this you conclude that Notch1 activation with SBHA or other drugs may represent an important approach to the treatment of patients with carcinoid tumors. Clearly, this would be a very important finding, as we all know that there is no effective chemotherapy for carcinoid tumors. Along these lines I have a few questions for you.

As you noted, Notch1 is overexpressed in a number of cancers, gastric cancer, colon cancer, pancreatic cancer, and esophageal cancer, and at this meeting there are a number of posters that say perhaps we should be inhibiting Notch1 for these cancers. Now, you, on the other hand, propose that we stimulate Notch1 for carcinoid tumors. Is there any chance that as we treat carcinoid tumors in this way we might actually be promoting the growth of the other cancers?

David Y. Greenblatt, M.D. (Madison, WI): Thank you, Dr. Staveley-O'Carroll. As you noted, Notch1 is overexpressed in a variety of cancers, including several GI malignancies. Earlier research has shown that Notch is overexpressed in cancer of the pancreas and colon, and a poster at this meeting reported that Notch is overexpressed in gastric adenocarcinoma as well. And so certainly it is a concern. We wouldn't want to cure a patient's carcinoid tumor and end up sparking the growth of an occult pancreatic adenocarcinoma. We have studied the effects of SBHA treatment in two pancreatic adenocarcinoma cell lines, Panc-1 and MiaPaCa-2, and at the concentrations that we used for this carcinoid study, there was no effect on Notch signaling or pancreatic cancer cell growth. So, while it is certainly a valid concern, we have no evidence that SBHA is likely to cause an increase in the growth rate of adenocarcinomas.

Dr. Staveley-O'Carroll: Have you treated other cell lines with SBHA and have you used other HDAC inhibitors such as valproic acid?

Dr. Greenblatt: We have. We have looked at several other HDAC inhibitors, including valproic acid, sodium butyrate, and trichostatin A. Our research with valproic acid has progressed the furthest to date, and essentially we found very similar patterns of response to treatment. When we treated carcinoid cells with valproic acid, there was a dose-dependent inhibition of carcinoid cell growth, and the mechanism was also cell cycle arrest.

Dr. Staveley-O'Carroll: What barriers do you see ahead as you move to in vivo studies or even clinical trials with SBHA and other HDAC inhibitors?

Dr. Greenblatt: We have conducted experiments using valproic acid in a mouse xenograft model of carcinoid tumors, and in that study we found that treatment with valproic acid at nontoxic doses did slow the growth of these tumors. So, on the basis of those findings, we are currently accruing patients for a pilot clinical trial of valproic acid for the treatment of patients with advanced carcinoid tumor disease. We believe that HDAC inhibitors such as SBHA, SAHA, and valproic acid may represent a new form of targeted therapy for carcinoids and other neuroendocrine tumors. We are eager to perform additional animal studies with SBHA and SAHA, with the goal of eventually taking these drugs to clinical trials.

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Underexpression of Mineralocorticoid Receptor in Colorectal Carcinomas and Association with VEGFR-2 Overexpression

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Abstract
Background The human mineralocorticoid receptor (MR) is a steroid receptor widely expressed in colorectal mucosa. A significant role for the MR in the reduction of vascular endothelial growth factor receptor-2 (VEGFR-2) mRNA levels has been demonstrated *in vitro*. To evaluate a potential contribution of MR to colorectal carcinoma progression, we analyzed the expression of MR in relation to VEGFR-2.
Methods Fresh human colorectal cancer tissue and adjacent normal mucosa were harvested from 48 consecutive patients. MR and VEGFR-2 mRNA expression levels were determined by real-time reverse transcriptase–polymerase chain reaction and correlated with clinicopathological parameters.
Results A decline of MR expression was observed in all carcinomas compared to normal mucosa. Expression of MR was a median of 11-fold lower in carcinoma compared to the normal mucosa, irrespective of the location, size, stage, and differentiation. MR was a median of 20-fold underexpressed in carcinomas with VEGFR-2 overexpression vs only 9-fold in carcinomas with VEGFR-2 underexpression ($p=0.035$, Mann–Whitney test).
Conclusions These findings support the hypothesis that reduction of MR expression may be one of the early events involved in colorectal carcinoma progression. The inverse association between MR and VEGFR-2 expression in carcinoma suggests a potential tumor-suppressive function for MR.

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Keywords Colorectal cancer · Mineralocorticoid receptor · Vascular endothelial growth factor receptor-2 · Angiogenesis

Introduction

The human mineralocorticoid receptor (MR) is a member of the steroid/thyroid/retinoid receptor superfamily mediating aldosterone action and is widely expressed in colorectal mucosa.[1,2] In addition to the well-known action of MR in stimulating electrolyte and water transfer in epithelia of the kidney and colon,[1,2] it has been shown that aldosterone exerts powerful effects on blood vessels, acting on endothelial and smooth muscle cells.[3–6] Recently, Marumo et al.[7] revealed a novel biological activity for aldosterone, showing a significant role for the MR in the reduction of vascular endothelial growth factor receptor-2 (VEGFR-2) mRNA in bone marrow-derived progenitor cells.

Angiogenesis is essential for tumor growth, in particular for the supply of oxygen, nutrients, growth factors, hormones, enzymes, and dissemination of cancer cells to distal sites.[8–10] VEGF and its receptors play a crucial role in normal and pathologic angiogenesis. Activation of the VEGF/VEGFR axis triggers a signaling network that results in endothelial cell survival, mitogenesis, migration, and differentiation, as well as vascular permeability and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation.[10,11]

Among the VEGF receptors, the VEGFR-2 (also known as kinase domain region of FlK-1) is the major mediator of the mitogenic, angiogenic, and permeability-enhancing effects of VEGF.[12] The importance of VEGFR-2 in angiogenesis and hematopoiesis is demonstrated by the lack of vasculogenesis and failure to develop blood-islands and organized blood vessels in FlK-1-null mice, resulting in death *in utero*.[13]

In human colorectal carcinomas, VEGFR-2 expression has been reported both in vascular endothelial and malignant cells.[14,15] Acting as a positive angiogenic signal transducer, VEGFR-2 is involved in the proangiogenic switch of colorectal tumors from the adenoma stage.[16]

To evaluate the intriguing hypothesis that MR expression levels may have a potential contribution to sporadic colorectal carcinoma progression, we analyzed the expression of MR in relation to VEGFR-2 mRNA levels in human carcinoma samples.

Material and Methods

Fresh sporadic colorectal carcinoma tissue and normal mucosa were obtained from 50 consecutive patients. Cancer tissue was harvested, avoiding the tumor margin where adenomatous components may be present. Normal-appearing mucosa was dissected from the underlying submucosa, at least 5 cm distant from either side of the carcinoma. In the case of rectal carcinoma, normal-appearing mucosa was obtained only proximal to the carcinoma.

Ischemic time of harvested tissue was carefully monitored to assure high quality RNA. It has been suggested that ischemic time less than 20 min after tissue extirpation provides relatively stable gene expression levels.[16] The average ischemic time before stabilization of colorectal samples using RNA*later*™ RNA stabilization reagent (QIAGEN Inc., Mississauga, Ontario, Canada) was 15.6 min (range 7–24 min, 95th percentile: 20 min).

Table 1 Patient Characteristics

Patient Characteristics	*N*=48
Age	
Mean value±SD	66.5±11.9
Range	31–86
Gender	
Male	26 (54.2%)
Female	22 (45.8%)
Carcinoma location	
Colon	30 (62.5%)
Rectum	18 (37.5%)
Proximal colon	18 (37.5%)
Distal colon* and rectum	30 (62.5%)
Carcinoma size (cm)	
Mean value±SD	4.5±1.7
Range	1.8–10
Histological type	
Adenocarcinoma, colonic type	42 (87.5%)
Mucinous carcinoma	6 (12.5%)
AJCC carcinoma stage	
I (pT1–2, N0, M0)	8 (16.7%)
IIA (pT3, N0, M0)	18 (37.5%)
IIB (pT4, N0, M0)	3 (6.3%)
IIIA (pT 1–2, N1, M0)	0
IIIB (pT 3–4, N1, M0)	10 (20.8%)
IIIC (any pT, N2, M0)	4 (8.3%)
IV (any pT, any N, M1)	5 (10.4%)
Carcinoma differentiation	
Well	2 (4.2%)
Moderately	34 (70.8%)
Poorly	12 (25.0%)
Lymphatic invasion	
Present	24 (50.0%)
Absent	24 (50.0%)
Venous invasion	
Present	24 (50.0%)
Absent	24 (50.0%)
Perineural invasion	
Present	16 (33.3%)
Absent	32 (66.7%)

*Distal to the splenic flexure

According to the study protocol, two patients were excluded: the first, as the patient had carcinoma associated with Crohn's disease, and the second because the final histology showed a tubulovillous adenoma with high-grade dysplasia, but no carcinoma. Thus, 48 patients (male/female: 26/22; mean age 67, range 31–86 years) with colon (n=30) or rectal (n=18) neoplasia were eligible. The demographic, clinical, and pathological characteristics of the patients are summarized in Table 1.

The study was approved by the local research ethics committee and informed consent was obtained from the patients.

Isolation and Analysis of mRNA Levels

RNA was extracted from tissue samples stored in RNA*later*™ RNA stabilization reagent at −20°C, using the RNeasy® Mini Kit (QIAGEN Inc.), according to the manufacturer's instructions. Concentration and purity of RNA was determined by spectrophotometry and $A_{260/280}$ ratios. Complementary DNA with integrated removal of genomic DNA contamination was generated with the QuantiTect® Reverse Transcription Kit (QIAGEN Inc.), according to the manufacturer's protocol.

The quantitative analysis of MR and VEGFR-2 mRNA expression levels was performed by real-time polymerase chain reaction (Stratagene Mx30000P® system) using the QuantiTect® SYBR® Green PCR Kit (QIAGEN Inc.). The 18S ribosomal RNA (QIAGEN Inc.) level was used for sample standardization. The primer sequences for the real-time polymerase chain reaction were as follows: MR sense, 5′-GAGGCTTCAGGATGCCATTA-3′; MR antisense, 5′-GCTCCTCGTGAATCCCTTTT-3′, with an expected product size of 238 bp; VEGFR-2 sense, 5′-GGTGTTT TGCTGTGGGAAAT-3′; VEGFR-2 antisense, 5′-AAAC GTGGGTCTCTGACTGG-3′, with an expected product size of 186 bp. The primers were obtained from Invitrogen™. The thermal cycling parameters were 95°C for 15 min for HotStarTaq DNA Polymerase activation, followed by 40 cycles of 15 s at 94°C for denaturation, 30 s at 60°C for annealing, and 30 s at 72°C for extension. Each sample was analyzed in triplicate. The PCR products were also separated on a 2% agarose gel for qualitative analysis (Fig. 1).

Statistical Analysis

The nonparametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables. Chi-square or Fisher's exact tests were applied for analysis of categorical variables. Median values were considered for continuous variables when their values' distribution was skewed. The level of statistical significance was set at $p<0.05$. The analyses were performed using statistical software (Stata for Windows, Stata Corporation; College Station, TX, USA).

Results

Decreased MR mRNA expression was observed in all carcinomas compared to normal mucosa samples. The carcinoma/mucosa MR mRNA expression ratio ranged from 0.00424 to 0.338 (mean value: 0.11; median value: 0.09) (Fig. 2), meaning that MR was 3- to 236-fold less expressed in carcinoma compared to the normal mucosa. In

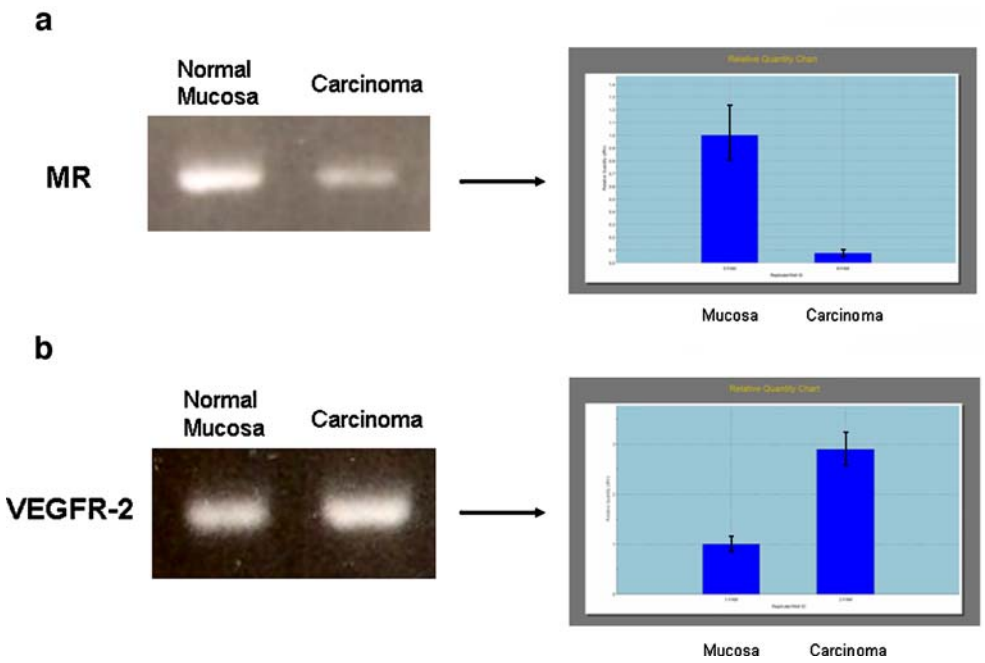

Figure 1 Representative examples of agarose gels of **a** MR and **b** VEGFR-2 reverse transcriptase PCR (RT-PCR) products are shown in the left panels. Values obtained by densitometric analysis of real-time RT-PCR for MR and VEGFR-2 in carcinoma are expressed as relative values to those obtained in the normal mucosa in the right panels. Each sample was analyzed in triplicate. The error bars reflects the deviation in the replicates.

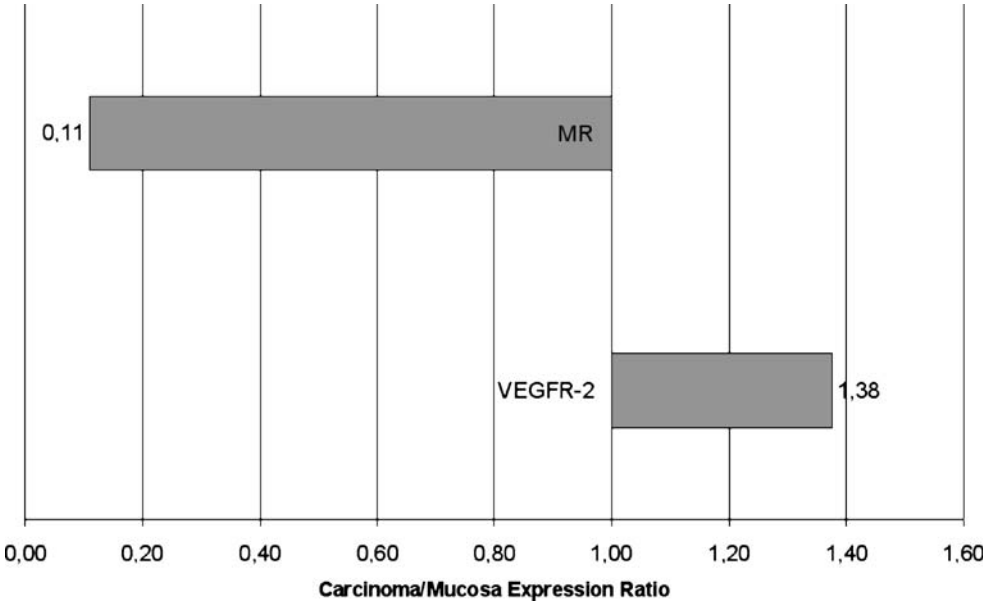

Figure 2 Expression of MR and VEGFR-2 mRNA in carcinoma (mean values). Carcinoma/mucosa expression ratio values of less than 1 denote that the carcinoma receptor is underexpressed compared to normal mucosa.

particular, the carcinoma/mucosa MR expression ratio was on average 0.08 (median value: 0.09) in early stage (stage I) carcinoma cases (Fig. 3).

No association was found between cancer MR expression and carcinoma location, size, stage, differentiation, and lymphatic, venous or perineural invasion.

The carcinoma/mucosa VEGFR-2 mRNA expression ratio ranged from 0.0792 to 11.5 (mean value: 1.38; median value: 0.95) (Fig. 2). The median carcinoma/mucosa VEGFR-2 mRNA expression ratio by stage was as follows: 0.4 in stage I, 1.1 in stage IIA–B, 1.1 in stage IIIA–C, and 1.4 in stage IV carcinomas (p=0.11; Kruskal–Wallis test). Carcinoma VEGFR-2 expression was significantly associated with lymphatic invasion (p=0.019, Mann–Whitney test). Specifically, carcinoma/mucosa VEGFR-2 mRNA expression ratio was a median of 0.6 in carcinomas without detectable lymphatic invasion and doubled (a median of 1.2) in carcinomas with lymphatic invasion.

No other demographic, clinical, or pathological variables showed a significant association with VEGFR-2 expression.

Two groups were defined in relation to VEGFR-2 expression: carcinomas with VEGFR-2 overexpression where the carcinoma/mucosa mRNA expression ratio was >1 and carcinomas with VEGFR-2 underexpression where the ratio was ≤1. Consequently, 15 cases (31%) showed VEGFR-2 overexpression.

Analyzing MR expression in relation to VEGFR-2 expression status, we found that MR expression was a

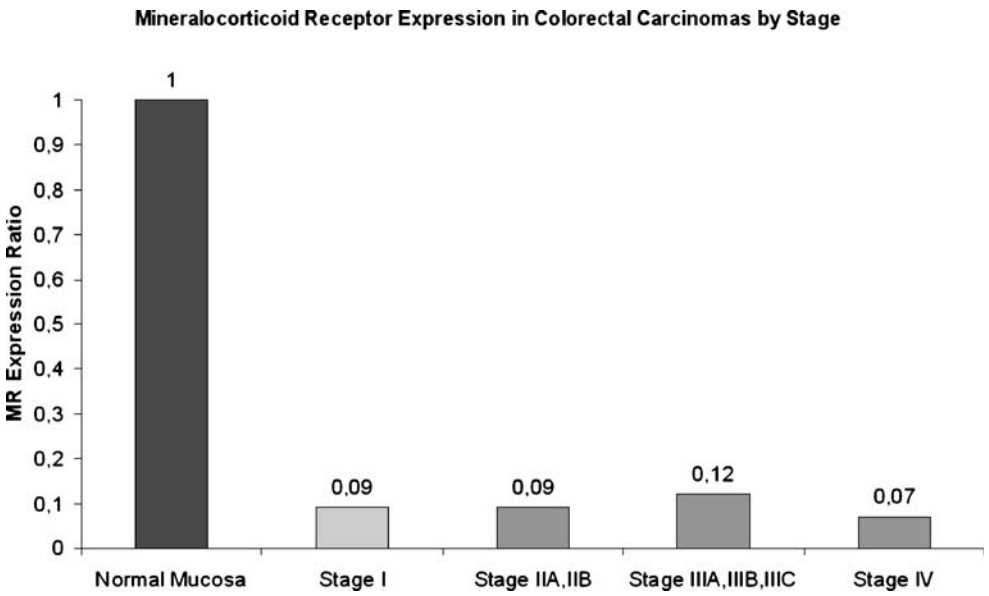

Figure 3 MR is markedly underexpressed even in early stage carcinomas compared to normal mucosa (median values).

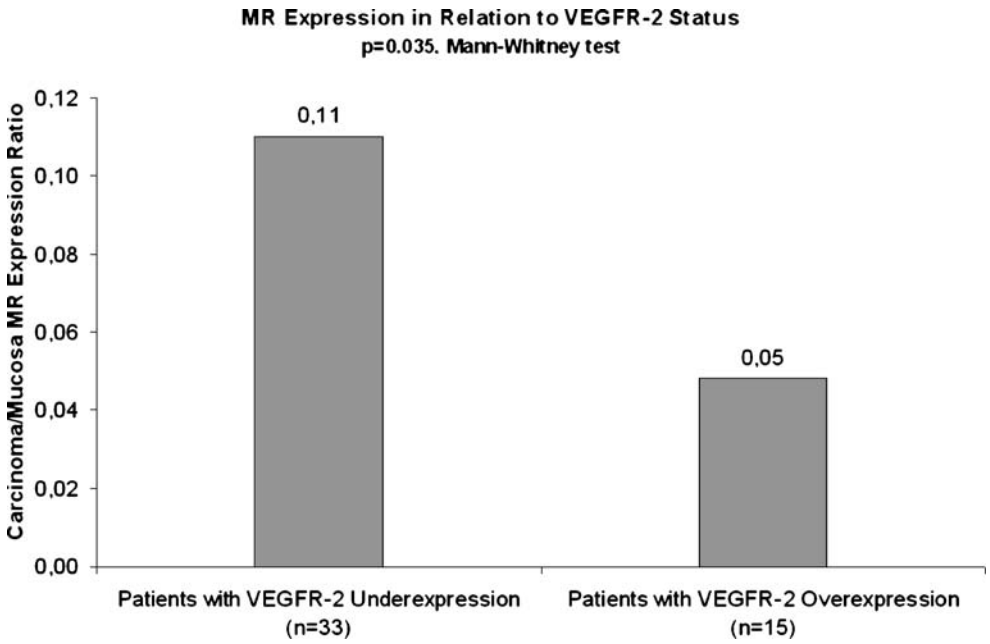

Figure 4 Expression of MR is more than twofold lower in colorectal carcinomas with VEGFR-2 overexpression (median values).

median 20-fold lower in carcinomas with VEGFR-2 overexpression vs only 9-fold lower in carcinomas with VEGFR-2 underexpression (p=0.035, Mann–Whitney test) (Fig. 4).

Thus, we analyzed the association between MR expression and VEGFR-2 status relative to various pathological variables, as shown in Table 2. Interestingly, MR expression was significantly lower in three categories of tumor with VEGFR-2 overexpression: right-sided (p = 0.019) (Fig. 5a), poorly differentiated (p = 0.040) (Fig. 5b), and lymph node metastatic carcinomas (p=0.021, Mann–Whitney test) (Fig. 5c).

Discussion

The present study demonstrates a significant inverse association between MR and VEGFR-2 expression in human colorectal carcinoma. In particular, expression of MR was more than twofold lower in colorectal carcinomas with VEGFR-2 overexpression. This observation may be compatible with a potential tumor-suppressive function for MR.

The role that MR expression may play in cancer progression is an intriguing current topic of research. Over

Table 2 Analysis of the Association Between MR Expression and VEGFR-2 Status in Relation to Pathological Variables

Variables	Carcinoma/Mucosa MR mRNA Expression Ratio, Median Values (Number of Cases)		
	VEGFR-2 Underexpression	VEGFR-2 Overexpression	p Value
Carcinoma location			
Colon	0.12 (n=21)	0.05 (n=9)	NS
Rectum	0.10 (n=12)	0.05 (n=6)	NS
Proximal colon	0.26 (n=9)	0.05 (n=9)	0.019*
Distal colon	0.09 (n=24)	0.05 (n=6)	NS
AJCC carcinoma stage			
I	0.09 (n=7)	0.08 (n=1)	NS
IIA, IIB	0.09 (n=15)	0.08 (n=6)	NS
IIIA, IIIB, IIIC	0.13 (n=9)	0.04 (n=5)	NS
IV	0.12 (n=2)	0.04 (n=3)	NS
Carcinoma differentiation			
Well–moderately	0.09 (n=26)	0.05 (n=10)	NS
Poorly	0.11 (n=7)	0.04 (n=5)	0.040*
Lymph node metastases			
Absent	0.09 (n=23)	0.08 (n=7)	NS
Present	0.13 (n=10)	0.04 (n=8)	0.021*

*Mann–Whitney test; NS: not significant.

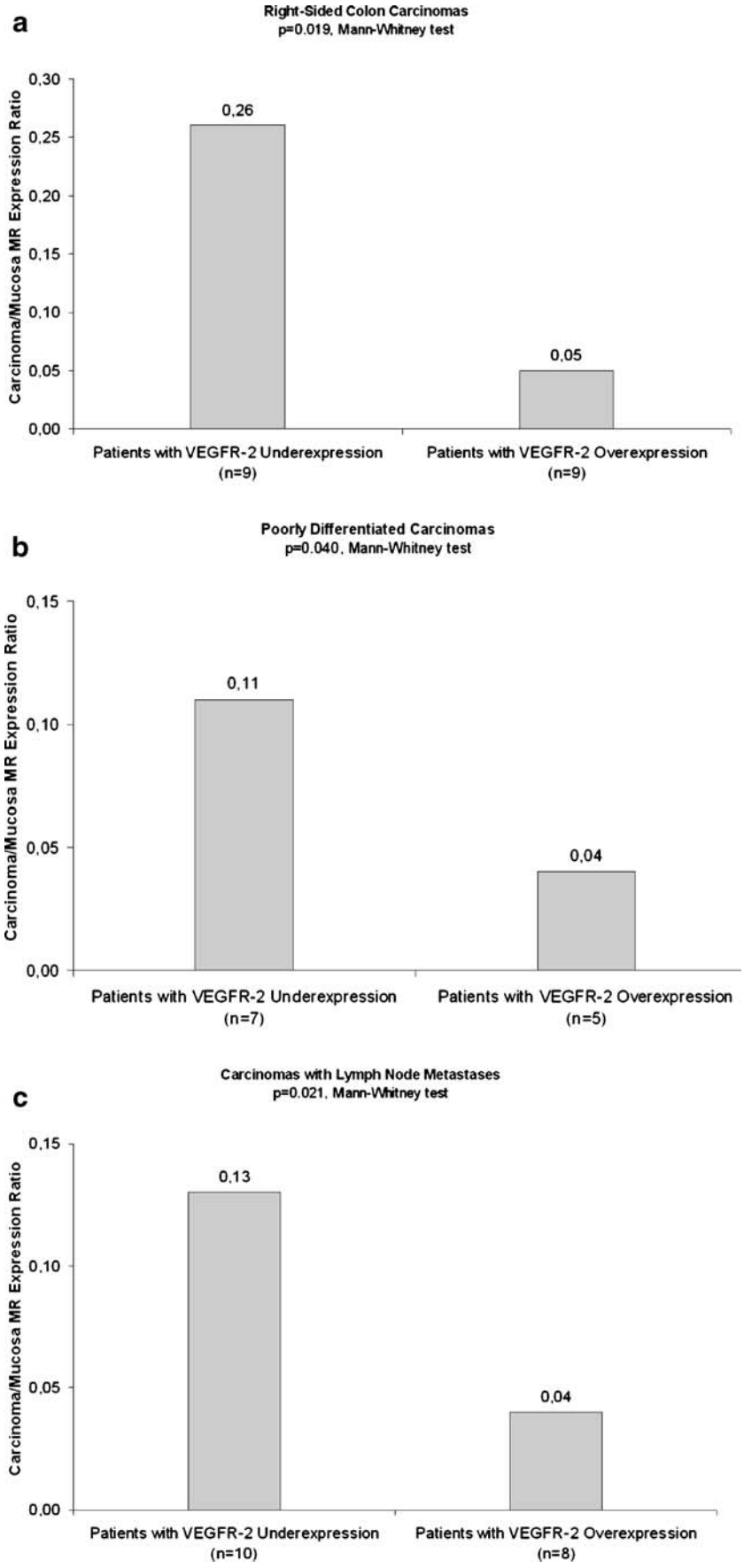

Figure 5 MR expression in relation to VEGFR-2 status in patients with **a** right-sided, **b** poorly differentiated, and **c** lymph node metastatic carcinomas (median values).

the past years, it has been shown that MR may act directly on the vascular endothelial cells.[3–6,17] Vascular endothelium is intimately linked to capillary formation, repair, and remodeling of microcirculation.[18,19] Some of these activities characterize angiogenesis. Neoangiogenesis is essential for tumor growth and dissemination of malignant cells to distal sites. This process is regulated by the VEGF/VEGFR pathway.[20,21] Recently, Marumo et al.[7] showed a significant role for the MR in the reduction of VEGFR-2 mRNA in bone marrow-derived precursor cells, which may have an inhibiting effect on endothelial progenitor cell differentiation. Increasing evidence has shown that endothelial progenitor cells play a crucial role in promoting new vessel formation in response to specific stimuli.[22] This implies a highly regulated signaling network between the cancer cells and tumor-associated stroma cells.[23]

Receptor expression analysis interestingly showed a marked decrease in MR mRNA expression in colorectal carcinomas, even in the early stages. In stage I carcinoma, the MR was a median of 11-fold less expressed compared to the normal mucosa. Indeed, this suggests that MR underexpression may be an early event in colorectal carcinoma progression. Very little data is available in the literature regarding MR expression in human colorectal carcinoma. As an indirect sign of MR expression, it has been shown that 11 beta-hydroxysteroid dehydrogenase, the enzyme that confers mineralocorticoid specificity in certain aldosterone target tissues, is associated with differentiation or maturation of human colonic epithelia.[24] However, in our study we did not find any association between MR expression and tumor stage or differentiation.

Among the pathological variables considered, we specifically analyzed differences in MR expression in relation to VEGFR-2 status in carcinoma (Table 2). We found that MR expression was significantly lower in right-sided, poorly differentiated, and lymph node metastatic carcinomas with VEGFR-2 overexpression. We may speculate that MR underexpression confers an advantage in enhancing VEGFR-2 expression in particular pathological patterns of malignancy, such as carcinomas with poor differentiation or lymph node involvement. Regarding the interesting finding in the right-sided colon carcinomas, there is wide support for the existence of different carcinogenesis pathways in left- and right-sided colorectal carcinomas.[25] This may involve differential hormonal responsiveness; however, the actual cause of the differences between right- and left-sided colon carcinomas still remains unclear.[25]

Our observation that MR expression is inversely associated with VEGFR-2 expression suggests that MR inhibition may enhance angiogenesis. In this respect, ambiguous results have been reported in the literature. It seems that spironolactone has antiangiogenic effects *in vitro* and *in vivo*. Interestingly, these effects have been shown to be unrelated to the antimineralocorticoid activity.[26,27] On the contrary, eplerenone, a more selective MR antagonist, seems to preserve capillary density after myocardial ischemia.[28]

Such discrepancies may be explained by the fact that angiogenesis is the result of a highly complex sequence of events that are pivotal for many physiologic and pathologic processes, including inflammation, ischemia, and malignancy.[20] In this respect, it is slowly being elucidated that while the stimulation of angiogenesis may benefit coronary pathology and diabetic limb ischemia, its inhibition may provide remission of diabetic retinopathy, arthritis, and neoplasia.[19]

Conclusion

This is the first report showing that a decrease in MR expression is found even in stage I colorectal carcinomas and may thus be an early event in cancer progression. Our observations support the hypothesis that the degree of MR underexpression may have a role in the proangiogenic switch of the tumor, by inducing VEGFR-2 overexpression. To further test this hypothesis and to establish the reciprocal role of epithelial and stroma cells, additional studies are warranted.

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Laparoscopic Surgery for Patients with Crohn's Colitis: A Case-matched Study

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Abstract

Introduction The purpose of this study was to compare short and long-term outcomes of laparoscopic colectomy with open colectomy in patients with Crohn's disease confined to the colon.

Materials and Methods We reviewed all patients undergoing laparoscopic colectomy for Crohn's disease at our institution between 1994 and 2005. Laparoscopic colectomies were matched to open colectomies by patient age, gender, American Society of Anesthesiologists score, type, and year of surgery. We excluded patients with concomitant small bowel disease.

Results Twenty-seven laparoscopic cases were matched with 27 open cases. There were seven conversions (26%). There was no mortality. Median operative times were significantly longer after laparoscopic colectomy (240 vs 150 min, $P<0.01$), and estimated blood loss was comparable (325 vs 350 ml, $P=0.4$). Postoperative complications were similar. Laparoscopic colectomies had shorter median length of stay (5 vs 6 days, $P=0.07$) and median time to first bowel movement (3 vs 4 days, $P=0.4$). When overall length of stay included 30-day readmissions, the difference in favor of laparoscopy became statistically significant ($P=0.02$). Recurrent disease requiring surgery was decreased after laparoscopy, although median follow-up was significantly shorter.

Conclusion Laparoscopic colectomy is a safe and acceptable option for patients with Crohn's colitis. Longer follow-up is needed to accurately establish recurrence rates.

Keywords Crohn's disease · Laparoscopy · Postoperative complications · Colitis · Colectomy

Introduction

Crohn's colitis is reported in 30–52% of patients with Crohn's disease[1–3] with rates of symptomatic recurrence in the order of 50%.[4] In spite of such a high incidence, the cases of Crohn's disease limited to the colon and rectum requiring abdominal surgery are relatively uncommon.

Increasing experience with laparoscopic colectomy (LC) has shown recovery benefits compared to open colectomy (OC) resulting in shorter hospital stay, more rapid return to bowel function, decreased use of postoperative narcotics, and lower rates of cardiopulmonary and wound complications.[5–7] Moreover, long-term recurrences after laparoscopic ileocolic resection for Crohn's disease were similar to open resections with the added advantage of reduced small bowel obstruction rates.[8,9]

Whereas most data on laparoscopic surgery for Crohn's disease is based on ileocolic disease, data on outcomes of laparoscopic colonic resection in patients with Crohn's colitis is still limited. Therefore, the purpose of this study was to compare open with laparoscopic colonic resections in patients with refractory Crohn's disease confined to the colon with respect to short and long-term outcomes.

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Material and Methods

We reviewed all consecutive patients undergoing elective LC for Crohn's disease of the colon at our institution between 1994 and 2005. Patients were identified from a

Table 1 Demographics and Details of Surgical Procedures

	LC	OC	*P* value
Total patients	27	27	
Age (years)[a]	35.5 (±18.5)	32.6 (±14.2)	0.65
Gender			
Male	15	15	
Female	12	12	1
ASA			
II	19	19	
III	8	8	1
BMI[a]	24.9 (±4.6)	26.7 (±5.2)	0.2
Type of surgical procedures			
Right-side colectomy	1	1	
Left-side colectomy	6	6	
Low anterior resection	1	1	
Total colectomy+IRA	10	10	
Total colectomy+EI	4	4	
Total proctocolectomy+EI	4	4	
Proctocolectomy IPRA	1	1	1
Previous surgery[b]	1	5	0.08

LC Laparoscopic colectomy, *OC* open colectomy, *IRA* ileorectal anastomosis, *EI* end ileostomy, *IPRA* ileal pouch-rectal anastomosis, *NS* not significant

[a] Mean (standard deviation)

[b] Details of specific surgical procedures in text.

prospective, IRB-approved institutional Crohn's disease database. LC cases were computer-matched to OC by patient age (±5 years), gender, American Society of Anesthesiologists (ASA) physical status classification, type of surgical procedure, and year of surgery (±3 years). Patients with concomitant small bowel disease or indeterminate colitis were excluded from the analysis. Both cohorts were compared for operative time, estimated blood loss (EBL), time to return to bowel function through anus or stoma, length of hospital stay, readmissions within 30 days of discharge, morbidity, mortality, and Crohn's disease recurrence episodes during follow-up. We defined postoperative ileus as a period of transient cessation of bowel function lasting longer than 5 days after surgery. Other data included demographics, duration of disease, medication use, and indication for surgery. Recurrence was defined as any endoscopic or radiological evidence of active Crohn's disease requiring medical or surgical treatment. Recurrences requiring surgery vs medical treatment were recorded separately. Data from the approved database were supplemented by direct chart review as necessary. Six and eight different colorectal surgeons performed LC and OC cases, respectively, during the study period. The discharge criteria were similar in both groups and included tolerance of three meals without nausea or vomiting, passage of flatus or stoma function, adequate pain control with oral analgesia, and independent ambulation. An intention-to-treat analysis was performed including, in the same group, all surgical procedures initiated laparoscopically whether they were completed laparoscopically or converted to open.

Statistical Analysis

Comparisons of the LC and OC groups were performed using chi-square or Fisher exact tests with respect to categorical data and using the Wilcoxon rank sum test with respect to quantitative data. The comparison with respect to recurrence was performed using a log-rank test with the Kaplan–Meier method used to estimate recurrence time. Parametric data were reported as means and nonparametric data as medians. A level of $\alpha=0.05$ was used to establish statistical significance of individual *P* values.

Results

Twenty-seven LCs were matched with 27 OCs. Thirty patients were males (56%). Groups were well matched for age, gender, ASA, BMI, and surgical procedures as shown in Table 1. Eight patients in each group had significant comorbidities (ASA III). Among these, five LC patients had cardiovascular disease, one insulin-dependent diabetes mellitus, one deep venous thrombosis, and one severe immunosuppression. With regard to the OC group, five patients had severe cardiovascular disease, one severe chronic obstructive pulmonary disease, and two insulin-dependent diabetes mellitus. A total of six patients had undergone previous abdominal surgical procedures (Table 1), involving either a single abdominal quadrant or a limited intra-abdominal area. In particular, one patient from each group had undergone creation of diverting loop ileostomy, which was subsequently converted to Brooke ileostomy at the time of their colectomy. One OC patient had also a previous diverting loop ileostomy, which was maintained for 3 months after proctectomy and coloanal anastomosis. Three additional OC patients had undergone appendectomy, open cholecystectomy, and transabdominal hysterectomy, respectively. The indications for surgery

Table 2 Indications for Surgery

	Total	LC	OC	*P* value
Stricture/obstruction	21 (38.9%)	11 (40.8%)	10 (37.1%)	0.8
Unresponsiveness to medical treatment	17 (31.4%)	9 (33.3%)	8 (29.6%)	0.8
Fistulas/abscess	9 (16.7%)	3 (11.1%)	6 (22.2%)	0.3
Dysplasia	7 (13%)	4 (14.8%)	3 (11.1%)	0.7

LC Laparoscopic colectomy; *OC* open colectomy

Table 3 Postoperative Morbidity

	LC	OC	*P* value
Postoperative ileus	4 (14.8%)	5 (18.5%)	0.8
Anastomotic leak	1 (3.7%)	1 (3.7%)	1
Intra-abdominal abscess	2 (7.4%)	2 (7.4%)	1
Wound infection	1 (3.7%)	2 (7.4%)	1
Intra-abdominal bleeding	1 (3.7%)	0	1
Deep venous thrombosis	0	1 (3.7%)	1
Portal vein thrombosis	1 (3.7%)	0	1
Acute renal failure	1 (3.7%)	0	1
Pneumonia	1 (3.7%)	0	1
Total complications	12	11	0.8
Patients with at least one complication[a]	7 (26%)	9 (33.3%)	0.5

LC Laparoscopic colectomy, *OC* open colectomy
[a] Some patients had more than one complication

were not statistically different between the groups (Table 2). There were seven conversions (26%). Causes of conversion were intra-abdominal phlegmon or abscess (six patients) and small bowel distension (one patient). Postoperative complications occurred in seven LC patients vs nine OC (26 vs 33%, respectively; $P=0.5$) as reported in Table 3. There were no deaths. Stoma creation was related to intractable rectal disease and/or extensive perianal involvement in 87% of cases. In the remaining two patients, the rectum was preserved, and a subsequent ileorectal anastomosis was performed.

Median operative times were significantly longer after LC (240 vs 150 min OC, $P<0.01$), and EBL was comparable (325 ml LC vs 350 ml OC, $P=0.3$). Median time to first flatus or stoma function was 3 days for LC vs 4 days for OC ($P=0.4$), and median length of stay was not significantly shorter after LC (5 days for LC vs 6 days for OC, $P=0.07$). Intraoperative results and postoperative morbidity are summarized in Table 4. One patient had a LOS of 68 days after LC because of multiple complications. One out of seven patients developed postoperative pneumonia as the only postoperative complication among laparoscopic cases requiring conversion. Thirty-day readmission rates were increased in OC group (Table 5). When overall LOS included 30-day readmissions, the difference in favor of LC became statistically significant ($P=0.02$, Table 4).

Table 5 Causes of 30-day Readmissions

	LC	OC	*P* value
Postoperative ileus	–	2	
Perianal abscess	–	1	
Total number (%)	0	3 (11%)	0.02

LC Laparoscopic colectomy, *OC* open colectomy

Three OC patients had incisional hernias vs none after LC during follow-up. One LC patient had a late adhesive obstruction requiring readmission and was managed without surgery. Two OC patients developed late adhesive obstruction, one had explorative laparotomy, and the other was treated conservatively (Table 6).

The overall recurrence rate was 37%, corresponding to 11 LC patients and 9 OC patients based on a median follow-up of 20 months (range 1–114 months). Recurrences requiring surgery or medical therapy occurred at the anastomosis in 69% of cases. Overall recurrence rates were similar between the two groups. Recurrent Crohn's disease requiring surgery was not significantly decreased after LC (one case vs six cases after OC, 4 vs 22%, respectively, $P=0.2$). However, the median follow-up was significantly longer after OC (12 vs 40 months; $P=0.02$). Summary of long-term outcomes is shown in Table 6.

Discussion

Our study shows that LC for Crohn's colitis had longer operative times but similar morbidity, shorter return to bowel function, and LOS when compared with OC in an intent-to-treat analysis. Whereas these differences were not statistically significant for primary LOS, they became significant when the total LOS was inclusive of hospital stays because of readmissions. In fact, despite their longer

Table 4 Intraoperative and Postoperative Results

Median (interquartile)	LC	OC	*P* value
Operative time (min)	240 (180–310)	150 (120–180)	<0.01
EBL (ml)	325 (200–450)	350 (250–540)	0.4
First flatus (days)	3 (2–4)	4 (3–4)	0.4
LOS (days)	5 (3–7)	6 (5–8)	0.07
Overall LOS (days)[a]	5 (3–7)	6 (6–10)	0.02

LC Laparoscopic colectomy, *OC* open colectomy, *EBL* estimated blood loss, *BM* bowel movement, *LOS* length of hospital stay
[a] Inclusive of 30-day readmission

Table 6 Long-term Outcomes

	LC	OC	*P* value
Incisional hernia[a]	0	3 (11.1%)	0.07
Adhesive obstruction[a]	1 (3.7%)	2 (7.4%)	0.5
Overall recurrence[a]	11 (41%)	9 (33%)	0.1
Recurrence requiring surgery[a]	1 (4%)	6 (22%)	0.2
Follow-up (months)[b]	12 (7–19)	40 (21–70)	0.02

LC Laparoscopic colectomy, *OC* open colectomy
[a] Patient (%)
[b] Median (interquartile)

LOS after surgery, readmissions were more common after OC. It is reasonable to presume that the small sample size did not allow detecting more striking variations. In addition, a reduction in our 26% conversion rate could have also optimized the recovery advantages in favor of laparoscopic surgery as reported in larger studies on ileocolic Crohn's disease.[8,10–12]

Our conversion rate is comparable to conversion rates reported in multicenter prospective randomized trials comparing LC and OC for colon cancer, which range from 17 to 29%.[5,6,13] However, it is higher than what was reported in two prospective randomized trials comparing laparoscopic and open ileocolic resections for Crohn's disease, which had conversion rates of 6 and 10%, respectively.[10,12] Other retrospective studies on Crohn's disease included small number of patients and a conversion rate ranging from 0 to 29%.[8,11,14–18] This wide variability encountered in the literature might be associated with both specific pathologic features of Crohn's disease and the effect of a learning curve in laparoscopic techniques.

With respect to the former, it should be noted that a substantial portion of our conversions occurred in the presence of pericolonic phlegmon or abscess. An unexpected intraperitoneal abscess or fistula was reported to predict conversion of laparoscopic ileocecal resections for Crohn's disease.[19] In our series, two out of our six converted patients had pericolonic phlegmons detected on preoperative CT scan obtained because of a clinical presentation concerning for intra-abdominal sepsis. An additional patient underwent preoperative CT scan for the same indication, which did not identify intra-abdominal infections. In spite of this, a phlegmon was subsequently detected at the time of surgery. Four more patients had a phlegmon identified intraoperatively and did not undergo preoperative CT scan.

With respect to the latter point, conversions of LC were reported by two out of the six laparoscopic surgeons included in the study at a relatively early stage of their laparoscopic experience. Unfortunately, an accurate measurement of previous laparoscopic experience is difficult for our study, which includes a variety of often complex surgical procedures. However, our findings would seem to confirm that conversion rates for LC are at least partially related to the learning curve for individual surgeons.[20–23] In spite of relatively high conversion rates, it is reassuring that our study showed appreciable recovery benefits deriving from LC, confirming the validity of this surgical approach. Furthermore, whereas based on small numbers, our series also suggests that LC might reduce incisional hernia and small bowel obstruction rates as previously reported.[7,24]

Our study design also optimizes the validity of our conclusions for Crohn's disease limited to the colon. Whereas in theory, a prospective randomized trial would be the most accurate study design to reach meaningful conclusions, this would not be practical to study a relatively uncommon condition requiring surgery such as Crohn's colitis without small bowel involvement. It is therefore not surprising that, while few prospective randomized trials were published on ileocolic Crohn's disease,[10,12] none has ever been produced for Crohn's disease limited to the colon. In fact, most of the literature on LC for Crohn's disease analyzes ileocolic resections alone or combined with colonic resections.[14,15]

On the other hand, whereas our design strengthens the accuracy of our study, a small sample size and an uneven follow-up between groups hamper the value of any conclusions regarding the ability of LC to reduce the incidence of recurrent Crohn's disease. With this regard, our recurrence rate requiring surgery was not significantly higher after OC (22 vs 4% after LC). However, our median follow-up was only 12 months for LC vs 40 months for OC. Therefore, our data is still insufficient to contradict what was reported by recent studies reporting that LC and OC for ileocolic disease have similar long-term recurrence rates[9] and result in comparable quality of life.[25]

Finally, our study was conducted over a long period of time, including different surgeons, practices, and available technology. Further studies for LC in Crohn's colitis with longer follow-up may help elucidate differences in recurrence rates and additional benefits to this patient population.

Conclusion

Laparoscopic colectomy is a safe option for patients with Crohn's disease limited to the colon and is associated with more rapid postoperative recovery. Longer follow-up is needed to accurately establish recurrence rates when compared to OC.

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Peritumoral Inflammatory Infiltrate is not a Prognostic Factor in Distal Rectal Cancer Following Neoadjuvant Chemoradiation Therapy

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Abstract
Background Peritumoral inflammatory response has been considered a good prognostic factor for colorectal cancer. However, this has not been evaluated in patients submitted to neoadjuvant therapy for distal rectal cancer. For this reason, we decided to study the effect of the presence of this pathological finding on disease recurrence and survival.
Methods The peritumoral inflammatory infiltrate from recovered pathological specimens of patients operated after neoadjuvant therapy for distal rectal cancer was graded (positive or negative). Patients were compared according to the presence of peritumoral inflammatory response.
Results Of the 168 patients, 63 (37%) patients had a peritumoral inflammatory response. The lack of peritumoral inflammatory response was significantly associated with the presence of mucinous component (13 vs 3%; $p=0.02$). Five-year overall survival (91 vs 81%) and disease-free survival (57 vs 48%) were not significantly different between patients with and without peritumoral inflammatory response ($p=0.5$ and 0.3, respectively).
Conclusions Peritumoral inflammatory response is not a favorable prognostic factor in patients with distal rectal cancer after neoadjuvant chemoradiation therapy. Possibly, the immunosuppressive action of chemoradiation therapy may lead to a loss of function of the immunological response, which may represent a disadvantage of the neoadjuvant approach for the management of distal rectal cancer.

Keywords Rectal cancer · Neoadjuvant therapy · Local inflammatory response

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Introduction

Final pathological disease stage, including tumor depth of penetration, lymph node and distant metastases remains the most significant prognostic factor for colorectal cancer. However, other pathological features have also been found to have a role in disease-specific survival. In fact, peritumoral inflammatory response has been considered a good prognostic factor possibly because of its immunological effects against cancer cell proliferation and dissemination.[1–9] For this reason, it has been suggested to be included during classification of colorectal cancer stage to improve accuracy of survival estimation.[10]

This pathological feature has not been studied in patients with distal rectal cancer submitted to neoadjuvant chemo-radiation therapy (CRT). Neoadjuvant CRT is considered the preferred initial treatment strategy for distal rectal cancer because of the observation of increased local disease control, significant tumor downstaging, increased rates of sphincter preservation, and improved functional results when compared to post-operative course.[1,11–14] However, survival improvements have not been demonstrated, and distant failure remains a significant challenge during rectal cancer management.

The neoadjuvant approach in rectal cancer with combined chemotherapy and radiation therapy has been associated with a significant increased risk of postoperative infectious complications.[15–19] Therefore, neoadjuvant CRT could possibly lead to inactivation of the immunological effects of the peritumoral inflammatory reaction, leading to both increased risk of local infectious complications and loss of survival benefit of these patients. For these reasons, we decided to determine the impact of peritumoral inflammatory infiltrate in distal rectal cancer after neoadjuvant CRT and radical surgery.

Patients and Methods

Patients with primary adenocarcinoma, located no more than 7 cm from the anal verge, were treated by neoadjuvant chemo-radiation therapy for 6 weeks including 50.4 Gy of radiation and 5FU/Lecovorin as described elsewhere.[20] Initial staging included complete physical examination, digital rectal examination, rigid proctoscopy, spiral abdominal and pelvic computed tomography (CT), endorectal ultrasound, carcinoembryonic antigen (CEA) level, and chest radiographs. Other radiological studies were performed in selected patients to rule out distant metastases. Patients with metastatic disease were excluded from this study. Complete colonoscopy was attempted either before or after CRT.

After at least 8 weeks from CRT completion, patients were staged to determine tumor response assessment. Patients with complete clinical response without any suspicious residual disease determined by clinical, endoscopic, and radiological studies were not immediately operated on and enrolled in a strict follow-up program. Patients with sustained complete clinical response for at least 12 months were considered clinical stage 0 and were excluded from the study and are reported elsewhere.[20,21]

Patients with incomplete clinical response identified during tumor response assessment or up to 12 months from CRT completion were referred to immediate radical surgery and were included in this study.

Operations included sphincter-saving operations (SSO) such as low anterior resection (AR) with coloanal or low colorectal anastomosis, or abdominal-perineal resection.

Final pathological staging (yp0-III) was performed according to the International Union Against Cancer (UICC) recommendations and reviewed by a single experienced pathologist (V.R.) to determine and grade the presence of peritumoral inflammatory reaction. Patients with absence or scant peritumoral inflammatory reaction were considered

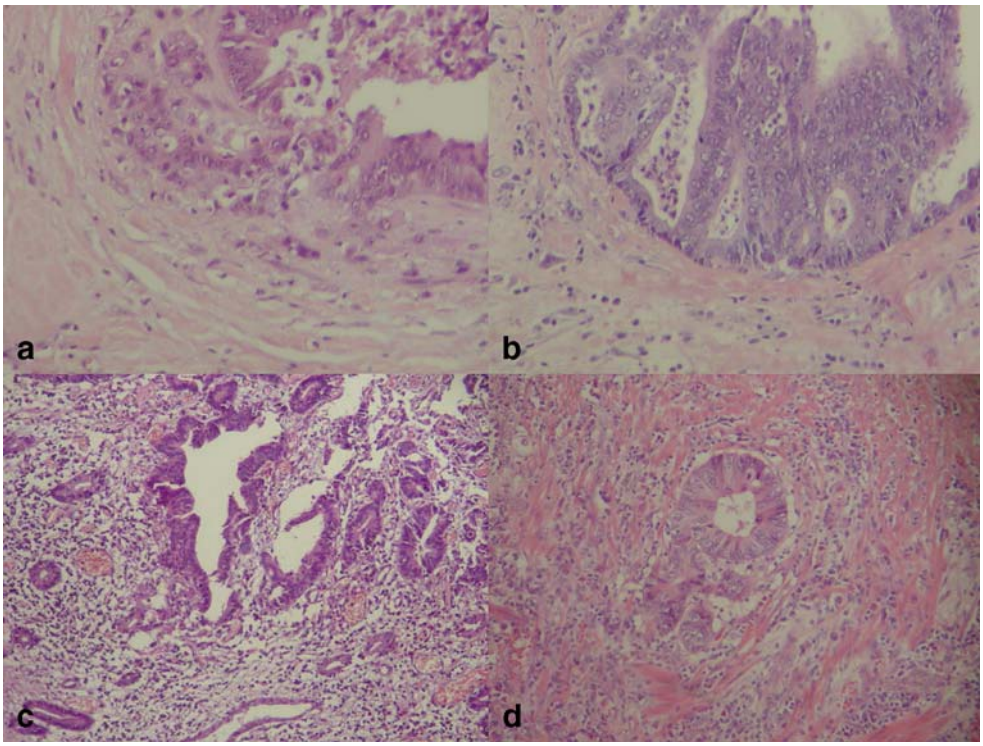

Figure 1 **a** and **b** Rectal cancer with absence of peritumoral inflammatory infiltrate. **c** and **d** Rectal cancer with positive peritumoral inflammatory infiltrate.

negative (Fig. 1a and b), whereas patients with moderate or intense peritumoral inflammatory reaction were considered positive (Fig. 1c and d).

Follow-up was performed with visits and CEA level determination every 3 months for the initial 24 months, every 6 months during the third and fourth year, and yearly thereafter. Patients with stage yp0-II were not referred to adjuvant chemotherapy. Patients with stage pIII were referred to medical oncology specialists for adjuvant therapy.

Neoadjuvant chemoradiation, staging, surgery, and follow-up were performed by a single group of colorectal surgeons and radiation oncologists in two institutions: University of São Paulo School of Medicine and Hospital Alemão Oswaldo Cruz.

Statistical analysis was performed using chi-square and Student's *t* test for comparison of variables between patients. Survival was determined by Kaplan–Meier curves using log-rank test. Differences were considered significant for p values <0.05.

Results

Overall, 230 patients managed in the period between 1991 and 2005 were eligible for the study. However, only 168 (73%) had pathological specimen available for HE revision and represent the final study population. The mean follow-up period was 39.6 months.

There were 102 (60.7%) male and 66 (39.3%) female patients. The mean age was 58.6±13.0 years, ranging from 22 to 88 years. Mean distance from anal verge of the primary tumor was 3.9±1.7 cm, and initial tumor size was 4.1 cm. Overall, 88 (52.7%) patients underwent abdominoperineal resection (APR), whereas 79 (47.3%) underwent SSO.

Final pathology revealed depth of penetration of the residual tumor (ypT) to be ypT0 in 8 (4.8%), ypT1 in 6 (3.6%), ypT2 in 54 (32.1%), ypT3 in 87 (51.8%), and ypT4 in 13 (7.7%). Lymph node metastases were present (ypN1-3) in 51 (30.3%) patients. Final disease stage was stage yp0 in 8(4.8%), ypI in 47 (27.9%), ypII in 63 (37.5%), and ypIII in 50 (29.8%) patients. Perineural invasion was observed in 55 (32.7%), lympho-vascular invasion in 40 (23.8%), and mucinous component in 19 (11.3%) patients.

Peritumoral inflammatory infiltrate was considered positive in 63 patients (37.5%), whereas negative in 105 patients (62.5%). The clinical characteristics and tumor characteristics according to the presence of a peritumoral infiltrate are summarized in Tables 1 and 2.

Table 1 Clinical Characteristics According to the Presence of Peritumoral Inflammatory Infiltrate

	Negative	Positive	*p* Value
Number of patients	105 (62.5)	63 (37.5)	
Age			
Mean	59.9± 12.3 years	56.1± 12.3 years	0.067
Sex			
Female	36 (34.3)	33 (52.4)	0.08
Male	69 (65.7)	27 (47.6)	
Surgery			
APR	55 (52.4)	30 (48.4)	0.28
SSO	50 (47.6)	32 (51.6)	

APR Abdominal perineal resection, *SSO* sphincter-saving operations

Table 2 Tumor Characteristics According to the Presence of Peritumoral Inflammatory Infiltrate

		Negative (n=105)	Positive (n=63)	p Value
Tumor characteristics				
Tumor size		3.4±1.9 cm	4.2±1.4	0.84
Perineural invasion		37 (35.2)	18 (28.6)	0.37
Lymphovascular invasion		23 (21.9)	17 (27.0)	0.45
Mucinous type		16 (15.2)	3 (4.8)	0.038
Staging				
ypT	0	3 (2.9)	5 (7.9)	0.58
	1	3 (2.9)	3 (4.8)	
	2	37(35.2)	17 (27.0)	
	3	55 (52.4)	32 (50.8)	
	4	7 (6.7)	6 (9.5)	
ypN	0	74 (70.5)	40 (63.5)	0.76
	Positive	30 (28.6)	21 (33.3)	
Stage	0	3 (2.9)	5 (7.9)	0.20
	I	31 (29.5)	16 (25.4)	
	II	42 (40.0)	21 (33.3)	
	III	29 (27.6)	21 (33.3)	

Positive vs Negative Peritumoral Infiltrate

There were no significant differences between patients with positive and negative peritumoral inflammatory infiltrate in terms of clinical characteristics, final pathological features, initial tumor size, and type of operation (Tables 1 and 2). However, patients with absent peritumoral inflammatory infiltrate exhibited more frequently mucinous component (4.8 vs 15.2%; p=0.04).

Recurrences and Survival

Overall, 59 patients (35%) experienced a recurrence during follow-up, being 41 (39%; 13% local and 26% systemic) among patients with negative and 18 (29%; 12% local and 17% systemic) among patients with positive peritumoral inflammatory infiltrate (p=0.7). Five-year overall survival rates were 80.6 and 90.5% for patients with negative and

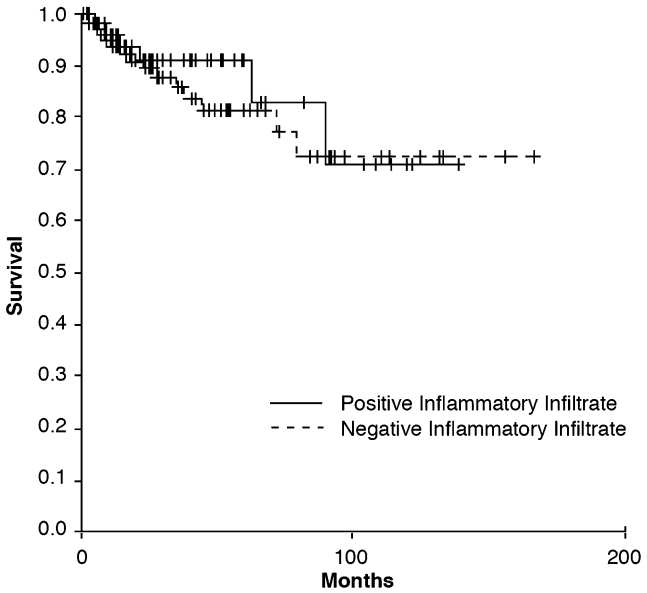

Figure 2 Overall survival according to the presence of peritumoral inflammatory infiltrate. Five-year overall survival rates were 80.6 and 90.5% for patients with negative and positive peritumoral inflammatory infiltrate, respectively (p=0.55).

positive peritumoral inflammatory reaction, respectively (p=0.55; Fig. 2). Similarly, there were no differences in terms of 5-year disease-free survival rates (47.9 vs 56.6%; p=0.53; Fig. 3). Also, when patients where stratified by disease stage, there were no significant differences in 5-year overall and disease-free survival rates.

Discussion

One of the physiological roles of the immunological system is the recognition and destruction of malignant transformed cells known as tumoral immunological surveillance.[22] Although the existence of such immunological anti-tumor effect has been questioned, it can be observed in both experimental and human studies.[23–26]

Peritumoral inflammatory infiltrate is considered to be one of the weapons of the immune system during the battle of the host against tumors. It seems that altered cell phenotype may result in a specific immunological reaction ultimately leading to a local influx of activated lymphocytes and other specific immune cells. On the other hand, tissue architecture disorganization may result in a non-specific native inflammatory process, usually localized in tumor surroundings.[1]

Indeed, peri-tumoral inflammatory infiltrate has been associated with improved survival and has been used for disease stage classification to improve prognosis determination.[10,27] Also, some studies have suggested that the stage-adjusted improved survival associated with hereditary nonpolyposis colorectal cancer (HNPCC) patients could be due to the more frequently observed and effective peritumoral Crohn's-like inflammatory infiltrate.[28–31]

Recently, neoadjuvant CRT has been shown to result in improved local disease control, significant tumor downstaging, increased rates of SSO, and improved functional results when compared to postoperative CRT during distal rectal cancer management. However, none of the studies have shown definitive survival benefits with this neoadjuvant CRT approach over postoperative CRT or surgery alone.[1,12] One of the possible explanations for this lack of survival benefit is the possible inactivation of peritumoral inflammatory response by neoadjuvant CRT, thus, abolishing the beneficial role in tumor surveillance and, ultimately, survival of specific and non-specific inflammatory and immunological effects.

In fact, studies have indicated increased rates of infectious complications in the postoperative period of these patients undergoing long-course CRT reflecting local and, possibly, systemic immunosuppression of these patients. These studies have demonstrated increased overall infectious as well as perineal wound failure rates.[32,33] Neoadjuvant short-course radiation therapy has also led to increased rates of readmissions because of infectious complications up to 6 months after radical surgery.[34]

Molecular studies have further contributed to the understanding of the possible detrimental effects of neoadjuvant CRT to patient's immunology.[35] Significant decreases in both pro-inflammatory cytokines, such as interleukin-6 precursor (IL-6) and tumor necrosis factor alpha (TNF-α),

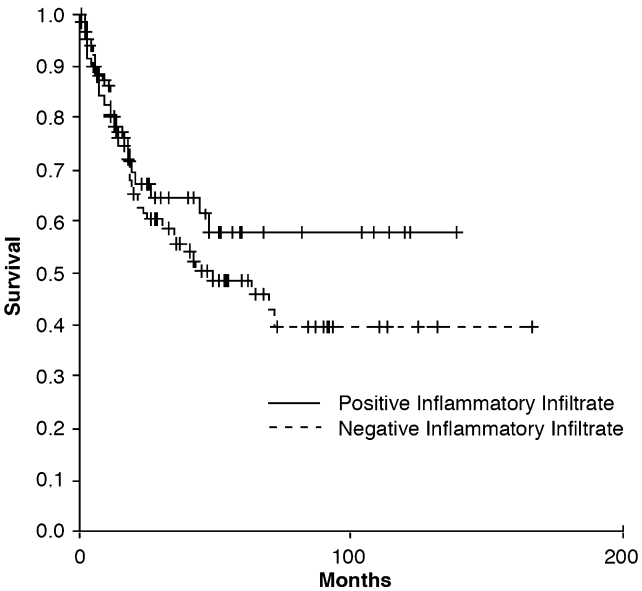

Figure 3 Disease-free survival according to the presence of peritumoral inflammatory infiltrate. Five-year disease-free survival rates were 47.9 and 56.6% for patients with negative and positive peritumoral inflammatory infiltrate, respectively (p=0.53).

and markers of cell-mediated immunologic response including specific lymphocyte subpopulations, granulocytes, and monocytes in patients managed by neoadjuvant CRT have been documented.[35] These results are of clinical interest, as these specific cells have been demonstrated to interfere with tumor cell growth during surgical manipulation.[36,37] Patients in this same study undergoing neoadjuvant CRT had CD4+ cell counts <200 μl, similar to patients with HIV infection considered to be advanced immune-impaired and requiring adjuvant immunological therapy. [35,38]

Other studies have also addressed specific peritumoral inflammatory infiltrate cell subpopulation in patients with rectal cancer after neoadjuvant CRT. These patients exhibit a different pattern of cell population with decreased neutrophil and T lymphocyte counts, although no differences were observed in terms of mastocyte, eosinophil, macrophage natural killer (NK) counts.[1,39]

Immunological features may interfere with tumor cell growth, and therefore, alterations determined by neoadjuvant CRT could affect disease survival. In our study, there were no differences between patients with the presence or absence of peritumoral inflammatory infiltrate in terms of final disease stage. In fact, tumor downstaging seems to be associated with CRT and is not expected to be affected by the presence of peritumoral infiltrate.

Interestingly, patients with absent peritumoral infiltrate presented more frequently mucinous-type adenocarcinoma compared to patients with absent peritumoral infiltrate (15.2 vs 4.8%, $p=0.045$). In fact, mucinous colorectal tumors have been shown to interfere with inflammatory and immunological host response, a feature that may have a role in the worse biological behavior of this particular histological subtype.[40] Also, patients with peritumoral infiltrate in our study had a trend toward younger age than patients without this feature and could reflect increased susceptibility to CRT-induced immunossupression.[41–44]

Finally, we did expect to find improved survival in patients with peritumoral infiltrate. However, this was not observed in our series, as overall and disease-free survival were similar in both groups even after stage-adjustment. In fact, the absence of survival benefit among patients with peritumoral inflammatory infiltrate observed in our study could be influenced by both insufficient sample size and short follow-up. Although a mean follow-up over 3 years is considered to be sufficient for the occurrence of more than 90% of colorectal cancer recurrences, the follow-up period in which most recurrences occur in patients with irradiated rectal cancer may be significantly longer, especially in terms of local recurrences.[21] The fact that survival curves among patients with positive peritumoral infiltrate were slightly better but not significant raises the question of inadequate sample size and underpowering of our study. In fact, the sample size in our study would be enough to demonstrate a significant difference of 20% in 5-year disease-free survival rates with a 95% confidence interval and 76% power. Interestingly, to demonstrate a significant difference of 10% in 5-year disease-free survival rates, a considerably larger series of 300 patients in each group would be required. Still, our study suggests that the role of peritumoral inflammatory response in rectal cancer may be at least attenuated after neoadjuvant CRT, supporting the observations of other detrimental effects of neoadjuvant CRT in immunological features among these patients.[35,39]

In conclusion, the presence of peritumoral inflammatory infiltrate is not a good prognostic factor in patients with distal rectal cancer managed by neoadjuvant CRT followed by radical surgery. The observation of detrimental effects of neoadjuvant CRT on the immune system, associated with the increased risk of developing local postoperative infection and requirement for readmission because of infectious diseases supports the hypothesis that CRT may inactivate the protective effects of the immune system in these patients. This may result in increased risk for infection and perhaps influence the benefit of improved survival associated with the presence peritumoral inflammatory infiltrate observed in colon and rectal cancer.

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Medical and Surgical Treatment of Chronic Anal Fissure: A Prospective Study

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Abstract
The aim of this prospective study was to assess the efficacy of different medical treatments and surgery in the treatment of chronic anal fissure (CAF). From 1/04 to 09/06, 156 patients with typical CAF completed the study. All patients were treated with 0.2% nitroglycerin ointment (GTN) or anal dilators (DIL) for 8 weeks. If no improvement was observed after 8 weeks, patient was assigned to the other treatment or a combination of the two. Persisting symptoms after 12 weeks or recurrence were indications for either botulinum toxin injection into the internal sphincter and fissurectomy or lateral internal sphincterotomy (LIS). During the follow-up (19±8 months), healing rates, symptoms, incontinence scores, and therapy adverse effects were prospectively recorded. Overall healing rates were 65.3 and 96.3% after GTN/DIL or BTX/LIS. Healing rate after GTN or DIL were 39.8 and 46%, respectively. Thirty-six patients (23.1%) responded to further medical therapy. Fifty-four patients (34.6%) underwent BTX or LIS. Healing rate after BTX was 81.8%. LIS group showed a 100% healing rate with no morbidity and postoperative incontinence. In conclusion, although LIS is far more effective than medical treatments, BTX injection/fissurectomy as first line treatment may significantly increase the healing rate while avoiding any risk of incontinence.

Keywords Chronic anal fissure · Surgery · Botulinum

Introduction

The cause of anal fissure is still unknown, but hypertonia of internal anal sphincter (IAS) associated with the passage of hard stools is likely one of the main factors implied. As a matter of fact, an elevated mean resting pressure of the IAS (measured during anorectal manometry) is the most consistent finding in patients with fissures. Lateral internal sphincterotomy (LIS) has proved highly effective in curing anal fissures in a number of randomized clinical trials[1–8], with success rates higher than 90%. Although LIS is currently considered the "gold standard" of treatment, it encompasses an overall risk of incontinence, which can be as high as 10%, as estimated in a systematic review of randomized surgical trials.[9] Hence, the interest, in the last two decades, in seeking new medical treatments is directed at lowering the tone of the IAS. Glycerin trinitrate (GTN), botulin toxin, and topical calcium channel blockers are all known to be able to lower the IAS tone. The efficacy of GTN has been evaluated in several randomized studies and although the overall healing rate for GTN estimated in a meta-analysis of the published randomized trials[10] is about 50%, it is established as a first line therapy in many centers because of convenience, safety, and costs. The main drawbacks of GTN treatment are recurrence, tachyphylaxis, anal burning, hypotension, and the risk of headache that can be so severe to cause many patients to abandon therapy. The botulinum toxin is injected directly into the IAS and produces a "chemical sphincterotomy." It appears to be the

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ideal agent to overcome the side effects of GTN, as it produces the same reduction of the anal sphincter resting pressure as GTN, there are no compliance issues, and adverse effects are infrequently reported. A meta-analysis of randomized clinical trials comparing medical treatments to placebo or surgery[10] has shown that GNT, botulinum toxin, and surgery have overall response rates of about 55, 65, and 85%, respectively, whereas the placebo healing rate is about 35% across all the studies. Medical treatment seems therefore a reasonable first line therapy for most patients with chronic anal fissure (CAF). Second-line use of botulinum toxin seems to heal only 50% of fissures resistant to.[11] It is likely that the fibrotic nature of chronic fissures resistant to GTN is not resolved by chemical sphincterotomy alone. Fissurectomy alone is not currently used in adults, but its combination with botulinum toxin injection has been recently used with success to treat fissures resistant to medical treatment.[12,13] with healing rates higher than 90%. The aims of our study were the assessment of the efficacy of different medical treatments, fissurectomy, and botulinum toxin injection, and LIS in lowering the anal sphincter tone and healing CAFs, and the development of a treatment algorithm for patients with CAF.

Material and Methods

Between January 2004 and September 2006, 156 consecutive patients with CAF were enrolled in the study. Diagnosis was made according to history and physical exam. CAF was defined by duration of symptoms longer than 3 months and the presence of a skin tag, a sentinel pile or fibrosis at the margins of the fissure. Exclusion criteria included atypical CAF associated with grade III/IV hemorrhoids, previous anal surgery, incontinence, inflammatory bowel disease, infection, or cancer. Patients with coexisting medical conditions requiring calcium channel blockers and oral, sublingual, or transdermal nitrates were also considered ineligible for this study.

During the outpatient visit, a complete explanation of the disease and the medical treatment options, benefits, and side effects were given to the patient.

After this, patient was assigned to an 8-week course of medical therapy with either 0.2% GTN or anal dilators (DIL) according to his/her preference. Patients of GTN group were instructed to apply the ointment twice a day to the edge and just inside the anal canal (morning and evening) after a warm sitz bath. The amount of crème to be applied was shown during the outpatient visit. If patients experienced side effects, he was instructed to use a finger glove for application or to reduce the amount to be applied.

Patients of DIL group were instructed to use an anal dilators set (Dilatan, Sapi Med, Alessandria, Italy) as follows. To ease the DIL introduction, after being heated for 15 min in water, patients lubricated the DIL with a preparation gel (Dilatan crema, Sapi Med, Alessandria, Italy) and introduced it fully into the anal canal and maintained the position for 10 min twice a day (morning and evening). Patient was invited to repeat this procedure for 3 weeks starting with small diameter dilators (20–23 mm), followed by medium size dilators (23–27 mm) and ending with the large (32 mm).

The primary end-point was fissure healing at last follow-up. Secondary end-points were symptomatic improvement, need for LIS, and side effects. Improvement was defined as absence of pain or bleeding. Healing was defined as complete epithelialization of the fissure base. Those patients in which no improvement in symptoms was observed after 8 weeks were crossed to the other treatment (either GTN or DIL) or switched to a combination of the two for additional 4 weeks. Botulinum toxin injection in the IAS associated to fissurectomy (BTX-F) or LIS were offered to patients who did not benefit from the 12-week treatment course with GTN or DIL or a combination of them, after full information about the risks and the benefits of either procedure. Patients with non-healed or recurrent CAF who refused surgery were offered a further medical treatment. Anorectal manometry was performed before either one of the procedures.

Either fissurectomy/Botox injection or LIS were performed in a day-surgery setting under sedation and local anesthesia in lithotomy position. Before surgery, all patients had a limited bowel preparation with one Sorbiclis (Sofar S.p.a, Milan, Italy). An Eisenhammer speculum was gently inserted, avoiding excessive sphincter dilatation. Fissurectomy was performed by minimal excision of the fibrotic edges of the fissure and curettage of its base just back to fresh, normal, non-fibrotic tissue. If present, the sentinel pile was excised with cutting diathermy. Once fissurectomy was performed, 25 U of botulinum toxin (Botox, Allergan, Milan, Italy) were injected as follows. A volume of 1.6 ml of saline solution was mixed into a 100-U vial of botulinum toxin, and 0.4 ml aliquot (equal to 25 U) was drawn up into a 1-ml syringe with a 27-gauge needle and injected equally into the IAS at 3 and 9 o'clock.

LIS was performed using the open technique with partial division of the IAS in the lateral position using coagulation diathermy. In all cases, fissurectomy was performed as previously described.[13]

Patients in both groups were discharged on the same day and stayed on a high-residue diet and stool softener for 7 days. A non-narcotic analgesic was also prescribed as needed, and patients were advised to take regular warm sitz baths. Patients were seen in outpatient clinic after 1 week and therefore at 1-, 2-, 3-, and 12-month intervals. Independently of these scheduled appointments, patients

were seen on request. Information about fissure healing, symptoms, complications, and adverse effects were prospectively collected. Wexner incontinence score was used to assess continence after the procedures.

Differences between treatment groups were evaluated by chi-square test.

Results

Patients' demographics, fissure characteristics, and treatment failures are shown in Table 1.

Median follow-up was 19±8 months ranging from 3 to 33 months.

Overall fissure healing after medical treatment with either GTN or DIL was observed in a total of 102 (65.4%) patients.

Figure 1a shows healing rates after 12 weeks treatment with GTN or DIL alone as well as recurrences and overall healing rates at the end of the study. Fig. 1b shows healing rates, recurrences, and overall healing after the switch. Healing after 12 weeks was observed in 52.7% of the patients for the GTN only group and in 50.8% of the patients for the DIL only group without significant differences. Recurrence rate after 12 weeks treatment was 24.5% for GTN only group and 9.4% for DIL only group respectively (p=0.09).

In particular, healing with no recurrence was observed in 37 out of 93 patients (39.8%) treated with GTN alone and in 29 out of 63 patients (46.0%) who underwent anal dilation only. In most of the patients, healing time ranged from 8 to 12 weeks after treatment course. No significant difference was noted between the two groups in terms of time to healing (p=0.1).

Seventy-five patients (48.1%) experienced non-healing or sudden recurring disease within the first 8 weeks observation period. Of those, 33 patients (previously treated with GTN) were switched to DIL and 22 (previously treated with DIL) to GTN for additional 4 weeks. The remaining 20 patients accepted a combined GTN/DIL treatment.

A total of 36 patients (23.1%) responded to this further medical therapy, and overall healing rate raised significantly from 42.3 to 65.4% (p=0.03). In particular, at the end of this further 4 weeks treatment, GTN after DIL resulted effective in 68.2% of the treated patients (15 out 22) and DIL after GTN in 36.4% (12 out of 33) (p=0.02). Of the 20 patients treated with combined DIL/GTN, 14 responded with healing (70%) (p=0.02 vs DIL and 0.90 vs GTN). During the follow-up recurrence rates were 16.7% for DIL after GTN, 7.1% for combined GTN/DIL, and 14.3% for GTN after DIL, with no significant differences among groups. Fig. 1b shows definitive healing after this further medical treatment. Definitive healing was observed in 10 out of 33 patients treated with DIL after GTN (30.3%), in 13 out of 22 patients treated with GTN after DIL (59.1%), and in 13 out of 20 patients treated with combined GTN/DIL (65%). Combined GTN/DIL and GTN after DIL treatments were similar in terms of definitive healing and significantly better than DIL after GTN treatment (p=0.003).

At the end of the study, overall medical treatment success was 60.2% (56 out of 93 patients) and 73% (46 out of 63 patients) respectively for patients initially treated with GTN or DIL. No significant differences were observed between the groups.

Overall incidence of GTN side effects was 12.8% (15 patients), mostly mild headache (9 patients) and *pruritus ani* (6 patients). Five patients (4.2%) discontinued therapy and were switched to DIL.

A total of 107 patients were treated with DIL (63 patients as initial treatment and 44 patients after GTN treatment) and 12.1% interrupted the DIL course (13 out 107) because of

Table 1 Patients' Demographics, Fissure Characteristics, and Treatment Failures Resume

	GTN	DIL	GTN/DIL	BOTOX/fissurectomy	LIS
Number	93	63	20	22	32
Mean age (years)	37	41	39	34	43
Sex (M/F)	42/51	29/34	8/12	10/12	11/21
Fissure position					
Post	74	49	13	19	28
Ant	14	11	5	2	3
Both	4	3	2	1	1
Other	1	0	0	0	0
Sentinel pile *N*/%	61/65.6%	39/61.9%	14/70%	15/68.2%	27/84.4%
Single treatment (12 weeks) success *N*/(%)	49/93 (52.7%)	32/63 (50.8%)	NA	NA	NA
Recurrence	12/49 (24.5%)	3/32 (9.4%)	NA	NA	NA
After cross-over healing *N*/%	12/33 (36.4%)	15/22 (68.2%)	14/20 (70%)	NA	NA
Recurrence	2/14 (14.3%)	2/15 (13.3%)	1/14 (7.1%)	NA	NA
Overall success *N*/%	47/93 (50.5%)	42/63 (66.7%)	13/20 (65%)	18/22 (81.8%)	32/32 (100%)

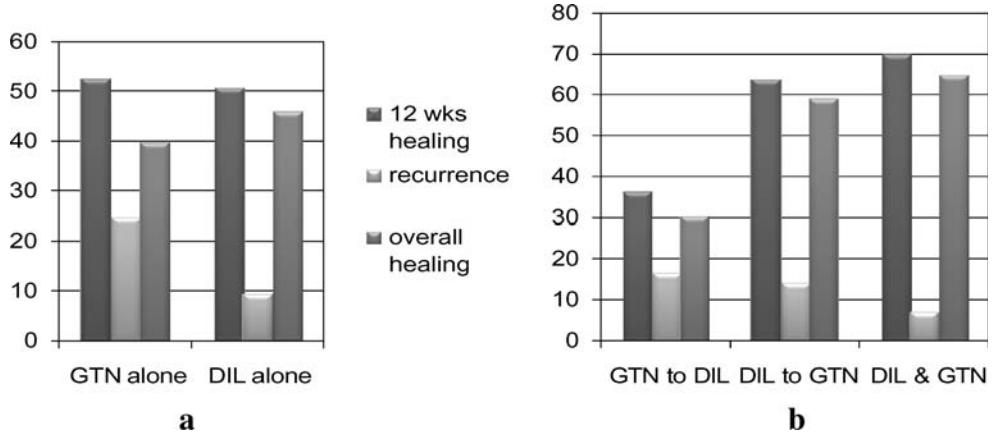

Figure 1 Healing after 12 weeks, recurrence rates, and overall definitive healing after single medical treatment (**a**) and after the switch (**b**). Data is expressed as percentage of treated patients.

severe discomfort. After non-healing or recurrence, surgery was offered to 53 patients (34%). One patient refused either botulinum treatment or surgery, and further medical treatment was offered with minimal beneficial effect. Of the remaining 52 patients, 22 underwent fissurectomy/Botox injection and 30 to LIS. Healing was reported in 18 out of 22 (81.8%) patients after fissurectomy/Botox injection. This percentage was significantly higher compared to GTN alone course (p=0.008), to DIL alone treatment (p=0.02) or to overall combined/cross-over groups (p=0.01). One patient (4.5%) experienced transitory flatus incontinence. Non-healing was observed in one patient (4.5%) and recurrence in 3 (13.6%). Two out four subsequently required LIS because of recurrent disease (one patient) or failure of therapy in promoting fissure healing (one patient) and had complete healing. The remaining two patient refused further surgical treatment and remained on periodical medical treatment.

All 32 patients treated with LIS showed complete healing with no morbidity or postoperative incontinence.

Comparing the different treatment groups, there were no significant differences in terms of healing rates between males and females, presence or absence of sentinel pile, or previous GTN or/and DIL treatment.

Discussion

The most recent theories on etiopathogenesis of anal fissures have focused on increased tonicity of the IAS, which contains smooth muscle fibers whose contraction is controlled by neural influences and myogenic mechanisms.[14,15] IAS contraction is mediated by increased cytosol calcium levels. Nitric oxide serves as the main neurotransmitter in the IAS causing relaxation of the muscle fibers.[15] Numerous clinical evidences pointed out the role of an elevated resting pressure of the IAS in patients with anal fissures.[16,17] Factors causing IAS hypertonia are not well understood, but a significant role in perpetrating the muscle spasm is played by the trauma caused by the passage of hard stools on the mucosa.[18] Spasm of the sphincter not only promotes constipation (thus setting up a vicious cycle) but also leads to compression of the terminal arterioles supplying the mucosa of the anal canal.[19] Impaired blood flow in this already poorly perfused area prevents fissure healing.

Since the introduction of the posterior internal sphincterotomy by Eisenhammer[20] in 1951, CAF has been managed with surgery once conservative measures failed. The more safe lateral sphincterotomy, popularized by Notaras[21] in 1969, has until recently been the mainstay of treatment to reduce the pathologically raised pressure profile within the anal canal. Despite that surgery is highly efficacious and succeeds in curing CAF in more than 90% of patients (often exceeds 95% with high patient satisfaction), postoperative impairment of continence is not uncommon.[10,15] The incidence is not well documented and varies between 0 and 35% for flatus incontinence, 0 and 21% for liquid incontinence, and 0 and 5% for solid stool incontinence.[22–25] As indicated by Nelson in a recent systematic review of randomized surgical trials, the overall risk of incontinence is about 10%,[9,10,26] mostly to flatus without any specification of the duration of this problem (transitory or permanent). However, it is a common belief that the risk of permanent incontinence is about 1%. Nonetheless, this does not take into account normal weakening of the sphincter with age and the possibility of future anorectal surgery, radiation, or obstetrical trauma. Therefore, the risk of incontinence after LIS should be considered lifelong, to an often young, otherwise healthy person.

To minimize this risk, several authors have tried a more limited division of internal sphincter, a tailored or controlled sphincterotomy, but additional remarkable data is needed.[27,28]

In the late 1990s when alternatives to surgery were sought because of risk of incontinence, costs, and time for recovery, newer medications directed at relaxing increased sphincter tone or enhancing mucosal blood flow were investigated. These included nitroglycerin ointment, calcium channel blockers (either given as tablets or topically), and recently, injection of botulinum toxin.

GTN causes sphincter relaxation by acting as a nitric oxide donor and improves anodermal perfusion.[29] Topical calcium channel blockers like diltiazem and nifedipine induce IAS by decreasing cytosolic calcium concentration.

Despite that early trials (including both acute and chronic fissure) of conservative medical treatments showed overall healing rates and pain relief close to surgery, usually results with medical treatments are only marginally better than placebo or conservative therapies alone (fiber, Sitz baths, and topical lidocaine) with healing rates between 36 to 68% and relapses rates as high as 35%.[30,31] According to Nelson's meta-analysis, a marginal advantage in using GTN (55%) over placebo (35%) exists, but no statistical difference was found comparing GTN to either botulinum toxin or calcium channel blockers.

We used GTN ointment in addition to conservative approaches (fiber and Sitz bath) as first line treatment because of its safety, convenience, and cost. The dosage and number of applications previously reported ranges from 0.2 to 0.5% and from twice to four times per day.[32,33] Dose escalation or use of a transdermal patch has not been shown to improve the healing rate.[34,35] The principal side effect is headache, seen in up to 50% of patients and less commonly anal pruritus.[31,36–38] Hence, compliance issues are observed in up to 72% of patients, and about 20% of patients will discontinue therapy.[26,35,39]

As 0.2% dosage seems to be as effective as 0.5% dosage, with less side effects, we decided to offer a 0.2% twice a day treatment. Our healing rate after GTN alone treatment was close to 40% increasing to only 50.5% when DIL course was added. We also observed a 24.5% recurrence rate, significantly higher compared to DIL use only or combined GTN/DIL. In our series, the incidence of side effects associated with GTN application was lower (12.8%) than the common incidence of at least 20–30% reported in literature. Only 4% of the patients discontinued the therapy and were switched to DIL. Surprisingly, in our series, the most common reason to discontinue GTN therapy was anal pruritus, observed in 5% of patients.

We believe that the low incidence of side effects and good compliance to treatment program showed by our groups of patients is the result of reduced number of applications (twice a day) and the accuracy of instructions given to the patient at the time of the outpatient visit.

The rationale for the use of anal dilators (DIL) is the finding that they induce muscle relaxation with consequent reduction in sphincter hypertonia. Moreover, blood flow is improved in the IAS, thus favoring fissure healing. When the DIL is heated, the relaxing effect is enhanced.[38] Short-term healing rates are reported as high as 95% when used in combination with GTN, with about 10% reduction after 2 years follow-up. However, little evidence on the efficacy of anal dilators is present in the literature. Recently, Schiano et al.[38] reported healing rates of 75% with DIL only and 93.7% with combined GTN/DIL treatment. In our experience, the DIL-only treatment was associated with a 46% healing rate, slightly superior to GTN use only. However, recurrence rate was significantly lower.

When DIL group was switched to GTN because of non-healing, the success rate increased to 66.7% significantly higher than the success rate of 50.5% observed when GTN course was followed by DIL. We explain this difference with a shorter healing time observed with GTN compared to DIL course that needs few weeks of applications of different size dilators. A 4-week DIL course may not be sufficient to significantly increase the healing rate after GTN, thus reducing the likelihood of surgery. An indirect evidence of this is observed in patients simultaneously treated with DIL and GTN who showed a definitive healing rate of 65% with a very low recurrence rate (7%). This result might be indicative of a possible synergic effect of the two. Schiano et al. reported a 93.5% healing rate; however, our follow-up was longer. In our experience, DIL use is safe, healing rates are comparable to GTN treatment, but compliance is lower. In our experience, 12.1% of the patients interrupted the DIL course because of severe discomfort preferring "less invasive" approaches. The reluctance in using DIL after GTN failure and the reduced compliance may also explain the low healing rate observed in this group.

Injection of botulinum toxin into the internal sphincter produces a temporary chemical sphincterotomy that allows fissure healing.

The botulinum toxin is believed to act at the postganglionic level reducing noradrenaline output from sympathetic neural terminals in the internal sphincter and possibly also by reducing myogenic tone in this tissue.[28] A single botulinum injection is well tolerated, with minor side effects, thus eliminating non-compliance issues. It reduces maximum resting pressure by a similar proportion to that of GTN (25–30%)[39] over a 2- to 3-month period of time.[22]

The most common side effect is transient incontinence to flatus (up to 10%) or feces (up to 5%).[40]

Recurrence are common but may be easily treated with a good rate of healing even if up to 20% of patients will need LIS.[26,41,42]

There is no consensus on dose, site, or number of injections.[43] However, a dosage between 20 and 25 U, and anterior injection seems more effective and causes no additional side effects.[14,15,37] A transient decrease in mean squeeze pressure can also be observed when higher doses are used.[40,44] Conversely, higher doses are not proven to be more effective.[45]

Despite that early trials have shown healing rates as high as 90% for acute and chronic fissures, the enthusiasm

was tempered by the disappointing results on CAF. Lindsey et al.,[11] in a prospective study of 40 patients with GTN-resistant fissures treated with 20U of botulinum, reported a healing rate of only 43%. Similarly, Minguez et al.[46] did not show healing rates as high as surgery after botulinum injection with a 42 months follow-up, while Arroyo et al. [47] and Mentes et al.[48] observed 1-year recurrence rates after botulinum injection approaching, respectively, 50 and 40%. Higher healing rates are observed if botulinum is given early, before the chronic fibrosis of the fissure is established.[39] As botulinum injection treats only the internal sphincter spasm, Lindsey et al.[22] have proposed to add fissurectomy to chemical sphincterotomy, reporting a healing rate of 93% for medically resistant CAF. In a more recent study, Scholz et al.[12] reports excellent results with implementation of the fissurectomy–Botox injection technique, which proved to be effective in treating fissure recurrences, too.

Fissurectomy enhances healing by removing the fibrotic fissure edges, unhealthy granulation tissue at the base, and the sentinel pile when present.[22]

We adopted this novel sphincter-sparing procedure as second line treatment after failure of GTN and/or DIL course. We observed a long-term healing rate of 81.8%, significantly higher than the one reported after all other approaches. Along with Lindsey et al, we believe that fissure healing is significantly higher with fissurectomy–botulinum toxin injection compared to medical treatment alone because with this treatment, we are able to address both elements of chronic fissure, chronic fibrosis, and internal sphincter spasm. We observed a single case of transitory incontinence, and our data confirm the safety of this treatment. The main drawback of this approach is the need of an operating theater and the costs. Although four patients of this group experienced fissure recurrence or non-healing, with two requiring subsequent LIS, fissurectomy and botulinum injection reduces significantly the need of LIS. The paucity of minor side effects associated to the good healing rates indicate that botulinum injection/fissurectomy may be used as first line approach for selected CAF even without previous medical treatment. Along with Lindsey et al., our study confirms that medical treatment alone for chronic, well-established fissures might be inappropriate, merely delaying definitive fissure healing.[13] Features of chronic fissure such as a fibrotic tissue, skin tag, or sentinel pile predict poor healing with medical therapy, and disappointing results of medical therapies for CAF, often similar, or just superior to placebo in different clinical trials, strengthen this observation. As a consequence of our experience and literature evidence, we believe that BTX/fissurectomy should be offered as first line treatment for patients with typical CAF even without previous medical/conservative treatments. Patients at high risk for anal incontinence, young female patients, and patients with previous anal surgery can also be treated with BTX/fissurectomy. Botulinum toxin injection associated to a gentle fissurectomy seems to be very safe, reducing greatly the likelihood of surgery and abolishing the risk of incontinence. The main drawback of BTX/fissurectomy is the need of surgery and the costs. However, we believe that the prompt and excellent healing rates (close to LIS) and the absence of severe side effects or complications might justify the costs.

Failure of BTX/fissurectomy or recurrence indicate the need of LIS.

Our study confirms that LIS represents the most effective approach to CAF. Although transitory postoperative incontinence can been observed in up to one third of patients, in our experience, we did not incur in any. Nonetheless, we did not observe any permanent incontinence. Although the proximal extent of the LIS continue to be a topic of debate, in our experience, by 'tailoring' the amount of sphincter to be divided to the length of the fissure, the risk of incontinence is minimized and the fissure healing achieved. To enhance and accelerate healing, we also believe that an accurate fissurectomy should always be added to LIS.

Conclusions

Although surgery (LIS) may be appropriately offered without a trial of pharmacological treatment after failure of conservative therapy as indicated by the "Practice parameters for the management of anal fissure", being incontinence as a lifelong risk, a step-wise approach would be appropriate and a trial of topical GTN and/or DIL should be offered. However, as refractory CAF with fibrotic tissue may heal with fissurectomy and botulinum injection only, abolishing the risk of incontinence, this approach should also be offered especially if patients are reluctant to undergo LIS or at high risk for incontinence. Moreover, according to our experience, this approach as first line medical treatment seems to be rational, safe, and effective, but further data is needed.

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Prognostic Significance of Pathologic Nodal Status in Patients with Resected Pancreatic Cancer

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Abstract

Background The purpose of this study was to evaluate the significance of pathologic nodal assessment and extent of nodal metastases on patient outcome in patients with pancreatic adenocarcinoma.

Materials and Methods A prospectively maintained pancreatic cancer database was reviewed, and 696 consecutive patients were identified who underwent resection for pancreatic adenocarcinoma between 1995 and 2005. Overall survival was compared to lymph node (LN) status, absolute number of pathologically assessed LN, and LN ratio expressed as the number of positive LN to the total LN assessed.

Results Of the 696 patients, 598 (86%) had pancreaticoduodenectomy (PD), and 96 (14%) had distal pancreatectomy (DP). For all patients, median follow-up was 13 months (range, 0–122 months), and estimated 5-year survival was 16%. A total of 243 (35%) patients were LN-negative (N0) and had a median survival of 27 months. When assessed as a continuous variable, the number of pathologically assessed LN did not correlate with survival for N0 patients undergoing either PD or DP. The median survival for the 453 patients with node-positive (N1) disease was 16 months. When analyzed as a continuous variable, the absolute number of positive LNs was a significant predictor of survival for N1 patients with a linear relationship up to eight positive LNs. LN ratio, as a continuous variable, also predicted survival with a linear relationship up to a ratio of 0.35. A ratio of 0.18 was associated with a 19-month median survival and served as the best cutoff, $p<0.01$.

Conclusions The absolute number of positive LNs and LN ratio are strong predictors of survival for patients with node-positive pancreatic adenocarcinoma. Inadequate surgical lymphadenectomy or pathologic LN assessment understages node-negative patients.

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Keywords Pancreas · Adenocarcinoma · Lymph nodes · Survival

Introduction

Over one half of the patients diagnosed with adenocarcinoma of the pancreas will harbor metastatic disease at the time of presentation, and one half of the remaining patients without metastatic disease will have locoregionally advanced disease that precludes surgical resection.[1,2] Even for patients with localized, surgically resectable disease, long-term survival after treatment for pancreatic adenocarcinoma is poor. The estimated 5- and 10-year survival for patients after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma is 18 and 11%, respec-

tively, and the actual 5-year survival rate for these patients has been reported as 4–10%.[3–7]

Based on a large clinical database containing clinicopathologic factors associated with outcome, a prognostic nomogram has been developed to predict survival for individual patients after resection for pancreatic adenocarcinoma.[8] Verifiable factors that are associated with patient outcome include the following: tumor size, tumor differentiation, surgical margin status, and lymph node status.[7–10] In addition to lymph node status, the number of pathologically detected positive lymph nodes has been incorporated into the nomogram as a strong predictor of outcome for patients who undergo surgical resection for pancreatic adenocarcinoma.[8]

Similar to other gastrointestinal malignancies, accurate stage-based prediction of survival after resection for pancreatic adenocarcinoma appears to be dependent on the degree to which regional lymph nodes are assessed.[11] Retrospective studies have shown that the total number of positive nodes identified, the total number of negative nodes identified, and the ratio of positive to total lymph nodes assessed after pancreaticoduodenectomy all correlate with survival for patients with resected pancreatic head cancer.[12–14] These findings suggest that more accurate stage-specific survival is obtained in the setting of high negative lymph node counts (or a lower ratio of positive/negative nodes) because of the greater likelihood that the extent of nodal disease has been accurately determined. Patients with higher ratios may have incompletely documented nodal disease (e.g., one positive node out of two assessed) or a substantially greater burden of disease (e.g., 12 positive nodes out of 24 assessed).

Using an extensive, single-institution cancer database with long-term clinical follow-up, we performed a retrospective review of a prospective dataset to examine the influence of pathologic lymph node assessment on patient survival after resection for pancreatic adenocarcinoma.

Materials and Methods

Patients

Over a 10-year period from 1995 to 2005, 696 consecutive patients underwent surgical resection for pancreatic adenocarcinoma at Memorial Sloan-Kettering Cancer Center (MSKCC). Permission for studying these patients was obtained from the MSKCC Institutional Review and Privacy Board according to institutional policy for protected health information. All patients were identified from a prospectively maintained pancreatic cancer database containing demographic, clinical, operative, pathological, and follow-up data. Thirteen attending surgeons were included in this study, and three surgeons accounted for 54% of the pancreatic resections. Complete postoperative treatment-related and follow-up data were available for 92% of the patients. Clinical status during patient follow-up was categorized into four groups as follows: no evidence of disease (NED), alive with disease (AWD), dead of disease (DOD), and dead of other causes (DOC). Follow-up time was calculated from the date of pancreatic resection to the date of last clinical interaction.

Pathology

Final pathology reports were reviewed retrospectively to confirm the presence of a primary pancreatic adenocarcinoma in each of the surgical specimens included in this study. Primary tumor size was recorded as the largest diameter axis through the sectioned specimen. Histologic grade was categorized into two groups for analysis: poor/undifferentiated or moderate/well-differentiated. The absence of microscopic disease involving any pancreatic resection margin was considered a margin-negative (R0) resection. The total number of examined lymph nodes and the number of histologically positive metastatic lymph nodes within each surgical specimen were recorded. For node-positive (N1) cancers, a lymph node ratio (LNR) was calculated as the number of metastatic lymph nodes divided by the total number of lymph nodes within the surgical specimen. Cancer staging was based on pathologic findings referenced to the sixth edition of the AJCC guidelines for pancreatic exocrine cancer.[15]

Statistics

Statistical analyses were performed appropriately with SPSS version 12.0 for Windows (Statistical Package for the Social Sciences, Inc., Chicago, IL) and/or SAS version 9.1 (Statistical Analysis System, Cary, NC). Continuous variables were expressed as median or mean±standard deviation and were compared using a two-sample t test. Categorical variables were compared using a χ^2 test. Survival probabilities for clinical, pathological, and treatment variables were estimated using the Kaplan–Meier method and compared using a log–rank test. The effect of number of negative nodes, number of positive nodes, and LN ratio on survival were examined using local regression, and optimal cutoffs were determined using the maximal chi-square method.[16,17] Significant univariate factors were included in a Cox proportional hazards regression model to determine multivariate significance.

Results

A total of 696 patients with a median age of 70 years underwent pancreatic resection (Table 1). Final histopathology was graded as poorly differentiated in 34% of patients. The average tumor diameter was 3.2 cm. Pathologically positive lymph nodes were detected in 453 patients (65% of

Table 1 Patient and Pathologic Characteristics

Characteristics	
Total patients	696
Median age (range)	70±10 years (39–92)
Gender	
Male	339 (49%)
Female	357 (51%)
Site of pancreatic cancer	
Head	596 (86%)
Body	48 (7%)
Tail	52 (7%)
Type of operation	
Pancreaticoduodenectomy	598 (86%)
Distal pancreatectomy	96 (14%)
Total pancreatectomy	2 (0.3%)
Margin status	
Negative	502 (72%)
Positive	194 (28%)
Resection margin	127 (18%)
Retroperitoneal margin	81 (12%)
Tumor stage	
T1	16 (2%)
T2	164 (24%)
T3	516 (74%)
Mean tumor diameter (range)	3.2±1.6 cm (0–15)
Histologic grade	
Well/moderate differentiated	457 (66%)
Poor/undifferentiated	239 (34%)
Nodal stage	
N0	243 (35%)
N1	453 (65%)
Total LN count[a] (range)	
All patients	17±9.5 (0–61)
N0 patients	13±8 (0–41)
N1 patients	19±10 (3–61)
Positive LN count[a] (range)	
N1 patients	4±3 (1–21)
Cancer stage	
IA	11 (2%)
IB	55 (8%)
IIA	177 (25%)
IIB	444 (64%)
IV	9 (1%)
Median follow-up (range)	13 months (0–122)
90-day mortality	28 (4%)

[a] Number of pathologically assessed lymph nodes (LN) in surgical specimen (expressed as mean number)

all resections). Seventy-four percent of cancers were T3, and 64% of patients were stage IIB.

Pancreaticoduodenectomy was performed in 598 patients, 86% of the pancreatic resections. A margin-negative (R0) pancreatic resection was achieved in 502 patients (72%). Clinical follow-up data were available for 92% of the patients (n=640) with a median follow-up of 13 months. The 90-day patient mortality rate was 4%. The median follow-up for 3- and 5-year survivors was 52 and 75 months, respectively.

Table 2 Multivariate Analysis[a] of Predictors for Survival After Resection

Risk Factor	Hazard Ratio	95% C.I.	p value
Positive lymph nodes	1.81	1.44–2.25	<0.001
Histological grade (poor or undifferentiated)	1.63	1.34–2.05	<0.001
Positive resection margin	1.41	1.14–1.75	0.014

[a] Cox proportional hazards regression model (included in multivariate analysis: type of procedure, T stage, tumor diameter (numerical), N stage, histologic grade, and margin status)

Multivariate analysis of pathologic variables, previously established as predictors of survival, was performed to validate the dataset included in this study.[8,9] The hazard ratio associated with each of these variables is listed in Table 2.

Total LN Assessment for N0 and N1 Patients

The total number of pathologically assessed lymph nodes were recorded from the final pathology report for each surgical specimen. The mean number of assessed lymph nodes for all specimens was 17. There was a significant difference in the total lymph node count for patients with or without nodal metastases (Table 1; mean lymph node count 19 versus 13, respectively, p=0.02).

In this study, 243 patients had no histopathologic evidence of lymph node metastases (N0). Among these

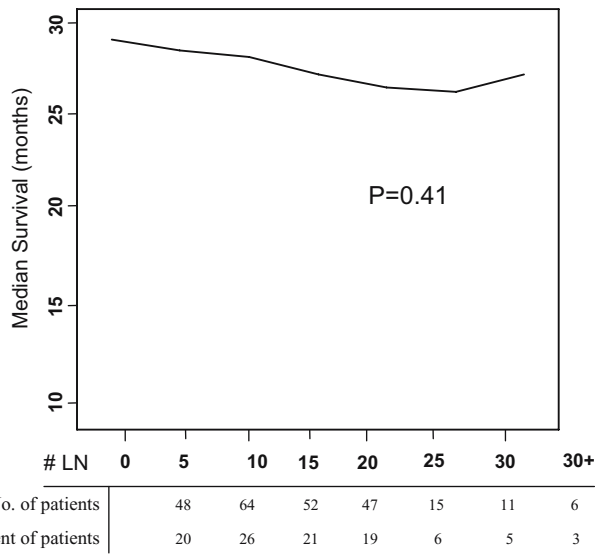

Figure 1 Relationship between the total number of lymph nodes examined and median survival for 243 patients pathologically staged with N0 disease after pancreatic resection. Patients are grouped according to total lymph node counts of 0–5, 6–10, 11–15, 16–20, 21–25, 26–30, and >30.

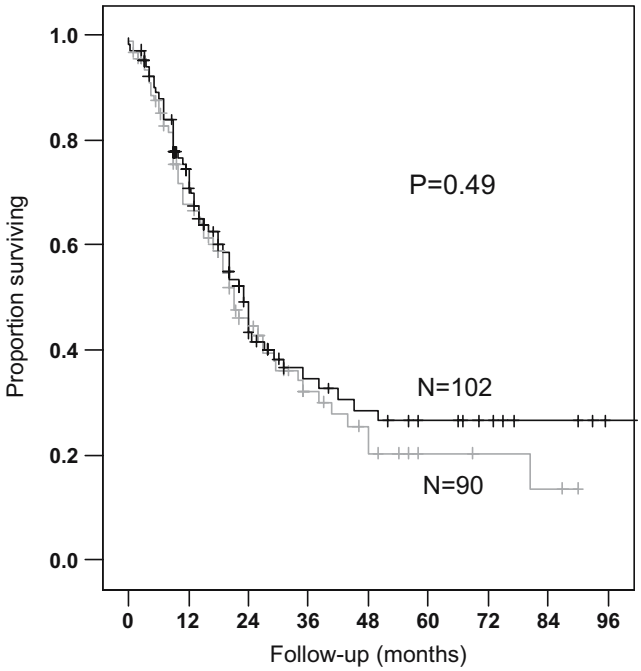

Figure 2 Kaplan–Meier plot of overall survival (in months) for pathologically staged N0 patients who underwent an R0 resection for pancreatic adenocarcinoma. Patients who had <12 lymph nodes (N=90) examined are represented by the *gray curve*. Patients with ≥12 lymph nodes (N=102) examined are represented by the *black curve*. The estimated 3- and 5-year survival for patients with ≥12 lymph nodes examined was 35 and 26%, respectively.

patients, the mean and median number of assessed lymph nodes was 13 and 12 (range, 0–41 nodes), respectively. The median survival for N0 patients, as a group, was 27 months. For patients who underwent pancreatic resection and were node-negative, the total number of assessed lymph nodes was not found to be associated with survival (Fig. 1). Similar results were obtained for patients who either underwent pancreaticoduodenectomy or distal pancreatectomy. There was not an association between survival and the total number of assessed lymph nodes for subgroups of node-negative patients categorized according to margin status, type of operation, tumor size, tumor stage, or histologic grade. When the median number of total lymph nodes (i.e., 12 nodes) was used as a cutoff value, there was no significant separation in the Kaplan–Meier survival curves for N0 patients who underwent an R0 resection for pancreatic adenocarcinoma (Fig. 2). Arbitrary cutoff points at 10, 15, and 20 total lymph nodes failed to generate a survival difference in the N0/R0 patients.

For patients who had less than 12 lymph nodes assessed pathologically, the presence of one or more positive lymph nodes was not associated with a worse overall survival compared to node-negative patients (Fig. 3a). However, the 3-year survival for node-negative patients who had at least 12 lymph nodes assessed was significantly better than that for node-positive patients, 39 versus 22% (p=0.02), respectively (Fig. 3b).

In this study, 125 patients were staged as node-positive on the basis of one pathologically detected metastatic lymph node and represented 28% of all node-positive patients. The median and 3-year survival for patients with a solitary nodal metastasis out of a minimum of 12 total lymph nodes were 22 months and 31%, respectively (Fig. 4). The observed overall survival for these patients was similar to that observed for N0 patients who had fewer than 12 lymph nodes assessed (Fig. 3a). When less than 12 total lymph nodes were assessed, there were no long-term survivors among a group of 38 patients with a single positive node (Fig. 4).

Positive LN Number as a Predictor of Survival

On average, patients with node-positive pancreatic cancer had four positive lymph nodes (range, 1–21 nodes). As an entire group, the median survival for node-positive patients was 16 months. There was a linear relationship between the number of metastatic lymph nodes and median survival for

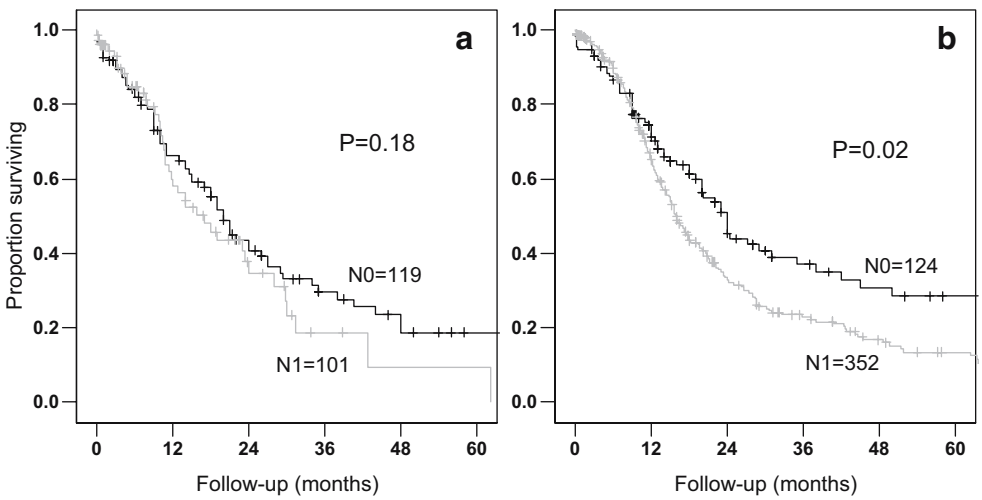

Figure 3 Overall survival of patients with pathologically staged N0 (*black curve*) or N1 (*gray curve*) pancreatic adenocarcinoma. **a** comparison of N0 versus N1 patients who had <12 lymph nodes examined. **b** comparison of N0 versus N1 patients who had ≥12 lymph nodes examined. The estimated 3- and 5-year survival for N0 patients with ≥12 lymph nodes examined was 39 and 29%, respectively. In comparison, the estimated 3- and 5-year survival for N1 patients with ≥12 lymph nodes examined was 22 and 13%, respectively.

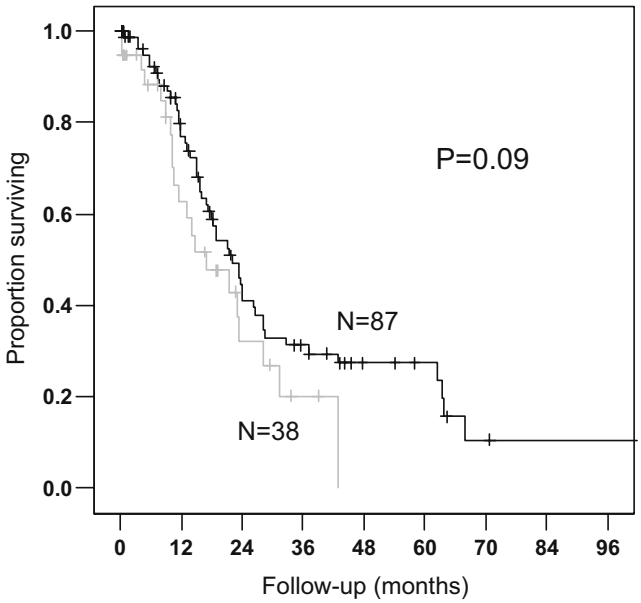

Figure 4 Overall survival of 125 N1 patients who had a single pathologically detected lymph node metastasis. Patients who had ≥12 total lymph nodes examined (*black curve*) were compared to patients who had <12 total lymph nodes examined (*gray curve*). The estimated 3- and 5-year survival for patients with a single positive lymph node out of =12 total lymph nodes was 31 and 27%, respectively.

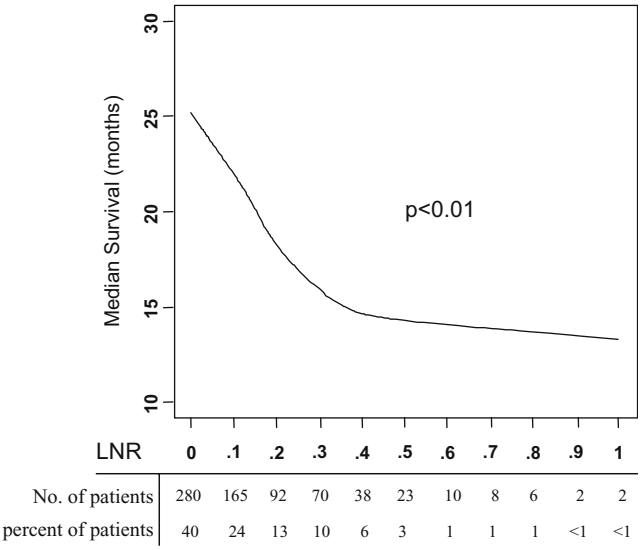

Figure 6 Relationship between lymph node ratio (*LNR*) and the median survival for 696 patients undergoing resection for pancreatic adenocarcinoma. LNR was calculated as the number of metastatic nodes among the total number of lymph nodes examined. The number and percentage of patients in each LNR group (rounded to the nearest ratio) are listed.

patients with node-positive disease. The presence of two positive lymph nodes was associated with a median survival of 20 months and represented the most significant point of separation in survival, $p=0.01$ (Fig. 5). The linear relationship between the number of positive lymph nodes and survival was lost after eight metastatic lymph nodes. Only 33 patients had more than eight positive lymph nodes.

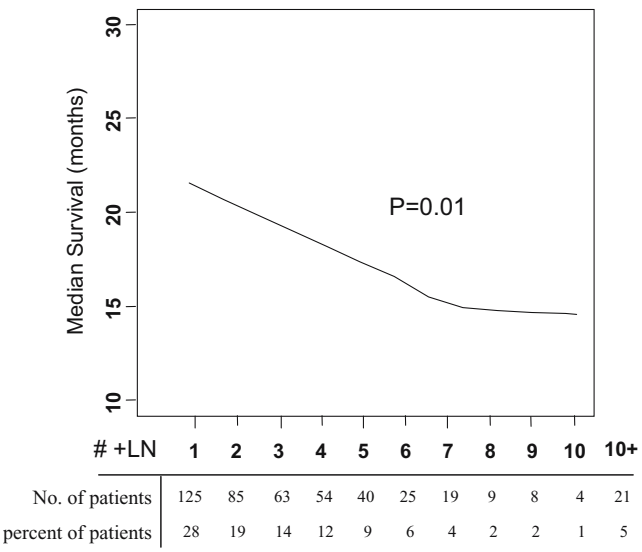

Figure 5 Relationship between the absolute number of metastatic lymph nodes and median survival in 453 patients pathologically staged with node-positive pancreatic adenocarcinoma. The number and percentage of patients with each number of positive lymph nodes are indicated.

LN Ratio as a Predictor of Survival

Lymph node ratio, as a continuous variable, was associated with survival. The linear relationship between LNR and median survival was highly significant and was observed up to a ratio of 0.35 (Fig. 6). LNR of 0.18 was the best cutoff value and was associated with a median survival of 19 months. Only 7% of patients had a LNR greater than 0.4.

Discussion

Complete surgical resection remains the only potentially curative treatment for adenocarcinoma of the pancreas. Even after R0 resection, the majority of patients with pancreatic adenocarcinoma will develop recurrent disease locally, regionally, and/or distantly. Several pathologic factors, including nodal status, margin status, tumor size, and histologic grade, have been established as predictors of poor survival after curative resection.[7–10,18,19] For pancreatic adenocarcinoma, the presence of metastatic lymph nodes has been associated with relatively poor prognosis that does not seem to be improved with extended lymphadenectomy for therapeutic intent.[20–23]

The purpose of this study was to further examine the influence of pathologic lymph node assessment on the stage-specific outcome for patients with resected pancreatic adenocarcinoma.

Retrospective studies have examined the relationship between survival and the extent of lymph node assessment after resection for various gastrointestinal malignancies including pancreatic adenocarcinoma.[11,13,14,24–26] A recent review of 1,666 patients with clinicopathologic data, contained within the Surveillance, Epidemiology, and End Results (SEER) database for pancreatic cancer between 1973 and 2000, reported a significant influence of the total number of examined lymph nodes on the estimation of stage-based survival after resection for pancreatic adenocarcinoma.[11] The most significant survival differences among N0 and N1 patients in the SEER database were observed when patients were subgrouped according to total lymph node counts of 11 and 14, respectively. Higher cutpoints for the total number of lymph nodes (e.g., total node count greater than 25) were not associated with a significant survival difference for patients with any-stage disease and possibly reflects the inclusion of only 65 patients with more than 25 total lymph nodes assessed. Selective analysis of SEER data from 14 cancer registries over three decades faces many limitations including incomplete pathologic data, lack of information regarding the adequacy of surgical resection, and questionable relevance to contemporary clinical outcomes.

Improving the accuracy of stage-specific survival probabilities through more extensive pathologic nodal assessment (i.e., stage migration) has not translated into improved survival with more extensive operative nodal dissection (i.e., therapeutic effect). Prospective randomized controlled trials have not reported improved survival in patients undergoing extended nodal dissection for pancreatic adenocarcinoma.[20–23] However, these randomized trials have not reported stage-specific survival, and some have included different histopathologic entities. The influence of extended lymph node dissection on stage migration, and possibly on disease-specific survival, remains unclear.

Our retrospective analysis of a contemporary single-institution dataset did not demonstrate a continuous relationship between the total number of lymph nodes examined and survival for resected patients with node-negative disease. Among a relatively favorable group of 109 patients, who underwent R0 resection for small (<3 cm) primary cancers with negative nodes, increased pathologic nodal assessment was not found to be associated with a difference in survival.

Within the group of patients with node-negative disease, there was evidence of stage migration with more extensive nodal assessment. Patients who were deemed node-negative with fewer than 12 lymph nodes assessed had a similar survival to patients with a single positive node and greater than 12 nodes assessed. The median, 3- and 5-year survival for patients with one positive node out of a minimum of 12 total lymph nodes, assessed were 22 months, 31 and 27%, respectively. Similarly, the observed overall survival for N0 patients who had less than 12 lymph nodes assessed experienced a median, 3- and 5-year survival of 21 months, 32 and 18%, respectively. With more extensive nodal assessment (i.e., ≥12 nodes assessed), patients with node-negative disease had improved survival compared to those with a single positive lymph node (Fig. 4). This observation may provide an explanation for previous reports that have failed to demonstrate a significant survival difference between patients with a single lymph node metastasis and those with N0 disease.[27,28]

Prior studies have suggested that survival after resection for pancreatic adenocarcinoma declines significantly when two or more lymph nodes are detected pathologically compared to a single nodal metastasis.[27,28] In the current study, we were able to demonstrate a relationship between the absolute number of metastatic lymph nodes and survival for patients with N1 disease. The presence of two positive lymph nodes was associated with the most significant difference in median survival for N1 patients, but the linear relationship between the number of positive lymph nodes and survival persisted until eight or more metastatic lymph nodes were present. We were also able to show that lymph node ratio was associated with survival for patients with N1 disease. A LNR value of 18% was associated with the most significant difference in median survival for node-positive patients in this study and was comparable to previous reports citing an optimum cutoff LNR value at 15–20%.[13,14] The linear decrement in survival associated with LNR for node-positive patients was observed up to a ratio of 35%. Pawlik et al.[12] recently reported that LNR remains an independent predictor of disease-specific survival even after adjusting for established factors associated with poor outcome (e.g., poor histologic grade, margin positivity, perineural invasion, and tumor size larger than 2 cm).

We were not able to determine the comparative strength of positive lymph node number versus LNR as an independent factor that stratifies survival for patients with N1 disease. Intuitively, LNR should be associated with more accurate survival estimation given the wide standard deviation in the mean number of lymph nodes assessed in node-positive patients (e.g., mean 19±10). Schwarz et al.[11] in their SEER review demonstrated that stage-based estimation of overall survival for resected pancreatic cancer was associated with the absolute number of negative lymph nodes in addition to total lymph node count.

In conclusion, the results of the current study suggest that pathologic assessment of more than 12 lymph nodes may

provide more accurate survival estimates for patients who are resected with node-negative disease. Inadequate surgical lymphadenectomy and/or pathologic assessment appears to understage N0 patients as these patients have similar outcomes to patients with a single positive node out of a minimum of 12 lymph nodes assessed. Both the absolute number of positive lymph nodes and LNR are predictors of survival for patients with node-positive pancreatic adenocarcinoma. A thorough assessment of regional lymph nodes in resected specimens should be performed in an attempt to provide more accurate prognostic information.

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The Impact of Perioperative Dexmedetomidine Infusion on Postoperative Narcotic Use and Duration of Stay after Laparoscopic Bariatric Surgery

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Abstract Dexmedetomidine (Precedex, Hospira, Lake Forest, IL) is an alpha-2 receptor agonist with sedative and analgesic sparing properties. This medication has not been associated with respiratory suppression, despite occasionally high levels of sedation. For 10 months, all patients undergoing a laparoscopic bariatric procedure received a dexmedetomidine infusion 30 min before the anticipated completion of the procedure (n=34). A control group was comprised of a similar number of patients to have had laparoscopic bariatric surgery in the time period immediately before these 10 months (n=37). All pathways and discharge criteria were identical for patients in each group. A total of 73 patients were included in this retrospective chart review. Two gastric bypass patients were excluded for complications requiring additional surgery (one bleed and one leak). Gastric bypass patients who received a dexmedetomidine infusion required fewer narcotics (66 vs 130 mg of morphine equivalents) than control patients and met discharge criteria on post-op day (POD) 1 more often (61% discharged POD 1 vs 26% discharged POD 1, p=0.02). Vital signs and pain scores were similar in all groups. Dexmedetomidine infusion perioperatively is safe and may help to minimize narcotic requirements and decrease duration of stay after laparoscopic bariatric procedures. This may have important patient safety ramifications in a patient population with a high prevalence of obstructive sleep apnea. A well-organized prospective, randomized, double-blinded trial is necessary to confirm the benefits of dexmedetomidine suggested by this study.

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Introduction

The prevalence of obesity is escalating at an alarming rate in the USA.[1] Increasingly, obese Americans are turning to bariatric surgery as a means of significant and durable weight loss.[2] Due to the strong association between obesity and certain medical conditions, bariatric surgery patients are at increased risk for a variety of medical complications after surgery. Obstructive sleep apnea is extremely common in obese bariatric surgical candidates. Studies have indicated that the incidence of this comorbid medical condition may be as high as 77% in those seeking surgery.[3] Narcotic pain medications can decrease upper airway tone and unmask or exacerbate sleep apnea.[4] Apneic episodes precipitating heart block perioperatively in bariatric surgery

patients have also been documented.[5] For these reasons, the American Society of Anesthesiologists task force on perioperative management of patients with obstructive sleep apnea recommends minimizing or avoiding perioperative narcotic administration to these patients.[6]

Dexmedetomidine (Precedex, Hospira, Lake Forest, IL) is a highly selective alpha-2 adrenergic receptor agonist with sedative and analgesic properties.[7] Dexmedetomidine has not been associated with respiratory depression, despite occasionally profound levels of sedation.[8] For these reasons, this medication may be useful in achieving an adequate level of pain control in bariatric surgery patients while minimizing the use of narcotics and avoiding respiratory suppression and the potential sequelae in patients prone to apnea. Minimizing perioperative narcotics may also allow patients to meet discharge criteria sooner. We sought to determine the impact of a perioperative dexmedetomidine infusion on narcotic requirements and duration of stay after minimally invasive bariatric surgery.

Materials and Methods

In September of 2005, we began to administer a perioperative dexmedetomidine infusion to all patients undergoing a laparoscopic bariatric surgical procedure as part of a new clinical protocol. The infusion was started 30 min before the anticipated completion of either a laparoscopic adjustable gastric band or a laparoscopic gastric bypass. Dexmedetomidine was loaded at 1 mcg/kg IV over 10 min and continued until the end of the operation at 0.2–0.7 mcg kg^{-1} h^{-1} IV to maintain systolic blood pressure >90 mmHg. Infusion was discontinued in the post-anesthesia care unit (PACU).

Minimally invasive bariatric surgery patients to have received this infusion over a 10-month period (September 2005 to June 2006) were compared to a similar number of patients to have had surgery immediately before this interval without a dexmedetomidine infusion. Due to the fundamentally different nature of gastric band surgery and a gastric bypass, comparisons were made only between patients to have had the same procedure. Narcotic doses, antiemetic requirements, patient self-assessed pain scores, perioperative vital signs, and duration of stay were the variables of interest. These parameters were compared by a retrospective chart review and utilizing a comprehensive hospital computerized data warehouse. All pathways and discharge criteria were identical for patients in each group. Patients chronically taking prescription narcotic medications preoperatively were excluded. Patients who experienced major complications that may have contributed to a prolonged hospital stay or increased pain (intestinal leak or bleeding for example) were also excluded. This study was approved by the University of Wisconsin Institutional Review Board. Statistical analysis was conducted using MStat 4.01, University of Wisconsin, Madison, WI.

Results

Charts from 73 patients meeting the above criteria were reviewed. Two gastric bypass patients were excluded for major complications (one intra-abdominal bleed and one leak, both requiring a second procedure), one in each study group. Dexmedetomidine was administered to 23 gastric bypass patients and 11 gastric band patients. The control group consisted of 19 gastric bypass patients and 18 gastric band patients who did not receive a dexmedetomidine infusion. For the gastric bypass patients, each group was similar with regards to age (41 years dex vs 46 years control, $p=0.3$), sex (83% female dex vs 84% female control; $p=1$), and initial body mass index (BMI; 52 kg/m^2 dex vs 51 kg/m^2 control; $p=0.46$). For the gastric band patients, each group was similar with regards to age (46 years dex vs 42 years control; $p=0.33$), sex (82% female dex vs 56% female control; $p=0.15$), and initial BMI (45 kg/m^2 dex vs 45 kg/m^2 control; $p=0.82$).

In the laparoscopic gastric bypass patients, a similar level of pain control was attained in each group. Study patients in the dexmedetomidine group were administered less narcotic pain medications during their hospital stay, and these patients met discharge criteria on post-op day (POD) 1 more often and were discharged home from the hospital slightly sooner than patients in the control group (Table 1). As Table 1 also demonstrates, perioperative vital signs did not differ for gastric bypass patients regardless of their treatment group. In the gastric band patients, a similar level of pain control and comparable vital signs were observed for each study group (Table 2). Duration of stay and total milligrams of morphine equivalents required were similar for each gastric band study group. Unlike in the gastric bypass patients, there was a slightly decreased need for antiemetic medications in the gastric band patients to receive a dexmedetomidine infusion.

The mean number of dexmedetomidine bottles administered in this protocol was 1.7 per patient (range, one to three bottles). The Average Wholesale Price (AWP) for one bottle is $69 (average, $117/patient).

Discussion

In this retrospective study, we have demonstrated that a dexmedetomidine infusion can safely be administered perioperatively to morbidly obese patients. Furthermore, we have also provided data suggesting that a perioperative

Table 1 Outcomes in Laparoscopic Gastric Bypass Patients According to Dexmedetomidine Infusion Status

	Dex (n=23)	Control (n=19)	p value
MSO4 equiv total (mg)	66*	130*	0.04
MSO4 equiv/day (mg)	47	67	0.53
Duration of stay (days)	1.4*	1.9*	0.02
D/C criteria met POD 1	14/23 (61%)*	5/19 (26%)*	0.02
Pain score PACU (0–10)	3.5	2.7	0.37
Pain score floor day 0	2.4	3.3	0.15
Antiemetic doses	3.0	2.7	0.83
Mean HR PACU	75	72	0.21
Mean SBP PACU (mmHg)	121	124	0.63
Initial RR PACU	17	16	0.58

MSO4 equiv Morphine equivalents; *D/C* discharge; *PACU* Post-anesthesia Care Unit; *HR* heart rate; *SBP* systolic blood pressure, *RR* respiratory rate

*p<0.05, statistically significant

dexmedetomidine infusion may result in less need for narcotics and earlier discharge, particularly after laparoscopic gastric bypass surgery.

The analgesic properties of alpha-2 adrenergic agonists were first described more than 30 years ago, when nociceptive thresholds in rats given clonidine were noted to be increased.[9] Dexmedetomidine is a highly selective alpha-2 agonist with an approximately eight times higher affinity for the alpha-2 adrenoreceptor than clonidine. Dexmedetomidine has been associated with what has been termed "arousable sedation." Patients receiving dexmedetomidine can typically respond to commands and perform psychomotor tests when lightly roused from their sedate state without a need to decrease or stop the dexmedetomidine infusion.[10] Dexmedetomidine has been approved for use in the ICU, but its role in contemporary intra-operative anesthesia has yet to be established.[11] After intravenous infusion, dexmedetomidine is largely bound to plasma proteins, and the serum concentration has been demonstrated to be unaffected by body weight or BMI. Metabolism occurs primarily in the liver and decreased dosages may be required in those with hepatic impairment.[12] Despite these facts, this is the first study to objectively examine the impact of a dexmedetomidine infusion on narcotic requirements specifically in a morbidly obese patient population. Further research is necessary to confirm the potential beneficial effects of a dexmedetomidine infusion for bariatric surgery patients.

We first became interested in the potential benefits of perioperative dexmedetomidine in bariatric surgery patients after reading a manuscript published by McCarty et al.[13] These authors safely discharged 84% of a case series of 2,000 laparoscopic gastric bypass patients within 23 h. In the McCarty series, very few patients were readmitted within 30 days (1.7%), and the early complication rate was quite low as well (1.9%). The standard pathway in the later portion of this case series included a perioperative dexmedetomidine infusion. Although multivariate analysis did not demonstrate that a dexmedetomidine infusion was associated with early discharge, we felt that any narcotic

Table 2 Outcomes in Laparoscopic Adjustable Gastric Band Patients According to Dexmedetomidine Infusion Status

	Dex (n=11)	Control (n=18)	p value
MSO4 equiv total (mg)	19	33	0.06
MSO4 equiv/day (mg)	18*	33*	0.03
Duration of stay (days)	1.1	1.0	0.2
D/C criteria met POD 1	10/11 (91%)	18/18 (100%)	0.38
Pain score PACU (0–10)	4.1	3.6	0.91
Pain score floor day 0	2.7	2.4	0.75
Antiemetic doses	1.5*	2.2*	*0.04*
Mean HR PACU	69	69	0.98
Mean SBP PACU (mmHg)	114	125	0.09
Initial RR PACU	15	17	0.23

MSO4 equiv Morphine equivalents; *D/C* discharge; *PACU* Post-anesthesia Care Unit; *HR* heart rate; *SBP* systolic blood pressure, *RR* respiratory rate

*p<0.05, statistically significant

sparing effects of this medication would be beneficial from a patient safety perspective. The McCarty study does not objectively examine the association between narcotic requirements and dexmedetomidine, but several other published studies have looked at this relationship in a variety of patient populations and clinical settings.

Gurbet et al.[14] recently published the results of a prospective, randomized, double-blinded study evaluating the impact of an intra-operative dexmedetomidine infusion on morphine requirements postoperatively in 50 women undergoing total abdominal hysterectomy. Patients to receive a dexmedetomidine infusion required significantly less morphine in the recovery room and on the ward than patients randomized to receive a 0.9% saline infusion. Patients in the treatment group also reported less nausea and itching than patients in the placebo group. Patients with a weight exceeding 100 kg were excluded from this study.

Shahbaz et al.[15] conducted a prospective randomized double-blinded trial designed to compare the analgesic efficacy of dexmedetomidine with that of morphine in the early perioperative period. Patients undergoing elective inpatient surgery were randomized to receive either dexmedetomidine or morphine sulfate infusion 30 min before the anticipated completion of each procedure. End points were vital signs, visual analogue pain scores, sedation levels, and requirements for additional morphine in the recovery room to achieve adequate pain control. These investigators determined that the dexmedetomidine-treated patients required significantly less supplemental morphine to achieve equivalent analgesia and that these patients had a significantly slower heart rate in the recovery room. Other vital signs and sedation levels were similar in each study group. As in the Gurbet study, morbidly obese patients were excluded. The Shahbaz trial also excluded patients with sleep apnea.

Conclusions

Perioperative dexmedetomidine infusions can be safely administered to bariatric surgery patients. Adequate pain control with a ‘narcotic sparing’ effect can be observed. This factor may have important safety ramifications in a population of patients with a high prevalence of obstructive sleep apnea. In minimally invasive bariatric surgery, particularly for gastric bypass, a perioperative dexmedetomidine infusion may be associated with discharge criteria being met sooner and a decreased duration of stay. Further study is necessary to confirm these conclusions.

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Outcomes of Cocaine-Induced Gastric Perforations Repaired With an Omental Patch

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Abstract
Crack cocaine has been associated with acute gastric perforation. The appropriate surgical treatment and long-term outcomes remain unclear. A retrospective chart review of all gastroduodenal perforations associated with crack cocaine use was performed. Data abstracted included details of short- and long-term outcomes. Kaplan–Meier methods were used to evaluate surgical outcomes. Over the 14-year period ending December 2005, 16 cases of crack-induced gastric perforations were identified. Most (75%) were treated with an omental patch. The other patients underwent a formal antiulcer operation, including one vagotomy and pyloroplasty (V&P), one vagotomy and antrectomy, one subtotal gastrectomy, and one ulcer excision and V&P. All patients after antiulcer procedures were followed for a median of 63 months (range 27–120) with no recurrences. Follow-up data were available in 75% of the omental patch patients. Recurrence of disease was observed in 56% of these omental patch patients at a median of 20 months (range 11–39). Those without recurrence were followed for a median of 67 months (range 12–96). The recurrence rate was borderline lower in the antiulcer group (P=0.072). Omental patch closure results in a recurrence rate over 50% compared with no recurrence for formal antiulcer procedures.

Keywords Peptic ulcer perforation · Crack cocaine · Gastrectomy

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Introduction

About 6.3 million US residents consumed cocaine on at least one occasion during calendar year 2002.[1] Crack cocaine, a cheaper and smokable form of cocaine, made by mixing cocaine with baking soda in boiling water, became widely available in the mid-1980s. The relatively low cost of crack has allowed it to become common among low-income inner-city African-Americans.[2] Both cocaine and crack have been linked to a variety of adverse health events, including seizure, stroke, myocardial infarction, pulmonary disease, and psychiatric disorders.[3–8] There is also evidence to support more severe health problems when the cocaine is injected or smoked.[9] Anecdotal reports of young, mostly male crack users presenting with acute juxtapyloric gastric perforations began appearing in the literature in 1989.[10] Since that time, several other reports have appeared documenting this phenomenon.[11–15] No long-term follow-up of these patients is reported. Although the etiology remains unclear, the pathogenesis is most commonly attributed to local ischemia caused by crack cocaine-induced profound vasoconstriction. Regardless of etiology, this is an important disease entity now facing

surgeons caring for patients in areas where crack cocaine use is prevalent.

At The University of Miami affiliated Jackson Memorial Hospital, an apparent high rate of recurrence of perforated juxtapyloric ulcers was identified in this patient population when omental patches were used as the sole repair. Formal antiulcer operations may offer a potential advantage over patch repair as a more durable solution without increased morbidity or mortality in this otherwise relatively young and healthy cohort. We, therefore, undertook this review of our experience treating perforated gastroduodenal ulcers associated with crack cocaine use.

Material and Methods

After approval by the University of Miami Institutional Review Board, all patients undergoing emergency operation for perforated ulcer disease between January 1991 and December 2005 at Jackson Memorial Hospital were identified from the operative logs. Charts were reviewed to identify patients whose onset of abdominal pain was temporally associated with the use of crack cocaine. For those patients with associated crack cocaine use, charts were reviewed for data of initial presentation, operative findings and procedures, and postoperative course. Long-term follow-up data were obtained by reviewing data from office records and subsequent hospital admissions for similar or unrelated medical issues. Patient demographics and variables were compared using the *t*-test and chi-square where appropriate. Kaplan–Meier cumulative recurrence curves were generated to compare omental patch repairs and antiulcer operations. The log-rank test was used to determine significance ($p<0.05$).

Results

Over the 14-year period ending December 2005, 143 emergency upper gastrointestinal cases were identified from the operative logs at Jackson Memorial Hospital. After detailed chart review, 16 cases (11%) were identified as crack-related ulcer perforations. Patients were predominantly men (88%) and most presented with acute onset abdominal pain (75%; Table 1). One patient presented with hematemesis and, in the remaining documentation, was absent; seven had peritonitis on physical exam. The average age was 45 (range 32–57). Five patients had a history of peptic ulcer disease, six were concomitantly abusing alcohol, and five were infected with the human immunodeficiency virus. Twelve patients had free intra-abdominal air on x-ray, whereas the remaining patients were operated on for peritonitis alone. At operation, 13 of the patients had pyloric channel perforations, whereas 2 were antral, and the remaining, ulcer was located at the gastroesophageal (GE) junction.

Table 1 Characteristics of Patient Presentation, Hospital Course, and Outcome

	Omental patch	Anti-ulcer procedure	*p* value
n	12	4	
Age	45	46	0.37
% male	100	50	≤0.01
Concomitant alcohol use	5	1	NS
Prior peptic ulcer disease	3	2	NS
Length of stay (days)	15	10	0.36
ICU Length of stay	1.7	0	0.13
H. pylori infection	3 (3 tested)	0 (0 tested)	
Early complications	1	2	NS
Number recurred (%)	5 (42%)	0 (0%)	0.072
Length of follow-up (months)	67	63	

NS Not significant

Most patients (75%) were treated with omental patch closure, whereas the others had formal antiulcer operations. Antiulcer operations performed included one vagotomy and pyloroplasty (V&P), one vagotomy and antrectomy (V&A), one subtotal gastrectomy, and the GE junction ulcer was treated with V&P and ulcer excision. All patients were functionally independent on admission, and all were discharged home with the exception of one patient discharged to an acute rehabilitation facility. Average length of stay was 14 days (range 4–87) with only three early complications, one wound infection, one early small bowel obstruction, and one entero-cutaneous fistula. In comparing early outcome variables between groups, there were no statistically significant differences. Three patients in the omental patch group were tested for *Helicobacter pylori* by antibody assay. All three were positive, and all were discharged on medical therapy, although data on compliance were not available. No patients in the antiulcer surgery group were tested for *H. pylori*.

No recurrence of disease was identified in the four patients who underwent an antiulcer procedure and were followed for a median 63 months (range: 27–120). Recurrence of disease was identified in 56% of patients treated with an omental patch closure at a median of 20 months (range: 11–39). The 44% without recurrence were followed for a median of 67 months (range: 12–96). Cumulative Kaplan–Meier proportions with recurrence in the simple patch group were 11.1% at 12 months, 36.5% at 24 months, and 71.9% at 36 months (Fig. 1). The recurrence rate was borderline lower in the antiulcer group, $P=0.072$.

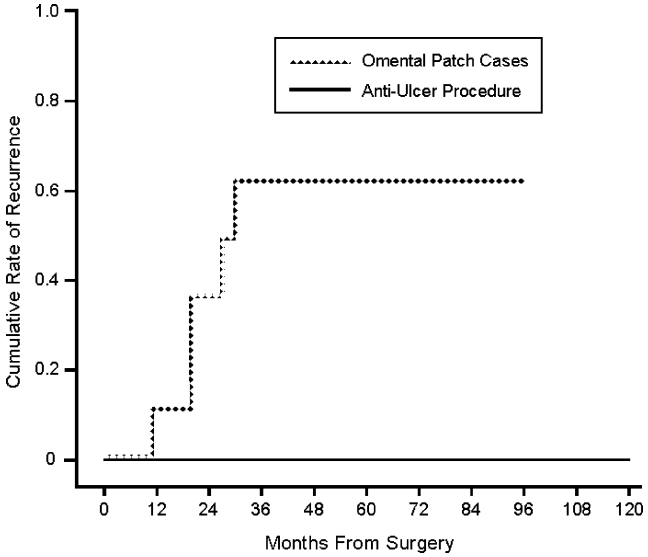

Figure 1 Kaplan–Meier plot of time to recurrence after omental patches and formal antiulcer procedures.

Discussion

Although the treatment of perforated duodenal and pyloric channel ulcers has evolved over the last several decades, the initial management remains controversial. Since Graham's description of the omental patch repair in 1937,[16] it has become the most commonly employed procedure in these patients.[17,18] This is most likely because of the reports documenting higher mortality rates when antiulcer operations are performed in elderly patients with multiple comorbidities, the most common patient population with this disease entity. Suture plication and omental patch repairs have been criticized for their long-term failure rate despite lower initial mortality when compared to definitive ulcer operations.[19] However, since the introduction of H_2 receptor antagonists, long-term failure of omental patch repair has decreased significantly as long as patients are compliant with ongoing medical therapy.[20]

The etiology of ulcer perforation in crack cocaine users remains unknown. In fact, the description of this phenomenon as an "ulcer" may not be correct, as there is no certainty this is a mucosal-based process. Multiple authors have reported on their experience treating this group of patients.[11–15] A wide range of theories have been proposed by these authors and others, including focal ischemia,[11,14] in-situ mesenteric thrombi,[14,21–23] elevated ACTH,[14,15,24] delayed gastric emptying,[12,15] and increased aerophagia resulting in increased intra-abdominal pressure.[13,15] *H. pylori* infection has also been proposed as a contributing factor.[15] The proposed mechanisms that seem most plausible are those that involve the ischemic and thrombotic effects of cocaine. The significance of *H. pylori* infection is also questionable, as perforations occurring in the course of standard peptic ulcer disease do not seem to be related to *H. pylori*. This conclusion is based on similar rates of *H. pylori* infection in perforated ulcer patients and the general population.[25,26]

As omental patches have been demonstrated to produce good long-term outcomes after peptic ulcer perforations and an etiology of crack cocaine-induced perforations has not been identified, which would contraindicate ometal patch repair, this has been proposed as the standard of care for perforation after cocaine ingestion.[14,15] However, the current data demonstrate higher rates of recurrent perforation in patients treated with omental patches. A recurrence rate of nearly 72% at 3 years was identified in patients treated with an omental patch, whereas no recurrences occurred when a formal antiulcer procedure was performed. To our knowledge, this is the first report of long-term follow-up in this patient population.

There are several caveats associated with these data. First, as outlined above, the mechanism of these perforations remains unclear. Combining this with a lack of data regarding compliance with prescribed antiulcer and *H. pylori* eradicating medications leaves open the possibility that, if a patient is compliant with these therapies, their risk of recurrent perforation may be low. In addition, if patients enter treatment programs and discontinue the use of crack cocaine, recurrent perforation risk may be significantly reduced. Our two groups were quite similar in their presentation with the exception of gender. This potentially may have also been a confounding factor if one is to believe women are more likely to permanently abstain from cocaine use. Women, however, have not been shown to be more likely than men to sustain cocaine abstinence.[27]

The types of antiulcer operations performed also varied in our study group by the extent of resection. Essentially, there were two procedures that removed the most at-risk area for perforation and two that did not. Small numbers prevent us from making a recommendation regarding the appropriate antiulcer operation. However, it would seem appealing to reason that removal of the area of perforation would decrease subsequent perforation risk.

Crack cocaine carries significant risk for adverse health events requiring treatment in the emergency department.[28] The low cost and ease of use have made crack cocaine common among inner-city, low income, African-Americans, and there is no indication of improvement in this epidemic.[29] The juxtapyloric gastric perforations associated with crack cocaine use, which have been identified in this group of patients, will remain a problem facing surgeons treating these patients for years to come. Simple omental patch closure is not optimal because of a recurrence rate of up to 72% compared with no recurrence when a formal antiulcer operation is performed. Only in older patients with significant comorbidities and patients who present in shock

should omental patches be considered.[19] Until further data are available, a formal antiulcer procedure should be the operation of choice in this patient population. The antiulcer operation chosen should remain with the operating surgeon based on patient and perforation characteristics given the paucity of data comparing efficacy of one procedure over another.

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Can Surgeons Think and Operate with Haptics at the Same Time?

Caroline G. L. Cao · Mi Zhou · Daniel B. Jones · Steven D. Schwaitzberg

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Abstract Much effort has been devoted to incorporating haptic feedback into surgical simulators. However, the benefits of haptics for novice trainees in the early stages of learning are not clear. Presumably, novices have less spare attentional resources to attend to haptic cues while learning basic laparoscopic skills. The aim of this study was to determine whether novice surgeons have adequate cognitive resources to attend to haptic information. Thirty surgical residents and attendings performed a TransferPlace task in a simulator, with and without haptics. Cognitive loading was imposed using a mental arithmetic task. Subjects performed 10 trials (five with cognitive loading and five without) with and without haptics. Results showed that all subjects performed significantly slower (27%) when they were cognitively loaded than unloaded, but equally accurately in both cases, suggesting a speed–accuracy tradeoff. On average, subjects performed 36% faster and 97% more accurately with haptics than without, even while cognitively loaded. Haptic feedback can not only enhance performance, but also counter the effect of cognitive load. This effect is greater for more experienced surgeons than less experienced ones, indicating greater spare cognitive capacity in surgeons with more experience.

Keywords Haptic feedback · Cognitive loading · Surgical training

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Introduction

Laparoscopic surgery has very important advantages over open surgery to patients in that it minimizes tissue trauma, shortens recovery time, reduces the length of hospital stay, and hence health care costs. It is a preferred alternative to open surgery in many procedures. However, it presents considerable challenges for surgeons such as distorted haptic feedback from long-stemmed instruments, reduced depth perception caused by the loss of stereopsis, poor hand–eye coordination as a result of reduced degree of freedom of motion and the fulcrum effect created by the pivot point at the abdominal wall. In laparoscopic surgery, surgeons have learned to adapt to the reduced haptic and visual feedback. However, this process of adaptation is time-consuming and costly in terms of patient safety. Higher injury rates, compared to open surgery, have been documented.[1,2]

Recently, a transformation in the approach to surgical training has taken place, with technological innovation such as surgical simulators and virtual reality simulation playing an increasingly important role.[3–5] Simulators have emerged as the preferred choice for training environments for both

practical and ethical reasons. For example, the simulator can be used over and over to practice the same skills without incurring the costs associated with animal models. Through advances in computer modeling techniques, virtual environments can be developed and modified to simulate unusual anatomy or rare scenarios. Another advantage of using simulation for training is that trainees can practice their skills in an ultimately safe environment. Furthermore, additional aids, such as navigational aids for colonoscopy or force feedback for laparoscopic tissue dissection, can be provided to the trainee to enhance the learning experience. A number of simulators (e.g., GI Mentor, ProMIS, LapSim Simulation, MIST-VR, XiTact SA) have been developed and marketed, and some have been validated by demonstrating successful transfer of skills to the OR environment.[4] The implementation of simulators into surgical training programs as part of a standard curriculum is expected in the near future.

One of the most controversial dilemmas in VR training simulator design is the incorporation of haptic feedback. The role of haptic feedback is of special interest because it is critical in the discrimination of healthy versus abnormal tissues, identification of organs, and motor control. In laparoscopic surgery, haptics is reduced and distorted by the long tools and the friction in the trocar seal.[6,7] Some surgeons maintain that they are able to determine shape, texture, and consistency even in the absence of visual feedback using laparoscopic tools,[8,9] whereas others attribute the large numbers of injuries to excessive forces being applied to the tissues as a result of distorted haptics.[2,10]

To improve the surgical performance in laparoscopic surgery, many researchers have attempted to restore haptic feedback by adding force sensors to the instrument,[11] or designing new laparoscopic tools with force feedback capabilities.[12] Also, much effort has been devoted to the integration of force feedback functions into VR surgical simulators.[13–15]

Although force feedback has been shown to improve performance for telemanipulation tasks, the benefits of force feedback for training are not clear.[16] For example, force feedback has been shown to improve robot-assisted knot-tying with fine suture.[17] Visual and force feedback together is better than only visual feedback or only force feedback for tissue grasping and pulling.[18,19] Other research comparing the performance between different force feedback gains also showed that force feedback improves performance by reducing the overall forces applied and the number of accidental incursions into sensitive structures, but the rate and precision of dissection were not significantly enhanced with force feedback.[20] A similar study indicated that the impact of force feedback is dependent on the task to be performed.[21] For example, when the mechanical efficiency is high, performance in determining tissue properties was improved, but performance in holding tissue was not.

However, Higgins and Champion[22] noted in their review of aviation training literature that "irrelevant" stimuli in a high-fidelity simulation actually made task learning more difficult, as the novice trainee had to learn to ignore these stimuli. Experts, however, expect more realism and are likely to have more problems with immersion in abstract, low-fidelity environments. Some have suggested that the level of simulator fidelity be matched to the stage of skill acquisition. Low-fidelity simulators may be appropriate for cognitive stage learners as initial or sustaining training, whereas high-fidelity trainers may be appropriate for advanced or autonomous stage learners.[22,23] As current surgical training simulators are low in fidelity with respect to visual and task representation (i.e., using peas or graphical spheres to represent tissue), the notion of realistic haptic feedback may be treated as an "irrelevant" stimulus for the novice trainee. Presumably, novices have less spare attentional resources to attend to haptic cues while learning basic laparoscopic skills.

Therefore, to improve the training of MIS surgeons through technological innovation capable of providing haptic feedback, we need to know if haptics is useful during the skill acquisition stage of training. We hypothesized that haptic feedback is more useful to the expert than the novice surgeon because of the difference in cognitive capacity as a result of experience. We expect that more experienced surgeons will be able to perform faster, with fewer errors, compared to less experienced surgeons. We also expect that the difference in performance measures caused by haptics will be greater as the subjects are more experienced. To test the hypotheses, we conducted a controlled experiment using two surgical simulators, one of which provided haptics, whereas the other did not. In addition, as cognitive capacity was presumed to be a covariate with experience, and the underlying mechanism in the utility of haptic information, we also varied the degree of cognitive loading on subjects while performing on the simulators.

Methods

The experiment was conducted in the Shapiro Simulation and Skills Center at Beth Israel Deaconess Medical Center. This project was approved by the institutional review board (IRB).

Subjects

Thirty surgical residents and attendings (six PGY1s, six PGY2s, six PGY3s, six PGY4/PGY5s and six fellows/

Figure 1 MIST-VR (left) and ProMIS (right) systems.

attendings) participated in this experiment. Two of the subjects were left-handed, 27 subjects were right-handed, and one subject was ambidextrous. All residents had no previous experience with the ProMIS simulator, and minimal to no prior experience with the MIST-VR simulator used in this study. All residents had approximately 10 hours' training annually in the Skills Lab on a box trainer and in the SAGES FLS program. Fellows and attendings had minimal to no experience in the Skills Lab.

Materials and Procedures

Two surgical simulators were used in this study. The MIST-VR system (see Fig. 1, left) is a virtual reality system, which has no haptic feedback. It is made up of a computer, a monitor, and laparoscopic tool base and costs approximately $35,000 USD. The ProMIS system (see Fig. 1, right) is a physical simulator consisting of a life size model of the upper torso with a light source, a computer, monitor, and laparoscopic tools. The ProMIS offers haptic feedback similar to that in actual surgery. The base unit and software options cost approximately $50,000 USD.

A transfer-place task was used to compare the effect of haptics on performance as a function of subject experience. In the MIST-VR system, a graphical ball was grasped by one tool, transferred to another tool, and placed in a graphical box. The procedure was then repeated with the opposite tools until a total of six error-free transfer-place tasks were achieved in each trial. In the ProMIS system, a visually similar environment was constructed using metal ball bearings and cups as receptacles for placing the balls. These metal balls were covered in a layer of soft material for ease of grasp. At the beginning of each test session, a demonstration of the task was shown to the subject, accompanied by a verbal explanation by the researcher. Then, subjects practiced until one target drop error-free trial was achieved on each simulator.

Cognitive load in the form of mental arithmetic problems were given to the subjects in half of the trials on each simulator. In the loaded condition, the subject was asked to solve as many medium-level math problems (such as 21 × 11) as possible, while performing the transfer-place task. Each subject performed 10 trials in each haptic condition, with five cognitively unloaded trials and five loaded trials. The experimental session lasted approximately 1 hour.

Experimental Design

The experimental design was a 2 (haptics) × 2 (cognitive loading) × 5 (experience) mixed design. The order of haptic conditions (Haptics, and No Haptics) was counterbalanced, whereas the order of cognitive loading conditions was randomized.

Dependent Measures and Data Analysis

Three performance measures were obtained: time-to-task completion, number of errors, and the total number of math problems completed. The independent factors were haptics (haptics and no haptics), cognitive load (loaded and unloaded), and experience (PGY1, PGY2, PGY3, PGY4/PGY5, fellow/attending). Performance data were analyzed using analysis of variance (ANOVA). Pearson correlation was used to examine the relationship between the number of math problems completed and time or number of errors.

Table 1 Significant Results

	Time-to-Task Completion (Seconds)									Error (Frequency)	
	Haptics		Cognitive Load		Experience					Haptics	
	Haptics	No haptics	Unloaded	Loaded	PGY1	PGY2	PGY3	PGY4/5	Attending/ fellows	Haptics	No haptics
Mean	54.24	85.49	57.93	73.6	81.06	69.74	65.46	55.3	57.27	0.05	0.98
Standard deviation	17.54	23.89	19.48	26.58	25.71	26.11	18.61	19.69	22.87	0.21	1.53
F value	631.59		192.32		22.42					95.35	
p value	<.001		<.001		<.001					<.001	

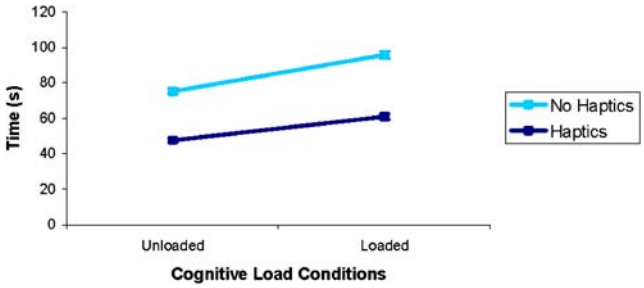

Figure 2 Interaction between haptics variable and cognitive load variable on time-to-task completion, collapsed across experience levels. *Error bars* represent standard deviation.

Results

Time-to-Task Completion

There were significant main effects for haptics [$F(1, 145) = 631.59$, $p<.001$], cognitive load [$F(1, 145) = 192.32$, $p<.001$], and experience [$F(4, 145) = 22.42$, $p<.001$] (see Table 1). There was a significant interaction between haptics and cognitive load [$F(1, 145) = 13.50$, $p<.001$], showing that when subjects were cognitively loaded, there was a larger increase in time-to-task completion without haptics than with haptics (see Fig. 2). There was a significant interaction between haptics and experience [$F(4, 145) = 3.16$, $p<0.016$] (see Fig. 3), indicating that experienced surgeons showed greater improvement with haptics than the less experienced surgeons. The slope of linear regression of the performance in haptics condition as a function of experience, across cognitive load conditions, was larger than the slope in no-haptics condition (see Fig. 3). There was also a significant interaction between cognitive load and experience [$F(4, 145) = 2.48$, $p<0.046$] (see Fig. 4).

Errors

There was a significant main effect for haptics [$F(1, 145) = 95.35$, $p<0.001$] (see Table 1), but not for cognitive load.

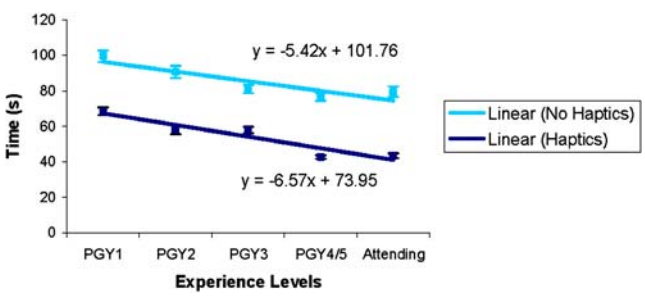

Figure 3 Performance of time-to-task completion in haptics and no haptics conditions, collapsed across cognitive load conditions. *Error bars* represent standard deviation.

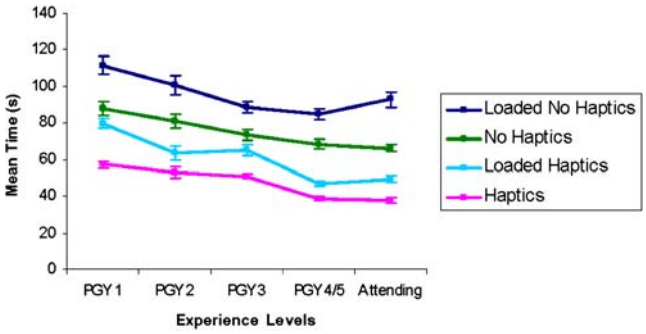

Figure 4 Effects of cognitive loading and haptics on time-to-task completion in simulated laparoscopic surgery. *Error bars* represent standard deviation.

Number of Math Problems Solved

Pearson correlation showed a slight positive correlation between time-to-ask completion and the number of math problems in haptics condition ($r=0.24$), and in the no-haptics condition ($r=0.26$).

Discussion

Effects of Haptics and Cognitive Load

In general, subjects performed significantly faster (37%) and more accurately (95%) with haptics than without. Haptic feedback plays an important role in improving the accuracy and the speed of task performance. Similarly, subjects performed significantly faster (21%) when they were not cognitively loaded, showing that the mental math problem was competing with the laparoscopic task for cognitive resources. However, subjects performed equally accurately in both cases, suggesting a speed–accuracy tradeoff. Indeed, it was observed that surgeons tended to pause work while mentally solving math problems. Similar results have been reported in the

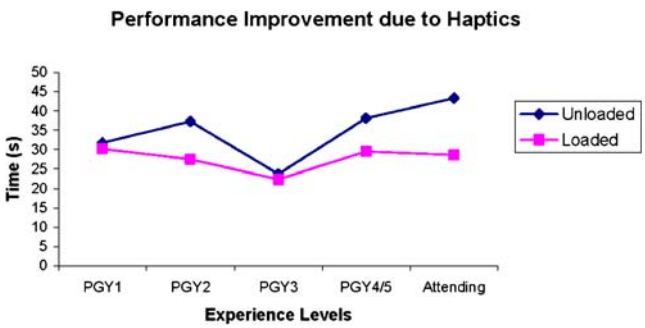

Figure 5 Performance improvement (time-to-task completion) as a result of haptics when cognitively loaded and unloaded.

literature.[24] Although subjects who tended to pause their task would take longer to perform the task, movements during such a pause were slight and caused no error whatsoever. The shift of attention away from and back to the task did not lead to more errors. This is in contrast to the results of other studies where distractions that caused an attention shift led to increased errors in performance of both cognitive and motor tasks.[25,26] As the subjects were all surgeons, it may be presumed that accuracy in surgical performance was their priority, whereas speed of performance could be judiciously sacrificed. This result was reflected in the positive correlation between the number of math problems subjects solved and the time-to-task completion in the haptics condition.

When not cognitively loaded, subjects performed 37% faster and 94% more accurately with haptics than without. Interestingly, even while cognitively loaded, subjects performed 36% faster and 97% more accurately with haptics than without, suggesting that haptics not only enhances performance, but counters the effect of cognitive loading (see Fig. 4).

Effects of Experience

In general, more experienced surgeons performed faster ($p<.001$), but not more accurately than less experienced surgeons. Our results suggest that haptics is beneficial even to less experienced surgeons, but more experienced surgeons are able to better take advantage of haptics (see Fig. 3). Our hypothesis that novice surgeons have relatively limited spare cognitive resources available to utilize haptic information was supported.

Indeed, when cognitively loaded, all surgeons showed similar improvement as a result of haptics, indicating that the haptic information was not fully utilized. Conversely, when not cognitively loaded, the performance improvement with haptics was much greater for the more experienced surgeons than the less experienced surgeons (see Fig. 5), suggesting that experts had more spare cognitive resources to utilize the haptic information. More experienced surgeons, having mastered the surgical skills to the level of automatic responses, have the spare cognitive resources to attend to the subtle haptic cues. Given the myriad of difficulties associated with performing laparoscopic surgery, less experienced surgeons are still in the learning stages and may not have the spare cognitive capacity to utilize, or benefit from, the subtle force feedback in the system. However, the only group that did not conform to this trend was the PGY3s. The residents in this group of residents were classified as PGY3, but in reality, had only completed 2 years of surgical residency and were working on research during their third year in the program. Therefore, it is possible that their smaller performance improvement with haptics was a function of lack of practice with surgical techniques over the last 6 months.

Conclusion

In general, haptic feedback not only enhances performance, but also counters the effect of cognitive loading. Haptic feedback plays an important role in improving the accuracy and the speed of task performance. Haptics is beneficial for simple surgical training task performance. Experienced surgeons are able to take more advantage of the haptic feedback in the system. Based on these results, it is unclear whether it would be worthwhile to provide haptic feedback in surgical training simulators to novice trainees, especially when learning complex surgical tasks, such as suturing, for the first time. Future research to investigate the utility of haptic information during early stage learning is warranted.

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Mucin-producing Bile Duct Tumor of the Caudate Lobe Protruding into the Common Hepatic Duct

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Abstract Mucin-producing tumor in the bile duct is referred to clinically as mucin-producing bile duct tumor (MPBT). Intraductal papillary neoplasm of the biliary tract that resembles an intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a rare category of MPBT and is not well characterized. We, herein, report a case of MPBT of the caudate lobe of the liver that showed papillary growth and communicated with the bile duct of the caudate lobe and protruded into the common hepatic duct. Histologically, MPBT cells showed papillary overgrowth with abundant mucinous secretions, resembling an IPMN of the pancreas. The MPBT cells showed the same immunostaining pattern as that of cells from IPMN of the pancreas.

Keywords Bile duct · Intraductal papillary neoplasm · Mucin-producing bile duct tumor

Case Report

A 50-year-old Japanese woman presented with sudden fever, and liver dysfunction was detected. Ultrasonography revealed a cystic lesion, 7 cm in diameter, in the middle segment and caudate lobe of the liver. The patient was admitted to our hospital for further examination and treatment. Computed tomography confirmed the presence of a relatively well-demarcated cystic lesion, approximately 7 cm, containing a papillary tumor in the middle segment and caudate lobe of the liver (Fig. 1). Peripheral intrahepatic bile duct dilatation of the lateral segment was observed. Magnetic resonance cholangiopancreatography also detected a cystic lesion filled with an irregular tumor. T1-weighted magnetic resonance imaging showed a low-intensity tumor in the cystic component; the same tumor was of high signal intensity on T2-weighted images. Endoscopic retrograde cholangiography revealed a widely opened ampulla of Vater and mucin pooling in the common bile duct, and a papillary protrusion was observed near the left hepatic duct. The cystic lesion communicated directly with the common hepatic duct. However, there was no communication between the cystic lesion and the bile duct of the medial segment. These findings indicated that the lesion originated from the caudate lobe. We then performed intraductal ultrasonography, which revealed that the papillary tumor was located in the cystic lesion and that the papillary tumor was also present in the common hepatic duct. The presence of the papillary tumor in the common hepatic duct was confirmed by peroral cholangioscopy. A tumor biopsy specimen obtained with the use of the peroral cholangioscope showed proliferating columnar to cuboidal cells with large eosinophilic cytoplasm forming papillary growth. On the basis of these findings, cystadenoma or cystadenocarcinoma was suspected, and surgery was planned for the treatment.

Upon laparotomy, neither ascites nor peritoneal dissemination was found. The tumor was not exposed on the surface of the liver; intraoperative ultrasonography detected an well-defined cystic tumor, and the middle hepatic vein was shifted to the right. Left lobectomy, total caudate lobectomy, and resection of the extrahepatic bile duct were performed. The surgical specimens contained an 8.3 × 7.0 cm cystic lesion with a papillary tumor. Upon gross

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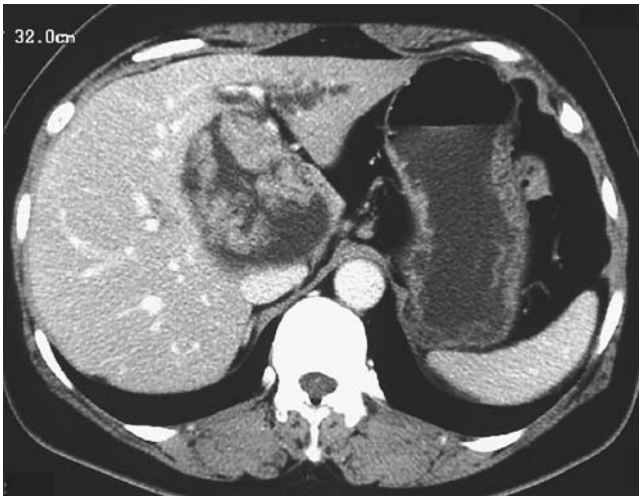

Figure 1 Computed tomography scan shows a cystic lesion containing a papillary tumor.

examination, the cystic lesion appeared to originate from the bile duct of the caudate lobe of the liver. The main tumor was located in the cystic lesion in the caudate lobe (Fig. 2A), and the papillary protrusion continued to the left hepatic duct (Fig. 2B).

Microscopically, atypical cells proliferated, forming papillary structures with abundant mucinous secretions (Fig. 3). The tumor cells were localized in the cystic cavity in most areas; however, downward stromal growth was noted in one area, and this lesion was diagnosed as carcinoma. The tumor cells showed strong immunohistochemical staining for MUC5AC and weak staining for MUC2, however, cells were negative for MUC1 and p53 staining. There was no ovarian-type stroma such as that observed with mucinous cystic neoplasms of the pancreas. There was no lymph node metastasis. The patient was doing well 9 months after surgery, with no signs of recurrence, and neither chemotherapy nor radiation was performed.

Discussion

Mucin-producing tumors of the bile duct are referred to clinically as mucin-producing bile duct tumors (MPBTs).[1] These tumors of the peripheral bile duct, which include benign and malignant lesions, have also been referred to as intraductal growth (IG)-type peripheral cholangiocarcinomas,[2] mucin-producing cholangiocellular carcinomas,[3] intraductal papillary neoplasms (IPNs) of the biliary tract,[4] IPNs of the liver,[5] or IPNs of the bile duct.[6] MPBTs showing papillary growth are rare and not fully understood. MPBTs are classified as either columnar-type or cuboidal-type MPBT on the basis of histopathologic findings, morphometric data, Ki-67 labeling, and mucin expression profiles. Survival of patients with columnar-type carcinoma

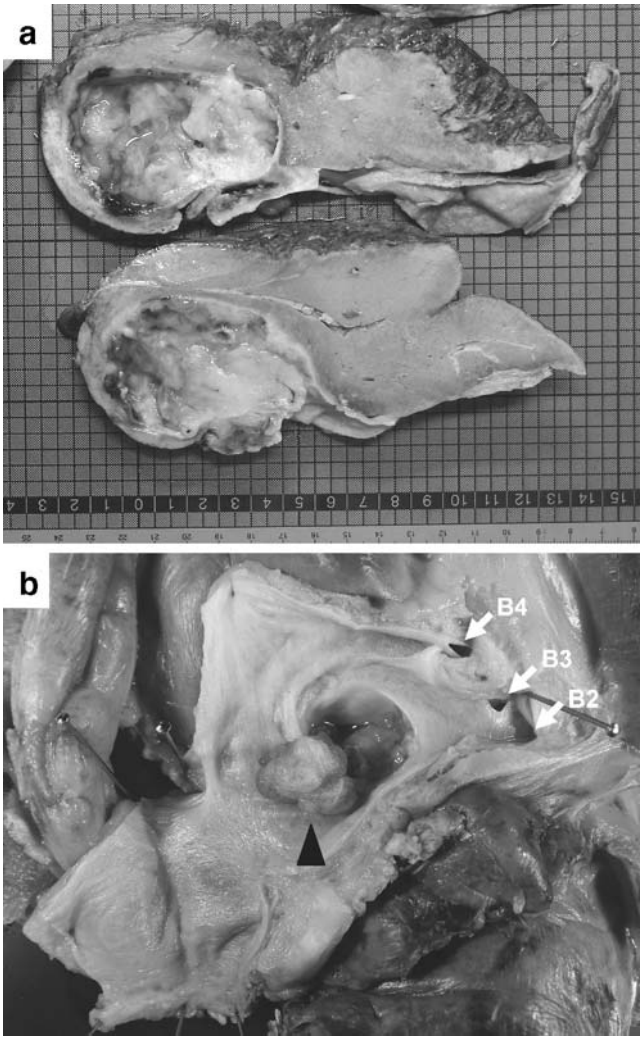

Figure 2 **a** Photograph of the resected left lobe of the liver shows a well-demarcated cystic lesion containing a papillary tumor. **b** The papillary protrusion (*black arrowhead*) from the bile duct of the caudate lobe continues to the common hepatic duct.

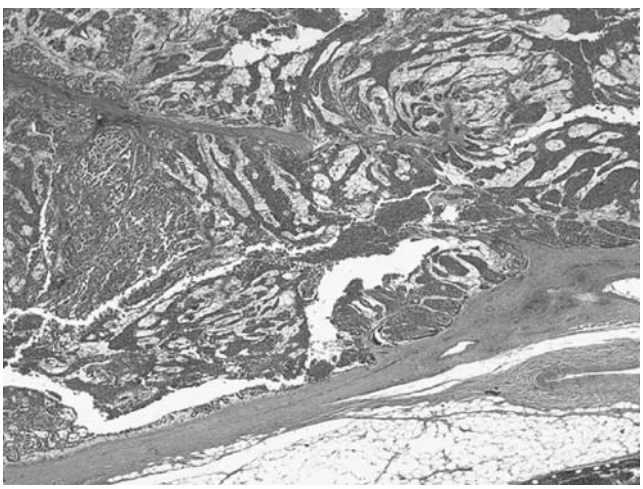

Figure 3 Histologic findings (hematoxylin and eosin stain, original magnification ×40). Atypical cells proliferate, forming papillary structures with abundant mucinous secretions.

is significantly poorer than that of patients with cuboidal-type carcinoma.[1]

Mucobilia found upon common bile duct exploration, which was observed in our case, is significant for the early diagnosis of intrahepatic bile duct carcinoma with mucin production. Suh et al.[2] reported that 16 of 112 patients (14.3%) with peripheral cholangiocarcinoma (PCC) were classified as having the IG-type according to gross morphology, and the 5-year survival rate of patients who underwent curative resection for IG-type PCC was significantly higher than that of patients treated by surgical resection for non-IG-type PCC.[2] Chen et al.[3] also reported that survival of patients with mucin-producing cholangiocellular carcinoma (MPCCC) was significantly better than that of patients with non-MPCCC.[3]

Molecular and immunohistochemical analyses of 14 cases of IPN of the biliary tract were performed by Abraham et al.[4] Several genetic alterations in the histologically similar pancreatic IPMNs have been well characterized and include relatively high frequencies of K-ras gene mutations, p53 protein accumulation, p53 gene mutations, allelic loss and a low frequency of DPC4 inactivation. The frequency of K-ras gene mutations is lower (29%) in biliary IPNs than in pancreatic IPMNs (approximately 60%); however K-ras mutations occur early in tumorigenesis.[4]

It is widely known that intraductal papillary growth of neoplastic biliary epithelia resembling IPMN of the pancreas is occasionally associated with hepatolithiasis.[5,6] Bile stasis and repeated cholangitis may lead to the development of periductal inflammation, followed by biliary dysplasia, papillary hyperplasia with dysplasia, and in situ and invasive cholangiocarcinoma.[5] Mucobilia observed in patients with MPBT may lead to the same inflammatory condition and adenoma–carcinoma sequence.

An immunohistochemical analysis of intrahepatic bile duct tumors revealed that invasive cholangiocarcinoma (ICC) with a poor outcome expressed MUC1 but not MUC2, whereas bile duct cystadenocarcinoma or ICC with a favorable outcome was MUC1-negative and MUC2-positive.[7] MUC5AC expression is correlated with tumors that show an expansive growth pattern and low degrees of invasion and metastasis[8], and IPMNs that express high levels of MUC2 and MUC5AC may, therefore, confer a better chance of survival and have a lower tendency to metastasize.[9]

Although the tumor in our case was classified as a bile duct cystoadenocarcinoma in accordance with the World Health Organization classification,[10] the morphologic features were not typical, and the histologic features were similar to those of cuboidal cell-type MPBT.[1]

We conclude that the tumor in our case should be classified as an intraductal papillary mucinous carcinoma of the bile duct.

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A Composite Adenoendocrine Carcinoma of the Stomach Arising from a Neuroendocrine Tumor

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Abstract Gastric neuroendocrine tumors (carcinoids) are relatively uncommon neoplasms. Some 70 to 80% of these lesions occur in patients with autoimmune body gastritis. This disorder, however, is also a risk factor for the development of conventional gastric adenocarcinomas. We report a case of a patient with autoimmune body gastritis and a well-differentiated neuroendocrine tumor of the stomach, which was removed with endoscopic full-thickness resection in sano upon signs of invasive growth several years after its first diagnosis. Histological examination surprisingly showed a composite glandular-endocrine gastric carcinoma. We discuss the histopathological genesis of the tumor and provide evidence that endoscopic full-thickness resection might be an oncologically appropriate minimally invasive treatment for such gastric lesions.

Keywords Stomach neoplasms · Carcinoma · Neuroendocrine · Carcinoid tumor · Adenocarcinoma · Surgical procedures · Minimally invasive

Introduction

Neuroendocrine tumors are uncommon neoplasms with a predominant manifestation in the gastrointestinal tract.[1] Approximately 9% of enteric neuroendocrine tumors occurs in the stomach and their incidence has risen over the last decades to 1–2.5 cases per 1,000,000 persons per year.[2] They are commonly classified into three different types.[3,4]

Type I, representing 70–80% of gastric neuroendocrine tumors, arises from atrophic mucosa in achlorhydric autoimmune body gastritis (ABG).[3] The clinical course is generally benign, but there are occasional instances of invasive growth and metastases.[5] The causal condition for type II gastric neuroendocrine tumors, accounting for about 5% of cases, is Zollinger–Ellison syndrome.[3] Although prognosis is favorable in most cases, regional lymph nodes are involved in almost one third of cases and tumors may progress to neuroendocrine carcinomas.[6,7] Type III tumors occur without predisposing condition.[3] Metastatic spread into lymph nodes and the liver is common and directly linked to tumor size.[7]

Current treatment guidelines advocate endoscopic follow-up and, if possible, endoscopic or local resection for types I and II gastric carcinoids. Tumor resection through total or subtotal gastrectomy is recommended only when invasive growth into the muscular layer, repeated recurrence, or histologically malignant transformation is present. For type III tumors, immediate radical resection is the treatment of choice.[4]

The current WHO classification of stomach tumors clearly separates neuroendocrine tumors from gastric adenocarcinoma.[8] There is, however, evidence that neuro-

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endocrine cells might be involved in the genesis of gastric adenocarcinoma, particularly so in a low-acid milieu.[1] A proportion of gastric adenocarcinomas shows neuroendocrine features on immunohistochemistry. Some very rare tumors comprise both endocrine and glandular characteristics by morphology. Their histogenesis is not fully clear, but they might develop from common precursor cells or coincidental changes in two cell types.[9]

Case Report

A 53-year-old man was diagnosed with a tumor of the gastric corpus with a diameter of 1 cm during gastroscopy performed for epigastric pain. Histology showed a type I gastric neuroendocrine tumor in the context of ABG, which was controlled through regular endoscopies and remained histologically unaltered for years. Ten years after first diagnosis, a biopsy showed tumor infiltration of the submucosal layer and another biopsy for the first time also revealed high-grade intraepithelial neoplasia of the gastric mucosa (data not shown).

Given the signs of starting invasive growth, we decided for resection. Because endosonography showed no lymph node involvement, we were hesitant to perform total gastrectomy with lymphadenectomy, a procedure that bears a nonnegligible morbidity and mortality.[10] In line with current treatment guidelines for neuroendocrine tumors,[4] we decided to perform endoscopic full-thickness gastric wall resection, a minimally invasive procedure recently developed by our group.[11] With this technique, we removed the tumor and surrounding gastric wall. Histology showed a tubular adenocarcinoma intimately intermingled with an unequivocal, well-differentiated, neuroendocrine tumor/carcinoid (Fig. 1). Both components infiltrated the submucosa. There was no invasion of lymphatic or blood vessels, and all resection edges were free of tumor. The intervention was well tolerated and the patient was discharged after 2 days. Regular follow-up examinations showed remaining neuroendocrine proliferation surrounding the scar of the full-thickness resection without any sign of invasive growth or recurrence of the adenocarcinoma. There was no hint of metastases in the lymphatic tissue or other organs 22 months after endoscopic surgery.

Discussion

We reported on a patient with recurrent carcinoid in the context of long-standing ABG. When the lesion after many years became invasive and required surgery, the neuroendocrine tumor was found to be intimately intermingled with a concomitant gastric adenocarcinoma. Although long-standing ABG is a well-known risk factor predisposing the development of nonneuroendocrine gastric adenocarcinomas,[12] the combination of adenocarcinoma and a neuroendocrine neoplasm within the same lesion is an exceedingly rare finding. Lewin[13] proposed a classification for such neoplasms distinguishing (1) composite (or mixed) glandular-endocrine tumor with both elements in more or

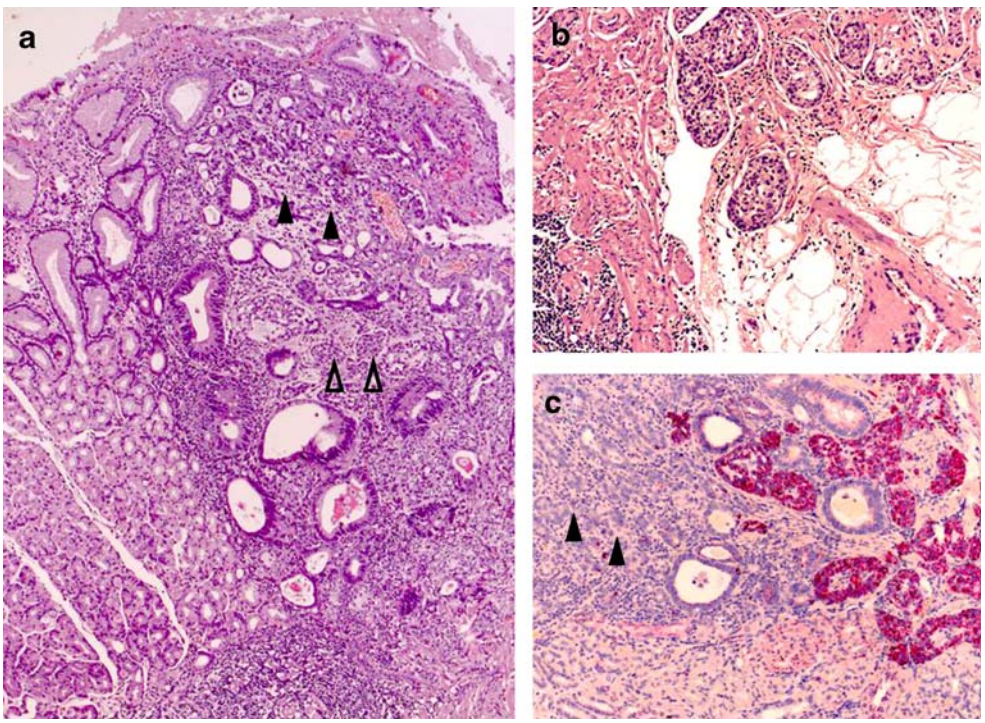

Figure 1 Histology of the excised specimen revealed **a** a neoplasm with a poorly differentiated conventional glandular gastric carcinoma with diffuse growth pattern (filled arrow heads) in combination with a synchronous carcinoid with tubular and nodular growth pattern (open arrow heads), **b** the latter invading the submucosal lamina. **c** Immunohistochemical staining for chromogranin A highlighted the carcinoid (red) in vicinity of the glandular gastric carcinoma (filled arrow heads) (original magnification ×200).

less equal proportions, (2) amphicrine tumors with dual differentiation within the same cell, and (3) collision tumors where the two components are juxtaposed but not admixed. According to this classification, our case was a composite glandular-endocrine carcinoma. The histological origin of such tumors has remained mostly unclear. In rats with hypergastrinemia, enterochromaffin-like cells had the capacity to dedifferentiate and become potential precursors of gastric adenocarcinoma.[14,15] Some authors postulated proliferation of a pluripotential precursor cell,[16,17] and studies describing common genetic alterations in the glandular and neuroendocrine component of mixed tumors may support the latter hypothesis.[18] However, because there were no morphological transitions between the two components in our case, morphology per se was also compatible with the independent proliferation and "collision" of two different glandular and endocrine cell clones.

In this particular case, minimally invasive surgery through endoscopic full-thickness gastric wall resection without radical gastrectomy and lymphadenectomy was sufficient to remove the tumor in sano. Tight follow-up examinations have not shown any sign of recurrence, lymphatic involvement, or distant metastases for almost 2 years after resection. Thus, we strongly believe that in selected patients, this novel technique is a highly attractive alternative to more invasive open surgical procedures because it yields comparable oncological outcomes with a significantly lower intervention-specific morbidity and mortality. Studies on more patients and longer follow-up periods are, however, needed before expressing a conclusive judgment and introducing this technique as a new standard into clinical routine.

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Pseudomyxoma Peritonei Presenting with Femoral Hernias and Peritonitis

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Abstract Pseudomyxoma peritonei is a rare disease characterized by intraperitoneal accumulation of mucinous ascites produced by neoplastic cells, which mostly originate from an appendiceal adenoma. The clinical presentation of the disease varies, and preoperative diagnosis is often difficult. This report describes a 76-year-old female patient with pseudomyxoma peritonei who presented with lower abdominal pain and bilateral femoral masses. Computed tomography revealed bilateral femoral hernias and fluid collection in the peritoneal cavity. Laparotomy was performed, during which we found extensive diffuse gelatinous material mixed with purulent ascites, and the diagnosis of pseudomyxoma peritonei was confirmed. The disease is rarely associated with femoral hernias or peritonitis. Its clinical presentation, including the characteristic findings on computed tomography, and surgical management are briefly reviewed.

Keywords Pseudomyxoma peritonei · Appendiceal adenoma · Computed tomography · Femoral hernias · Peritonitis

Introduction

Pseudomyxoma peritonei (PMP) is a rare disease characterized by slow, progressive accumulation of mucinous ascites. Although the clinical and pathological definitions of PMP are still controversial, most cases are associated with a mucinous neoplasm of low malignant potential in the appendix.[1–3]

The common presentation of PMP is abdominal pain, similar to that of acute appendicitis, and increased abdominal girth.[4] However, because the symptoms of the disease vary, preoperative diagnosis is often difficult, and, in many cases, the diagnosis is made during surgery. In this report, we describe a case of PMP presenting with femoral hernias and peritonitis, and discuss the surgical management of the disease.

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Case Report

A 76-year-old woman was referred to our hospital with complaints of nausea and lower abdominal pain, which had worsened over the previous 2 days. She had been treated with medication for depression. On admission, her body temperature was 38.0°C. Physical examination revealed masses in the bilateral femoral regions, indicative of femoral hernias, with tenderness on the left side. Blood examination showed a white blood cell count of 11,300/mm^3 and C-reactive protein level of 21.18 mg/dl. Computed tomography (CT) demonstrated bilateral femoral and left inguinal hernias, with calcification in the left femoral hernia and fluid collection in the peritoneal cavity (Fig. 1).

She was diagnosed with peritonitis, possibly because of incarceration of the left femoral hernia. Laparotomy was performed, which revealed diffuse gelatinous fluid in the peritoneal cavity and severe inflammatory pelvic adhesions. By freeing the intestines from the adhesions, the abscess cavity was opened, and purulent ascites mixed with mucinous material was drained. The appendix was enlarged, the tip of which was perforated in the abscess cavity. We found bilateral inguinal and femoral hernia sacs filled with purulent gelatinous fluid, whereas there was no sign of hernia incarceration. There was no tumor in the ovaries. Under the diagnosis of PMP and pelvic abscess secondary

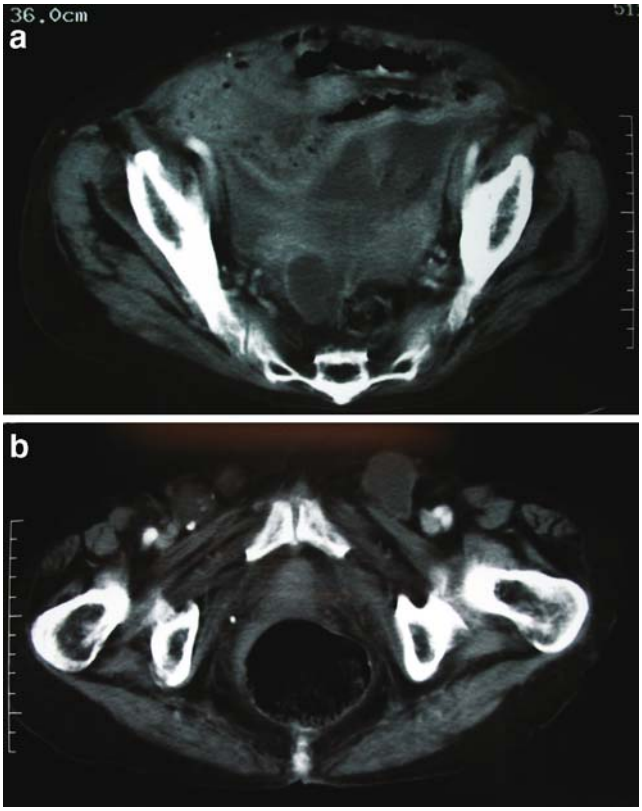

Figure 1 Preoperative CT shows fluid collection in the peritoneal cavity (**a**) and bilateral femoral and left inguinal masses indicative of hernias, with calcification in the left femoral hernia (**b**).

to perforation of the appendix, we performed appendectomy, and the bilateral inguinal and femoral hernia sacs were resected. The peritoneal cavity was lavaged with 10 l of saline to remove as much gelatinous fluid as possible.

The postoperative course was uneventful. Pathological examination revealed mucinous cystadenoma of the appendix, whereas no tumor cells were detected on the surface of the resected hernia sacs.

Discussion

Pseudomyxoma peritonei is a clinical condition characterized by diffuse collection of gelatinous material in the peritoneal cavity and mucinous implants on the peritoneum.[1,3] Because of the rarity of the disease, with an estimated incidence of 2 in 10,000 laparotomies,[5] the pathogenesis of the condition remains unclear. Recent developments in immunohistochemistry have shown that PMP is associated with primary appendiceal adenoma.[6,7] It is now generally thought that PMP is caused by neoplastic mucus-secreting cells of low-grade malignancy arising in the appendix. As the tumor grows, the lumen of the appendix becomes occluded by mucus and tumor cells. Eventually, the appendix ruptures, and the mucus-containing epithelial cells are disseminated in the peritoneal cavity, leading to extensive accumulation of gelatinous material.[1–3] Although lymphatic or hematogenous metastasis does not occur, PMP leads to a fatal condition because of the progression of bowel obstruction and starvation.[3]

The clinical presentation of the disease varies, which makes preoperative diagnosis difficult. The diagnosis is often made during laparotomy for suspected appendicitis or an ovarian tumor. Esquivel and Sugarbaker[4] demonstrated that suspected acute appendicitis was the most common presentation of PMP, followed by increased abdominal girth, ovarian mass, and development of inguinal or umbilical hernia. They reported that in 25% of male and 4% of female patients the diagnosis was made when gelatinous material was found during hernia repair. Our patient presented with femoral hernias and abdominal pain indicative of peritonitis, which are both uncommon symptoms for PMP, and made the diagnosis even more difficult. Sulkin et al.[8] reported the usefulness of CT in diagnosing PMP. "Scalloping" of visceral surfaces, especially that of the hepatic and splenic margins, is the diagnostic sign of mucinous ascites. Septa and calcification within the low-attenuation gelatinous ascites are also characteristic of the disease. Central or posterior displacement of small bowel can be seen after increase of mucinous ascites. These signs were not evident in our patient except for slight calcification in the left femoral hernia, probably because the mucinous material was relatively small in volume, and was mixed with purulent ascites associated with the pelvic abscess.

The treatment of PMP remains controversial. The traditional approach is repeated surgical debulking of tumor cells and mucinous ascites. This surgery is not curative, but reduces symptoms caused by the massive mucus. Sugarbaker[9,10] introduced cytoreductive surgery (CRS), which includes greater and lesser omentectomy, splenectomy, bilateral subphrenic peritonectomy, pelvic peritonectomy, rectosigmoid resection, and distal or total gastrectomy. There have been several reports supporting the effectiveness of CRS combined with intraperitoneal chemotherapy.[11–13] Esquivel and Sugarbaker[14] suggested that CRS should be performed within a year if PMP was diagnosed during hernia repair. On the other hand, Smeenk et al.[15] demonstrated relatively high risk of the procedure, especially in patients over 70 years old, and reported that patients should be selected to reduce treatment-related complications. Taking into account her age and probable severe intrapelvic adhesions, we consider that it would be difficult to perform radical surgery in our patient, and she is now under close follow-up.

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