Neoadjuvant Chemoradiotherapy Is Not Associated With a Higher Complication Rate Vs. Surgery Alone in Patients Undergoing Esophagectomy

Scott T. Kelley, M.D., Domenico Coppola, M.D., Richard C. Karl, M.D.

Recent studies have claimed a higher rate of perioperative complications related to the use of neoadjuvant chemoradiotherapy in the treatment of esophageal cancer. We tested the hypothesis that neoadjuvant chemoradiotherapy has no significant effect on the perioperative complication rate. Data on 155 patients with esophageal carcinoma treated between 1996 and 2001 were collected in a prospective database. This included 61 patients (40%) treated with neoadjuvant chemoradiotherapy (group I) and 94 patients (60%) who underwent esophagectomy alone (group II). Neoadjuvant therapy consisted of two courses of cisplatinum and continuous-infusion 5-fluorouracil with radiation followed by esophagectomy. Ivor-Lewis esophagectomy was performed in 146 (94%) and a transhiatal resection in nine (6%). The two groups (I vs. II) were comparable in terms of age (61.3 ± 11 years vs. 64.8 ± 11 years), diagnosis (adenocarcinoma: 82% vs. 83%; squamous cell carcinoma:11% vs. 16%), and stage (stage 0 to I: 39% vs. 38%; stage II: 25% vs. 34%; stage III: 30% vs. 24%; and stage IV: 6% vs. 4%). The neoadjuvant group had 23 complete responses, 11 partial responses, and 27 nonresponses. There were 39 complications (25.1%) for the cohort, which included three deaths (1.9%) and four anastomotic leaks (2.6%) demonstrated by Gastrografin swallow (1 in group I vs. 3 in group II. Only one leak required reoperation (group II); all others responded to conservative treatment. Group I had 14 complications (22.9%) vs. 25 (26.5%) in group II (P = NS). Groups were comparable with respect to the rate of pulmonary events (4.9% vs. 6.3%), arrhythmias (6.5% vs. 8.5%), and stricture formation (6.5% vs. 7.4%). Neoadjuvant chemoradiotherapy in patients with esophageal cancer was not associated with increased perioperative morbidity or mortality. Complete response to chemoradiotherapy also did not affect the complication rate (26% vs. 22%). (J GASTROINTEST SURG 2004;8:227–232)

KEY WORDS: Esophageal cancer, neoadjuvant therapy, complications

The incidence of adenocarcinoma of the esophagus has increased markedly over the past 25 years. The change is most marked among Caucasian men in whom it has increased 350% since the mid-1970s.[1] Although surgical mortality for esophageal resection has been reduced, the rate of cure and 5-year survival are poor, particularly for patients with T3 and/or N1 disease (American Joint Committee on Cancer [AJCC] stages IIb, III, and IV disease).[2] The optimal treatment of adenocarcinoma of the esophagus is unknown. Although surgery may prove successful in removing the primary tumor, most patients will develop recurrent disease. Only about 20% to 30% survive 2 years.[3] Factors that contribute to this outlook include the presence of locally advanced disease and undetected metastatic cancer at diagnosis. Because of the high rates of locoregional and distant failure, there is much interest in the combination of systemic chemotherapy with local radiotherapy and surgical treatment.[3]

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From the H. Lee Moffitt Cancer Center (S.T.K., R.C.K.), Tampa, Florida; and the Departments of Surgery and Pathology (D.C.), University of South Florida, Tampa, Florida.

Reprint requests: Scott T. Kelley, M.D., Assistant Professor of Surgery, H. Lee Moffitt Cancer and Research Institute, University of South Florida, 12902 Magnolia Drive, Tampa, FL 33612. e-mail: kelleyst@moffitt.usf.edu

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The expected benefits of preoperative chemoradiotherapy are the preoperative elimination of potential systemic micrometastases in patients with both locoregional and locally advanced tumors, and the lowering of the stage of the primary tumor. Such a regimen may increase the R0 resection rate in patients with locally advanced tumors and may reduce the rate of local and distant recurrences, thereby increasing the chances for long-term survival.[4]

This potential activity of chemotherapy as well as the radiosensitizing properties of some chemotherapeutics form the basis for the combination. In locally advanced disease, such a combination might more effectively downstage the tumor and make possible an R0 resection.[4] In fact, approximately 15% to 20% of patients experience a complete pathologic response to preoperative chemoradiation therapy and no tumor is found in the pathologic specimen at the time of resection.[4] Increased rates of long-term survival are to be expected in the subset of patients who do have a complete response to such therapy.[4] Several studies report 3-year survival rates as high as 100% in this group.[5] Partial response is also associated with improved survival.[4]

Although adjuvant chemotherapy and radiotherapy, either combined or given individually, have failed to increase survival,[1] there is increasing evidence that esophageal cancer (both adenocarcinoma and squamous cell types) responds to neoadjuvant chemotherapy or combination chemoradiation therapy. Two-year survival rates as high as 30% to 40% have been described with preoperative chemotherapy followed by surgery.[6] Recently the Medical Research Council in the United Kingdom has shown, in a randomized controlled trial, that two cycles of preoperative cisplatin (CDDP) and 5-fluorouracil (5-FU) achieved a significantly better 2-year survival of 43% compared with the rate in the surgery-alone group (34%).[6]

There has been some controversy in the literature as to whether neoadjuvant chemoradiotherapy is associated with an increased rate of complications when compared to that in patients undergoing immediate esophagectomy.[7–10] Many have claimed that patients with carcinoma of the esophagus exhibit a higher postoperative morbidity and mortality after preoperative radiochemotherapy.[8] In a randomized trial, patients with esophageal cancer undergoing resection after chemoradiation had more severe complications (pneumonia, infection, and anastomotic leaks with higher postoperative mortality) than patients undergoing surgery alone.[9] Recently, in a study from Munich,[10] neoadjuvant therapy in general was associated with significant immunosuppression in the host, specifically with defective proliferation of T cells after chemoradiotherapy, when compared to patients undergoing immediate esophagectomy. This deficiency has been hypothesized to impair the host response to subsequent surgery and has been proposed to explain the higher risk of surgery after neoadjuvant therapy.

Given this state of the literature, and the fact that we have not appreciated a similar increase in morbidity and mortality after neoadjuvant therapy, we sought to determine the validity at our institution. Neoadjuvant therapy consisting of continuous 5-FU, CDDP, and 5040 cGy local radiation is given routinely for tumors greater than T2N0 at our institution. We tested the hypothesis that neoadjuvant chemoradiotherapy would fail to increase the morbidity, mortality, or rate of complications when given prior to esophagectomy in patients with esophageal cancer.

METHODS

Between January 1996 and August 2001, a total of 155 consecutive patients (132 men and 23 women) with esophageal carcinoma or high-grade dysplasia (n = 16) underwent surgical resection at Moffitt Cancer Center. Data collected included patient demographics, and pretreatment tumor staging workup included physical examination, routine blood work, thoracic, abdominal, and pelvic CT scans, endoscopy with biopsy, and endoscopic ultrasound.

The inclusion criteria at Moffitt Cancer Center (initiated after mid-2000) for neoadjuvant therapy were patients with distal or gastroesophageal junction tumors with tumor $\geqslant$T2 or any T, N1 tumors assessed by pretreatment endoscopic ultrasound and CT scans. Sixty-one patients (40%) underwent neoadjuvant chemoradiotherapy prior to resection. Neoadjuvant therapy for most patients consisted of two courses of chemotherapy with 5-FU and CDDP. The first course of 5-FU was given at a dosage of 1 g/m^2 per day and was given from day 1 to day 4. CDDP was given at a dosage of 75 mg/m^2 per day and was given from day 2 to day 5. The second-course dose of 5-FU was given from day 21 to day 24, and the full dose of CDDP was given from day 22 to day 25. Concomitant radiotherapy was administered in 25 fractions, to a total dose of 5040 cGy. Surgery was performed 4 to 6 weeks after the completion of therapy (see Fig. 1 for overall design).

Tumor histology and stage were determined by the TNM classification system.[11] On day 7 after surgery, an esophagram was performed with meglumine diatrizoate followed by thin barium after an Ivor-Lewis esophagectomy, or with only thin barium after a transhiatal procedure. Complications, 30-day mortality

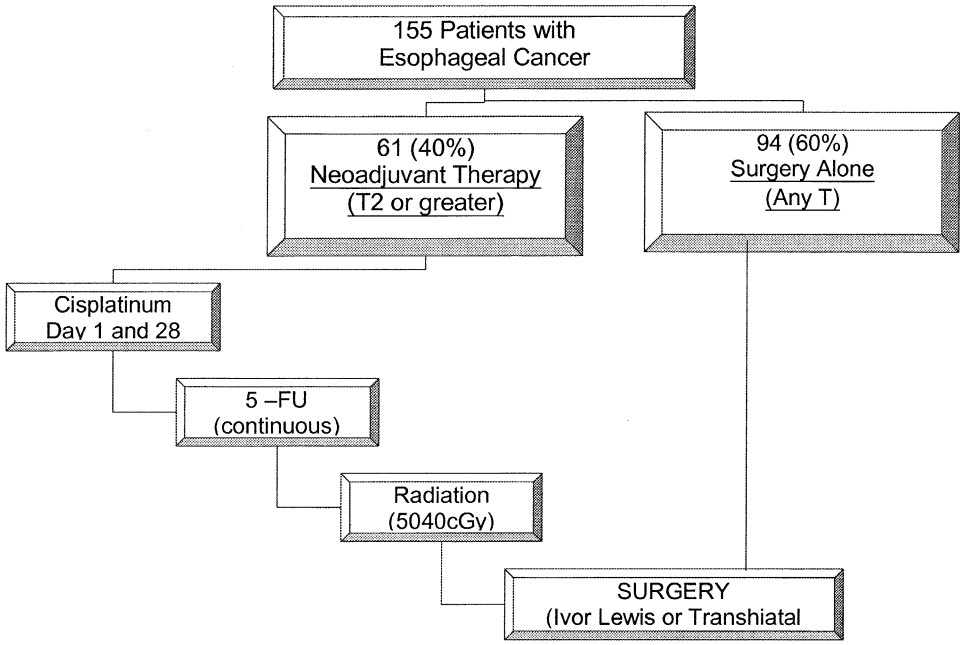

Fig. 1. Study design.

rate, esophageal leakage rate, and length of hospital stay were tabulated. For the purpose of group comparisons, patients were divided into two groups: neoadjuvant therapy vs. surgery alone. Statistical analyses included chi-square test, Student's *t* test, and Mann-Whitney U test for nominal, continuous, or ordinal variables. Results were considered significant at $P < 0.05$.

RESULTS

Neoadjuvant therapy was successfully tolerated with only mild side effects (<1% required hospitalization)

Table 1. Patient characteristics

Category	Entire cohort	Neoadjuvant group	Surgery alone	*P* value
Total patients	155 (100%)	61 (40%)	94 (60%)	—
Males	132 (85%)	49 (80%)	83 (88%)	0.78
Females	23 (15%)	12 (20%)	11 (12%)	0.44
ASA score (mean)	2.2	2.1	2.2	0.62
Squamous	19 (13%)	10 (18%)	9 (10%)	0.79
Adenocarcinoma/Barrett's	136 (87%)	51 (82%)	85 (90%)	0.56
Mean hospital stay (days)	12.7	11.1	13.0	0.82
Ivor-Lewis esophagectomy	146 (94%)	58 (95%)	88 (94%)	0.67
Transhiatal	9 (6%)	3 (5%)	6 (6%)	0.72
AJCC stage (pathologic)				
0	39 (25%)	23 CR (37%)	16 dysplasia/BE (17%)	
I	21 (14%)	1 (2%)	20 (21%)	
II	47 (30%)	15 (25%)	32 (34%)	
III	41 (26%)	18 (30%)	23 (24%)	
IV	7 (5%)	4 (6%)	3 (4%)	
AJCC stage (EUS)				
I	11 (7%)	0	11 (12%)	
II	39 (25%)	16 (26%)	23 (24%)	
III	48 (31%)	32 (52%)	16 (17%)	
IV	0%	0	0	
NO EUS	57 (37%)	13 (22%)	44 (47%)	

ASA = American Society of Anesthesiologists; CR = complete response; BE = Barrett's esophagus; EUS = endoscopic ultrasound.

Table 2. Complications

Complications	Entire cohort No. of patients	Neoadjuvant Group No. of patients	Surgery alone No. of patients	*P* value
All	39 (25.1%)	14 (22.9%)	25 (26.5%)	0.26
Death	3 (1.9%)	2 (3.3%)	1 (1.1%)	0.17
Leak	4 (2.6%)	1 (1.6%)	3 (3.2%)	0.19
Arrhythmia	12 (7.8%)	4 (6.5%)	8 (8.5%)	0.73
Pneumonia	9 (5.8%)	3 (4.9%)	6 (6.3%)	0.51
Stricture (over 1 yr)	11 (7.1%)	4 (6.5%)	7 (7.4%)	0.53

in all patients who received it. Patient characteristics are reported in Table 1. Patients in both groups did not differ in terms of routine demographic characteristics—specifically, age, American Society of Anesthesiologists score, length of hospital stay, and type of operation performed. Table 1 also summarizes the range of both radiologic and pathologic stages within each of the two groups. Results represent final pathologic staging of resected specimens and therefore were not compared across groups because the neoadjuvant group included a significant number of complete responses to therapy.

Tumor Staging and Response to Treatment

Of the 61 patients treated with neoadjuvant chemoradiation, 23 (38%) experienced a complete pathologic response to treatment. Specifically, the patient's pathologic specimen was found to contain no residual tumor cells (cases range from T4N0 to T2N0; data not shown). In addition, 11 patients (18%) experienced a partial response to neoadjuvant therapy with significant downstaging of their tumors on final pathologic review as compared to their preoperative stage (evaluated via endoscopic ultrasound). There were an additional 27 patients (44%) who did not respond to neoadjuvant therapy.

Surgical Resection and Postoperative Complications

A total of 155 patients underwent esophageal resection. Of these, 146 patients (94.1%) underwent Ivor-Lewis esophagectomy (via right thoracotomy and abdominal incision) and nine (5.9%) underwent transhiatal esophagectomy with anastomosis in the neck. There were 39 postoperative complications (25.1%), which are listed in Table 2. Analysis of the overall and individual complication rates between the neoadjuvant group and the surgery-only group revealed no significant differences (see Table 2).

There were two deaths in the neoadjuvant group (one patient experienced a massive pulmonary embolus in the recovery room, and another died of multiorgan system failure due to aspiration pneumonia) vs. one in the surgery-only group (large acute myocardial infarction in a patient with known coronary artery disease who had undergone coronary stent placement preoperatively).

Anastomotic leaks were more prevalent in the surgery-only group than in the neoadjuvant group (3.2% vs. 1.6%, respectively). Furthermore, the one leak in the neoadjuvant group was the result of a transhiatal esophagectomy and responded to neck drainage alone. Only one patient in the surgery-only group required reoperation (pleural flap, drainage), whereas the other two were managed nonoperatively, with complete resolution in all and no deaths.

There were a total of 12 episodes of arrhythmia (4 neoadjuvant; 8 surgery only) documented; all were supraventricular and all responded to medical management. Finally, there were three pneumonia/pulmonary complications (4.9%) in the neoadjuvant group (2 were simple aspiration events that responded to antibiotics; the third was the patient who died of multiorgan system failure) vs. six events (6.3%) in the surgery-only group (4 simple aspiration pneumonias and 2 patients who had episodes of mucous plugging requiring extended intubations of 2 and 3 days).

Within the neoadjuvant group, patients who had a complete response proved no more or less likely to encounter a postoperative adverse event than nonresponders (Table 3).

DISCUSSION

The early results of patients who underwent esophagectomy for cancer of the esophagus carried a

Table 3. Tumor response to neoadjuvant therapy

Response	Entire neoadjuvant cohort No. of patients	Complications No. of patients	*P* value
Complete response	23 (38%)	6 (26.1%)	—
Partial response	11 (18%)	2 (18.2%)	0.52
No response	27 (44%)	2 (22.2%)	0.39

very high operative morbidity and mortality and low rates of resection.[2] More recent studies have improved results; however, with the advent of neoadjuvant therapy came the question of whether such manipulation of the tissue and immune system prior to surgery might result in a higher rate of adverse events. Our data did not show an increased propensity for complications in this select group of patients. The present study is a review of our experience in treating esophageal cancer at a single, high-volume institution. The majority of our patients were older men with adenocarcinomas of the gastroesophageal junction or distal esophagus. The majority of the patients underwent Ivor-Lewis esophagectomy, with or without neoadjuvant chemoradiotherapy. We believe that in the setting of esophageal cancer, treatment with neoadjuvant therapy effectively facilitates resection in a large number of patients (both complete responders and partial responders), allows timely administration of systemic treatment for what is likely a systemic disease, and adds very little, if any, increase in the risk to the patient in the form of postoperative complications.

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Discussion

Dr. A. Lowy (Cincinnati, OH): It is really an impressive series with great results and low mortality. I would love to know how you get just a 5% pulmonary complication rate in patients undergoing an Ivor-Lewis esophagectomy. Do you do some type of preoperative pulmonary therapy for these patients, because our experience has been nowhere near that good?

The second question really relates to your low incidence of anastomotic strictures. I think most practitioners believe that neoadjuvant chemoradiation may predispose to those types of complications because the irradiated esophagus is left behind and constitutes a large portion of the anastomosis, and possibly even irradiated stomach.

Can you tell us anything about the radiation fields that are being used, and do you do anything specifically to try to ensure that you have excised radiated tissue that is going to be incorporated into the anastomosis?

Dr. S. Kelley: I will answer your second question first. We do not do anything specifically with the stomach or the area that we are going to anastomose. However, for the Ivor-Lewis procedure obviously we do not need to stretch the stomach out and put it on a very tenuous blood supply. There is a great deal of stomach that we can use, and I think we just cut back the stomach to a point where it is very clearly able to bleed well. Our stricture rate is a little bit lower than probably other series have shown.

Reporting of strictures is also an issue, and I presented patients who were "symptomatic" with strictures, so they clearly were the worst of the worst. I think that most of our patients end up having some difficulty swallowing that may be due to a small stricture, and they tend to get away with it.

In terms of your first question, the pulmonary complication issue, any patient who has any underlying lung disease, any history of smoking, or chronic

obstructive pulmonary disease, we tend to send to our pulmonologists. All of our patients undergo preoperative pulmonary function testing, and they also get some coaching in terms of quitting smoking and some exercises they can do. I think that helps a great deal just in terms of getting them ready for surgery. I have not looked at the specifics of whether it has had any effect on our pulmonary complications, but it is an interesting point to maybe look at in the future.

Mr. P. McCulloch (Liverpool, UK): Most series, unfortunately, do not provide data that can support your conclusions because they are not randomized either, and you must select patients for chemoradiation on some basis. There is already a hint that the age is a difference. Can you tell us about your fitness criteria?

Dr. Kelley: We are not trying to screen the healthy or the sicker patients. We are now basically sending anyone with a T2N1 lesion or greater for neoadjuvant therapy, so patients with T2N1 or T3 lesions are receiving neoadjuvant therapy.

I agree with you that this is not a randomized study and thus it is not easy to draw conclusions, but this is essentially a retrospective review of one surgeon's experience. With the advent of newer neoadjuvant therapies, patients are tolerating treatment better, and there are studies out there that are starting to find just as low a complication rate in both groups. Several studies have been published recently (e.g., *Journal of Clinical Oncology* 19:305–313, 2001).

Mr. McCulloch: If the chairman would permit me, I should point out that the British recently abandoned a prospective randomized trial with chemoradiation because the pilot study showed a sudden leap in postoperative mortality, and that is our concern.

Invited Discussion—Expert Commentator

David G. Fromm, *M.D.* (Detroit, MI): In this esophageal cancer study, if one excludes deaths, twice as many complications occurred in those patients who did not receive neoadjuvant chemoradiotherapy compared to those who did receive such treatment. On the one hand, this is surprising because the European Organisation for Research and Treatment of Cancer (EORTC) randomized trial (reported in 1997) comparing patients who were also treated with neoadjuvant chemoradiotherapy and surgery to those who were treated with surgery only found almost the same incidence of nonfatal postoperative complications. On the other hand, the differences in complications reported by Dr. Kelley and his associates may be due to a selection bias in that some patients, during the course of their neoadjuvant therapy, develop complications and/or progressive disease that excludes them from operative treatment. Thus, better-risk patients are referred for surgery. Of note is that the EORTC had a 12% postoperative mortality in the neoadjuvant therapy arm compared to 4% in the surgery-alone arm; the recent literature reports range from 3% to 12%. The present study had an overall mortality of 1.9%, which is not only a reflection of patient selection but also surgical skill. Randomized trials of preoperative radiotherapy alone have not demonstrated an improvement in resection rate or overall survival. Randomized trials of preoperative chemotherapy alone and randomized trials of neoadjuvant chemoradiation therapy have given mixed results. These conflicting outcomes may be due to patient variables and differences in drug and radiation doses.

Factors Affecting Quality of Life After Minimally Invasive Heller Myotomy for Achalasia

Yannis Raftopoulos, M.D., Ph.D., Rodney J. Landreneau, M.D., Fernando Hayetian, M.D., Pavlos Papasavas, M.D., Keith S. Naunheim, M.D., Steven R. Hazelrigg, M.D., Ricardo Santos, M.D., Daniel Gagné, M.D., Philip Caushaj, M.D., Robert J. Keenan, M.D.

The effect of prior nonoperative treatment, type of fundoplication, and surgical approach on quality of life after minimally invasive Heller myotomy (MIHM) for achalasia in not known. MIHM for achalasia was performed in 105 patients (primary 102; redo 3). Sixty-five patients had prior nonoperative treatment (dilations in 41; botulinum toxin injections in 13; dilations and botulinum toxin injections in 11). Primary laparoscopic MIHM with fundoplication (Dor in 32; Toupet in 56) was performed in 88 patients and thoracoscopic MIHM without fundoplication in 14. Achalasia and quality-of-life–related symptoms were evaluated prospectively with a visual analogue scoring scale. Median follow-up was 25 months. There was a trend toward a higher incidence of intraoperative esophageal perforation and recurrent dysphagia in patients with prior nonoperative treatment. Patients with prior nonoperative treatment had significant improvement in achalasia-related symptoms postoperatively. Patients with prior botulinum toxin injections with or without dilations had no improvement in quality of life after MIHM. The operative success of MIHM may be compromised if prior nonoperative treatment is used. Botulinum toxin injections may blunt the beneficial effect of MIHM on quality of life. The outcome of MIHM is good regardless of the type of fundoplication or surgical approach. (J GASTROINTEST SURG 2004;8:233–239)

KEY WORDS: Achalasia, minimally invasive, Heller myotomy, quality of life

Current therapies for achalasia aim at palliating dysphagia rather than restoring normal esophageal motility. As a result, some symptoms may persist or new symptoms may develop postoperatively, thereby affecting quality of life. Minimally invasive Heller myotomy (MIHM) is a highly effective treatment for achalasia.[1] Quality of life and dysphagia improve significantly after MIHM.[2] MIHM in patients with prior nonoperative treatment (dilation or botulinum toxin injection), although technically challenging, is feasible and safe if the procedure is performed carefully.[3] The effect of such treatments on quality of life after MIHM is not known because reports of such studies are lacking in the literature. In addition, there is no consensus as to whether to perform an anterior or posterior fundoplication.[4] Short of randomized trials, the use of quality of life and achalasia-specific instruments to assess the impact of prior nonoperative treatment, type of fundoplication, and surgical approach (thoracoscopic or laparoscopic) on patients' quality of life after MIHM for achalasia might allow for some valid conclusions.

MATERIAL AND METHODS

From May 1992 to July 2002, a total of 105 patients (primary 102; redo 3) underwent MIHM at three institutions (Western Pennsylvania Allegheny Health System [WPAHS], n = 66; St. Louis University

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From the Department of Minimally Invasive Surgery, Western Pennsylvania Allegheny Health System (Y.R., R.J.L., F.H., P.P., R.S., D.G., P.C., R.J.K.), Pittsburgh, Pennsylvania; Department of Cardiothoracic Surgery, St. Louis University (K.S.N.), St. Louis, Missouri; and Department of Cardiothoracic Surgery, Southern Illinois University (S.R.H.), Springfield, Illinois.
Reprint requests: Yannis Raftopoulos, M.D., 494 Gettysburg St., Pittsburgh, PA 15206-4530. e-mail: iraftopoulos@hotmail.com

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{SLU], n = 22; and Southern Illinois University [SIU], n = 14). Data regarding age, sex, preoperative symptoms, diagnostic workup, operative time, type of fundoplication (Toupet or Dor), surgical approach (thoracoscopic or laparoscopic), length of hospital stay, complications, postoperative gastroesophageal reflux, and recurrence of dysphagia were prospectively collected in a similar fashion by each institution. The study was approved by the institutional review board of WPAHS (RC #3318).

There were 54 males and 48 females whose mean age was 46 years. Preoperative symptoms included dysphagia (99%), weight loss (29.2%), regurgitation (26.4%), chest pain (16%), and respiratory abnormalities (6.6%). All patients underwent preoperative manometry, upper endoscopy, and barium swallow study. Prior nonoperative treatment had been offered in 65 patients. Forty-one patients were treated with dilations (D group; median 2 per patient, range 1 to 12), 13 with botulinum toxin injections (B group; median 2 per patient, range 1 to 4), and 11 with a combination of dilations and botulinum toxin injections (DB group). Thirty-seven patients did not receive any treatment prior to MIHM (N group). Thoracoscopic Heller myotomy without fundoplication was performed at only one institution (SIU) in 14 (13.8%) of 102 patients. Laparoscopic Heller myotomy with fundoplication was used in the remaining 88 (86.2%) of 102 patients. All patients from SLU (n = 22) underwent a Dor fundoplication. Ten patients from WPAHS underwent a Dor fundoplication, of which seven were performed during our early experience and three to buttress an esophageal perforation. A Toupet fundoplication was performed in the remaining patients (n = 56) from WPAHS.

SURGICAL TECHNIQUE

The surgical technique used at the three institutions was similar, as previously described.[5] In brief, patients are placed preoperatively on a liquid diet for 5 days to allow for clearance of as much solid debris from the esophagus as possible. At the time of surgery, a fiberoptic esophagogastroduodenoscopy is performed first to remove any residual esophageal debris and to assess the esophagus. Laparoscopic Heller myotomy is performed with the patient in a lithotomy position, and the legs abducted at a 45-degree angle with Allen stirrups. Five ports (four 10 mm and one 5 mm) are placed, two of which (surgeon) are placed at a horizontal line inferior to the costal margin, one slightly to the right of the midline (5 mm), and one at the left midclavicular line. Three additional ports are placed at the right (liver retractor) and left (assistant) anterior axillary line 2 cm below the costal margin and one (laparoscope) in line with the anatomic location of the esophageal hiatus at the same horizontal level with the liver retractor and assistant's ports. The gastrohepatic ligament is divided, and the left and right crura are dissected. Myotomy begins with the harmonic scalpel, 1 cm proximal to the gastroesophageal junction, and is extended 3 to 4 cm proximally and 2 cm distally onto the gastric cardia. Endoscopic evaluation of mucosal integrity and adequacy of the myotomy is undertaken next. The procedure is completed with a Dor or a Toupet fundoplication. The latter requires, in addition, creation of a retroesophageal window and division of the upper short gastric vessels. Thoracoscopic Heller myotomy is performed with the patient in a right lateral decubitus position under double-lumen endotracheal anesthesia and contralateral single-lung ventilation. Four ports are placed in two nearly parallel vertical rows at the left anterior and posterior axillary line. Myotomy is performed in a similar fashion, as in the laparoscopic approach, under endoscopic guidance. No fundoplication is performed.

Follow-up Protocol

Achalasia-related symptoms and quality of life were assessed with a questionnaire previously designed by our group.[5] Our questionnaire assesses six achalasia-related gastrointestinal symptoms—heartburn, dysphagia, regurgitation, chest pain, gas/bloating, and diarrhea—and includes two health-related quality-of-life questions regarding level of activity, or lifestyle and sense of well-being. A visual analogue scoring scale (0 = no symptoms/great = 10 severe symptoms/poor) is used. Routine follow-up evaluation occurred in the early postoperative period, 6 months after the operation, and then on an annual basis. Follow-up protocol was similar among the three institutions. Patients who had not been seen in our clinic for more than a 1-year period were contacted by telephone. Follow-up data were available in 101 (99%) of 102 patients. The median follow-up was 25 months (range 1 to 90 months).

Statistical Analysis

The symptom scores at the time of the last clinic visit were used. Patients who required esophagectomy because of recurrent dysphagia were included in the analysis, as these were considered complications of the original operation. The last symptom scores prior to the second surgical intervention were used. Patients with intraoperative esophageal perforations were excluded from the comparison of complications between the Dor and Toupet fundoplications,

because their occurrence was directly related to the myotomy technique and influenced the choice of fundoplication. Surgical outcome was assessed by operative time, length of hospital stay, and incidence of intraoperative esophageal perforation, complications, and recurrent dysphagia.

GraphPad (GraphPad Software, Inc., San Diego, CA) software was used for statistical analysis. Mean symptom scores were calculated. Comparison of continuous and categorical data was performed by means of Student's *t* test and chi-square test, respectively. One-way analysis of variance and Kruskal-Wallis tests were used for comparison of more than two variables. $P < 0.05$ was considered significant.

RESULTS

Mean operative time was 166 (±60) minutes and the hospital stay averaged 2.7 (±2.3) days. The perioperative morbidity was 4.9% with no deaths. Esophageal perforations occurred in 3 (2.9%) of 102 patients; these were sutured laparoscopically with an uneventful postoperative course. Seventeen (16.6%) of 102 patients had dysphagia postoperatively; seven had mild symptoms and required no treatment, six were treated with dilations, and four required further surgical intervention. One patient underwent a redo laparoscopic Heller myotomy on postoperative day 1 because of persistent achalasia symptoms consistent with incomplete myotomy, and three eventually required a transhiatal esophagectomy because of subsequent stricture formation and severe esophageal dilation. There were no significant differences in any preoperative characteristics in the patients who required further surgical intervention compared to the entire group. Postoperative gastroesophageal reflux requiring medical treatment occurred in 14 (13.7%) of 102 patients. There was a statistically significant improvement in heartburn ($P < 0.0001$), regurgitation ($P < 0.0001$), dysphagia ($P < 0.0001$), chest pain ($P = 0.02$), level of activity ($P = 0.03$), and sense of well-being ($P < 0.0001$) scores after MIHM (Fig. 1).

Preoperative lower esophageal pressure was significantly higher ($P = 0.0019$) in patients with previous botulinum toxin injections (B group) (56.9 ± 8.6 mm Hg) compared to patients in the N group (33.4 ± 17.5 mmHg), D- (32.2 ± 16.4 mm Hg) and the DB group (39.2 ± 20.9 mm Hg). There was no significant difference in preoperative symptom scores among the D, B, DB, and N groups with the exception of dysphagia, which was higher ($P = 0.02$) in the D and DB groups. Prior nonoperative treatment had no significant effect on surgical outcome (Table 1). There was a trend, however, toward a higher incidence of intraoperative esophageal perforation and recurrent dysphagia in patients with prior nonoperative treatment. Patients without prior nonoperative treatment reported a significant improvement in heartburn ($P = 0.0007$), regurgitation ($P < 0.0001$), dysphagia ($P < 0.0001$), chest pain ($P = 0.02$), and sense of well-being ($P < 0.0001$) postoperatively (Fig. 2). Patients in the D group had a significant improvement in heartburn ($P = 0.01$), regurgitation ($P < 0.0001$), dysphagia ($P < 0.0001$), and sense of well-being ($P < 0.0001$) postoperatively (see Fig. 2). In contrast, patients in the B group had significant improvement only in dysphagia ($P = 0.001$) and patients in the DB group only in regurgitation ($P = 0.003$) and dysphagia ($P = 0.0005$) postoperatively (see Fig. 2). Postoperative level of activity ($P = 0.008$) and sense of well-being scores ($P = 0.01$) were significantly poorer in the DB group compared to the other groups.

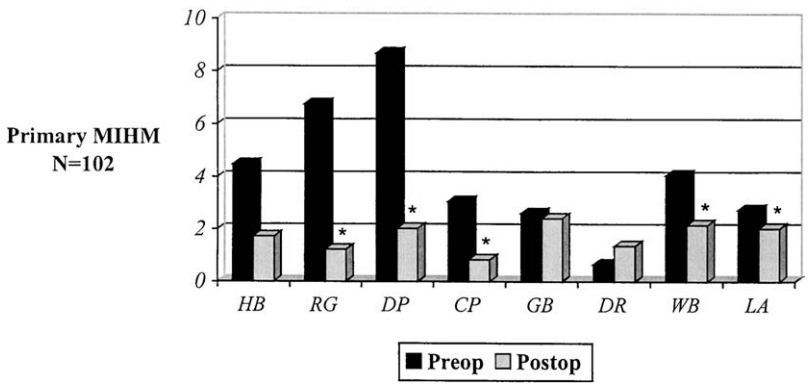

Fig. 1. Improvement in postoperative symptom score over baseline. * = $P < 0.05$; scale: 0 (none/great) to 10 (severe/poor). HB = heartburn; RG = regurgitation; DP = dysphagia; CP = chest pain; GB = gas/bloating; DR = diarrhea; LA = level of activity; WB = sense of well-being.

Table 1. Effect of prior nonoperative treatment on surgical outcome

Group	OT (min)	LOS (days)	Esophageal perforation	Postoperative complications	Recurrent dysphagia
D	181	2.9	2/41 (4.8%)	1/41 (2.4%)	5/41 (12.1%)
B	156.5	3.6	1/13 (7.6%)	0	3/13 (23%)
DB	198	2.5	0	0	2/11 (18.1%)
N	172	2	0	1/37 (2.7%)	7/37 (18.9%)
	NS	NS	NS	NS	NS

D = dilation; B = botulinum toxin injection; DB = dilation and botulinum toxin injection; N = no previous treatment; OT = operative time; LOS = length of hospital stay; NS = not significant.

The type of fundoplication had no significant effect on surgical outcome (Table 2). Toupet fundoplication was associated with significantly lower heartburn ($P = 0.005$), regurgitation ($P < 0.0001$), dysphagia ($P < 0.0001$), sense of well-being ($P < 0.0001$), and level of activity ($P = 0.01$) scores postoperatively. Dor fundoplication was associated with a significant improvement in heartburn ($P = 0.0009$), regurgitation ($P < 0.001$), dysphagia ($P < 0.0001$), and sense of well-being ($P = 0.04$) (Fig. 3). Although symptom scores were reduced significantly after MIHM, regardless of the type of fundoplication, postoperative dysphagia scores were higher in patients with Dor fundoplication ($P = 0.02$).

Operative time was significantly shorter after thoracoscopic Heller myotomy compared to laparoscopic Heller myotomy (96 vs. 177 minutes; $P < 0.0001$). No significant difference in length of stay, complications, and dysphagia recurrence rates was noted between the two approaches (Table 3). Laparoscopic Heller myotomy was associated with significant improvement in heartburn ($P = 0.0004$), regurgitation ($P < 0.0001$), dysphagia ($P < 0.0001$), chest pain ($P = 0.01$), and sense of well-being ($P < 0.0001$) postoperatively. With the exception of chest pain, postoperative heartburn ($P = 0.04$), regurgitation ($P = 0.008$), dysphagia ($P < 0.0001$), and sense of well-being ($P = 0.04$), scores were significantly improved after thoracoscopic Heller myotomy as well (Fig. 4). Postoperative symptom score reduction was similar for both approaches.

DISCUSSION

This study shows that quality of life and gastrointestinal symptoms related to achalasia improve significantly after MIHM. Other investigators, as well as our group, have previously reported that quality of life improves after laparoscopic Heller myotomy.[2,5–7] A telephone survey assessing symptoms and quality of life after laparoscopic Heller myotomy with anterior fundoplication concluded that this procedure improves patients' symptoms and results in excellent patient satisfaction.[8] In addition, compared to open Heller myotomy, laparoscopic Heller myotomy has comparable success and causes less early detriment to quality of life.[9]

According to our results, achalasia-related symptom scores improved significantly after MIHM regardless of whether or not prior nonoperative treatment was used. However, patients without prior nonoperative treatment had significant improvement in more achalasia-related symptoms after MIHM than the other groups, suggesting that the operative success may be somewhat compromised if previous treatments have been used. Prior nonoperative treatment may also blunt the beneficial effect of MIHM on quality of life. The degree of postoperative improvement in quality of life, as measured by sense of well-being and level of activity, was impaired in patients with a history of botulinum toxin injections, compared to the other groups. Furthermore, this study provides evidence that the benefit of MIHM on quality of life can even be reversed in patients who had a combination of dilations and botulinum toxin injections prior to MIHM, as such patients reported worsening of their sense of well-being and level of activity scores postoperatively. Longer duration of symptoms preoperatively, fibrosis of the lower esophageal sphincter as previously reported,[10] and a higher (as shown in this study) preoperative lower esophageal sphincter pressure in patients with previous botulinum toxin injections may play a role. On the other hand, treatment of achalasia with dilations prior to MIHM did not have a negative effect on quality of life postoperatively. A previous study comparing six patients who had preoperative dilations with 34 patients who had no prior nonoperative treatment showed that a history of dilations had no influence on preoperative and postoperative achalasia-related symptoms and quality-of-life scores.[2]

This study did not show any significant differences in surgical outcome and degree of postoperative improvement on quality of life and achalasia-related symptom scores in relation to the type of fundoplication or surgical approach. It is possible that the inclusion of patients from three different institutions may

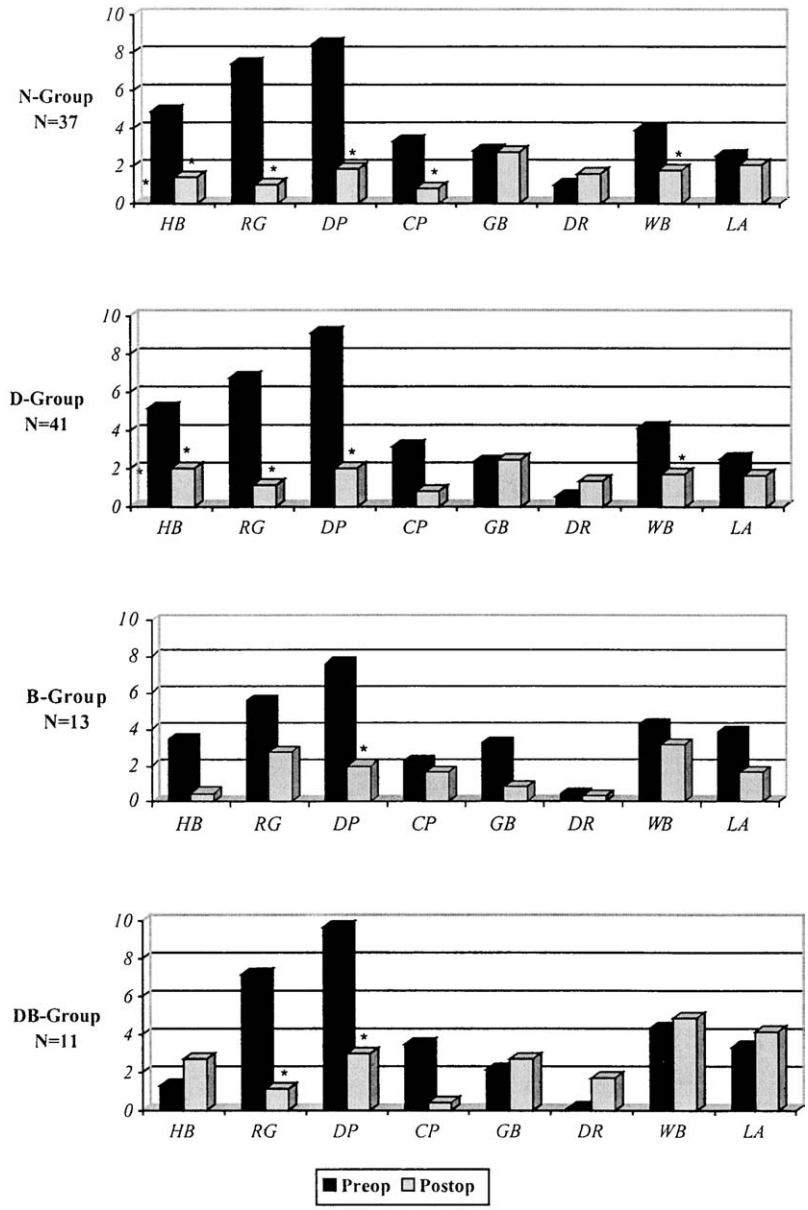

Fig. 2. Effect of prior nonoperative treatment on pre- and postoperative symptom scores. * = $P < 0.05$; scale: 0 (none/great) to 10 (severe/poor). N = no treatment; D = dilation; B = botulinum toxin injection; DB = dilation and botulinum toxin injection; other abbreviations as in Fig. 1.

Table 2. Effect of type of fundoplication on surgical outcome

Group	OT (min)	LOS (days)	Postoperative complications	Recurrent dysphagia
Toupet	190	2.3	1/56 (1.7%)	9/56 (16%)
Dor	172	3.1	1/32 (3.1%)	2/32 (6.2%)
	NS	NS	NS	NS

OT = operative time; LOS = length of hospital stay; NS = not significant.

have concealed differences among the procedures. It is important to emphasize that the techniques used for the myotomy, fundoplication, and surgical approach were similar. In addition, variations with regard to the choice of fundoplication and approach were mostly among the institutions, and to a lesser extent among patients originating from the same institution. It is also possible that because of the retrospective nature of this study, the sample size may not have been large enough to detect differences between the

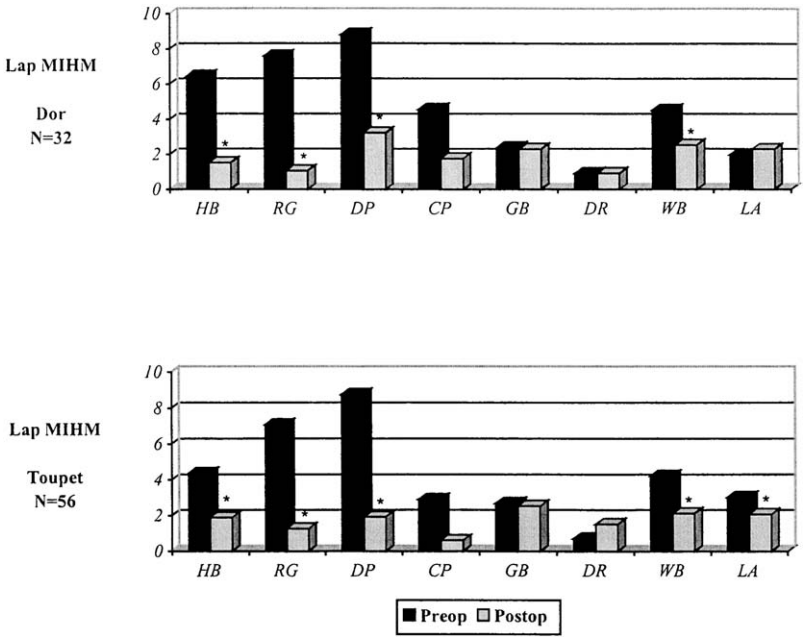

Fig. 3. Preoperative and postoperative symptom scores in relation to type of fundoplication. * = $P < 0.05$; scale: 0 (none/great) to 10 (severe/poor). Lap = laparoscopic; other abbreviations as in Fig. 1.

various subgroups examined. Achalasia, however, is a relative rare condition, and a review of the literature shows that there are only a few studies with larger patient populations (110 to 168 patients). In addition, sample sizes in studies reporting data on quality of life after MIHM are even smaller (19 to 56 patients). A multicenter collaborative study could allow for more valid conclusions.

The results of this study should be viewed with some caution, however, as the questionnaire used to assess achalasia-related symptoms and quality of life has not been validated yet. Certain validation criteria, however, such as reliability, validity, and responsiveness have been met.[11] The same results on repeated examinations define the reliability of an instrument. Although reliability was not directly tested, improvement of achalasia-related symptoms and quality-of-life scores, as measured by our questionnaire, was similar in this report and our previous report.[5] Validity is defined by the instument's ability to measure what it claims to measure. Validity can be assessed in an informal way, so-called "face" validity, or in a formal way so-called "construct validity."[11] In our opinion, face validity is fulfilled because our questionnaire examines the most common symptoms of achalasia. Quality of life is also reliably assessed. A previous study showed that disease-specific instruments might be more sensitive than generic instruments in assessing quality of life for surgical diseases.[12] This same study demonstrated that only the domains of physical functioning and general health of the SF-36 were significantly affected in patients with gastroesophageal reflux disease who undergo antireflux surgery when compared with a validated gastroesophageal reflux disease–specific quality-of-life scale. The domains of physical functioning and general health are represented in our questionnaire by the questions regarding level of activity and sense of well-being. Sensitivity is defined by the instrument's ability to detect changes in quality of life over time.

Table 3. Effect of surgical approach on surgical outcome

Group	OT (min)	LOS (days)	Esophageal perforation	Postoperative complications	Recurrent dysphagia
Laparoscopic	177	2.6	3/88 (3.4%)	2/88 (2.3%)	16/88 (18.1%)
Thoracoscopic	96	2.5	0	0	1/14 (7.1%)
	$P < 0.0001$	NS	NS	NS	NS

OT = operative time; LOS = length of hospital stay.

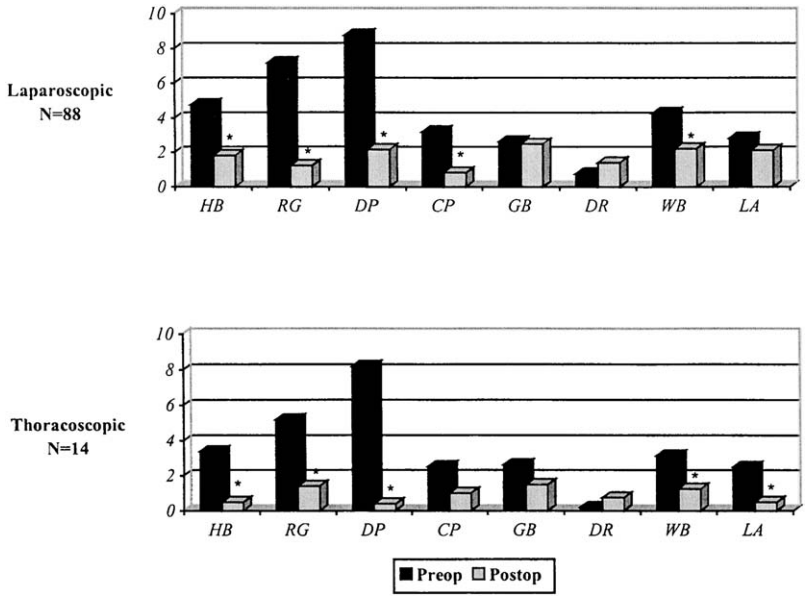

Fig. 4. Preoperative and postoperative symptom scores in relation to surgical approach. * = $P < 0.05$; scale: 0 (none/great) to 10 (severe/poor). Abbreviations as in Fig. 1.

Our study shows that all achalasia-related symptom scores improved significantly after MIHM.

CONCLUSION

MIHM offers excellent long-term relief of achalasia-related symptoms and significant improvement in quality of life. The outcome of MIHM is good regardless of the type of fundoplication, or surgical approach. Prior nonoperative treatment may blunt the success of MIHM. Botox pretreatment should not be used in patients who are good operative candidates because it may increase the technical difficulty of MIHM and have a negative effect on quality of life.

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Clinicopathologic Characteristics of Gastric Cancer in a Young Patient Population

Antonio Ramos-De la Medina, M.D., Noel Salgado-Nesme, M.D., Gonzalo Torres-Villalobos, M.D., Heriberto Medina-Franco, M.D.

The aim of this study was to analyze the clinicopathologic characteristics of young patients with gastric cancer with special attention to hereditary gastric cancer in a tertiary referral university hospital. Charts from all patients 40 years of age or younger at the time of diagnosis, during the period from January 1, 1987 to December 31, 2001, were retrospectively reviewed. Demographic variables, family history of gastric cancer, clinicopathologic characteristics, and treatment-related variables were analyzed. Overall survival was the main outcome variable. Survival curves were constructed by means of the Kaplan-Meier method, univariate anlaysis was performed with the log-rank test, and multivariate analysis with Cox regression. Significance was considered at $P < 0.05$. During the study period, 558 cases of gastric cancer were seen at our institution, 83 (14.8%) were in patients 40 years of age or younger. Mean patient age was 33.2 years. Forty-five patients (54.2%) were male. Fourteen patients (16.9%) had a family history of gastric cancer. Five patients (6%) fulfilled the criteria of hereditary gastric cancer. Surgery was performed in 88% of patients, but only 35% of the operations had a curative intent. Operative mortality was 2.4%. On univariate analysis, advanced tumor stage, hypoalbuminemia, low performance status, diffuse type, pangastric tumor location, noncurative surgery, and lack of adjuvant chemotherapy had a significant negative impact on survival. On multivariate analysis, advanced tumor stage, pangastric tumor location, and absence of adjuvant chemotherapy were significantly associated with poor prognosis. Family history of gastric cancer or hereditary gastric cancer did not have any impact on prognosis. There is a high frequency of gastric cancer in young patients at our institution. Most patients present in advanced stages, which favors a poor overall survival. Family history of gastric cancer or hereditary gastric cancer did not have a significant impact on survival. Complete resection and adjuvant chemotherapy appeared to confer the only chance of prolonged survival. (J GASTROINTEST SURG 2004;8:240–244)

KEY WORDS: Hereditary gastric cancer, young patients, E-cadherin

Gastric cancer is the second most common malignancy in the world.[1] In Mexico, gastric adenocarcinoma is the most frequent gastrointestinal neoplasm.[2] The proportion of young patients at our institution is the highest reported thus far in the literature.[3] The prognosis in young patients with gastric cancer has been a subject of debate, with some series reporting poorer prognosis for these individuals and others finding no difference between young and elderly patients.[3,4] Differences between young patients with hereditary gastric cancer and those with sporadic occurences have not been described. Criteria for defining familial gastric cancer syndromes have been proposed and include review of histopathologic findings and pedigree analysis of any family with an aggregation of cases of gastric cancer.

The present study represents a retrospective analysis of all patients 40 years of age or younger with gastric cancer seen and managed at the National Institute of Medical Sciences and Nutrition "Salvador Zubirán" in Mexico City during a 15-year period. The objective was to describe the clinicopathologic

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From the Department of Surgery, National Institute of Medical Sciences and Nutrition "Salvador Zubirán," Mexico City, Mexico.
Reprint requests: Heriberto Medina-Franco, M.D., Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán," Departamento de Cirugía, Vasco de Quiroga 15, Tlalpan, Mexico DF 14000. e-mail: herimd@hotmail.com

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characteristics of gastric cancer in a young patient population with a main focus on hereditary gastric cancer.

PATIENTS AND METHODS

A retrospective review of charts from patients 40 years of age or younger with a diagnosis of gastric cancer, who were seen at the National Institute of Medical Sciences and Nutrition in Mexico City, was conducted. The study period was January 1, 1987 to December 31, 2001. Demographic, clinical, histopathologic, treatment, and survival data were reviewed and analyzed. All deaths within 30 days after surgery were considered to represent surgical mortality. The American Joint Committee on Cancer (AJCC) staging criteria was used for clinical and pathologic staging. The criteria used to define hereditary gastric cancer included the following: two or more documented cases of gastric cancer in first- and second-degree relatives, with at least one of them diagnosed before the age of 50, or three or more cases regardless of age at diagnosis. Survival curves were constructed according to the Kaplan-Meier method[5] and compared by means of the log-rank test. Multivariate analysis was performed with the Cox regression model using the SPSS 10.0.1 statistical package (Chicago, IL). Differences were considered significant at $P < 0.05$.

RESULTS

A total of 558 patients with gastric adenocarcinoma were identified from the tumor registry during the study period. Eighty-three patients (14.8%) were 40 years of age or younger; these patients comprised the study group. There were 45 male (54.2%) and 38 female (45.8%) (ratio 1.2:1) patients. Forty-four patients (53%) were 35 years of age or younger, and 27 (32.5%) were less than 30 years of age. Of these 27 patients, 13 were male and 14 were female (ratio 0.9:1). Among the patients over 30 years of age, 32 were male and 24 were female (ratio 1.3:1). The mean age at diagnosis was 33.2 years (range 15 to 40 years). The mean age for males and females was 34 and 32.3 years, respectively. Fourteen patients (16.9%) had a first-degree relative with a history of gastric cancer. Five patients (6%) fulfilled the criteria of hereditary gastric cancer. All patients were symptomatic. The mean duration of symptoms from onset to diagnosis was 8.4 months (range 2 to 48 months). Abdominal pain was the most common symptom, reported by 88% of patients, followed by weight loss in 70%. All symptoms at presentation are shown in Table 1. Thirty-nine percent of patients had a Karnofsky score of less than 90, and 56% had a body mass index below 20. Although only 26% of patients reported gastrointestinal bleeding, 46% had hemoglobin levels below 12 g/dl. Thirty percent of patients had albumin levels below 3.0 g/dl at the time of diagnosis. All of the patients underwent upper endoscopy with biopsy of the tumor. This study was the most useful diagnostic test with a sensitivity of 97%. Computed tomography and endoscopic ultrasound were performed in 90.4% and 10.8% of the patients, respectively. Histologic findings were as follows: 88% of patients had diffuse gastric cancer, followed by 10.8% with intestinal-type, in 1.2% (one case) with mucinous-type cancer. By definition, all hereditary gastric cancers were of diffuse type. Surgery was performed in 88% of patients, but only 35% of the operations had a curative intent. Operative morbidity was 20.5%. The most frequent complications were intra-abdominal abscess and anastomosis leak/fistula. Infectious complications (intra-abdominal abscess, pneumonia, wound infection and urinary tract infection, mediastinitis, and empyema) developed in 15.6% of cases. The postoperative mortality rate was 2.4% (2 of 83 patients). Tumor locations are shown in Fig. 1. Pathologic tumor stages were divided as follows: stage I–II 9.6%; stage III 26.5%; and stage IV 63.9%. Forty-one patients (49.4%) received some type of adjuvant chemotherapy and in four cases (4.8%) postoperative radiotherapy was used. There were no significant differences in clinicopathologic characteristics between patients with and without a family history of gastric cancer.

Median survival for the entire cohort was 10 months (95% confidence interval 5.92 to 14.08) with actuarial survival at 1, 3, and 5 years of 43.3%, 16.4%, and 10%, respectively. Mean follow-up was 15.1 months (range 1 to 99 months). There was no significant difference in survival for patients with or without a family history of gastric cancer. Median survival for

Table 1. Symptoms at presentation

Symptom	%
Abdominal pain	87.9
Weight loss	69.9
Vomiting	60.2
Upper gastrointestinal bleeding	26.4
Dysphagia	21.6
Abdominal distention	18.0
Ascites	3.6
Early satiety	2.4
Jaundice	1.2

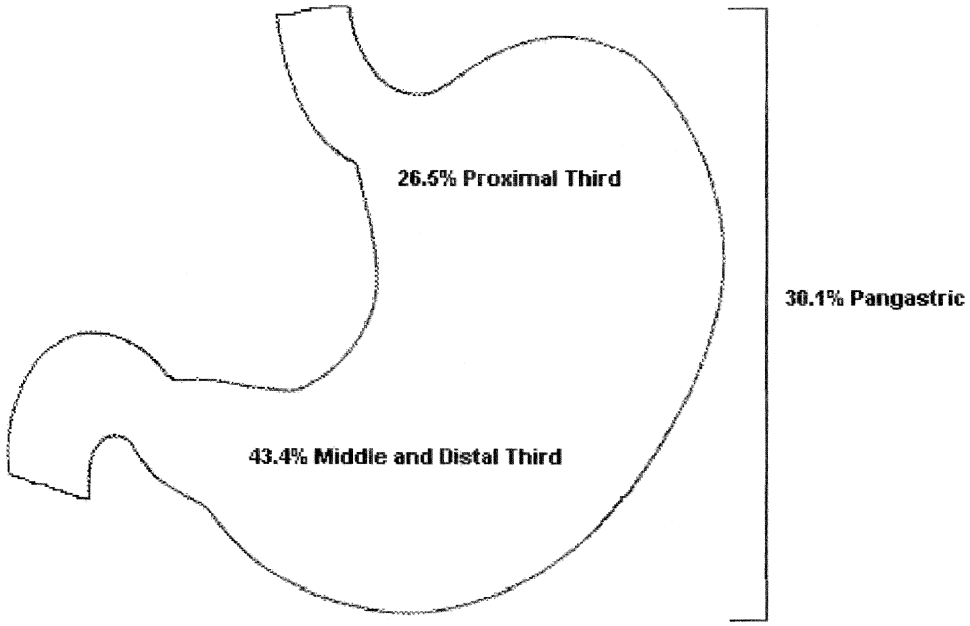

Fig. 1. Tumor location according to surgical and pathologic notes. Tumors in the middle and distal thirds were grouped together.

patients with hereditary gastric cancer was 5 months compared to 10 months for patients with sporadic cases; nevertheless, the difference was not significant. Patients with symptoms for less than 12 months had a median survival of 6 months compared with 27 months for patients with symptoms for more than 12 months ($P = 0.08$). On univariate analysis, advanced tumor stage, low performance status, linitis plastica hypoalbuminemia, and diffuse histologic findings were significantly associated with poor prognosis, whereas curative surgical resection and adjuvant chemotherapy had a positive significant impact on survival.

On multivariate analysis, advanced stage, tumor location, and chemotherapy retained their significance (Table 2).

Recently germline mutations in the E-cadherin/CDH1 gene have been identified in families with an autosomal dominant inherited predisposition to gastric cancer of the diffuse type. E-cadherin mutation analysis was performed in only 22 patients and was positive in three. Among the few cases in which E-cadherin analysis was performed, its mutation had a tendency to predict poor survival, with 15 months for patients not showing expression of this gene vs. 2 months for those testing positive for gene expression ($P = 0.02$).

DISCUSSION

Some reports have suggested that certain malignancies present a decade earlier in Mexico compared to other countries.[6] The proportion of young patients with gastric cancer at our institution is one of the highest that has been reported in the literature (14.8%). It has come down since a previous publication in which a rate of 16.2% was reported.[3] In contrast, several studies have stated that the frequency of gastric cancer in young patients has remained stable representing approximately 4% of all gastric cancers. Bonacini and Valenguela[7] reported a sevenfold increase in the incidence of gastric cancer from 1972 to 1976 and from 1982 to 1986 in Hispanic patients less than 30 years of age.

Gastric cancer in patients under the age of 30 is considered very rare.[8] In our series, 32.5% of young patients were less than 30 years of age. Young patients with gastric cancer in the United States are more likely to be black, Asian, or Hispanic.[9,10] All patients in this study were of Hispanic origin. These patients have a tendency to present in advanced stages, and some investigators have blamed this on delayed diagnosis due to lack of suspicion, whereas others theorize that a more aggressive disease is the culprit. Our findings suggest that patients with an abbreviated duration of symptoms have a shorter mean survival than patients with symptoms lasting longer than 12 months. This is consistent with previous reports, although statistical analysis did not show this correlation to be significant in our series.[8,11] Surgically treated patients have also shown better survival rates the longer the duration of symptoms prior to

Table 2. Survival analysis

	Median survival (mo)	95% CI	Univariate *P* value	Multivariate *P* value
Tumor stage			0.0001	.001
1	NR			
3	19	9.22–28.78		
4	4	2.91–5.09		
Albumin				
⩾3.5 g/dl	13	9.72–16.28	0.0002	NS
<3.4 g/dl	4	3.25–4.75		
R0 resection				
Yes	33	14.21–51.79	0.001	NS
No	5	0–14.64		
Karnofsky				
⩾90	14	10.9–17.10	0.00001	NS
<90	4	3.01–4.99		
Lauren				
Diffuse	9	5.27–12.73	0.04	NS
Intestinal	27	8.48–45.52		
Tumor location				
Distal	13	4.69–21.31	0.0006	0.01
Proximal	12	7.81–16.19		
Linitis plastica	3	1.94–4.06		
Chemotherapy				
Yes	14	10.82–17.18	0.01	0.01
No	4	2.44–5.56		
Family history				
Yes	11	0–24.09	NS	NS
No	10	6.32–13.68		

CI-confidence interval; NR-not reached; NS-not significant.

treatment.[12] As suggested by Armstrong and Dent,[11] this difference in behavior may represent subsets of disease, one of which is biologically more aggressive. Gastric cancer tends to present more frequently in men than in women (male:female ratio 2:1). Others series have noted that this relationship changes in young patients and particularly in patients under 30 years of age where the male:female ratio becomes reversed.[8,13] In our series, the male:female ratio for all patients 40 years of age or younger was 1.2:1 and for patients younger than 30 the ratio was 0.9:1. The reason for this increase in the number of women in the younger age group is not known. Yamachika et al.[14] recently correlated the expression of intestinal trefoil factor (ITF) with poor prognosis in patients with gastric cancer. In this report, although women were more likely to express ITF, it was mainly in men that expression of ITF was correlated with a more aggressive tumor phenotype (tumor stage, infiltrative growth pattern, positive lymph nodes) and a significantly worse survival. ITF expression seems to be induced by estrogen in breast cancer cells[15] and has been associated with expression of estrogen receptors in mucinous skin cancers, a nontargeted organ of estrogen.[16]

A family history of gastric cancer was found in 16.9% of the cases. A previous report from our institution found that only 2.6% of patients over 70 years of age report a family history of gastric neoplasms.[3] There is increasing evidence in the literature on heredity in gastric cancer. First-degree relatives of persons with gastric cancer have a two- to threefold increase in risk,[17,18] especially those diagnosed before the age of 50.[19] The Scandinavian Twin Study also showed an increased risk of gastric cancer in the twin of an affected person.[20] In only two patients were we able to find a reference to *H. pylori* in the pathology report. *H. pylori* infection may be lost with the development of atrophic gastritis, and atrophy is present in many patients with gastric cancer, so retrospective studies need to be interpreted with caution.[21]

In our series, survival was influenced by stage, tumor location, histologic findings, performance status, hypoalbuminemia, surgical resection, and adjuvant chemotherapy, as shown by univariate analysis. All of these variables have previously been reported in the literature as significant prognostic factors of survival.[3,21–25] Of interest, in a subset of our patient population where E-cadherin analysis was obtained,

its mutation had a negative predictive value on survival.

On multivariate analysis, only advanced stage, tumor location, and chemotherapy sustained significance. In summary, family history of gastric cancer and hereditary gastric cancer are variables without a significant impact on survival. We acknowledge that the small number of patients with a family history of gastric cancer (n = 14), hereditary gastric cancer (n = 5), and advanced disease stage at the time of surgery in the majority of patients may underpower the statistical analysis. Women under 30 years of age are a group with a higher risk of gastric cancer than was previously thought. The only interventions that can improve survival in this group of patients are prompt diagnosis and aggressive surgical treatment.

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Choledochal Cysts in Western Adults: Complexities Compared to Children

Michael Nicholl, M.D., Henry A. Pitt, M.D., Patrick Wolf, M.D., Janice Cooney, N.P., Munci Kalayoglu, M.D., Joel Shilyansky, M.D., Layton F. Rikkers, M.D.

Choledochal cysts occur most frequently in East Asian children and rarely in Western adults. Over the past two decades, pediatric treatment has been standardized, but relatively little information is available on the management of Western adults with choledochal cysts. Therefore the aims of this analysis were to compare the presentation, management, and late results of Western adults and children with choledochal cysts. Records were reviewed of patients with choledochal cysts at three academic institutions in Wisconsin. Fifty-seven patients were identified, and 51 of these patients (89%) were managed surgically. Thirty-one patients (54%) were adults, and the adults were more likely to be male (29% vs. 4%, $P < 0.02$). Pain (81% vs. 42%, $P < 0.01$) and cholangitis (35% vs. 15%) were more common in adults. Forty-one patients (71%) had type I cysts, but type IVa or V cysts with dilated intrahepatic ducts were more common in adults (39% vs. 15%, $P = 0.05$). Seventeen adults had undergone biliary surgery prior to referral compared to only four children (59% vs. 15%, $P < 0.01$). Preoperative endoscopic or percutaneous stents were employed more commonly in adults (42% vs. 15%, $P < 0.01$). Hospital mortality was 0%, and morbidity was low in both adults and children (25% vs. 8%). An associated biliary malignancy correlated with age ($P < 0.05$): 0 to 30 years (0%), 31 to 50 years (19%), and 51 to 70 years (50%). In addition, adults were more likely to have late problems with cholangitis (19% vs. 4%, $P < 0.07$) and secondary biliary cirrhosis (13% vs. 4%). This analysis suggests that compared to children, Western adults with choledochal cysts are more likely to have (1) type IVA or V cysts, (2) undergone prior surgery, (3) preoperative biliary stents, (4) an associated biliary malignancy, and (5) late hepatobiliary problems. We conclude that surgery in Western adults with choledochal cysts is frequently complicated and should be performed by specialists in complex biliary surgery. (J GASTROINTEST SURG 2004;8:245–252)

KEY WORDS: Biliary cysts, cholangiocarcinoma, choledochal cysts, gallbladder cancer

Choledochal cysts are dilatations of the extrahepatic and/or intrahepatic bile ducts that are believed to be of congenital origin. Most reported cases have been in female Asian children.[1] However, even in this patient population, choledochal cysts are uncommon. In comparison, choledochal cysts are very rare in children in the United States[2] and Europe.[3] Even more rare has been the presentation of choledochal cysts among Western adults.[4–6] Moreover, comparisons between children and adults with biliary cysts from Asia[7] or the United States[8] have rarely been reported.

Surgical treatment of choledochal cysts is undertaken to reduce the incidence of complications including pancreatitis, cholangitis, and biliary tract malignancy.[1–3,7–11] Even with adequate surgical treatment, long-term complications develop and include anastomotic stricture, cholangitis, biliary cirrhosis, and biliary tract malignancy.[12–14] Over the past two decades, pediatric treatment has been standardized and entails cholecystectomy, extrahepatic cyst excision, and Roux-en-Y hepaticojejunostomy.[1,2,11,15] However, the low incidence of choledochal cysts in Western adults has resulted in little information regarding management in this patient population. Thus the aims of this study were to compare the presentation, management, and late results in Western adults and children with choledochal cysts.

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From the Department of Surgery, Medical College of Wisconsin (M.N., H.A.P., P.W., J.S.,), Milwaukee, Wisconsin; and Department of Surgery, University of Wisconsin (J.C., M.K., L.F.R.), Madison, Wisconsin.

Reprint requests: Henry Pitt, M.D., Department of Surgery, Medical College of Wisconsin, 9200 West Wisconsin Ave., Milwaukee, WI 53226. e-mail: hapitt@mcw.edu

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METHODS

Patient Population

After institutional review board approval was obtained, a retrospective chart review was conducted of available records for the past 20 years at two Medical College of Wisconsin hospitals, Froedtert Memorial Hospital and Children's Hospital of Wisconsin, as well as at the University of Wisconsin Hospitals and Clinics. Search criteria included ICD 9 codes 576.9 and 751.9. Additionally, the radiology and endoscopic retrograde cholangiopancreatography (ERCP) databases were searched for the following key words: choledochal cyst, choledochocele, Caroli's disease, and abnormal pancreaticobiliary junction. Fifty-five patients were identified with the diagnosis of biliary cyst disease. Two patients were treated initially as children with cyst drainage or resection procedures at Children's Hospital of Wisconsin and subsequently returned as adults with long-term complications. Data from these patients were collected from both the children and adult groups, as appropriate, yielding a total of 57 patient encounters. Adults were defined as patients aged 18 years and older, and their mean age at presentation was 36.4 years. Children were defined as patients from birth to 18 years, and their mean age at presentation was 3.9 years. Adults comprised 54% (31 of 57) of the patient population (Table 1). Eighty-two percent (47 of 57) of the patients were female. However, adults were more likely to be male (29% vs. 4%, $P < 0.02$).

Table 1. Patient characteristics

	Children (n = 26)	Adults (n = 31)	Total (n = 57)
Age and sex			
Mean age (yr)	3.9	36.4	21.6
Female	96%	71%*	82%
Presenting symptoms			
Pain	42%	81%†	63%
Jaundice	42%	23%	32%
Fever	23%	35%	30%
Vomiting	23%	19%	21%
Mass	19%	0%*	9%
Associated diagnosis			
Cholangitis	15%	35%	26%
Pancreatitis	15%	19%	18%
Biliary malignancy	0%	19%*	11%
Biliary stricture	0%	3%	2%
Prior procedures			
Surgery	15%	55%†	37%
Stenting	4%	42%†	24%

*$P < 0.02$ vs. children.
†$P < 0.01$ vs. children.

Presentation

Pain was the most common presenting symptom (63%) and was reported more frequently in adults than in children (81% vs. 42%, $P < 0.01$) (see Table 1). Jaundice occurred in 32% of patients, and fever was present in 30% with no significant difference between adults and children. An abdominal mass was noted in 19% of children but was not found in any adult ($P < 0.02$). Cholangitis or pancreatitis was an associated diagnosis in 26% and 18% of patients, respectively, with no significant differences between adults and children. However, biliary malignancies were more common in adults (19% vs. 0%, $P < 0.02$).

Radiology

Sixty percent of patients underwent CT imaging, with adults slightly more likely than children to have a CT scan (65% vs. 54%). Ultrasound examinations were performed in 51% of patients, with adults less likely than children to have an ultrasound examination (32% vs. 75%, $P < 0.01$). Conversely, ERCP was performed in 42% of patients, with adults more likely than children to undergo ERCP (68% vs. 8%, $P < 0.01$). Nuclear medicine (HIDA) scans were obtained in only 13% of patients, all of them children (0% vs. 29%, $P < 0.01$). Magnetic resonance cholangiopancreatography (MRCP) was performed in 11% of patients, slightly more often in adults (16% vs. 4%). Radiology reports commented on the length of the common channel between the bile duct and the pancreatic duct in only 16 patients (28%). The common channel was long (>1.0 cm) in 75% of patients, adults (60%) and children (82%).

Cyst Type

Cysts were classified according to the Todani modification[16] of the system of Alonso-Lej et al.[17] Seventy-two percent of the cysts were type I cysts (Fig. 1), which are completely extrahepatic. Adults were less likely to present with type I cysts (61% vs. 85%, $P < 0.05$). No patients with type II, type III, or type IVB cysts were found. Ten patients had type IVA cysts, which are both extrahepatic and intrahepatic, and six patients had type V cysts, which are entirely intrahepatic. Adults were more likely to present with either a type IVA or V cyst (39% vs. 15%, $P < 0.05$).

Prior Surgery and Stenting

Seventeen adults and four children (55% vs. 15%, $P < 0.01$) had undergone prior biliary tract surgery (see Table 1). Eighty-two percent of adults who had prior surgery underwent cholecystectomy before receiving definitive treatment for their choledochal

cysts. Five adults and no children underwent preoperative endoscopic biliary stenting (16% vs. 0%, $P < 0.03$), and eight adults and one child underwent percutaneous biliary stenting (26% vs. 4%, $P < 0.02$). Overall, 13 adults and only one child had preoperative biliary stents (42% vs. 4%, $P < 0.01$) (see Table 1) (Fig. 2).

Statistical Analysis

Statistical analysis was performed with SPSS 11.0 for Windows software (SPSS Inc., Chicago, IL). Discrete variables were compared by chi-square analysis. All P values <0.05 were considered statistically significant.

RESULTS

Surgery

Fifty-one patients (89%) underwent surgical treatment including the vast majority of adults and children (84% vs. 96%) (Fig. 3). Most patients (82%) underwent cyst resection with Roux-en-Y cholangio- or hepaticojejunostomy in both adults and children (81% vs. 84%). Cyst drainage procedures were performed in three children (12%) and no adults. Four adults (15%) underwent palliative operations for advanced biliary tract malignancy. If not previously performed, cholecystectomy was undertaken at the time of surgery in most adults and children (74% vs. 88%). Intrahepatic or extrahepatic bile duct stones were found with equal frequency in adults and children (12% vs. 11%).

Mortality and Morbidity

No hospital deaths occurred in adults or children (Table 2). Overall morbidity was 18% and was higher in adults (23% vs. 12%), but this difference was not significant. Six adults incurred infectious postoperative complications with cholangitis (8%), abscess (4%), and wound infection (4%) being the most common. One adult patient had multiple postoperative complications. Postoperative complications occurred in three children; these included a biliary fistula, a biloma, and pancreatitis.

Biliary Malignancies

Six adults had a biliary malignancy compared to none of the children (19% vs. 0%, $P < 0.05$). These six patients ranged in age from 38 to 68 years with a median of 43 years. Four (67%) were women, which was similar to the entire adult group (71%). Five (83%) of these six adults had type I cysts, and one had a type IVA cyst. This distribution of cyst types was no different from that in the overall adult group (see Fig. 1). Three of these six patients had undergone prior biliary surgery. Two had undergone choledochal cyst duodenostomies 34 and 36 years previously when they were ages 4 and 8, respectively. One patient had undergone resection of a type I cyst elsewhere at age 29, which was 13 years before presenting to us with an unresectable cholangiocarcinoma. Thus, of the 43 patients undergoing cyst resection, only one (2%) developed a subsequent biliary malignancy. The other three adults with a biliary malignancy had

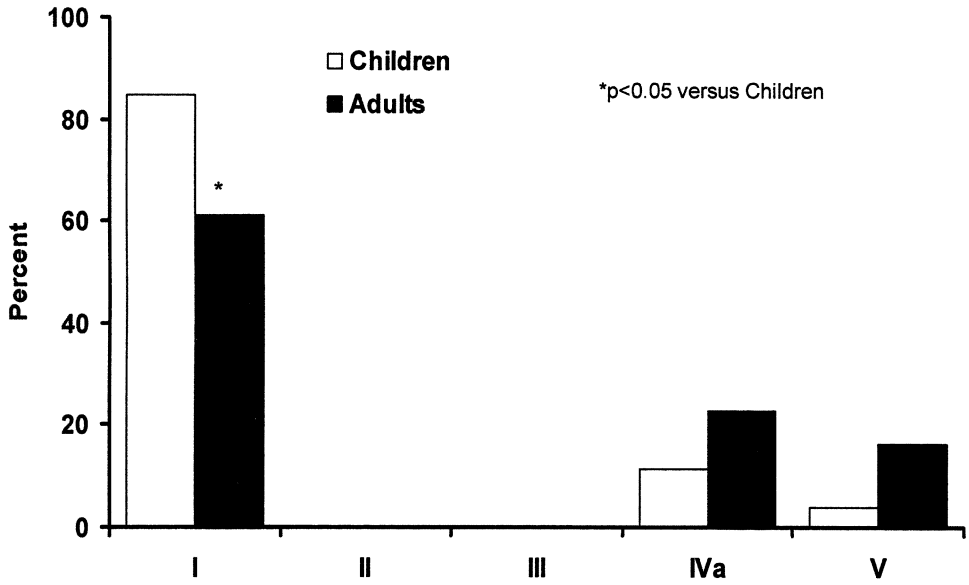

Fig. 1. Choledochal cyst type in children and adults. Type I cysts were less common ($P < 0.05$) and type IVA and V cysts were more common ($P < 0.05$) in adults.

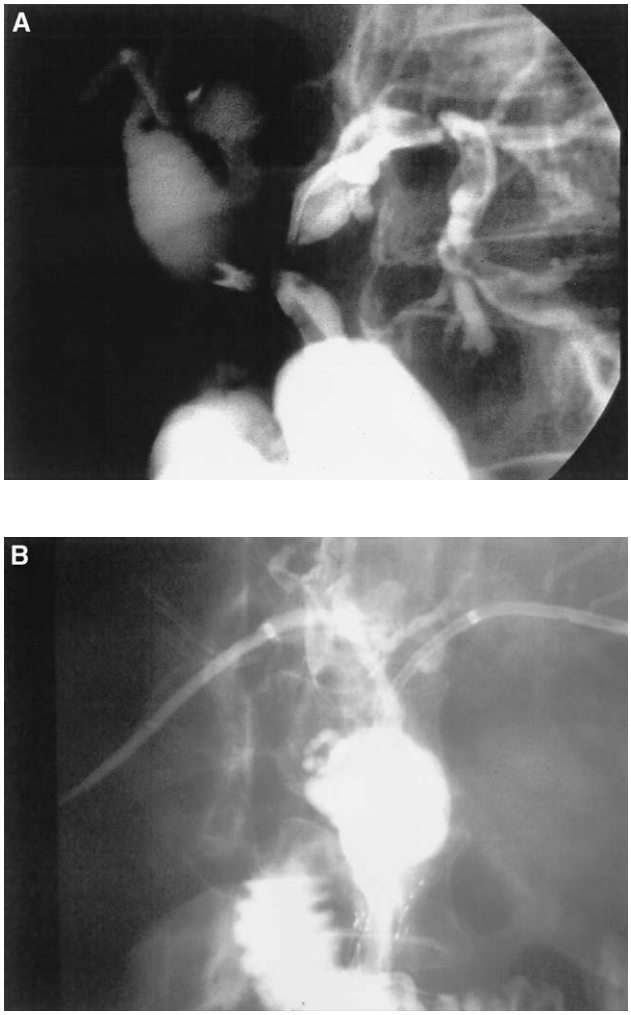

Fig. 2. A, Transhepatic cholangiogram demonstrating a type IVA cyst with intrahepatic stones and strictures in a patient previously managed with a metallic endoscopic stent. **B**, Preoperative cholangiogram after placement of bilateral transhepatic stents through the cysts and metal stent into the duodenum.

this problem at the time of their initial presentation. Five of the adults with a malignancy had cholangiocarcinomas (16%), whereas one had gallbladder cancer (3%). Two of the five cholangiocarcinomas were resected, and four patients underwent palliative surgery.

Late Complications

Late complications occurred in 28 patients (49%) including 18 adults and 10 children (58% vs. 38%). The most common late complications were cholangitis (12%), cancer (11%), cirrhosis (9%), and bowel obstruction (5%) (Fig. 4). Adults were more likely to have cholangitis (19% vs. 4%, $P < 0.07$), cancer (19% vs. 0%, $P < 0.05$), and cirrhosis (13% vs. 4%). However, children were more likely to develop bowel obstruction (0% vs. 12%, $P < 0.07$). As mentioned earlier, six adults had a biliary malignancy. The incidence of malignancy increased with age (Fig. 5). No patient under the age of 30 years developed a biliary tract malignancy. Nineteen percent of patients between the ages of 31 and 50 years developed a biliary cancer, and 50% of the patients aged 50 to 70 years developed a biliary tract malignancy. Four percent of adults and 8% of children developed an anastomotic stricture. Three percent of adults and 4% of children developed recurrent pancreatitis.

DISCUSSION

This analysis reports the experience with biliary cyst disease in adults and children at three academic medical centers in Wisconsin. Of the 57 patients with choledochal cysts or Caroli's disease, 31 (54%) were adults. Adults were more likely to be male ($P < 0.02$) and to present with pain ($P < 0.01$) and cholangitis ($P < 0.09$). Adults also were more likely to have intrahepatic cysts ($P = 0.05$) and to have undergone prior biliary tract surgery ($P < 0.01$) and preoperative biliary stenting ($P < 0.01$). In addition, adults were more likely to have a biliary tract malignancy ($P < 0.05$). Operative mortality (0%) and morbidity (18%) were low in both adults and children. However, adults were more likely to have late postoperative problems with cholangitis ($P < 0.07$) and biliary cirrhosis, whereas children were more likely to develop bowel obstruction ($P < 0.07$). This Wisconsin experience with choledochal cysts suggests that Western adults frequently have complicated disease that can be managed safely by specialists in complex biliary surgery.

In Japan and other East Asian countries, biliary cysts are diagnosed most frequently in childhood in females.[1,7,11,16] In comparison, in the United States and Europe an increasing number of adult patients are being diagnosed and treated.[1,4,6,8,18–20] In adults the classic triad of jaundice, right upper quadrant pain, and a palpable mass is unusual. In this and other series, pain was more common in adults, but this finding may be due to the fact that small children are unable to express this symptom.[1,8,13,21] Lipsett et al.[8] from Johns Hopkins University found that adults were more likely to present with cholecystitis and pancreatitis, but this observation was not confirmed in this Wisconsin series. In addition, the finding that Wisconsin adults were more likely to present with cholangitis may be due to the fact that they had relatively more type IVA and V cysts and were more likely to have preoperative biliary stenting. However,

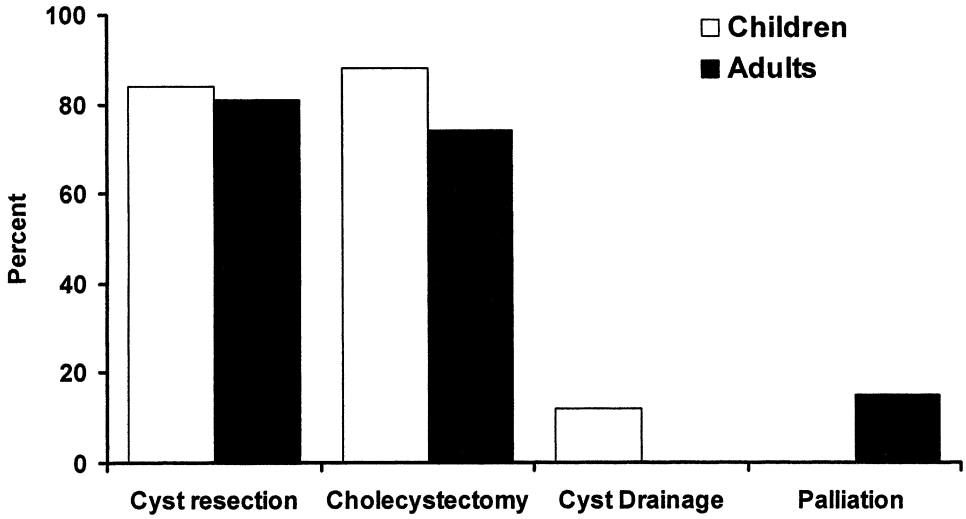

Fig. 3. Operations in children and adults.

the overall distribution of cysts in this series, with types I and IVA being most common is similar to many other reports.[1,8,9,18,19,21]

Once considered, the diagnosis of biliary cyst disease is easily established with modern imaging studies. Ultrasound has the advantages of imaging intrahepatic stones and avoiding radiation exposure but does not provide sufficient detail regarding vascular and pancreatobiliary duct anatomy. CT and MRI, therefore, are preferred. In addition, MRCP should be able to detect pancreatobiliary malfunction without the risks of pancreatitis and cholangitis associated with ERCP. Of note, the importance of an anomalous pancreatobiliary junction in the etiology of choledochal cysts was first described in 1969 by Babbitt,[22] a radiologist at the Children's Hospital of Wisconsin. This report confirms that most adults and children with choledochal cysts have a pancreatobiliary malfunction.

Factors to be considered when operating on patients with biliary cystic disease include (1) age, (2) presenting problems, (3) cyst type, (4) associated biliary stones, (5) prior biliary surgery, (6) intrahepatic strictures, (7) hepatic atrophy/hypertrophy, (8) biliary cirrhosis, (9) portal hypertension, and (10) associated biliary malignancy. As documented in this and other reports, adults are more likely to have many of these factors, which complicate their surgical management.[1,4–8,23,24] In general, however, surgery should include cholecystectomy and excision of extrahepatic cyst(s).[1,2,3–12,18–20,23,24]

Table 2. Operative mortality and morbidity

	Children (n = 25)	Adults (n = 26)	Total (n = 51)
Mortality	0%	0%	0%
Morbidity	12%	23%	18%
Cholangitis	0%	8%	4%
Abscess	0%	4%	2%
Wound infection	0%	4%	2%
Biliary fistula	4%	0%	2%
Biloma	4%	0%	2%
Pancreatitis	4%	0%	2%

Distally the intrapancreatic portion of the cyst should be excised taking care to avoid injuring the pancreatic duct or a long common channel. With respect to intrahepatic ducts, surgery should be individualized depending on whether (1) both lobes are involved, (2) strictures and stones are present, (3) cirrhosis has developed, or (4) an associated malignancy is localized or metastatic. In the absence of cirrhosis, hepatic parenchyma should be preserved even when strictures and stones are present. With advanced cirrhosis, which is unusual, transplantation may be indicated. If a malignancy has developed, oncologic principles should be followed.[1,25–27] When possible, resection of a localized tumor including adjacent hepatic parenchyma or the head of the pancreas and regional lymph nodes should be performed. However, as evidenced by this and other series, malignancies complicating biliary cystic disease are often diagnosed late and therefore have a low resectability rate and a poor prognosis.[1,8,28–32]

Resection of the gallbladder and the extrahepatic cysts clearly reduces the risk of subsequent biliary malignancy.[1,14] Thus in symptomatic adults and children, surgery is indicated. Occasionally a teenager or

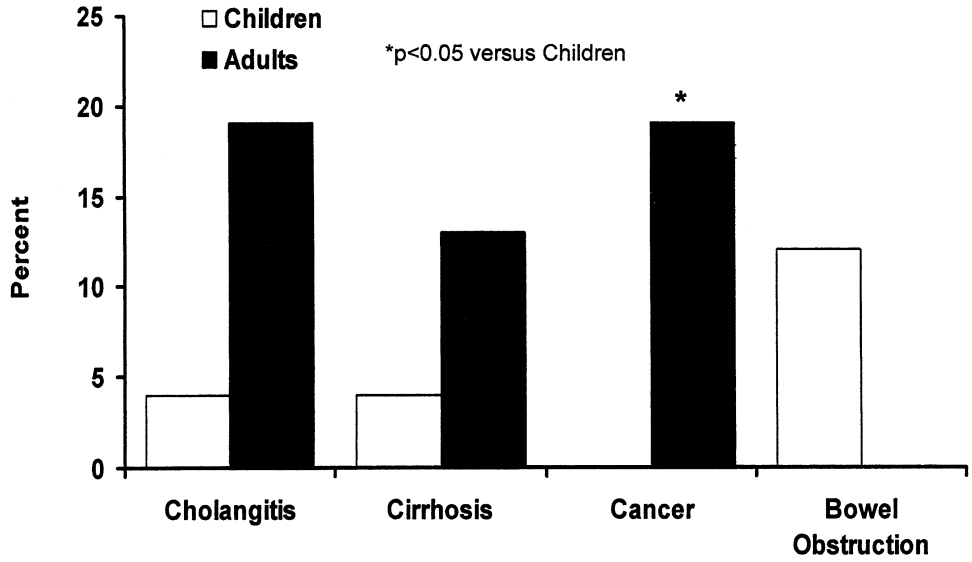

Fig. 4. Late complications in children and adults. Cancer ($P < 0.05$) and cholangitis ($P < 0.08$) were more common in adults, whereas bowel obstruction ($P < 0.07$) was more common in children.

young adult with minimal symptoms will be diagnosed, and the timing of surgery will be questioned. In this series, no malignancies were diagnosed in patients less than 30 years of age; however, the risk of malignancy in the gallbladder and bile ducts is increased in teenagers and adults in their 20s.[1,28–31] Thus, because of this increased risk of malignancy, surgery should not be delayed, even in asymptomatic patients. In addition, the morbidity and mortality of surgery in this and most reports is quite low.

Patients with choledochal cysts who have undergone surgery remain at increased risk for recurrent cholangitis, pancreatitis, intrahepatic strictures, stones, and malignancy. In some patients who present with recurrent cholangitis, febrile episodes may persist for several months postoperatively until the biliary

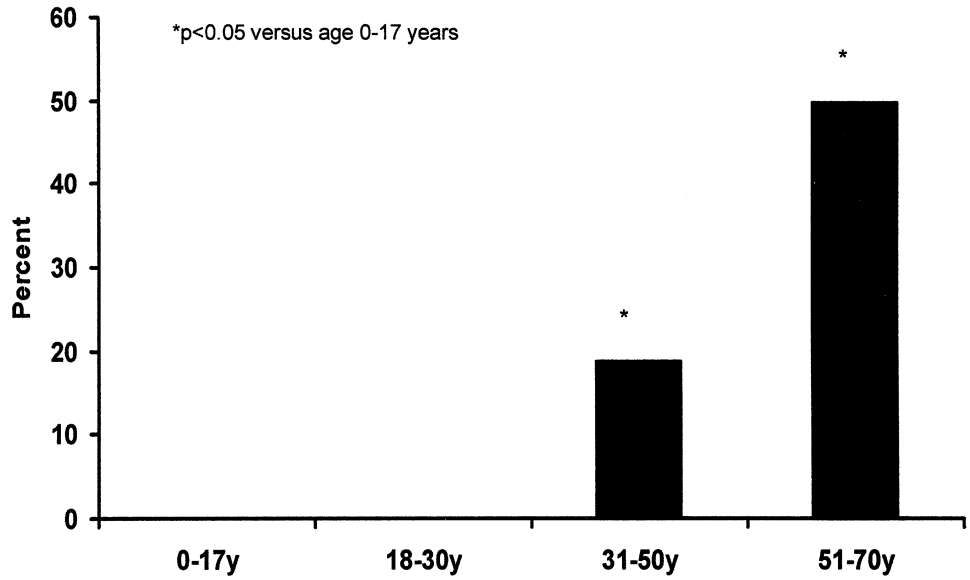

Fig. 5. Biliary malignancy by age. All malignancies were observed in patients over 30 years (adults vs. children, 19% vs. 0%; $P < 0.05$).

epithelium is repaired and a barrier to cholangiovenous and cholangiolymphatic reflux is reestablished. Patients with intrahepatic cysts are more likely to have late problems with cholangitis, as well as intrahepatic strictures and stones. In a recent report from Japan by Tsuchida et al.,[33] 4 of 10 patients with intrahepatic cysts developed late problems with cholangitis. These patients did not have stents placed, and the results are not as good as those reported with a strategy of long-term transhepatic stenting with large-bore silastic stents.[1,8,25–27,34] Recurrent pancreatitis also has been reported in Japanese children after choledochal cyst excision.[35] In this analysis, pancreatic duct abnormalities were reported in 47% of patients undergoing ERCP. In comparison, in this Wisconsin series only one adult (2%) and one child (2%) had postoperative pancreatitis.

CONCLUSION

When they are considered a possibility, biliary cysts are easily identified and treated. Surgery should include cholecystectomy, complete excision of extrahepatic cysts, and Roux-en-Y reconstruction. The pancreatobiliary malformation observed in the majority of these patients plays a significant role in their increased risk of gallbladder and bile duct malignancies.[14,30–33] Thus surgery should be undertaken in adults and children even when symptoms are minimal or prior cyst-enteric drainage without resection has been performed. In the hands of specialists in complex hepatobiliary surgery, operative morbidity is low and the long-term outlook for these patients is very good.

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2003 SSAT-AGA-ASGE Workshop on "Palliative Therapy of Rectal Cancer"

Summary Statement

Matthias Stelzner, M.D.

Questions Addressed by the Workshop

1. What are the indications and goals of palliative therapy for rectal cancer? How extensive should staging and clinical work-up be? Are endoscopic ultrasound and magnetic resonance imaging useful in the planning of palliative therapy?
2. What are the indications for palliative surgical therapy? What operative measures are most suited for patients with complications of the disease process? What is the role of diverting colostomies in light of the introduction of new interventional endoscopy techniques?
3. What are the indications and limitations of endoscopic rectal stenting? How successful is stenting in the palliation of cancer symptoms?
4. What are other endoscopic options? What are their strengths and weaknesses? When should they be used? Which methods are outdated?
5. What is the role of chemo-radiotherapy and chemotherapy? When are repeated courses with different agents indicated? Is chemotherapy useful to palliate rectal obstruction?
6. Is radiotherapy alone a good option? What are the indications? What is the role of intraoperative radiation therapy?

GENERAL SUMMARY

Cancer of the rectum is an important cause of cancer mortality in the United States. It is estimated that 20,000–30,000 patients require palliative care for rectal cancer annually. Palliative therapy of rectal cancer remains, thus, a major health issue in the United States.

Palliative care seeks to maximize the quality of remaining life. This goal requires a multidisciplinary approach. Optimal pain control, reassurance of the patient, and good communication about all aspects of the disease process are germane elements of palliative care. Every test or treatment should be intended to improve the patient's comfort. Whereas intravenous fluids may be helpful to increase patient comfort, total parenteral nutrition or enteral tube feedings in nonsurgical patients offer no proven benefit.

Diagnostic workup should assess the need for palliative treatment and identify factors that may limit palliative treatment options. In patients with advanced disease, workup should be minimized. Resectability and extent of abdominal metastases should be assessed with computerized tomography (CT) of the abdomen and pelvis. Endorectal ultrasound and magnetic resonance imagining (MRI) should be used only if resectability is uncertain. If the primary tumor is resectable and abdominal metastases are absent, further imaging studies (e.g., positron emission tomography) may be indicated. Diagnostic laparoscopy is occasionally useful to determine if palliative resection would be beneficial.

Resective surgery should be avoided in patients with nonresectable metastases or extensive locoregional disease and with a life expectancy of less than 3–6 months. The indication for surgical palliation depends on symptoms, extent of local disease, expected duration of life, and perioperative morbidity and mortality. Options may include resection, diversion, or local procedures. Pelvic exenterations are

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From the Department of Surgery, University of Washington and VA Puget Sound Healthcare System, Seattle, Washington.
Correspondence: Matthias Stelzner, M.D., University of California at Los Angeles, Department of Surgery, VA Greater Los Angeles (10H2-MS), 11301 Wilshire Boulevard, Los Angeles, CA 90073. e-mail: matthias.stelzner@med.va.gov

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rarely useful for palliation because of their high morbidity. For mid- and low-rectal lesions, transanal resection and/or electro-coagulation compare favorably to transabdominal procedures because of their lower morbidity of the transanal procedures.

Self-expandable metal stents may be indicated for obstructing tumors in patients who are not surgical candidates. Stents provide a good long-term resolution of symptoms and have low complication rates. Stenting is not suitable to palliate bleeding. Recurrent obstruction after stent placement may require argon beam, laser ablation, or restenting.

Laser ablation is most useful to palliate tumor-related bleeding. It can also be used for rectal obstruction. Palliation usually lasts up to 6 months. Laser therapy is not effective for treating pain, infiltration of the pelvic sidewall, or anal involvement. Endoscopic argon plasma coagulation is effective in palliating bleeding, but less effective in treating obstruction or other local symptoms.

Injection therapy with alcohol or sclerosing agents and endoscopic coagulation have been used as low-cost alternatives to laser ablation. Photodynamic therapy and cryotherapy are less suitable for palliation because of high rates of side effects or complications.

Chemotherapy and chemo-radiation therapy are useful for palliation in the absence of rectal obstruction. They may achieve a "down-staging" of the tumor to allow for palliative resection. In unresectable patients, both modalities are frequently useful in controlling effects of local tumor compression or infiltration including pain. Repeated courses of chemotherapy with newer agents (e.g., irinotecan, oxaliplatin) may increase or prolong the palliative effects and may offer a survival benefit.

External beam radiation without chemotherapy can be expected to relieve pain and bleeding in about 75% of patients with advanced pelvic disease. Palliation from radiation alone is shorter-lived compared to chemo-radiation and lasts usually not longer than 3–9 months. Future clinical studies are needed to improve clinical definitions and databases, to develop educational tools and decision aids for patients, and to compare different treatment options. It may be difficult to conduct such studies because of the variation of disease and the heterogeneity of the patient population.

INTRODUCTION

Cancer of the rectum ranks among the important causes of cancer mortality in the United States. It is estimated that there are 42,000 new cases of rectal cancer and 8,500 deaths from it every year. In most series, about three-quarters of the patients with rectal cancer are treated with curative intent. The remaining 25% of patients are treated for palliation and half of these will undergo abdominal surgery as part of their palliative treatment. Of the patients treated with curative intent, approximately 40% will develop cancer recurrences which cannot be treated with curative intent. Based on these data, it can be estimated that 20,000–30,000 patients per year will require palliative care for rectal cancer. Palliative therapy of rectal cancer remains, thus, a major health issue in the United States.

INDICATIONS FOR PALLIATIVE TREATMENT

Rectal cancer may be deemed incurable for several reasons. The patient may have advanced locoregional disease or distant metastases. There may be significant comorbidities rendering the patient unfit for surgery or the patient may decline the extent and consequences of radical surgery (e.g., construction of a permanent colostomy or urostomy). Finally, a few patients will decline surgery altogether even if the cancer is otherwise curable.

Operative palliative therapy is generally indicated if the patient will tolerate the procedure and if the operation has a high likelihood of relieving cancer-related symptoms and maintaining normal functions to maximize the quality of life.

Nonoperative palliative therapy may include chemotherapy, radiation therapy, interventional gastroenterologic measures, pain control, and other measures directed at increasing patient comfort. Therapeutic efforts are generally indicated for severe symptoms from locoregional disease (e.g., bowel obstruction, fistulas, or sciatic nerve compression).

GOALS OF PALLIATIVE CARE

The primary goal of palliative therapy is to maximize the quality of remaining life. Palliative care is a complex undertaking and requires close collaboration of a multidisciplinary team of surgeons, physicians, nurses, clergy, and spiritual counselors. There is evidence that cancer patients tend to overestimate the probability of long-term survival. This puts great responsibility on clinicians to provide the patient with a realistic prognosis and a choice of treatment options. This advice should be based on a thorough evaluation of the patient's general health and an accurate staging of the cancer. The treatment plan should

focus on pain and symptom management and treatments should be commensurate with the expected improved quality of life. Most patients with incurable rectal cancer fear the development of severe pain. Reassurance and good communication about all aspects of the disease process in combination with optimal pain control by modern pain management methods should play a pivotal role in the palliative treatment regimen.

CLINICAL EVALUATION

Diagnostic workup of a patient with incurable rectal cancer is based on physical findings and symptoms. It should determine whether palliative therapy is needed and identify factors that may limit palliative treatment options. If clinical findings suggest very advanced disease, workup should be minimized. In all other cases, a CT of the abdomen and pelvis is done to determine resectability and the extent of abdominal metastases. Endorectal ultrasonography and pelvic MRI may be used if physical exam and a CT scan are unable to determine resectability. If the pelvic disease seems resectable, additional imaging (e.g., chest CT) may be indicated to exclude distant metastases. In some instances, diagnostic laparoscopy is useful to identify widespread disease not amenable to palliative resection.

SURGICAL TREATMENT OPTIONS FOR PALLIATION OF RECTAL CANCER

Whereas surgical removal is the preferred curative treatment for rectal cancer, surgical intervention is only one of several options for palliation. Surgical resection of rectal cancer should be avoided if there is extensive pelvic disease, lower extremity lymphedema, invasion into iliofemoral vessels, or extensive lymphatic involvement. Surgery is also not an option in patients with nonresectable metastases or for patients with a life expectancy of less than 3–6 months. Anterior resection with anastomosis is considered if the rectal remnant is longer than 3 or 4 cm. Increased risks of anastomotic breakdown due to preoperative radiation, the disadvantage of a temporary proximal stoma, and the time to achieve good anal function should be taken into account. A Hartmann operation is often a better alternative if the patient is willing to accept a permanent colostomy. Whereas posterior vaginectomy and hysterectomy are not a deterrent to palliative rectal resection, more extensive pelvic exenterations are rarely performed because of their high morbidity and diminished quality of life. Surgical treatment for patients with unresectable cancer is frequently limited to construction of a sigmoid colostomy for fecal diversion; this is now often performed laparoscopically. Construction of an end stoma with an adjacent small mucous fistula avoids the disadvantages of a loop colostomy such as stoma recession and incomplete diversion of the fecal stream. Loop stomas are useful for patients with short life expectancy and with significant obesity. In a number of patients, colostomies are being replaced by endorectal debulking and endorectal stenting particularly for mid- and low-rectal lesions. These lesions are amenable to local transanal excision with conventional techniques or by transendoscopic excision (TEM). Both techniques compare favorably to transabdominal resective measures because of their lower morbidity.

RECTAL STENTING

Self-expandable metal stents have become a useful addition to the palliative armamentarium in the past decade. Stent placement is indicated in patients with obstructive rectal carcinoma who have extensive disease, who are poor surgical candidates, and who have incurable recurrent disease after resection. Stent placement does not palliate rectal bleeding. In experienced centers, stents are successfully placed in approximately 90% of cases. Stents provide good long-term resolution of obstruction (9 months and longer) and reported migration rates are below 15%. The interaction between stent placement and radiotherapy or chemotherapy is not well defined. However, case reports seem to indicate that stented tumors can be irradiated and radiated tumors can be stented without adverse effects. Recurrent obstruction may require endoscopic argon beam, laser ablation, or restenting. There are reports indicating that covered stents provide excellent palliation for rectovaginal or rectovesical fistulas.

OTHER ENDOSCOPIC METHODS

Older endoscopic methods of palliating obstruction from rectal cancer have largely been replaced by expandable metal stent placement. However, laser ablation is still a useful therapy for some patients particularly when the predominant symptom is rectal bleeding. In patients with obstructive rectal cancer, several repeated treatment sessions may be necessary to achieve initial luminal patency and further sessions will become necessary every few months or as symptoms recur. Palliation of obstructive symptoms is achieved after 2–5 laser sessions in 80%–90% of patients. In general, palliation is not long lasting and

symptoms often recur within 6 months. Complications occur in 5%–15% of patients and are mostly minor although perforation, sepsis, and death have been reported. Laser therapy is an important adjunct in patients with recurrent obstruction after self-expanding metal stent placement. Laser ablation is not effective for treating painful tumor infiltration of pelvic nerves.

Argon plasma coagulation is a cost-effective alternative to laser treatment for control of bleeding, but it is less useful for treating rectal obstruction. Injection therapy of rectal cancer using alcohol or sclerosing agents has the great advantage of being low cost and simple. Photodynamic therapy, endoscopic electrocoagulation, and cryotherapy cannot be recommended because of the side effects or high complication rates. Photodynamic therapy is limited by the cutaneous phototoxicity of the systemically administered hematoporphyrin sensitizing agent.

CHEMOTHERAPY AND RADIATION THERAPY

Chemotherapy and external beam radiation therapy play an important role in the palliation of incurable rectal cancer. Whereas tumors that are obstructing or near-obstructing on endoscopic examination require palliative surgery or stenting, those lesions that are asymptomatic or minimally symptomatic can be managed with chemotherapy or with chemotherapy and radiation. As a rule, tumors that are unlikely to obstruct in an 8–10 week period will not require palliative mechanical management before initiation of chemotherapy. Most chemotherapy will be assessed for efficacy at 6–8 weeks into treatment and tumor regression will decrease the risk of obstruction substantially. Modern combination regimens may achieve responses in excess of 75% for chemotherapy-naive rectal cancers and offer a considerable chance for palliation. The addition of pelvic radiation therapy should be made dependent on the extent of

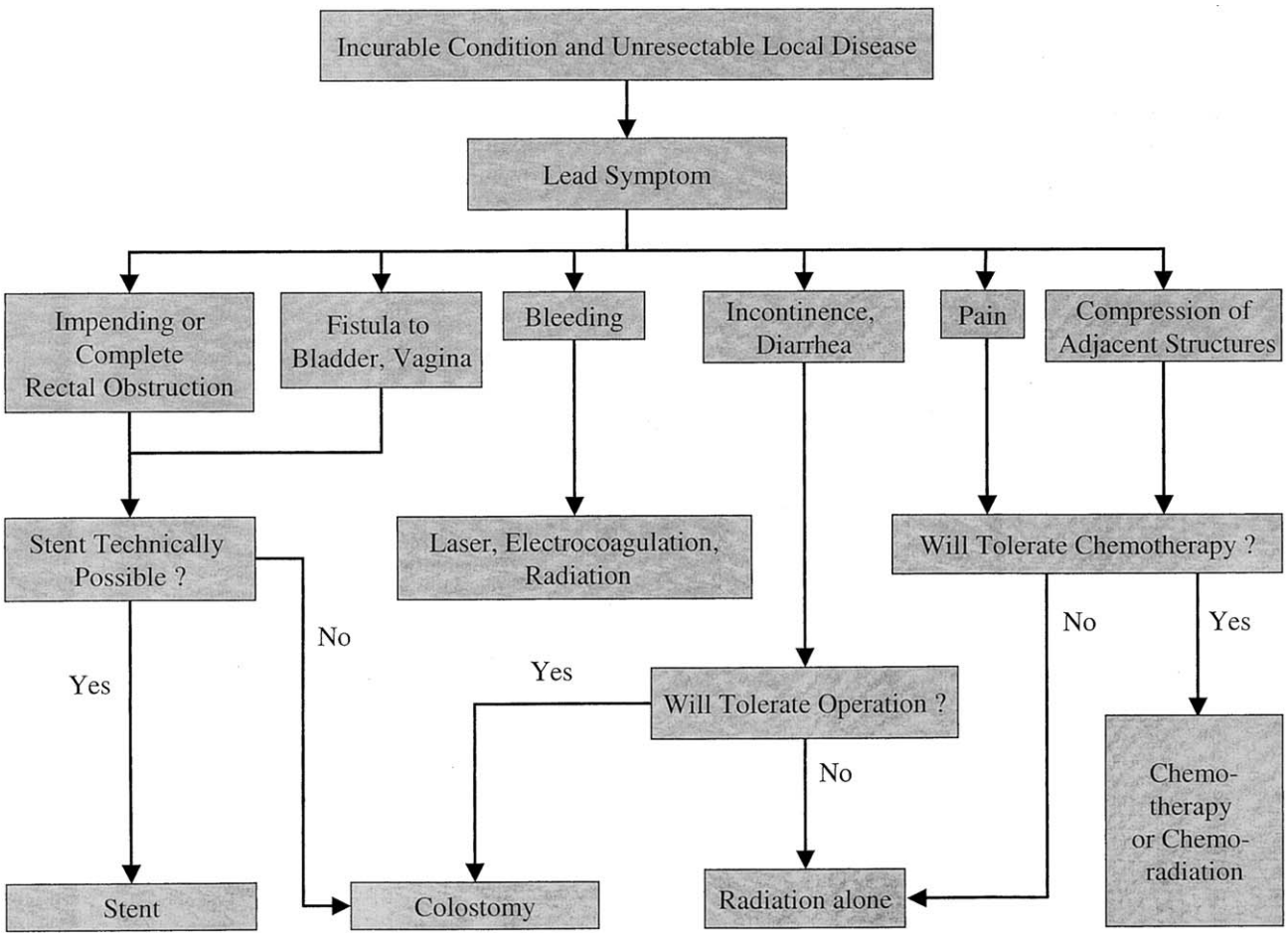

Fig. 1. Algorithm for palliative care of patients with locally unresectable rectal cancer.

extra-pelvic metastases and the size of the rectal tumor. For example, patients with small volume, asymptomatic distant metastases, and a larger rectal tumor are at greater risk of developing pelvic complications and should be offered pelvic radiation. This decision should be made by an experienced treatment team, because the addition of radiation generally requires the use of a less effective chemotherapy regimen.

Even radiation alone without chemotherapy has definite benefits in relieving symptoms. Pain and bleeding can be treated with success in 75% of patients with low doses of radiation. However, symptom relief is relatively short-lived and can be expected to last for only 3–9 months. It is most useful in patients with advanced disease and a short life expectancy. Radiation therapy does not offer a survival benefit. Addition of chemotherapy will generally increase long-term survival. Because of the poor results with external beam therapy alone, attempts have been made to improve palliation in patients with locally recurrent rectal cancer by combining surgery with external beam and intraoperative radiation therapy. Available evidence indicates that this is most beneficial when the tumor can be completely resected with negative margins. However, data for patients with metastatic disease are not available.

OTHER RECOMMENDATIONS

The presence of medical comorbidities should affect decisions about palliative treatment options. Patients should not be considered for surgery, chemotherapy, or radiation treatment if they have significant preexisting medical conditions, are unable to maintain alimentation because of metastatic disease, or are so debilitated in their performance status that they are limited to a bed-to-chair existence. Parenteral administration of fluids may provide some additional comfort, however, total parenteral nutrition or enteral tube feedings have not been shown to be of

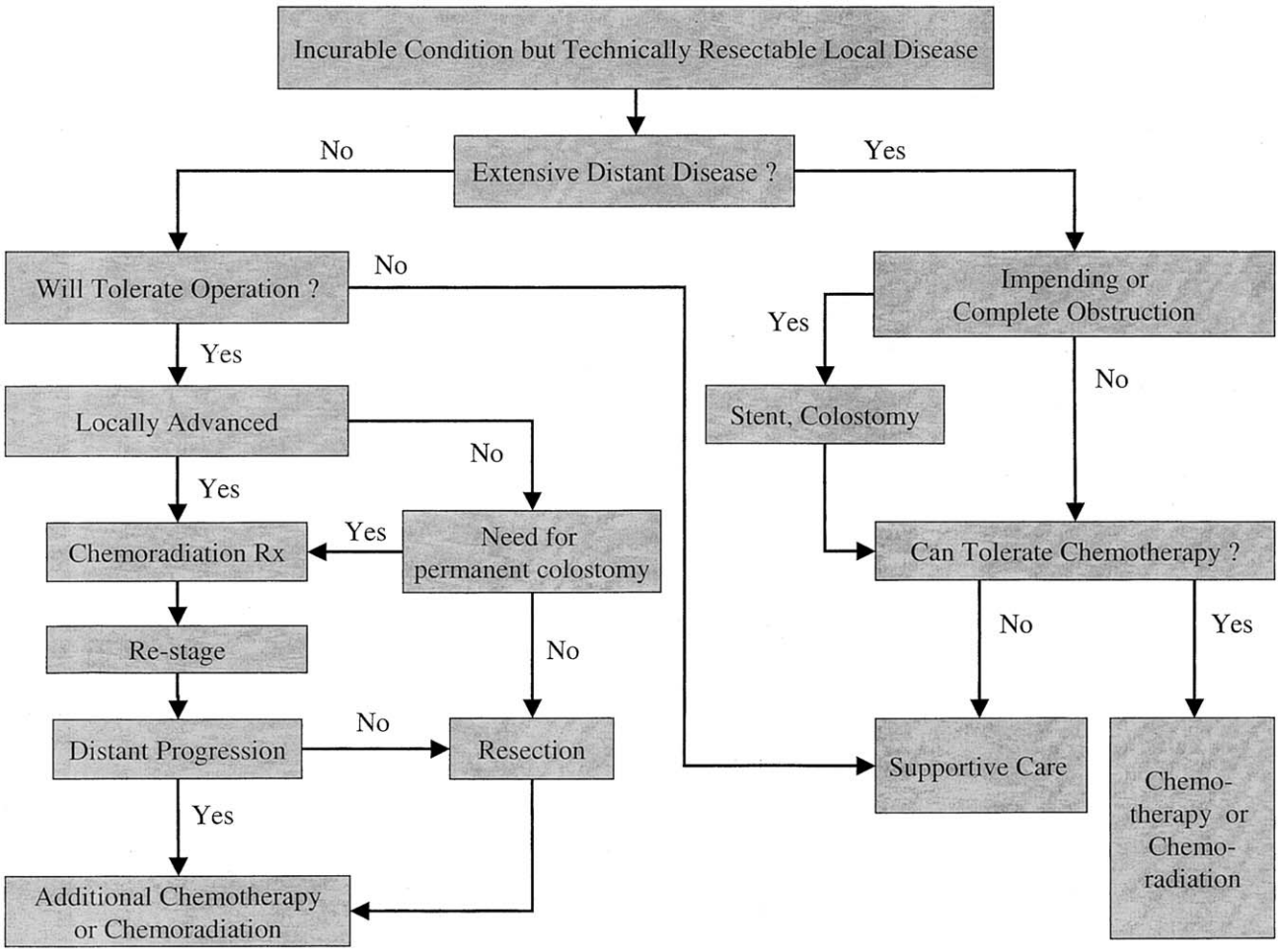

Fig. 2. Algorithm for palliative care of patients with resectable rectal cancer.

benefit in the nonsurgical cancer patient. Routine use of these latter modalities is discouraged.

FUTURE DIRECTIONS

Scientific progress in the palliative treatment of rectal cancer is limited by the lack of universally accepted definitions of extent of the disease, comorbidities, and factors influencing the patients' performance status. Future efforts are needed to improve these clinical definitions and to supply better and more stratified databases. In addition, the effectiveness of our current methods of informing patients about the state of their disease is not well understood. Further research should explore the patients' preferences, investigate the communications between patient and health-care providers, and also focus on the development of improved educational tools and decision aids. Other studies should examine and compare the effect of different palliative therapies. Further scientific evidence is especially desirable in the following areas: (1) comparison of combining radiotherapy with stent placement vs. stent placement alone, (2) comparison of self-expandable metal stents vs. colostomies for palliation of obstruction, (3) comparison of metal stents vs. colostomies for palliation of cancer-related fistulas, (4) comparison of different interventional endoscopic measures for palliation, and (5) exploration of the usefulness of intraoperative radiation therapy. It is conceivable that some of these issues will never be studied in controlled randomized trials as it may prove very difficult to conduct such studies because of the variation of disease and the heterogeneity of the patient population.

TREATMENT ALGORITHMS

During the conference, the panel members developed two treatment algorithms for palliative treatment of rectal cancer. These flow diagrams give an outline of state-of-the-art therapy options for incurable rectal cancer in the presence of unresectable local disease (Fig. 1) and for incurable rectal cancer in the presence of technically resectable local disease (Fig. 2).

MEMBERS OF THE WORKSHOP

Todd H. Baron, M.D.
Department of Gastroenterology, Mayo Clinic, Scottsdale, AZ
Herbert Chen, M.D.
Department of Surgery, University of Wisconsin, Madison, WI
Victor W. Fazio, M.D.
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH
Carlos Fernandez-Del Castillo, M.D.
Department of Surgery, Massachusetts General Hospital, Boston, MA
Aaron S. Fink, M.D.
Department of Surgery, Emory University and Atlanta VAMC, Atlanta, GA
W. Scott Helton, M.D.
Department of Surgery, University of Illinois at Chicago, Chicago, IL
Michael Kimmey, M.D.
Division of Gastroenterology, University of Washington, Seattle, WA
Walter Koltun, M.D.
Department of Surgery, Penn State University, Hershey, PA
Robin S. McLeod, M.D.
Department of Surgery, University of Toronto-Mount Sinai Hospital, Toronto, Ontario, Canada
David A. Rothenberger, M.D.
Department of Surgery, University of Minnesota, Minneapolis, MN
Leonard B. Saltz, M.D.
Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY
Matthias Stelzner, M.D.
Department of Surgery, University of Washington and Seattle VAMC, Seattle, WA
Christopher G. Willett, M.D.
Radiation Oncology Service, Massachusetts General Hospital, Boston, MA

Overview: Epidemiology, Indications, Goals, Extent, and Nature of Work-up

David A. Rothenberger, M.D.

Each year in the United States, it is estimated that there will be 42,000 new cases of rectal cancer and 8,500 deaths.[1,2] Some patients present with an incurable rectal cancer but more often death follows development of recurrent rectal cancer after failed curative-intent therapy. Knowledge of the natural history of rectal cancer and limitations of treatment options coupled with sound clinical judgment and compassion are essential prerequisites for the clinician providing palliative care. (J GASTROINTEST SURG 2004;8:259–261)

KEY WORDS: Rectal cancer, palliation, recurrent rectal cancer, incurable rectal cancer

EPIDEMIOLOGY

In most series of rectal cancers, curative-intent resections are performed in 70%–90% of cases, sometimes after neoadjuvant chemoradiation. The remaining 10%–30% of patients are treated for palliation. It is logical to assume that the percentage of patients requiring palliative care is higher among those presenting with late-stage disease, but the epidemiology of late-stage rectal cancer is not well characterized. Morris and Baxter[3] used the Surveillance Epidemiology and End Results (SEER) database that represents 14% of the new cases in the United States to assess new colorectal cancer patients between 1988 and 1999. Among patients of known stage in the SEER database, 31,341 patients (17%) had stage IV disease at presentation (colon cancer = 23,865; rectal cancer = 7,476). One third of the 31,341 patients with stage IV colorectal cancer did not undergo resection and were presumably treated for palliation. The SEER database does not record the intent of therapy for the two-thirds of patients with stage IV colorectal cancer treated by resection but it is reasonable to assume that at least some of these resections were palliative.

In addition to palliation in the setting of a primary rectal cancer, approximately 40% of patients who previously underwent curative-intent therapy of rectal cancer will develop recurrence. Of those with recurrence, the vast majority cannot be retreated with curative intent. Thus, palliative care for rectal cancer patients remains a major health issue.

INDICATIONS

Palliative therapy is indicated for all patients with incurable rectal cancer and may be operative or nonoperative. Palliative-intent operations leave local or metastatic residual cancer, varying from a small microscopic focus causing no symptoms to an extensive tumor producing major symptoms. Operative palliative therapy is indicated if a patient is judged able to tolerate a surgical procedure that has a high likelihood of relieving significant symptoms and/or maintaining normal functions to maximize the quality of remaining life. For some, extirpative radical surgery is the most likely way to provide relief of symptoms without undue morbidity. For others, operative palliation is achieved by symptom-relieving but less radical surgery.

Nonoperative palliative therapy may include chemotherapy, radiation therapy, pain control measures, and other comfort care. Nonoperative palliative therapy is generally indicated for locoregional disease if work-up shows that the pelvic cancer has caused sciatic nerve pain, bilateral ureteral obstruction, extensive pelvic side wall involvement (especially if in the upper 2/3 of the pelvis), neural or bony involvement

From the Department of Surgery, University of Minnesota, Minneapolis, Minnesota.
Reprint requests: David A. Rothenberger, M.D., Department of Surgery, University of Minnesota Medical School, 420 Delaware St. SE, Mayo MC 806, Minneapolis, MN 55455. e-mail: rothe002@maroon.tc.umn.edu

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at or higher than S1–S2, bilateral lymphedema, or deep venous thrombosis. Nonoperative palliative therapy is also indicated for patients who present with multiple peritoneal metastases, metastases fixed, or invading vital structures not amenable to safe resection or multiple metastases to the liver, lungs, or other organs. Such patients have a dismal prognosis and comfort measures are generally the only therapy of value.

Whereas incurability is most often a function of the patient's cancer status, general health and treatment preferences are also important factors. Curative therapy may have to be compromised because of the patient's debility and/or comorbidities and a palliative approach taken instead. Similarly, palliative treatment may be necessary to accommodate a patient's refusal to accept the morbidity of a proposed curative therapy.

In many cases, the need for a palliative approach is obvious after pretreatment evaluation. Counseling and treatment can be tailored accordingly but in a surprising number of cases, despite intensive investigations and modern imaging, the surgeon finds that the extent of disease was understaged and the need for palliative therapy is not apparent until laparotomy. The decision-making in these two scenarios is quite different. In the former, the morbidity of a laparotomy can be avoided whereas in the latter, the patient has already been subjected to the morbidity of a major operation before it is recognized that cure is impossible.

GOALS

The two primary goals of palliative therapy for rectal cancer are (1) to maximize the quality of remaining life by controlling symptoms and preserving normal bodily functions and (2) to help the patient, their family, and friends develop realistic expectations about their impending death from the incurable cancer. Most patients with incurable rectal cancer fear development of severe pain. They can be reassured that pain control is achieved in almost all cases with modern pain management. Other symptoms such as obstruction, tenesmus, urgency, incontinence, and bleeding can usually be controlled as described below. Preservation of anorectal and genitourinary functions is desirable but often a colostomy and/or urostomy with or without concomitant tumor resection can eliminate miserable symptoms and improve the quality of remaining life.

Creating realistic expectations about the natural history of incurable rectal cancer and its treatment is a complex undertaking made more difficult by the fact that cancer patients tend to overestimate the probability of long-term survival.[4–6] There is no convincing evidence that palliative resection improves survival. Weeks et al.[7] performed a prospective cohort study of 917 patients hospitalized because of advanced stage lung or colorectal cancer. They found that physicians estimated the prognosis accurately but their patients overestimated their survival probabilities and that these estimates influenced their preferences about treatment. Patients who thought they were going to live for at least 6 months were more likely to favor life-extending therapy over comfort care compared with patients who thought there was at least a 10% chance they would not live 6 months. Patients who preferred life-extending therapy were more likely to undergo aggressive treatment but after controlling for known prognostic factors, their 6-month survival was no better.

For some patients with a small focus of microscopic residual cancer, survival of high quality can be anticipated for a reasonable period of time. Realistic counseling regarding the pros and cons of palliative therapy options in this setting is difficult. Unfortunately, there is little hard data on which to base a recommendation. Steele's review from the National Cancer Database on colorectal cancer noted that 42% of patients with metastatic colorectal cancer received chemotherapy but 58% did not.[8] The decision-making process is unclear.

For other patients, a large burden of residual cancer makes death imminent. A multidisciplinary team including the treating physicians, pain control experts, nurses, clergy, and spiritual counselors can help create realistic expectations essential to shared decision-making as death approaches. The team needs to be aware of cultural sensitivities and psychological states that may make acceptance of some palliative measures such as construction of a colostomy unacceptable. It is essential that all personnel involved in palliative care communicate a clear message to the patient, the family, and others caring for the patient without prematurely removing hope of meaningful survival. This is time consuming and emotionally draining but an ethical imperative for our profession.

The surgeon has the responsibility of making certain that the physical and psychological burdens of palliative measures are commensurate with the hoped-for improved quality of life achieved by such treatments. Palliative operations for colorectal cancer have been associated with a mortality as high as 10% so it behooves the clinician to fully evaluate the patient, accurately stage the extent of disease, and provide the patient with a realistic prognosis and alternative treatment options.[9] Every test or treatment should be intended to improve the patient's comfort.

WORK-UP

Clinical evaluation and diagnostic testing should provide information needed to answer four fundamental questions: (1) Is palliative therapy necessary?, (2) What is the patient's prognosis and what component of their disease is most likely to cause significant symptoms in the near-term?, (3) Do prior treatments, underlying comorbidities, or patient choices limit palliative options?, and (4) Of the palliative options available, which will be most likely to provide meaningful palliation with the least morbidity?

The distinction between curative and palliative therapy is blurring because of the ability of some centers to safely conduct major resections such as pelvic exenterations and the ability to treat and control more than one sight of distant metastasis. Clinical judgment is needed to realistically estimate the patient's prognosis. In general, the more radical the contemplated treatment, the more extensive the work-up must be to assure that the treatment's morbidity is justified by the expected outcome. Conversely, when clinical findings such as significant malnutrition, ascites, extensive lymphadenopathy, and palpable metastases make it obvious that the prognosis is guarded, work-up is minimized. In between these two extremes are many patients who benefit from a limited work-up focused on (1) confirming the clinical impression that curative-intent therapy is not possible, (2) understanding the etiology of the patient's symptoms, and (3) obtaining additional information to appropriately tailor a palliative treatment plan.

Symptoms and physical findings should direct the work-up. For example, if obstructive symptoms dominate the clinical presentation, endoscopy and contrast gastrointestinal studies are indicated to define the areas of intrinsic or extrinsic obstruction. If digital rectal and pelvic examinations identify a fixed rectal primary cancer or a recurrence invading pelvic sidewalls or other adjacent viscera in a patient who is a candidate for radical surgery, a computed tomograph of the pelvis ± endorectal ultrasonography (ERUS) are done to determine resectability. If these studies are equivocal or do not confirm the clinical impression, additional studies, such as a pelvic MRI, may better define the pelvic mass.

If pelvic imaging studies suggest there is a realistic consideration of performing radical surgery, CT of the abdomen and chest and positron emission tomographic scanning are done to exclude distant metastases. Their presence generally precludes undertaking a potentially morbid radical resection. A negative work-up for distant metastases may lead to a laparotomy to determine whether palliative resection would benefit the patient. In some instances, diagnostic laparoscopy is useful to identify widespread disease not amenable to palliative resection.

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Indications and Surgical Alternatives for Palliation of Rectal Cancer

Victor W. Fazio, M.B., M.S., F.R.A.C.S., F.R.C.S

The goals of palliation of rectal cancer are relief of disabling symptoms and maximizing quality of life. Surgical intervention is appropriate in specific situations, where the selected procedure is chosen based on likelihood of achieving these goals, balanced against morbidity and recognition of the patient's limited life expectancy. Locally unresectable rectal cancer may be treated by transanal procedures where obstruction is the major feature; techniques used include local resection, self-expanding metal stents, and laser debulking of tumor where the rectal lumen is compromised. As well, colostomy may be used with or without external beam radiation therapy but is preferred when transanal techniques are unsuitable. Resective techniques such as anterior proctosigmoidectomy and anastomosis, Hartmann's resection, or abdominoperineal rectal excision are preferred in fit patients where local clearance is possible and longevity expectations are deemed reasonable—e.g., six months or more. Decisions for performing restorative procedures are based on risk assessment for anastomotic leak and quality of anal function. In rare cases, palliative exenteration is an option, although controversial. Recognition of contraindications to resection will minimize the risk of disabling or lethal complications of these procedures. (J GASTROINTEST SURG 2004;8:262–265)

KEY WORDS: Palliation, rectal cancer, surgery

Rectal cancer is typically treated by resection and usually a curative operation is performed. The range of rates of curative resection varies but commonly averages about 85%. A further number of patients will undergo treatment—these include chemo/radiation therapy and local procedures to debulk or disobstruct certain lesions. The focus of this presentation is on those 15% of patients not eligible for curative resection and, in particular, those who are managed by palliative abdominal surgery. Usually this involves resection of the primary tumor.

Palliation of colon cancer from a surgical strategy viewpoint may be achieved using more options (internal bypass, fecal diversion, segmental resection, abdominal colectomy, with/without anastomosis) than palliation for rectal cancer, and this can be done with less difficulty than palliative surgery for rectal cancer. In the case of rectal cancer, the anatomical restrictions of the pelvis (frequently irradiated) and the tumor extension/fixation to major structures (iliac vessels, prostate, ureter, bladder, nerve roots) make for greater difficulty as a rule than in palliative surgery of colon cancer. Additionally, aside from carcinomatosis, frequently colon cancer can be completely removed locally despite distal metastases. In certain cases, the metatastic colon cancer patient may have few symptoms, for example, cecal or ascending colon cancer, and may pose a dilemma for the clinicians to decide not to perform surgery until local symptoms develop. Possibly this occurs when the patient is least fit for operation.

VARIATIONS IN PRESENTATIONS OF INCURABLE RECTAL CANCER

Rectal cancer may be deemed incurable by the following:

- Patient declining surgery (otherwise curable)
- Significant comorbidity, unfit patient
- Locally extensive cancer (inability to achieve Ro status with resection)
- Can provide Ro status but with unacceptable risk of tolerance for surgery or injury to pelvic structures or patient refuses (e.g., a permanent colostomy or urostomy is unacceptable to the patient)
- Distal metatastic disease

From the Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, Ohio (V.W.F.).
Reprint requests: Victor Fazio, M.D., Department of Colorectal Surgery, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195. e-mail: faziov@ccf.org

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This has several clinical variations. With increasing use of positron emission tomography (PET) and magnetic resonance imaging (MRI), whole body-oncoscint scans, patient with metastases apparently confined to the liver or lung or both may be offered a potentially curative procedure (e.g., radio-frequency ablation [RFA] of one or more metastases or segmental liver resection).

Where there is clear evidence of nonresectable metastases (e.g., bilateral hepatic lobe, extensive disease, extensive mesenteric nodal metastases, multiple lung metastases, carcinomatosis), strong consideration is given to the avoidance of rectal resection if the prognosis is very limited (e.g., less than 3–6 months life expectancy). Alternatives such as chemotherapy, radiation therapy, and local procedures are usually preferred, especially for locally extensive disease. Finally, recurrence in the pelvis after curative resection usually involves palliative treatment, and this may or may not involve resective surgery.

INDICATIONS FOR SURGERY AND GOALS OF TREATMENT

Goals of treatment are to provide relief or improvement of symptoms, especially those deemed by the patient to be disabling. As well, treatment choices are taken into consideration. Quality of life may be affected positively by relieving symptoms or negatively by complications, functional anal problems, or patient's attitude regarding ostomy surgery.

INDICATIONS FOR SURGERY

Where distal metastases are present and the following are present:

- Obstruction of bowel
- Perforation of rectum—localized sepsis, supralevator abscess
- Fistula (e.g., rectovesical, rectoprostatic, rectovaginal)
- Rectal bleeding
- Obstructive uropathy
- Fecal incontinence, disabling diarrhea
- Pain (e.g., sphincter, or sacral, nerve root involvement by the primary cancer may lead to the need for surgical intervention)

Local extent of disease may mandate en bloc resection of adjacent structures with the increased likelihood of postoperative disability or complications. There remains a widely accepted view that palliative extensive resection and particularly anterior or posterior or combined pelvic exenteration are contraindicated.

In cases where locally extensive disease affects certain structures, resective surgery is best avoided. These factors include the following:

- Bilateral ureteric obstruction
- Fixation of primary tumor to lateral pelvic side wall (confirmed on CT/MRI scan) and an exam under anesthesia and/or trial dissection of the rectum
- Invasion of sacrum (e.g., S2 or above) where aggressive resection produces spinal instability and/or major intraoperative complications
- Lower limb lymphedema
- Invasion—extension or encasement of primary cancer to major vascular structures (ileo–femoral thrombosis)
- Extensive retroperitoneal nodal involvement

The considerations favoring nonresective surgery thus relate to the following:

- Diminished life expectancy
- Resection is a major intervention
- Complications prolong the time to recovery in a situation where longevity, especially that with a reasonable quality of life, is already very limited
- Functional impairment regarding anal sphincters may be very disabling, with low colorectal coloanal anastomosis producing incontinence
- Patient's (major) aversion to fecal diversion in many cases

OPERABLE ALTERNATIVES

Operable alternatives may be local or resective procedures.

Local Transanal Excision

A variety of procedures have been used including local excision with conventional techniques or with transendoscopic excision (TEM). Usually advanced tumor precludes local excisional techniques that may be inappropriate where palliation is defined on the basis of widespread metastases and the primary tumor otherwise lends itself to local excision.

The resectoscope, a urological instrument, has been used to prevent impending obstruction by debulking the tumor or enlarging the channel for defecation. This is proposed as an alternative to anterior resection, abdominal perineal resection, or colostomy alone. In one study from Oxford, 49 patients with rectal cancer had unresectable liver metastases and

24 patients underwent resectoscope debulking to achieve a hemostatic and patent lumen. Outcomes were compared to 25 patients having palliative abdominal resection of rectum. Overall survival and time spent out of the hospital were similar in the two groups. Morbidity for the anterior section APR group was higher (24% vs. 4% for local treatment [$P = 0.049\%$]).

Laser therapy, cryotherapy, and endoscopic stents are topics being addressed elsewhere in the panel.

Abdominal Approaches to Palliation

Colostomy. Perhaps the widest used procedure for palliation is colostomy. The procedure is used for most of the complications—indications listed above, particularly obstruction (due to lack of experience, expertise, or availability of other techniques applied locally). The usual procedure is that of sigmoid colostomy (to leave the least column of stool proximal to the obstructing lesion). A loop colostomy is usually performed. In obese patients, a loop transverse colostomy may be used. Then, in the event that total occlusion occurs, proximal collection of mucus, secretions, or blood have an exit point through the recessive end of the colostomy. This has significance in situations where an end stoma is considered desirable. A patient with septic complications or fistula may not have long-term relief with a loop colostomy due to stoma recession and the nondefunctioning nature of the procedure. In such cases, an end stoma is made, but if the tumor remains in situ, a small mucous fistula of the distal side of the colon is brought up into the midline wound.

A cutaneous, skin-level venting colostomy may be all that can be done for patients with distal rectal obstruction where local procedures are not possible or desirable due to extent of malignancy limiting access to the bowel mobilization.

An uncommon clinical situation occurs where rectosigmoid cancer is associated with circumferencial local disease, major narrowing of the lumen, but extensive intraperitoneal metastases. Occasionally the colon can be brought up to the extra fascial plane and left unopened. A tattoo of the overlying skin is made so that in the event that later obstruction occurs, this can be done through a local procedure. In certain cases, the patient may succumb from the metastatic disease before acute obstruction becomes a problem, thus negating the need for colostomy construction. This procedure has been largely replaced by colonoscopic assisted laparoscopic colostomy.

In general, colostomies are largely being replaced by endorectal debulking or stents in the palliative management of obstructing neoplasm of the rectum, particularly mid- and low-rectal cancers. However, where local procedures are likely to be difficult—long strictures or where the lumen is particularly angulated—laparoscopic colostomy is often an attractive alternative.

Resective Techniques

Resective techniques are possible with a variety of the following alternatives:

- Anterior resection and anastomosis
- Hartmann resection and colostomy
- Abdominal perineal resection and colostomy
- Pelvic exenteration—total, anterior, posterior

The choice of procedure is guided by the following:

- Extent of preoperative comorbidity
- Extent of distant metastases (e.g., volume of extra rectal tumor involvement of distant organs)
- Resectability of the primary tumor to achieve local clear margins
- Height of lesions in the rectum
- Surgeon experience and preference

Thus, the surgeon will consider the anticipated longevity of the patient, the level of operative risk, and the ability to achieve local clearance with acceptable morbidity and mortality rates. Other issues that may bear on choices include a possible role for intraoperative radiotherapy, although this is dependent upon availability, experience with the technique, and surgeon preference.

Imaging techniques and/or evaluation of the primary lesion by examination under anesthesia are helpful adjuncts to assess the feasibility of obtaining local clearance. This can be difficult in distinguishing malignant involvement of adjacent structures vs. inflammatory or fibrotic changes post-radiation. Historically, a trial dissection of the presacral space has been done to assess posterior fixation/freedom of primary tumor from the sacrum. Mobility of the primary lesion may be assessed at operation, but may be difficult to assess in borderline cases. The surgeon will variably continue dissection in the assessment of mobility depending upon the overall assessment of anticipated longevity. These are difficult decisions and in the presence of distal metastases, continued attempts at resection are made with the above considerations in mind. This relates to the experience of the surgeon as well as the predictable morbidity of leaving the primary tumor in situ.

Anastomoses are considered if local clearance of the tumors is possible with sufficient distal rectal remnant (greater than 3–4 cm) and predictably adequate

anal sphincter function, taking into account the risk of performing an anastomosis where distal rectum has been irradiated. Placement of a temporary proximal stoma may negate some of the advantages of a bowel anastomosis (compared to a Hartmann procedure) considering that anal function takes time to achieve a steady state of acceptable function. Whereas fashioning a colonic reservoir (e.g., colonic J pouch or coloplasty reservoir) is widely acceptable as a means of improving anal function with low anastomoses, these maneuvers increase the surgeon's concern about suture line breakdown unless a proximal stoma is made.

The extended Hartmann operation has been used to advantage—particularly in nonobstructing cases—where anal sphincter function is poor or predictably a problem is likely when an anastomosis is done. This can be considered an alternative to palliative abdominoperineal resection (APR), where problems with healing of the perineal wound are frequent; however, when anal sphincter involvement is present or the tumor involves the low rectum, APR is the preferred option.

Pelvic exenteration is rarely performed for palliation of rectal cancer because of anticipated high morbidity rates and further diminishing quality of life, especially because longevity is limited. Absolute contraindications were listed above. Many surgeons will draw the line at synchronous resection of bladder-prostate or sacrum. However, posterior vaginectomy or hysterectomy is usually not a deterrent to rectal resection in this context.

SUMMARY

Few studies exist that compare alternative surgical treatment in the palliation of treatment of rectal cancer. The variables involved in comparative studies are large and quantification of risks and benefits is difficult. Thus, for evidence-based guidelines, the quality of studies are limited. This then requires an extensive discussion with the patient, family, and friends of options available. Collaboration of the surgeon with the medical oncologist and radiotherapist as well as radiologist and nuclear medicine imager will be highly desirable. In the event that resective surgery is chosen, principles of rectal resection are the same as for curative resection, namely total mesorectal or site-specific mesorectal excision.

Indications and Results of Endoscopic Rectal Stenting

Todd H. Baron, M.D.

Self expandable metal stents (SEMS) are a useful option to diverting colostomy for the palliation of malignant rectal obstruction. SEMS can be successfully placed in approximately 90% of cases with acceptable complication rates. Covered SEMS allow closure of malignant rectovaginal and rectovesical fistulae associated with rectal obstruction. The main drawback to these devices is the inability to palliate bleeding. (J GASTROINTEST SURG 2004;8:266–269)

KEY WORDS: Stents, palliative care, rectal neoplasms, intestinal obstruction

INTRODUCTION

Self-expandable metal stents (SEMS) are useful for nonsurgical palliation of malignant rectal obstruction. SEMS may be placed endoscopically or by interventional radiologists without the use of endoscopy. In experienced centers SEMS can be successfully placed in approximately 90% of cases. Although it is known that the placement of these devices is feasible, there are no prospective trials comparing stent placement for palliation of rectal obstruction to other endoscopic or surgical modalities. Additionally, there are no studies comparing the outcome of the method of placement (endoscopic vs. radiologic).

Primary or recurrent adenocarcinoma of the rectum may lead to the development of colonic obstruction. Traditional management of symptomatic malignant rectal obstruction involves creation of a surgical ostomy. The use of self-expandable metal stents (SEMS) for the relief of malignant rectal obstruction as an alternative or adjunct to surgery is becoming more widely accepted.

Self-expandable Metal Stents: General Principles

SEMS are composed of a variety of metal alloys with varying shapes and sizes, depending on the individual manufacturer and organ of placement. Colonic SEMS have lumenal diameters of 20–30 mm. The radial expansile forces and degree of shortening differ between stent types.[1] Tissue reactions to SEMS in vivo are known based on animal data as well as autopsy and surgical findings in humans.[2] Histologic findings specifically related to rectal self-expandable metal stents has been reported on two occasions.[3,4] Once deployed, the tissue response to SEMS seems to be consistent throughout the gastrointestinal tract. The stent material becomes incorporated into both the tumor and surrounding tissue by pressure necrosis. In the areas uninvolved by tumor above and below the stenosis, the stent incorporates deep into the wall of the organ. This reaction allows anchoring of the stent and helps to prevent stent migration. With the use of fully covered stents this integration does not always occur and a higher rate of stent migration is seen. At the present time, SEMS specifically designed for rectal use are uncovered. Covered esophageal stents have been used in the colon to combat problems with tumor ingrowth and to close fistulae.[5]

SEMS may produce imaging artifacts on both computer tomography (CT) and magnetic resonance imaging (MRI) localized to the area around the stent that may prevent accurate interpretation. Most SEMS materials appear safe for MRI, but factors such as stent shape, orientation to the magnetic field, and type of alloy composition influence signal intensity in vitro. Therefore, this information should be obtained before an MRI is performed in a patient who has undergone rectal stent placement.[6,7]

Rectal SEMS may be placed by interventional radiologists using fluoroscopy alone or by endoscopists using endoscopic techniques with or without fluoroscopic guidance. Many patients can be electively treated as outpatients. It is unknown whether the

From the Mayo Clinic, Rochester, Minnesota.
Reprint requests: Todd H. Baron, M.D., 200 First St., SW, Rochester, MN 55905. e-mail: baron.todd@mayo.edu

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success rates and complication rates differ between endoscopic and radiologic insertion.

Palliation of Malignant Rectal Obstruction

Patients with obstructive rectal carcinoma who have extensive local or metastatic disease, who are poor operative candidates for surgical resection, or who have recurrent disease after resection are candidates for colonic SEMS placement for palliation.[8–10] Several series have demonstrated successful palliation of rectal obstruction with avoidance of colostomy in 85%–100% of patients. In some series, the stents effectively palliated obstruction for more than 1 year.[11–13]

In a recent comprehensive review of all colonic stent literature published through December 2000 of 336 patients undergoing palliative colonic stent placement (of which 20% were rectal lesions), successful palliation was achieved in 302 (90%).[14] Although most of the stent literature contains patients with all forms and locations of colonic obstruction, there are several series devoted entirely to the treatment of rectal cancer.[15,16] The largest series of endoscopic stent placement for palliation of obstructive primary rectal and rectosigmoid obstruction was published by Spinelli et al.[16] Stents were successfully placed in 36 out of 37 patients. Three early migrations occurred. Twenty-eight of the remaining 33 patients had good long-term resolution of obstruction without need for further treatment. Similarly, Tack et al.[17] reported their follow-up results in 10 patients, 9 of whom had rectal carcinoma. They found median patient survival of 204 ± 43 days with stent occlusion due to ingrowth in 1 patient after 268 days.

Nearly all series have used uncovered stents. One study found an unacceptably high rate of migration using fully covered stents.[18] In a recent study using partially covered esophageal stents in 16 patients for palliation of malignant rectal and sigmoid obstruction, two stent migrations occurred.[19] At a mean follow-up of 21 weeks, no stent occlusion was seen. Although randomized comparative trials of stent placement vs. colostomy are lacking, it is difficult to deny terminal patients the option of stent placement to avoid permanent colostomy.

Palliation of Malignant Fistulae

Patients with rectal carcinoma may suffer from fistulae to the vagina or bladder. In this setting, covered esophageal stents have been used to close such fistulae and produce excellent palliation.[5,20]

Patient Education

After uncomplicated colorectal stent placement patients may resume intake by mouth immediately if there was no overt clinical obstruction or after clinical decompression if they presented with significant obstruction. After palliative colorectal stent placement, patients are advised to consume a low-residue diet and use stool softeners, mineral oil, or laxatives to avoid stent occlusion from stool impaction. Patients should be educated about the signs and symptoms of recurrent obstruction and are advised to contact their physicians should they occur.

COMPLICATIONS OF SEMS

Complications of colon SEMS placement may occur during the procedure or soon after placement (early complications) or late after insertion (Table 1). Early complications include perforation, migration, bleeding, stent malposition, and stent occlusion by stool impaction. Free perforation during SEMS insertion may be a devastating complication, because fecal material is spilled into the abdominal cavity, resulting in peritonitis. This may be more difficult to manage surgically as compared to diverting colostomy alone. Additionally, the patient may become more acutely ill, producing a potentially worse surgical outcome. Improper deployment of the stent or proximal stent migration after successful placement results in a stent floating freely within the lumen above the stricture. This is usually of no consequence assuming an additional stent(s) is properly placed to relieve the obstruction (personal experience). Stents placed very distally in the rectum may produce tenesmus, rectal pain, and fecal incontinence. Thus, patients with distal rectal obstruction should be advised of this possibility before stent placement. In general, stent placement greater than 2 cm proximal to the anal canal does not interfere with anal function. Late complications include distal stent migration, bleeding, and perforation.[21] Stent migration may be completely asymptomatic or result in rectal bleeding or tenesmus. Removal of distally migrated stents from the rectum is not technically difficult and is best performed using rat's tooth forceps and an endoscope overtube. Stent occlusion from tumor overgrowth,

Table 1. Complications of colorectal SEMS

Complication	Mean incidence[14]
Perforation	4%
Bleeding	5%
Reobstruction	10%
Migration	10%
Pain/tenesmus	5%
Death	1%

SEMS = self-expandable metal stents.

ingrowth, or stool impaction requires endoscopic intervention. Obstruction by tumor ingrowth or tissue hyperplasia may be treated by ablative therapies such as argon beam plasma coagulation (APC), laser, or restenting. Tumor overgrowth is usually managed with placement of additional stents through the original stent(s).

The effect of stent placement on delivery of radiation therapy to the rectum is not well defined. It is also unknown whether it is safe to administer radiation therapy after stent placement. There is one case report in which a patient with a distal obstructing rectal cancer received preoperative radiation. After a full course of chemoradiation therapy, the tumor and stent were resected. No adverse pathologic effects were seen in the resected specimen. It is assumed that the risk of stent migration increases after such treatment when tumor shrinkage occurs. Similarly, in patients who have received prior radiation therapy to the rectum, the safety of stent placement is unknown. Some patients with widely advanced rectal cancer and rectal obstruction may not improve after successful stent placement because of other unidentified sites of malignant gastrointestinal obstruction or diffuse peritoneal carcinomatosis with small bowel encasement.

Stent Types

Although any type of SEMS may be used within the rectum[22] including esophageal, tracheobronchial, and biliary stents, dedicated colonic SEMS are commercially available. Three different self-expandable colonic stents are approved by the food and drug administration (FDA) in the United States for treatment of malignant obstruction.[23] These are (1) the colonic Z-stent (Wilson–Cook Medical, Winston-Salem, NC) with diameters of 28 mm flanged ends and 25 mm mid-body; (2) the Enteral Wallstent (Microvasive Corp., Natick, MA) with dimensions of 20 and 22 mm diameters; and (3) the Ultraflex Precision Colonic Stent (Microvasive, Boston Scientific Corp., Natick, MA) with a 30 mm diameter proximal flare and 25 mm body. The advantage of using the Enteral Wallstent over the other colonic stents is the much longer and smaller diameter (10Fr) delivery system that allows passage of stents directly through the working channel of the endoscope. A theoretical advantage of the Wilson–Cook Z-stent and the Ultraflex Precision stent is the larger diameter of the lumen compared to the Enteral Wallstent. One further advantage of the Z-stent is that they do not shorten during deployment.

Limitations and Success Rate

The technical success rate for placement of rectal SEMS in experienced centers is close to 100%. Pooled data from a large review of all stent literature of 598 patients found a technical success rate of 92% (interquartile range 88%–100%).[14] Unsuccessful placement is usually due to the inability to pass a guidewire through the stricture.

Avoidance of Complications

Two important tips are helpful to avoid intraprocedural perforation. The first is limiting the amount of air insufflation during the exam, especially in patients with a dilated cecum. The second is avoiding pre-stent or post-stent dilation.[22] A recent review of all colonic stent literature compared perforation rates in studies where stricture dilation was performed with those where dilation was not performed. A significantly higher incidence of perforation was found in the group in whom dilation was performed (10% vs. 2%).[14]

CONCLUSIONS

SEMS are effective for the palliation of obstructing rectal cancer allowing avoidance of a permanent colostomy in approximately 90% of patients. Covered stent placement should be considered the treatment of choice to seal malignant rectovaginal and rectovesical fistulae. Stent placement does not palliate rectal bleeding. Future studies should focus on the ideal stent design that prevents tumor ingrowth but with a low rate of stent migration. Additionally, future studies are needed to determine the effect of combined radiation therapy with stent placement on outcome of palliation as compared to stent placement alone.

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Endoscopic Methods (Other Than Stents) for Palliation of Rectal Carcinoma

Michael B. Kimmey, M.D.

Patients with unresectable or metastatic rectal cancer may have symptoms of obstruction, bleeding, pain, or tenesmus. Insertion of a self-expandable metal stent is the most durable nonsurgical method for relieving obstruction and has been reviewed in the previous article. Other endoscopic methods of palliating obstruction have been largely replaced by expandable metal stent placement. However, laser ablation is still a useful therapy for some patients, particularly when the predominant symptom is rectal bleeding. The indications and results of endoscopic laser therapy along with other endoscopic treatments for the palliation of rectal cancer will be reviewed here. (J GASTROINTEST SURG 2004;8:270–273) © 2004 The Society for Surgery of the Alimentary Tract

KEY WORDS: Rectal cancer, laser, palliation

LASER ABLATION

Lasers have been used with flexible endoscopy over the past 30 years.[1] The ability to deliver a focused form of energy through a small caliber fiber made it an ideal modality for treating bleeding lesions and cancer with flexible endoscopes. Although a number of types of lasers have been adapted for endoscopic use, the neodymium yttrium argon garnet (Nd:YAG) laser has been used the most for the treatment of cancer over the past two decades.[2] The Nd:YAG laser has a wavelength of 1024 nm and is well suited for treating bleeding and vaporizing tumor tissue. Lower power settings result in coagulative necrosis of tissue with subsequent tissue sloughing, whereas higher power settings cause immediate vaporization of neoplastic tissue. Both types of tissue injury are useful in patients with rectal cancer who may have symptoms of bleeding and/or luminal obstruction.

Laser energy can be applied to the tissue using both contact and noncontact methods. The noncontact method is most commonly used in the palliation of rectal cancer. A special fiber with a quartz tip and lumen for gas cooling of the tip is placed through the accessory channel of a sigmoidoscope or colonoscope and aimed at the tumor using endoscopic vision. Treatment is usually begun at the proximal edge of the tumor and targeted to intraluminal bulky tumor masses and areas of bleeding. The amount of energy delivered to the tissue and hence the effect on the tumor is a function of the laser power setting, duration of laser activation, and proximity of the fiber tip to the tissue. Care must be taken to suction tissue vapor and cooling gas at frequent intervals to avoid excessive colonic distension. Treatments are usually repeated every few days until luminal patency is achieved. Repeat treatments are then performed when recurrent symptoms develop or every few months in patients with good performance status.

The indications for laser ablation of rectal cancer are the palliation of bleeding, obstruction, and rectal urgency, or tenesmus. Palliation of symptoms is achieved after 2–5 laser sessions in 80%–90% of patients (Table 1). Quality of life is improved for patients with symptoms of bleeding, diarrhea, mucus discharge, tenesmus, and obstruction.[15]

Patients with symptoms of bleeding and tenesmus require fewer laser sessions and have a more durable response than patients with obstruction.[4,14] Palliation becomes less effective as patients survive longer, dropping from 80%–90% initially to only 52% at 6 months and 42% at 12 months,[3] arguing for the use of other palliative methods (stents, radiotherapy, or surgery) in patients with longer predicted survivals. Laser ablation is more difficult and results are not as good in patients with long or circumferential tumors and those where endoscopic visualization is difficult due to angulation or edema.[5,16]

From the Department of Medicine, University of Washington, Seattle, Washington (M.B.K.).
Reprint requests: Michael B. Kimmey, M.D., Division of Gastroenterology, Box 356424, Room AA-103, 1959 NE Pacific Street, University of Washington, Seattle, WA 98195; e-mail: Kimmey@u.washington.edu

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Laser ablation is not effective for treating rectal pain, which may be caused by tumor infiltration of regional nerves.[14] Patients with tumor involvement of the anal canal or sphincter and those with advanced cachexia do not usually benefit from laser therapy.[15]

Complications of laser therapy occur in 5%–15% of patients (Table 1). Most complications are minor but perforation, sepsis, and death may occur, particularly in severely debilitated patients. Other complications include bleeding, development of rectovaginal and rectocutaneous fistulas, perirectal abscess, fecal incontinence, and rectal stenosis.

There are few comparative studies with other techniques, none of them controlled, for the palliation of rectal cancer. In two retrospective reviews, laser ablation was found to be as effective as palliative surgery but with shorter hospitalization times and lower costs.[9,17] There are no comparative studies of laser ablation with endorectal stenting or radiation therapy.

Laser ablation is often used in conjunction with other techniques. Lasers effectively stop bleeding and reduce obstructive symptoms while awaiting the cytoreductive effects of radiation therapy. The combination of laser with external beam radiotherapy reduces recurrent obstruction from 58% with laser alone to 15%.[18] Use of endorectal brachytherapy along with laser therapy has also been reported to reduce the pace of recurrent tumor obstruction and bleeding.[19] Lasers can help open the rectal lumen to facilitate placement of self-expanding metal stents, but are usually not needed for this purpose.[20] Recurrent obstruction or bleeding due to tumor in-growth through the mesh of expandable metal stents can also be treated effectively with laser ablation.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves the activation of a systemically delivered hematoporphyrin drug by laser light directed at tumor tissue. Drug activation produces singlet oxygen species that destroy blood vessels and result in tumor necrosis. Because tumors often have increased vascularity and vascular permeability, there can be relatively more drug concentrated within tumors, leading to destruction of more neoplastic tissue than normal tissue. Most studies with photodynamic therapy of rectal cancer have focused on the use of this modality as an adjunct to endoscopic resection for curing small rectal cancers in nonoperative candidates.[21]

There have only been small pilot studies of photodynamic therapy for the palliation of symptoms due to rectal cancer.[22,23] In one series, 5 of 6 patients had clinical and radiologic response to treatment.[22] In another group of 10 patients, response was more durable in patients with small local or anastamotic tumor recurrences.[23]

The main limitation of photodynamic therapy is cutaneous phototoxicity. Patients must avoid significant sun exposure for up to 6 weeks after administration of Photofrin II (Axcan Pharma, Montreal, Quebec, Canada), the only photosensitizer currently available in the United States. Newer porphyrin derivatives with shorter durations of photosensitivity may lead to more widespread use of photodynamic therapy for treating rectal cancer.[24]

ARGON PLASMA COAGULATION

Argon plasma coagulation (APC) has replaced laser therapy in many gastrointestinal endoscopy units because of its lower cost, portability, and ease of use. This

Table 1. Laser ablation for palliation of rectal cancer

Author (reference)	Year	No. of patients	Initial efficacy (%)	Median number of treatments (range)	Median survival or range (weeks)	Complications (%)
Van Cutsem[3]	1989	88	82	5 (1–10)	40	7
Mathus-Vliegen[4]	1986	181	89	3 (1–40)	10–24	9
Loizou[5]	1990	49	74	3	19	5
Daneker[6]	1991	37	84	1 (1–5)	32	9
Mandava[7]	1991	27	85	3 (1–9)	39	15
Chia[8]	1991	27	100	2	20	0
Tacke[9]	1993	37	95	1 (1–5)	32	8
Schulze[10]	1994	74	74	2 (1–11)	28	9
Mlkvy[11]	1994	126	71	3	18	2
Rantala[12]	1995	20	70	4 (1–8)	44	15
Brunetaud[2]	1995	272	85	?	41	2
Farouk[13]	1997	41	78	2 (1–6)	24	2
Gevers[14]	2000	219	92	5	52	13

technique involves the ionization of argon gas by electrocautery to fulgurate mucosal blood vessels and neoplasms. Surface coagulation for bleeding control can be accomplished very effectively, resulting in control of bleeding in most cases.[25] The depth of penetration with APC is limited, so this technique is usually used as a temporizing measure in patients with obstruction while awaiting a beneficial effect of radiation therapy or before stent placement.[25,26] Larger controlled comparisons of APC with Nd:YAG laser for palliation of rectal cancer are desirable.

ELECTROCOAGULATION

Electrocautery has been used as an ablative technique both for attempted cure of early cancers and palliation of advanced tumors.[27–29] The treatment has usually been applied through a rigid operating proctoscope under general anesthesia, necessary because of significant pain during the procedure. Complications of bleeding, strictures, urinary retention, electrical burns, and perforation in approximately 20% of cases along with an unpredictable depth of tissue injury has made this treatment less desirable than other palliative therapies such as laser ablation and stenting.

CRYOTHERAPY

Coagulation of rectal cancer with endoluminal application of cryoprobes has been described. Use of rigid proctoscopes is necessary with current probes and general anesthesia may be required. Rectal discharge is common after the procedure.[30] Relief of tumor-related symptoms has been reported in approximately 60%.[31] Laser ablation appears to provide better palliation with fewer adverse effects.[30] This technique has been abandoned in most centers for local therapy of rectal cancer, however its use in the ablation of liver metastases is receiving renewed interest.

INJECTION THERAPY

Alcohol and sclerosing agents have been injected directly into bulky rectal cancers in an effort to ablate the tumors with a very low cost and simple technique. Palliation of obstruction was described in 5 patients treated with injections of 3% polidocanol into the tumor using a sclerotherapy needle passed through the channel of a flexible sigmoidoscope.[32] Up to 25 cc was injected per session in 2–3 cc aliquots. Repeat injection sessions were necessary in 4 of 5 patients over a period of 4–31 months of follow-up. Injection treatment has not been formally compared to lasers and other ablative techniques.

DISCUSSION

Endoscopic laser therapy is the main endoscopic therapy available for the palliation of rectal cancer. It is primarily an adjunctive tool to other techniques. It is an effective treatment for bleeding and tenesmus caused by rectal cancer. Although it can also be used to restore lumen patency, the effect is not durable. Therefore, it is used primarily in patients with very advanced disease and short life expectancy or as an adjunctive therapy to other treatments such as radiotherapy or stenting.

Other endoscopic ablative therapies have not been well studied in patients with rectal cancer. Argon plasma coagulation is a simple and widely available technique used in many centers, but the lack of published series and especially comparative studies do not allow conclusions to be reached about the role of this technique in the palliation of rectal cancer. Photodynamic therapy, cryotherapy, injection therapy, and electrocautery cannot be recommended due to side effects or the high rate of complications.

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Palliative Management of Rectal Cancer: The Roles of Chemotherapy and Radiation Therapy

Leonard B. Saltz, M.D.

One of the first maxims of oncologic care is that we must never miss an opportunity to cure a patient. Perhaps an equally important corollary is that to provide the best possible care for each individual, it is necessary to accurately recognize when a curative option does not exist and to adjust our treatment recommendations accordingly. A discussion of palliative care in a patient with rectal cancer must therefore be based on the assumption that the patient does not have a realistic chance of undergoing a curative intervention. (J GASTROINTEST SURG 2004;8:274–276)

KEY WORDS: Rectal cancer, palliation, chemotherapy, radiation therapy

Palliative care of the patient with rectal cancer presents challenges that are quite different from those encountered in a patient with a potentially curable tumor. A good place to start in the determination of the appropriate treatment options for a patient with incurable rectal cancer is to identify the clinical issues that preclude curative management. Several of these determinants of incurability will be outlined and discussed below.

SYNCHRONOUS METASTATIC DISEASE

One of the most common reasons for a rectal cancer patient to be incurable on initial presentation is the existence of metastatic disease. Keeping in mind the importance of not abandoning any realistic chance for cure, a patient presenting with synchronous resectable liver or lung metastases is a candidate for a curative intervention and is not under discussion here. The initial management of the patient with a rectal tumor in place and concurrent metastases requires an assessment of the relative risk of the primary tumor for imminent obstruction. This is ideally done endoscopically using either a flexible or rigid scope. Tumors that are obstructing or near-obstructing require mechanical palliation either by palliative surgery or by placement of an endorectal stent. Tumors, which are asymptomatic or minimally symptomatic and are not at substantial risk for imminent obstruction, can be managed with chemotherapy or with chemotherapy and radiation. In general terms, if a tumor is felt on clinical assessment to be unlikely to obstruct in an 8 to 10-week period, then it does not require palliative mechanical management (palliative resection or mechanical stent) before the initiation of chemotherapy. The scenario that is of most concern is the development of an obstruction during a chemotherapy-related toxicity such as neutropenia or thrombocytopenia—toxicities which would substantially complicate the ability to perform an emergency surgical intervention. Most chemotherapy will be assessed for efficacy at 6–8 weeks into treatment. If the chemotherapy is effective, then the risk of obstruction will be substantially decreased. In patients with measurable metastatic disease, such as lung, liver, or nodal metastases, CT or MRI evaluation of the metastatic disease can give a realistic surrogate evaluation of the primary. If the liver metastases are shrinking, the danger of progression of the primary tumor is remote and the risk of obstruction is remote as well. If the metastatic indicator lesions are not responding, then further attention to the risk of primary obstruction must be paid.

The choice of whether to use chemotherapy alone or chemotherapy plus radiation therapy is complex

From the Colorectal Disease Management Team, Memorial Sloan Kettering Cancer Center, New York, New York (L.B.S.).
Reprint requests: Leonard B. Saltz, M.D., Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10021. e-mail: SaltzL@mskcc.org

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and must be individualized to each patient. Combination chemotherapy regimens of either irinotecan/fluorouracil/leucovorin or oxaliplatin/fluorouracil/leucovorin have consistently been reported to cause major objective response rates in the range of 50% or more. It is important to recall that the definition of a response is a 50% reduction in the bidimensional measurements of the tumor. A tumor that shrinks by 40% is not counted as a response, but such a regression may have significant favorable impact on the patient. Taking the major responses (greater than 50% reduction) and the more minor responses and disease stabilizations, the disease control rate for chemotherapy–naíve colorectal cancer is usually in excess of 75%. Thus, chemotherapy alone can offer a considerable chance for palliation of disease.

The potential role of radiation therapy is largely based on the relative risk to the patient of the primary vs. the metastatic disease. If a patient has bulky extra-pelvic metastases and a nonobstructing rectal tumor, then the greater risk to the patient's life is progression of the metastases and systemic chemotherapy is the best option. Put bluntly, such a patient is likely to die of his/her metastatic disease before progression in the pelvis becomes an issue and control of the metastatic disease to whatever degree possible is of paramount concern. Conversely, if a patient has relatively small volume asymptomatic metastases, then the likelihood of serious complications developing in the pelvis over time becomes the greater concern. Such a patient should probably be considered for pelvic radiation therapy.

The question of surgical resection after palliative pelvic radiation is also one which must take into account the likely failure pattern of the patient's disease. If the volume of metastatic disease is large or response to systemic therapy is poor such that the patient is likely to die of metastatic disease before pelvic recurrence becomes a problem, then there is no need to subject the patient to a palliative resection. If, however, the patient has small-volume metastatic disease or metastatic disease that is demonstrating a high degree of responsiveness to chemotherapy, then resection of an asymptomatic primary would potentially be warranted to protect the patient from the miseries of a pelvic recurrence. The location of the tumor and the ability to perform a sphincter-sparing resection or not may figure into the decision. The creation of a permanent colostomy in a nonobstructed patient may well not be viewed by that patient as desirable palliation.

Whereas radiation therapy is typically given with concurrent chemotherapy, the amount of chemotherapy is necessarily limited because of toxicity constraints. Firstly, use of irinotecan or oxaliplatin in combination with radiation therapy remains investigational and concurrent chemotherapy treatments are usually restricted to protracted infusion fluorouracil or fluorouracil plus leucovorin. Additionally, to accommodate the toxicity of radiation, the fluorouracil dose has to be decreased approximately 25%. The use of pelvic radiation with chemotherapy therefore concentrates effective therapy on the pelvic disease but does not provide optimal therapy to extrapelvic metastases.

Given the activity levels demonstrated with combination chemotherapy regimens, use of these regimens as initial therapy, with radiation plus fluorouracil used for either consolidation of a favorable response or salvage of an unfavorable response, would seem to be a reasonable approach in many patients with metastatic disease and nonobstructing rectal cancer.

UNRESECTABLE PELVIC RECURRENCE

Patients who develop recurrent disease after having received previous pelvic radiation present a special management problem in palliation. The dose of radiation administered to the pelvis in the treatment of resectable rectal cancer represents the lifetime tolerance of normal tissues in that area. Further radiation therapy at a later date is not, therefore, a realistic consideration. Also, palliative management is limited to diverting surgery or stenting, if indicated, and systemic chemotherapy. Response rates in previously irradiated fields tend to be lower, however, substantial tumor regressions to chemotherapy in this setting can be achieved in some cases.

MEDICAL COMORBIDITIES

One of the most important issues to consider in deciding on palliative treatment options is the overall treatability of a patient. Patients with severe debilitation secondary to either their cancer or those with significant preexisting medical conditions may be inappropriate for aggressive intervention. Patients with an inability to maintain alimentation due to metastatic disease or patients with a debilitated performance status such that they are leading a bed-to-chair existence are not realistic candidates for chemotherapy-based treatments, and supportive comfort-oriented care without specific anti-cancer therapy may be the most appropriate course of action. Attention to analgesia is of critical importance in these settings. Parenteral hydration may provide some comfort in this palliative setting, however, total parenteral nutrition in the nonsurgical cancer patient has not been

shown to be of benefit and routine use of this maneuver should be discouraged.

SUMMARY

Palliative management of the incurable rectal cancer patient must be individualized to each patient's clinical presentation and overall medical condition. Combination chemotherapeutic regimens for colorectal cancer have made substantial improvements over the past decade and should be considered as the primary palliative modality in patients with metastatic disease. Pelvic radiation therapy plays an important role in the consolidation of successful initial chemotherapy or as salvage for chemotherapy–refractory disease. Decisions regarding palliative surgery require consideration of the overall management plan and an assessment of the specific immediate and long-term risks presented by the cancer to the patient's health. The overall clinical presentation of disease and the patient's general medical and nutritional status must also be considered in the decisions regarding appropriateness of any antineoplastic therapies.

Palliative Treatment of Rectal Cancer: Is Radiotherapy Alone a Good Option?

Christopher G. Willett, M.D., Leonard L. Gunderson, M.D., M.S.

KEY WORDS: Rectal cancer, radiation therapy, intraoperative radiation therapy

A majority of patients who develop local or regional recurrence after curative resection of primary rectal or colon cancers are treated with palliative intent in most institutions in the United States and worldwide.[1] Exceptions include patients with a true anastomotic recurrence or female patients with a limited vaginal recurrence. In either instance, complete resection with negative margins may be feasible and postoperative external-beam radiation therapy (EBRT) plus chemotherapy can be given as indicated. Patients with prior resection of rectal or sigmoid cancers often present with pelvic pain, which is a manifestation of local recurrence involving nerve in the presacrum or pelvic sidewalls. Presentation with pain usually indicates that a surgical approach will be unlikely to yield negative resection margins. Distal sacrectomy with negative resection margins can occasionally be performed in patients with a central distal pelvic relapse. If relapse develops after abdominoperineal resection, male patients may also require a pelvic exenteration in view of bladder or prostate involvement. Most patients, however, either have no surgical resection or a subtotal resection with gross or microscopic residual in view of tumor fixation to presacrum, pelvic sidewalls, or both.

In a Mayo Clinic analysis of 106 patients with subtotal resection of a localized pelvic recurrence from rectal cancer, 12 patients were treated with surgery alone and the remainder had some type of irradiation.[2] Of the 12 with no irradiation, 3- and 5-year overall survival rates were 8% and 0%, respectively. If 8 patients who received EBRT with no planned spatial relationship to surgery are included, 3-year survival increases to 15%, but 5-year survival was still 0%.

External irradiation with or without chemotherapy has definite palliative symptomatic benefit for locally recurrent lesions, but long-term survival is infrequent.[3–11] Relief of pain and/or bleeding is achieved in approximately 75% of patients with doses as low as 20 Gy in 10 fractions over 2 weeks, but doses in most series vary from 40–60 Gy in 1.8–2.5 Gy fractions. Median duration of symptom relief is only 6–9 months and long-term survival is infrequent (0%–5% in most series).

In a series from Queen Elizabeth Hospital in Birmingham, England, 18 patients with local recurrence of colorectal cancer were treated by external beam radiation therapy for pain relief.[12] Seven received a fractionated course of 45 Gy and the remainder received single fractions of 10 Gy, a number being treated more than once. The median survival for all patients once recurrence had produced pain was 7 months. Treatment benefit was recorded in 71% treated by fractionated courses and in 66% by single fractions. The duration of pain relief was 3 months for each method.

Some data suggest a correlation between irradiation dose and duration of palliation.[8,13–15] In an analysis by Wang and Schulz[11] for residual, inoperable, or recurrent lesions, the percentage of patients who received palliation for 6 months or more increased with doses beyond 41 Gy (21–30 Gy: 3 of 24 or 12%, 31–40 Gy: 5 of 28 or 31%, 41–50 Gy: 7 of 12 or 58%). Correlation of response and irradiation dose level was also seen in series reported by Hindo et al.,[13] Rao et al.,[14] and Overgaard et al.[15] on groups of patients treated for palliation. In 110 patients, Hindo et al. reported successful responses in 20% of patients treated with a nominal single dose (NSD) of 400–700 ret, 67% with 701–1000 ret and 82%–89% in the other three dose divisions (1001–1300, 1301–1500, and 1501–1750 ret). Rao et al. treated 92 patients with successful palliation in only 12% with an NSD of 1000 ret or less, 49% 1000–1200 ret, 59% with 1200–1400 ret, and 87% with 1400–1700 ret.

From the Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts (C.G.W.); and Department of Radiation Oncology, Mayo Clinic, Scottsdale, Arizona (L.L.G.).
Reprint requests: Christopher G. Willett, M.D., Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114. e-mail: willett.christopher@mgh.harvard.edu

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Lybeert et al.[16] published data from a group of 95 locally recurrent rectal cancer patients in the Netherlands treated with EBRT with or without 5-FU for relapse after radical surgery. Seventy-six patients presented with loco-regional relapse only and 19 presented with loco-regional relapse and concomitant distant metastases. The total dose of EBRT was 44 Gy median (range 6–66 Gy) and 40 Gy median (range 6–50 Gy), respectively. Twelve of 76 with localized relapse received concomitant 5-FU with EBRT. In the patients with loco-regional relapse only, recurrence-free and overall survival rates after EBRT were, respectively, 23% and 61% at 1 year and 6% and 13% at 3 years. Recurrent or persistent disease inside the EBRT volume was an important clinical problem in 43 of 63 patients who were able to be evaluated or 68% (42 of 43 were diagnosed within 2 years). In the 76 patients with loco-regional relapse only, using recurrence-free survival as the end point, dose of EBRT was a significant multivariate prognostic factor ($P = 0.01$); using survival as the end point, dose of EBRT ($P = 0.005$), and grade of tumor differentiation ($P = 0.002$) were significant.

Investigators at Peter MacCullum Cancer Institute[17] retrospectively analyzed a group of 135 patients with locally recurrent nonmetastatic rectosigmoid cancer treated from 1981–1990 with three different dose ranges of radiotherapy: 50–60 Gy (radical group: 2-Gy fractions, no split), 45 Gy (high-dose palliative group: 3-Gy fractions with 1 wk split after 30 Gy in 10 fractions), and <45 Gy (low-dose palliative group). Symptomatic response rates of 85%, 81%, and 56% were achieved in the radical, high-dose palliative, and low-dose palliative groups, respectively. Objective response rates were assessed only in the radical and high-dose palliative groups and were 44% and 37%, respectively. Estimated median survival times were 17.9, 14.8, and 9.1 months for the radical, high-dose, and low-dose palliative groups, respectively.

Randomized trials from the Mayo Clinic have looked at the combination of radiation therapy with and without chemotherapy or immunotherapy in patients with locally advanced or recurrent colorectal cancers. In the first trial, a group of 65 patients with locally unresectable or recurrent colorectal carcinoma were treated with 40 Gy in 2-Gy fractions over 4 weeks plus placebo or 5-FU (15 mg/kg on the first 3 d of EBRT)[6]. Median survival time was 10.5 months in the placebo group vs. 16 months in those receiving 5-FU concomitant with EBRT ($P < 0.05$). Two-year survival was 24% vs. 38% and 3-year survival was 9% vs. 19%.

In a later trial, 44 patients with locally advanced rectal cancer (unresectable 7, resected but residual 7, locally recurrent 30) received 50 Gy split-course pelvic irradiation with or without adjuvant immunotherapy.[10] Site of initial tumor progression could be evaluated in 31 patients and local progression within the radiation field was diagnosed in 28 patients (90%). In 17 patients (55% of patients who could be evaluated), it was the only site of disease. Median survival time in both groups of patients was approximately 18 months. In this trial, 36 of 44 patients were experiencing significant pelvic or perineal pain before EBRT. Although 94% of patients experienced temporary improvement in pain after treatment, median duration of pain relief was only 5 months.

Because of these poor results with external beam radiation therapy only, investigators initiated studies evaluating the combination of external beam irradiation (EBRT), surgery, and intraoperative irradiation (IORT) for patients with recurrent rectal cancer in the 1970s. From June 1978 to February 1997, 49 patients with locally recurrent carcinoma of the rectum or rectosigmoid were treated with external beam radiation therapy[18], surgery, and IORT for recurrent rectal cancer at the Massachusetts General Hospital. The 5-year overall survival, local control, and disease-free survival rates of 49 patients who received IORT were 27%, 35%, and 20%, respectively. Of the 49 patients undergoing surgery and IORT, 34 patients had a complete gross resection.

The 5-year overall survival, local control, and disease-free survival rates of these patients were 33%, 46%, and 27%, respectively. Twenty-five of these 34 patients underwent a complete gross resection with pathological negative margins. For this group, the 5-year overall survival, local control, and disease-free survival rates were 40%, 56%, and 32%, respectively. The results were inferior for 24 patients undergoing partial resection. Their 5-year overall survival, local control, and disease-free survival rates were 14%, 17%, and 8%, respectively. Within this group of 24 patients, 15 patients had gross residual disease despite maximal resection. Their 5-year overall survival, local control, and disease free-survival rates were 13%, 12%, and 7%, respectively. Two of the 15 patients with gross residual disease survived more than 5 years (13%). Aggressive combinations of external beam radiation therapy, surgery, and IORT may benefit a subset of patients undergoing complete re-resection.

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Predicting Resectability of Periampullary Cancer With Three-Dimensional Computed Tomography

Michael G. House, M.D., Charles J. Yeo, M.D., John L. Cameron, M.D., Kurt A. Campbell, M.D., Richard D. Schulick, M.D., Steven D. Leach, M.D., Ralph H. Hruban, M.D., Karen M. Horton, M.D., Elliot K. Fishman, M.D., Keith D. Lillemoe, M.D.

The radiographic assessment of extent of tumor burden and local vascular invasion appears to be enhanced with three-dimensional computed tomography (3D-CT). The purpose of this study was to evaluate the impact of preoperative 3D-CT in determining the resectability of patients with periampullary tumors. Intraoperative findings from exploratory laparotomy were gathered prospectively from 140 patients who were thought to have periampullary tumors and were deemed resectable after undergoing preoperative 3D-CT imaging. CT findings were compared to intraoperative findings, and the accuracy of 3D-CT in predicting tumor resectability and, ultimately, the likelihood of obtaining a margin-negative resection were assessed. Of the 140 patients who were thought to have resectable periampullary tumors after preoperative 3D-CT, 115 (82%) were subsequently determined to have periampullary cancer. The remaining 25 patients had benign disease. Among the patients with periampullary cancer, the extent of local tumor burden involving the pancreas and peripancreatic tissues was accurately depicted by 3D-CT in 93% of the patients. 3D-CT was 95% accurate in determining cancer invasion of the superior mesenteric vessels. Preoperative 3D-CT accurately predicted periampullary cancer resectability and a margin-negative resection in 98% and 86% of patients, respectively. For patients with pancreatic adenocarcinoma (n = 85), preoperative 3D-CT resulted in a resectability rate and a margin-negative resection rate of 79% and 73%, respectively. The ability of 3D-CT to predict a margin-negative resection for periampullary cancer, including pancreatic adenocarcinoma, relies on its enhanced assessment of the extent of local tumor burden and involvement of the mesenteric vascular anatomy. (J GASTROINTEST SURG 2004;8:280–288)

KEY WORDS: Periampullary cancer, computed tomography, vascular invasion, resection

Although several imaging modalities are available to evaluate patients with suspected periampullary tumors, including endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, and magnetic resonance imaging (MRI), computed tomography (CT) has evolved as the predominant, single modality for diagnosis and preoperative staging.[1] Many patients with neoplasms arising from the periampullary region, especially pancreatic adenocarcinoma, present with advanced disease that is not amenable to curative resection.[1,2] Although the surgical management of localized periampullary cancer has

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From the Departments of Surgery (M.G.H., C.J.Y., J.L.C., K.A.C., R.D.S., S.D.L.), Pathology (R.H.H.), and Radiology (K.M.H., E.K.F.), The Johns Hopkins University School of Medicine, Baltimore, Maryland; and the Department of Surgery (K.D.L.), Indiana University School of Medicine, Indianapolis, Indiana.

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Reprint requests: Keith D. Lillemoe, M.D., Professor and Chairman, Department of Surgery, Indiana University School of Medicine, 545 Barnhill Dr., EH 203, Indianapolis, IN 46202. e-mail: klillemo@iupui.edu

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improved over the past two decades, less than 20% of patients with pancreatic adenocarcinoma will have resectable disease at the time of initial diagnosis.[1,3,4] In patients with pancreatic cancer, preoperative thin-section, contrast-enhanced CT, when used alone, can accurately predict tumor resectability in 70% to 88% of patients.[5–8]

The radiographic findings on dual-phase, contrast-enhanced CT that predict unresectability for periampullary tumors include distant extrapancreatic spread, ascites, encasement of the superior mesenteric artery, and occlusion of the superior mesenteric vein–portal vein confluence.[6,9] Despite the reliability of dual-phase, contrast-enhanced CT to assess extrapancreatic involvement, its accuracy for predicting subtle local vascular invasion remained unreliable until the introduction of multidetector CT technology. This latter technology can be used to generate detailed, volume-rendered helical CT data that can be processed and displayed in three dimensions.[10] Consequently three-dimensional computed tomography (3D-CT) enhances the assessment of vascular invasion by allowing periampullary structures to be viewed in image planes that correspond to the oblique orientation of the pancreas within the retroperitoneum.[10,11]

Several studies have investigated the accuracy of CT in staging periampullary cancer and predicting tumor resectability.[5,7,12–16] Different scanning techniques and varying degrees of experience with later-generation devices make it difficult to compare CT results between large-volume centers. Also, the designation of unresectability has been poorly defined, particularly by surgeons who advocate aggressive resection even with extensive portal vein involvement.[8]

The goal of preoperative evaluation of periampullary tumors is to identify patients who will most likely achieve a survival benefit as a result of operative intervention.[17–19] The ultimate goal of preoperative imaging is to predict which patients will eventually undergo a margin-negative resection. Therefore this single-institution, prospective study was performed to evaluate the accuracy of 3D-CT in determining resectability for periampullary neoplasms and specifically for predicting a margin-negative pancreaticoduodenal resection.

MATERIAL AND METHODS

Patients

After obtaining permission from the Johns Hopkins University institutional review board, we began a prospective study to assess patients who were first seen with periampullary lesions at our institution between September 2001 and December 2002. Patients were eligible for enrollment if they underwent surgical exploration for a suspected periampullary mass detected on preoperative imaging with 3D-CT. Intraoperative findings from exploratory laparotomy, performed with intent to proceed to pancreaticoduodenal resection, were then gathered prospectively for 140 patients who were deemed resectable after undergoing preoperative 3D-CT at our institution. Among the patients who were evaluated with 3D-CT preoperatively, the average age was 64 years (range 26 to 87 years), and approximately half of the patients (52%) were male.

Three-Dimensional CT Technique

All 3D-CT studies were performed at The Johns Hopkins Hospital with a Somatom Plus-4 scanner (Siemens, Iselin, NJ) according to a standard protocol.[11] Patients received 750 ml of water 30 minutes prior to helical CT scanning. Scan slices 3 mm thick were acquired 30 seconds (arterial phase) and 60 seconds (venous phase) after the intravenous infusion of 100 to 125 ml of Omnipaque-350 (Nycomed, New York, NY) at 2 to 3 ml/sec. Scanning data were transferred for reconstruction using Reality Engineering software (Silicon Graphics, Mountain View, CA), and images were interpreted by one of two senior radiologists (K.M.H. or E.K.F) who had extensive experience with three-dimensional pancreatic imaging. After retrieving the three-dimensional images from the Reality Engineering software program, radiologists required approximately 5 minutes to interpret the final 3D-CT scans.

CT Interpretation

Two radiologists (K.M.H. and E.K.F) reviewed all of the preoperative 3D-CT scans prior to surgical exploration and prospectively recorded their interpretations for tumor size, location, peripancreatic spread, distant metastases, regional lymphadenopathy (measuring at least 5 mm), and degree (percentage of vessel circumference) of tumor infiltration/encasement into adjacent major vessels (including the superior mesenteric artery (SMA), hepatic artery, celiac axis, superior mesenteric vein (SMV), and portal vein (PV). The presence of anomalous arterial anatomy was also recorded.

Preoperative imaging with 3D-CT was interpreted as demonstrating a resectable tumor if there was no radiographic evidence of metastatic disease, a clear tissue plane between the tumor and SMA, and $\leqslant 180^{\circ}$ circumferential involvement of the SMV-PV confluence. Patients with unequivocal metastates to the liver, ascites, invasion into the SMA, or total occlusion

of the SMV-PV confluence were not included in this study.

Tumor Resectability

Tumors, completely removed at the time of surgery, without gross evidence of residual tumor, were defined as resectable. Patients discovered intraoperatively to have metastatic disease to the liver, or tumor spread to the peritoneum, adjacent organs (excluding duodenum and colon), or distant lymph nodes (excluding peripancreatic and lymph nodes), were deemed unresectable. An experienced surgeon's determination of vascular involvement was based predominantly on gross intraoperative findings that were not necessarily confirmed with biopsy. None of the patients in this study underwent vein resection in order to obtain gross or microscopically negative margins.

Pathologic Evaluation

In addition to the surgeon's intraoperative assessment, histopathologic findings were recorded for resected specimens by a gastrointestinal pathologist (R.H.H.) who had extensive experience with pancreatic tumors. These findings included tumor size, histopathologic diagnosis, pathologic staging, and microscopic invasion of resection margins.

Statistical Analysis

3D-CT findings were recorded prospectively from patients with potentially resectable periampullary tumors, and comparisons were made between preoperative 3D-CT interpretations and intraoperative findings (documented immediately after surgery from a datasheet filled out by participating surgeons), specifically for the extent of tumor burden, presence of local or distant tumor spread, degree of tumor invasion of the local venous and arterial systems, and anomalous hepatic arterial anatomy. Sensitivity was defined as the percentage of positive intraoperative findings correctly diagnosed by 3D-CT, whereas specificity reflected the percentage of negative findings correctly diagnosed by 3D-CT. The negative predictive value represented the percentage of patients with negative 3D-CT findings (for example, no evidence of tumor invasion of the local venous and arterial systems, and absent hepatic artery anomalies) who were also found to have negative intraoperative findings. The positive predictive value was calculated as the percentage of patients with positive 3D-CT findings (for example, tumor invasion of the mesenteric vessels) who were also found to have positive intraoperative findings. Overall accuracy reflected the consistency between the 3D-CT and intraoperative findings. The sensitivity, specificity, predictive value, and accuracy of 3D-CT to predict tumor resectability and, ultimately, the likelihood of obtaining a margin-negative resection were also assessed.

RESULTS

Intraoperative and Pathologic Findings

Of the 140 patients who were thought to have resectable periampullary tumors after preoperative 3D-CT, 115 (82%) were subsequently determined to have periampullary cancer. The remaining 25 patients (18%) were found to have benign pancreatic disease and were not included in the subsequent analyses. The average time interval from 3D-CT scan to operation was 19 days. Table 1 includes the pathologic features of the patients undergoing preoperative 3D-CT. The average size of all periampullary cancers was 3.4 cm (range 0.5 to 9 cm). Pancreatic adenocarcinoma was confirmed pathologically in 85 (74%) of 115 periampullary cancer specimens. Positive lymph nodes were present in 53% and 73% of the periampullary and pancreatic cancers, respectively.

Resectability

Of the 115 patients with periampullary neoplasms who were thought to be resectable on preoperative

Table 1. Pathologic characteristics for patients undergoing preoperative 3D-CT

	No. of patients	Average tumor size (cm)	Lymph node status (%)*
Periampullary cancers			
Pancreatic adenocarcinoma	85 (74%)	3.2	73
Ampulla/common bile duct adenocarcinoma	13 (11%)	1.8	51
Pancreatic neuroendocrine tumor	12 (10%)	6.2	17
Duodenal adenocarcinoma	5 (4%)	3.8	30
	115	3.4	53
Benign pancreatic lesions			
Benign cystic tumors	15 (60%)	3.1	NA
Chronic pancreatitis	10 (40%)	NA	NA
	25	3.1 cm	NA

All 3D-CT scans were performed at The Johns Hopkins Hospital; NA = not applicable.

* Percentage of tumors with positive lymph nodes.

3D-CT, 95 (83%) were resected. A pylorus-preserving pancreaticoduodenectomy was performed in 82%, a classic pancreaticoduodenectomy in 14%, and a total pancreatectomy in 4%. No patients underwent vein resection during pancreaticoduodenectomy. The intraoperative findings that prevented resection in 20 patients (out of 115 patients thought to be resectable preoperatively) are listed in Table 2. Eight patients were found to have liver metastases that were undetected by 3D-CT. All liver metastases were less than 1 cm in diameter. Multiple sites of metastases were present in three fourths of the patients with liver involvement. Peritoneal implants were not found in any patient; therefore only 7% of patients had undetected systemic metastases. Patients who were unresectable because of SMV/PV or SMA invasion were those that the surgeon thought would have positive margins even with major vein resection.

The decision to perform exploratory surgery in a patient with a suspected periampullary neoplasm depended heavily, but not exclusively, on the preoperative 3D-CT findings.[17,20] In general, our surgical philosophy is to explore all patients with suspected periampullary cancer unless clear evidence of unresectability is present. Twenty-three patients with highly suspicious, albeit nondefinitive, 3D-CT criteria for unresectability, therefore had exploratory operations (20% of 115 patients). Of the 23 patients who had exploratory operations with equivocal 3D-CT findings, 18 (78%) were found to have unresectable disease. However, five of these patients with equivocal 3D-CT findings of unresectability were resected with negative gross margins. Table 3 indicates the sensitivity, specificity, and predictive values of 3D-CT, when used alone, for unresectable periampullary cancer. The negative predictive value reflects the ability of 3D-CT to predict a resectable periampullary neoplasm.

Table 2. Reasons for tumor unresectability in patients undergoing preoperative 3D-CT

	No. of patients
SMV/PV invasion	8 (40%)
Liver metastasis	8 (40%)
SMA invasion	2 (10%)
Root of mesentery invasion	2 (10%)
Total unresectable cases	20
Total resectable cases	95 (83%)
Total exploratory operations for periampullary cancer	115

SMA = superior mesenteric artery; SMV = superior mesenteric vein; PV = portal vein

Table 3. Accuracy of 3D-CT to assess periampullary tumors

	Unresectable periampullary cancer (%)	Margin-positive resection (%)
Sensitivity	90	54
Specificity	95	93
PPV	78	72
NPV	98	86
Overall accuracy	94	83

NPV (negative predictive value) predicts a resectable/margin-negative periampullary neoplasm; PPV (positive predictive value) predicts an unresectable/margin-positive periampullary neoplasm.

Margin-Negative Resectability

Ninety-five of the 115 patients (83%) with periampullary neoplasms were resected without residual gross disease (Table 4). If the 23 patients with equivocal 3D-CT findings of unresectability were excluded, the resectability rate for patients with periampullary cancers would have been 98%. However, 5 (22%) of these 23 excluded patients would have been denied an opportunity for curative resection. Within the resected group, results of final histopathologic examination revealed microscopically positive resection margins in 24 patients (25%). Eighty-eight percent of these margin-positive tumors had involvement of the celiac (hepatic) or superior mesenteric vessels. As shown in Table 4, the rate of margin-positive resections increased for patients with pancreatic adenocarcinoma, albeit nonsignificantly. Of the 67 resected pancreatic adenocarcinomas, 18 (27%) were associated with positive margins. In comparison, a positive margin was found in 6 (21%) of the 28 nonpancreatic periampullary cancers ($P = 0.61$). As a single modality, 3D-CT was 86% accurate in predicting a margin-negative resection for periampullary neoplasms (negative predictive value; see Table 3) but was less accurate for

Table 4. Resectability of periampullary tumors among patients undergoing 3D-CT

	Periampullary neoplasms[†]	Pancreatic adenocarcinomas
Resectability	95 (83%)	67 (79%)
Margin-negative resectability*	71 (75%)	49 (73%)
Total exploratory operations	115	85

* Among resectable cases only.
† Periampullary neoplasms include primary tumors of the pancreas, common bile duct, ampulla, and duodenum.

predicting a margin-negative resection for pancreatic adenocarcinoma (83%, P = NS). 3D-CT predicted a margin-positive resection for 7 of the 18 patients with pancreatic cancer who ended up with a positive margin, typically involving the uncinate/retroperitoneal margin. The radiologist predicted a margin-negative resection based on the presence of a clear tissue plane between the neoplasm and the SMA, and non-circumferential involvement of the SMV-PV confluence. The overall features of the neoplasm, including size, density, location, or adjacent tissue invasion, did not contribute to the radiologist's opinion regarding the likelihood for margin-negative resectability.

Positive lymph nodes were confirmed by pathologic examination in 53% of all periampullary cancers; however, 3D-CT detected enlarged lymph nodes (≥5 mm) in only 13 (21%) of 61 patients with lymph node–positive cancers. Although preoperative 3D-CT suggested lymph node involvement in 25 of the 115 patients with suspected periampullary cancer, lymph node positivity was confirmed pathologically in only 16 (64%) of these 25 patients. Furthermore, lymphadenopathy on 3D-CT was associated with eventual unresectability in only 11 of 20 patients.

Three-Dimensional CT Detection of Vascular Involvement

A major benefit of 3D-CT is its enhanced assessment of tumor invasion into local mesenteric vessels. For this study, tumor involvement of the SMV, PV, SMA, and celiac axis was assessed during exploratory laparotomy and compared to preoperative 3D-CT findings that were recorded prospectively. The surgeon's determination of vascular involvement was based predominantly on gross intraoperative findings that were not necessarily confirmed with biopsy. The assessment of vascular involvement at the time of the operation was made irrespective of the preoperative 3D-CT findings. The sensitivity, specificity, and predictive values of 3D-CT in detecting tumor involvement of the major splanchnic vessels are listed in Table 5. Vascular invasion of the SMV, PV, or SMV-PV confluence were grouped together to simplify the analysis. Fifty-three patients were thought by the surgeon at the time of operation to have vascular invasion of the SMV/PV, and 3D-CT findings were consistent with the surgeon's operative assessment of vascular invasion in 45 (86%) of these 53 patients. Even though resection was precluded in only 8 of these 53 patients, 24 (out of these 53) patients were resected with microscopically positive margins. Five patients (out of 115 with periampullary cancer), thought to have SMV/PV involvement on 3D-CT, did not have vascular invasion during operative exploration. Fig. 1 illustrates the 3D-CT findings for a pancreatic neoplasm encroaching on the SMV but without direct vascular invasion. During laparotomy, 22 patients were judged to have minimal gross tumor involvement of the SMA. Even though resection was precluded in only 2 of these 22 patients, a positive resection margin was present in 11 of the final surgical specimens from the remaining 20 patients. Based only on the surgeons' assessment of SMA involvement in the resectable patients, 3D-CT was a sensitive modality for detecting this minimal SMA invasion (Fig. 2 and Table 5). Likewise, 3D-CT detected involvement of the celiac axis in 13 (87%) of 15 patients with positive intraoperative findings. Not surprisingly, 21 (88%) of the 24 resectable patients with positive margins had intraoperative findings of celiac or mesenteric vessel invasion. Overall, the accuracy of 3D-CT for determining the presence or absence of local vascular invasion was greater than 90%.

Table 5. Detection of vascular involvement with tumor by 3D-CT

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)
SMV/PV	85	95	90	92	90
SMA	86	97	83	98	95
Celiac axis	87	99	93	98	98

SMV/PV = superior mesenteric vein/portal vein; SMA = superior mesenteric artery; PPV = positive predictive value; NPV = negative predictive value.

Three-Dimensional CT Detection of Arterial Anomalies

Variations of hepatic artery anatomy occur in approximately 10% to 20% of patients undergoing pancreaticoduodenectomy. In addition to detecting tumor invasion of the major mesenteric vessels, 3D-CT can accurately map out anomalous anatomy involving the hepatic artery and celiac axis (Fig. 3). In this study, anomalous hepatic arteries were detected by 3D-CT in 19 patients and included 15 replaced right hepatic arteries originating from the SMA and four replaced left hepatic arteries off the left gastric. The 3D-CT maps of hepatic artery variations were confirmed in all 19 patients, whereas no variations in hepatic artery or celiac axis anatomy were detected in the remaining 121 patients in this study. The overall accuracy of 3D-CT for arterial anomalies was 100%.

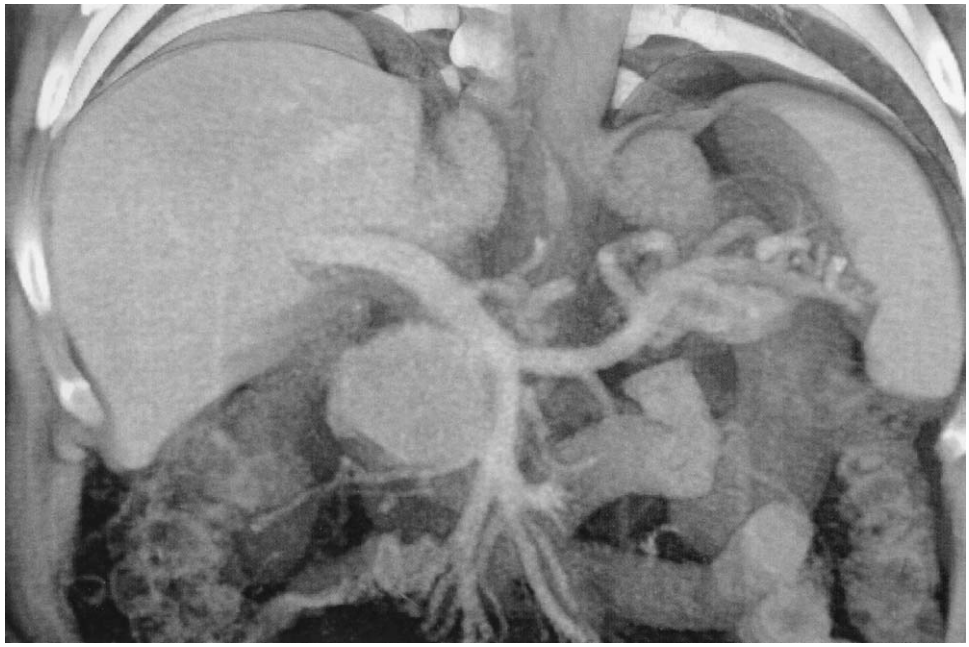

Fig. 1. Three-dimensional axial oblique reconstruction shows a low-density mass within the head of the pancreas that abuts but does not encase the superior mesenteric vein or portal vein. The vessels appear patent with no evidence of displacement. This pancreatic adenocarcinoma was resected without the need for partial superior mesenteric vein or portal vein resection.

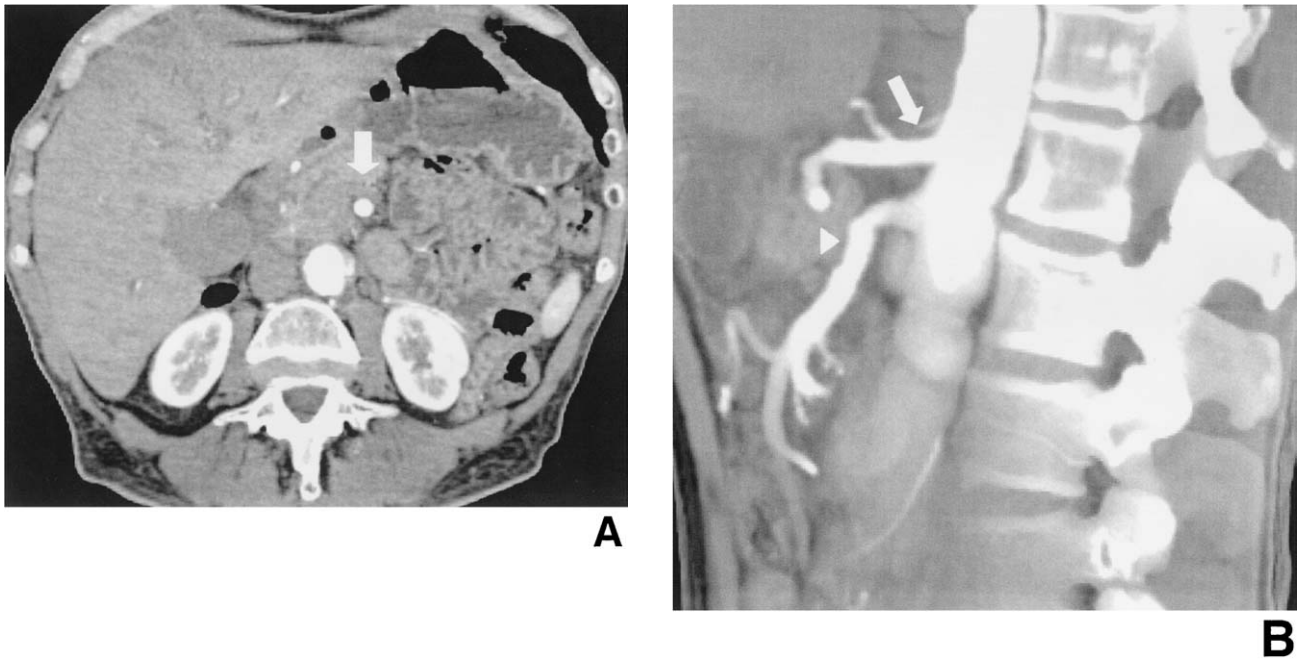

Fig. 2. A, Axial CT shows a 3 cm mass arising from the head of the pancreas. Arterial-phase axial images demonstrate loss of the periarterial plane over 90 degrees of the superior mesenteric artery (SMA) (*arrow*). SMA displacement is also present. **B**, Sagittal 3D-CT image confirms the intimate relationship of the pancreatic mass (*arrowhead*) with the SMA; however, the vessel remains completely patent. The mass does not involve the origin of the celiac axis (*arrow*). This patient underwent a margin-negative resection for pancreatic adenocarcinoma.

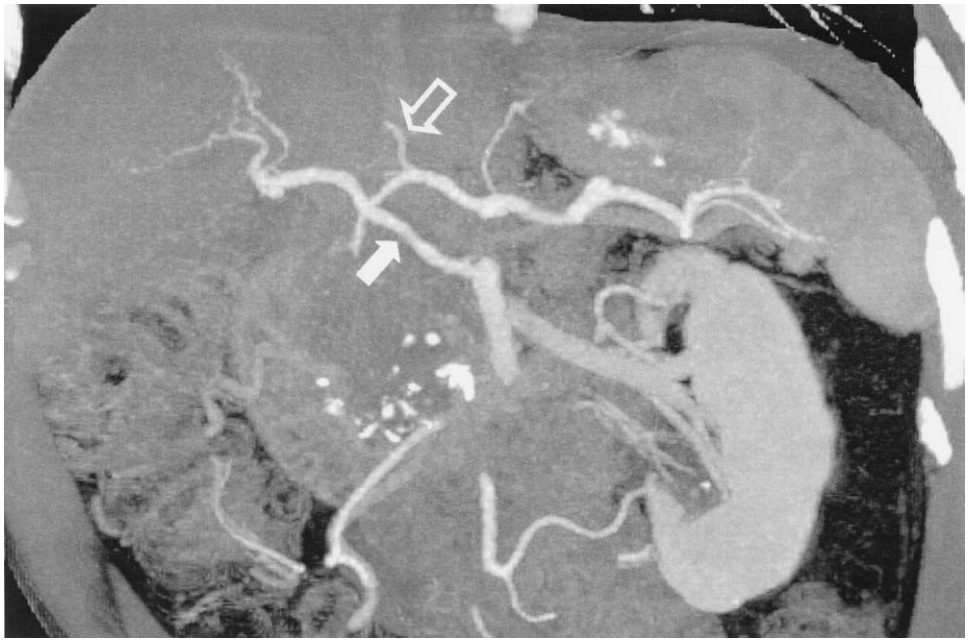

Fig. 3. A replaced right hepatic artery (*arrow*) arising off the superior mesenteric artery is readily seen during the arterial phase of 3D-CT. The left hepatic artery (*open arrow*) arises from the common hepatic artery off the celiac axis.

DISCUSSION

In this single-institution prospective study, 3D-CT was an accurate predictor of resectability for periampullary neoplasms. In the group of 92 patients with periampullary cancer who had 3D-CT scans that were interpreted unequivocally as showing resectability, resection was accomplished in 98%, whereas 22% of 23 patients with nondefinitive 3D-CT criteria of unresectability were resected. Perhaps more important, 3D-CT was an accurate predictor of a margin-negative resection for pancreatic cancer. 3D-CT predicted a margin-negative resection in 86% of patients with pancreatic adenocarcinoma. These results are superior to those from previous studies that reported predictive values for spiral CT for tumor resectability between 70% and 80%.[5,8,20] This apparent superiority of 3D-CT to predict tumor resectability is primarily due to its enhanced assessment of local vascular involvement compared to conventional spiral CT techniques.[11] In all of the patients who underwent preoperative 3D-CT and had exploratory operations, tumor involvement of the SMV, PV, SMV-PV confluence, or SMA was accurately assessed by 3D-CT in more than 90% of patients. Even though CT findings contributed to the consideration for surgical exploration during preoperative evaluation, equivocal radiographic criteria for unresectability (including, near-complete SMV-PV encasement with preserved patency or questionable SMA invasion with partial loss of a discernable fat plane) did not independently commit patients to a nonoperative treatment course.[17,21] Because 3D-CT was not used as the sole factor for surgical exploration, there was a discrepancy between the calculated predictive values of 3D-CT for resectability and the actual resectability rate for patients who underwent 3D-CT. Also, the intraoperative discovery of small hepatic metastases that were not seen by 3D-CT accounted for 8 of the 20 unresectable patients. Despite acquisition of 3 mm sections, current multidetector CT techniques fail to confirm liver metastases on the order of 2 to 10 mm in diameter. The routine use of laparoscopy may have avoided laparotomy in these eight patients with liver metastases, and the application of endoscopic ultrasound could have further delineated vascular invasion in patients with equivocal 3D-CT findings. The benefit of further imaging modalities and minimally invasive exploration needs to be addressed for patients with borderline 3D-CT criteria for unresectability.

The selective use of laparoscopy and/or endoscopic ultrasound for complete preoperative staging of periampullary carcinoma remains controversial. Our institution does not employ either of these modalities routinely during the preoperative evaluation of patients with suspected periampullary cancer; however,

we recognize the experiences of other large-volume centers that have been able to detect either metastatic disease or vascular invasion in approximately one third of patients with neoplasms of the head of the pancreas.[22,23] Eight (40%) of the 20 unresectable patients in this series were found to have hepatic metastases that went undetected on preoperative CT with 3 mm sections. This incidence of metastatic disease compares to previous studies from our institution in that metastatic disease to the liver accounted for approximately 50% of unresectable patients.[24,25] Despite these results, we have found that diagnostic laparoscopy in our hands would preclude open exploratory operations in only 2% to 3% of patients with periampullary cancer.[24]

In the absence of other factors precluding operative intervention, it has been the practice of our department to explore patients with suspected periampullary masses and with marginal or equivocal findings for unresectability on CT.[17,21] As a result, only patients with clear, unequivocal radiographic evidence of tumor unresectability were excluded from this study. Some may argue that this study should have included patients who had definitive radiographic evidence of unresectability and underwent exploratory operations; however, our strict criteria for judging unresectability and ethical issues prohibited exploratory laparotomy except in rare patients undergoing operative palliation after failed nonoperative interventions or impending duodenal obstruction. Also, previous retrospective studies of CT assessment of periampullary cancer have not recognized frequent instances of CT overstaging that would have prevented patients, with potentially resectable disease, from undergoing surgical exploration.[7]

In summary, 3D-CT is an accurate predictor of resectability for periampullary neoplasms and can predict which patients, with suspected periampullary adenocarcinomas, will eventually go on to have a margin-negative resection and derive a significant survival benefit. 3D-CT should be introduced to the preoperative evaluation of periampullary lesions that demonstrate equivocal findings of unresectability on high-quality spiral CT. Because 3D-CT can be performed with only minimal added cost to conventional multidetector CT, it should be employed as the imaging modality of choice for patients with suspected periampullary neoplasms.

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Does "Clonal Progression" Relate to the Development of Intraductal Papillary Mucinous Tumors of the Pancreas?

Keita Wada, M.D., Tadahiro Takada, M.D., Hideki Yasuda, M.D., Hodaka Amano, M.D., Masahiro Yoshida, M.D., Maki Sugimoto, M.D., Hiroshi Irie, M.D.

Intraductal papillary mucinous tumors of the pancreas show a unique histologic feature in that the wide spectrum of intraductal epithelium is observed in the same pancreas. The aim of this study was to clarify whether or not the "clonal progression" relates to the development of this tumor. A total of 210 intraductal epithelium samples were microdissected from 23 resected specimens of intraductal papillary mucinous tumors of the pancreas, including nine carcinomas, five borderline tumors, and nine adenomas. After histologic grading (grades 1 to 4) of the individual epithelium, the K-*ras* point mutation and loss of heterozygosity in 9p21(*p16*) and 17p13(*p53*) were investigated. From the distribution of the K-*ras* point mutation of 210 microdissected specimens, an identical sequence of K-*ras* was demonstrated in the precursor lesions in most cases. K-*ras* mutation showed a single pattern, and the multiple or heterogeneous mutation pattern was not seen in this study. In the same ways, the distribution of loss of heterozygosity in 9p21(*p16*) and 17p13(*p53*) of 210 microdissected specimens was shown to be mostly clonal, without the presence of the genetic alterations. Such distributions of the identical genetic statuses in the precursor lesions are consistent with the presence of clonal progression during the development of this tumor. (J GASTROINTEST SURG 2004;8:289–296)

KEY WORDS: Intraductal papillary mucinous tumor of the pancreas, clonal progression, K-*ras*, loss of heterozygosity

Intraductal papillary mucinous tumor (IPMT) of the pancreas is a relatively new entity and an increasingly recognized disease. IPMT is a papillary neoplasm that proliferates and spreads mainly in the pancreatic ducts, and secretes copious quantities of a thick mucin that fills the main and/or branch pancreatic ducts, thereby causing dilatation of the pancreatic ducts. In 1982, Ohashi et al.[1] first described "mucin-producing pancreatic cancer," defined as a dilatation of the main pancreatic duct with filling defects on a pancreatogram and an extrusion of mucin through an enlarged papilla of Vater. IPMTs are currently subdivided into three groups: benign (adenoma), borderline tumors (moderate dysplasia), and malignant (carcinoma), based on the histology of the intraductal lesions as established by the World Health Organization (WHO) classification.[2] Histologically they are frequently recognized over a wide spectrum of the intraductal epithelium, including normal, hyperplasia, dysplasia, and carcinoma in the same pancreas. The histologic variety observed within the same pancreas is considered to represent some unique clinical features of this disease, such as slow growth and a less aggressive nature with a favorable prognosis after treatment.[3–6] Furthermore, this also implies "clonal progression" is associated with the development of this tumor.

From adenoma to carcinoma, clonal progression has been clearly demonstrated in colorectal tumorgenesis.[7] At each step the activation of an oncogene or the inactivation of a tumor suppressor gene in a cell results in a selective growth advantage and clonal expansion of the cell.[7] The histologic variety of IPMT is similarly an excellent system in which to search

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From the Departments of Surgery (K.W., T.T., H.Y., H.A., M.Y., M.S.) and Pathology (H.I.), Teikyo University School of Medicine, Tokyo, Japan.
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Reprint requests: Keita Wada M.D. (Cassel Crag #305), c/o Virginia Mason Properties, 1006 Spring Street, Seattle, Washington. e-mail: k_wada@pg8.so-net.ne.jp

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and study the genetic alterations involved in the development. Although there have been reports on genetic or epigenetic events during carcinogenesis in the various neoplasms, only a few reports have focused on the genetic mechanism of the development of IPMT.[8–24] Previous studies have shown that some genetic alterations are frequently seen in IPMT in the same way as the ordinary type of ductal carcinoma of the pancreas.[25–26] We also previously reported that the K-*ras* point mutation was frequently detected in IPMT, and the loss of heterozygosity (LOH) of *p16* and *p53* was more common in malignant IPMT than in benign IPMT.[27] Therefore investigation of the relationship between the morphology of individual intraductal epithelia that were seen in the identical pancreas and their genetic status enables us to understand the mechanism of the development of IPMT.

In this study we collected 210 intraductal epithelium samples, ranging from normal epithelium to invasive carcinoma tissue, from 23 IPMTs by microdissection; we then examined K-*ras* mutation and the LOH of *p16* and *p53* to elucidate whether or not "clonal progression" is involved in the development of IPMTs.

MATERIAL AND METHODS

Patients

Between February 1992 and December 2000, a total of 23 patients with IPMTs (14 men and 9 women; mean age 64.3 ± 13.5 years [range 28 to 83 years]) who underwent pancreatic resections at Teikyo University Hospital, Tokyo, were studied.

Histologic Grading

For pathologic diagnosis, 10% formalin-fixed resected specimens of the whole pancreas were cut into 4 to 5 mm stepwise tissue blocks along with the main pancreatic duct and embedded in paraffin. Then 3 μm sections were cut, deparaffinized, and stained with hematoxylin and eosin. All pathologic findings were reviewed and diagnosed according to the WHO classification.[2] Because a wide spectrum of the intraductal epithelium was seen in the same pancreas, we divided the individual epithelium into four grades (grades 1 to 4) according to the classification of PanIN.[28] Grades 1, 2, and 3 corresponded to PanIN-1, PanIN-2, and PanIN-3, respectively, and grade 4 was determined to be the epithelium obtained from the invasive area (Fig.1).

Tissue Sampling and DNA Extraction

Tissue sampling was performed by microdissection. Appropriate tissue blocks were selected, and multiple serial sections (10 μm thick) were cut, deparaffinized, and stained with hematoxylin and eosin and viewed with an inverted microscope. Under an operating microscope, microdissection was performed using a 26-gauge sterilized needle, taking particular care to avoid contamination as much as possible. The sampling specimens were digested for 16 hours at 50C in a 20 μl buffer, which contained 200 μg/ml proteinase K, 10 mmol/L Tris-HCl (pH 8.0), 1 mmol/L EDTA, and 1% Tween 20 and inactivated for 8 minutes at 95C. This lysate was then directly used as a template for following the polymerase chain reaction (PCR).

K-*ras* Mutation

K-*ras* mutation at codon 12 and 13 was detected by a direct sequencing method as described previously.[27] The PCR reaction mixture consisted of 2 μl of DNA lysate, 10 pmol of each of the primers (sense: 5′GAC TGAATATAAACTATTCG 3′, antisense: 5′CTC TATTGTTGGATCATATT 3′), 1 × PCR buffer (Takara; Ohtsu, Kyoto, Japan), 0.2 mmol/L of dNTP, 2.0 mmol/L of $MgCl_2$, and 1.25 U Ex Taq polymerase (Takara) in a 25 μl total volume solution. After the initial denaturing at 95C for 5 minutes, PCR was carried out for 40 cycles of amplification at 95C (30 seconds) for denaturing, 52C (45 seconds) for annealing, and 72C (45 seconds) for elongation, followed by final elongation at 72C for 8 minutes. The sequence of K-*ras* point mutation at codon 12 and 13 was determined by the dideoxy chain termination method, using the BigDye Terminator Cycle Sequencing FS Ready reaction kit (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. The products after cycle sequencing reaction were analyzed by using the ABI Prism 3700 DNA Analyzer (Applied Biosystems).

Loss of Heterozygosity

LOH in 9p21(*p16*) and 17p13(*p53*) was detected using fluorescence-labeled microsatellite markers D9S319 and D9S304 for 9p21(*p16*), and D17S919 and D17S786 for 17p13(*p53*). LOH analysis was performed with the use of the ABI Prism 3700 DNA Analyzer (Applied Biosystems) and Gene Scan software (Applied Biosystems), as previously reported.[27]

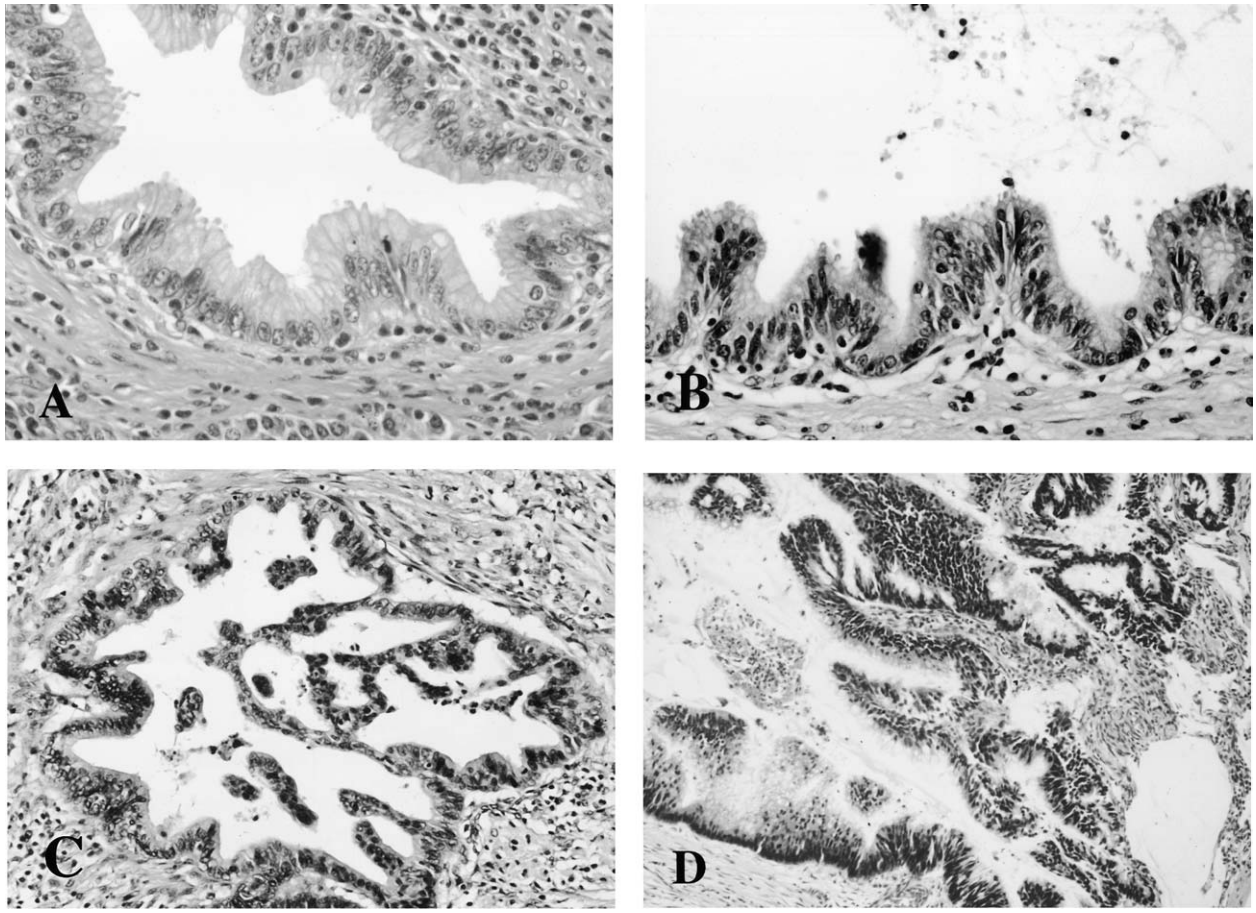

Fig. 1. Histologic grading of intraductal lesions in IPMT. **A**, Grade 1. Flat or papillary lesions consist of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are small and round to oval in shape without atypia (hematoxylin & eosin stain; ×40).These lesions are considered hyperplasia or adenoma. **B**, Grade 2. Flat or papillary mucinous epithelial lesions with some nuclear abnormalities, such as loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromatism (hematoxylin & eosin stain; ×100). These lesions are considered borderline malignancies. **C**, Grade 3. Papillary and micropapillary lesions with true cribriforming, budding off of small clusters of epithelial cells (hematoxylin & eosin stain; ×40). These lesions are considered severe dysplasia/carcinoma in situ. **D**, Grade 4. Invasive carcinoma (hematoxylin & eosin stain; ×40).

RESULTS

Histology of Intraductal Papillary Mucinous Tumors

Twenty-three IPMTs were diagnosed as nine carcinomas (6 invasive and 3 noninvasive), five borderline tumors, and nine adenomas as listed in Table 1. A total of 210 different epithelial lesions were microdissected from 23 pancreata (mean 9.1 lesions, range 3 to 13 lesions per pancreas) containing 42 normal epithelia, 92 grade 1 epithelia, 31 grade 2 epithelia, 25 grade 3 epithelia, and 20 grade 4 epithelia, respectively.

K-*ras* Mutation in Intraductal Papillary Mucinous Tumors

Fifteen (65.2%) of 23 cases of IPMT had K-*ras* mutation. All but one mutation were detected in codon 12, and the remaining mutation was detected in codon 13. The incidence of each subgroup was seven (77.8%) of nine carcinomas, four (80%) of five borderline tumors, and four (44.4%) of nine adenomas. The distribution of K-*ras* mutation of 210 microdissected specimens is shown in Table 2. All 15 cases of K-*ras* mutation showed a single pattern of the sequence in multiple samples obtained from the same pancreata; multiple or heterogeneous mutations were not seen in this study. All malignant and borderline cases had the identical mutation in the histologically less atypical epithelia that are considered to be the precursors. In 15 cases of K-*ras* mutation, the incidence was 31 (72.1%) of 43 grade 1 epithelia, 20 (83.3%) of 24 grade 2 epithelia, 19 (100%) of 19 grade 3 epithelia, and seven (87.5%) of eight grade 4

Table 1. Clinicopathologic data of intraductal papillary mucinous tumors

Patient	Age (yr)	Sex	Tumor location	Size of tumor (mm)	WHO classification	Follow-up (mo)	Clinical outcome
1	51	F	Head-body	Diffuse	Carcinoma	8	DOD
2	76	F	Head	45	Carcinoma	116	A
3	63	M	Head	7	Carcinoma	34	A
4	58	M	Head	50	Carcinoma	27	DOD
5	35	M	Head	35	Carcinoma	30	A
6	57	M	Head-body	Diffuse	Carcinoma	52	A
7	54	M	Head	36	Carcinoma	64	A
8	70	M	Head	24	Carcinoma	83	A
9	74	M	Body	55	Carcinoma	29	A
10	83	M	Head	20	Borderline	64	A
11	68	M	Head	34	Borderline	68	A
12	28	F	Body	40	Borderline	32	A
13	64	F	Body	30	Borderline	32	A
14	62	M	Head	23	Borderline	88	A
15	77	F	Head	7	Adenoma	1	DOO
16	76	M	Body	12	Adenoma	50	A
17	66	M	Tail	10	Adenoma	42	A
18	55	M	Head	35	Adenoma	87	A
19	70	F	Head	23	Adenoma	31	A
20	70	F	Head	21	Adenoma	28	A
21	80	F	Head	32	Adenoma	65	A
22	71	F	Head	11	Adenoma	56	A
23	72	M	Head	22	Adenoma	43	A

A = alive; DOD = died of disease; DOO = died of other disease.

epithelia, respectively (Table 3). None of the normal epithelia showed K-ras mutation.

Loss of Heterozygosity in 9p21(*p16*) and 17p13(*p53*) in Intraductal Papillary Mucinous Tumors

Eight (38.1%) of 21 informative cases had LOH in 9p21(*p16*). The incidence of each subgroup was six (75%) of eight carcinomas, one (20%) of five borderline tumors, and one (12.5%) of eight adenomas, respectively. The distribution of LOH in 9p21(*p16*) of 210 microdissected specimens is shown in Table 4. All five informative cases of invasive carcinoma had LOH. Among eight patients with LOH in 9p21(*p16*), six (Nos. 1, 2, 3, 5, 8, and 10) showed LOH in the precursor lesions, and the incidence of each histologic grade was 8 (80%) of 10 group 1 epithelia, 10 (83.3%) of 12 grade 2 epithelia, 15 (88.2%) of 17 group 3 epithelia, and 14 (77.8%) of 18 group 4 epithelia (see Table 3).

LOH in 17p13(*p53*) was only seen in all six cases of invasive carcinoma. The distribution is shown in the Table 5. Of six cases with LOH in 17p13, five showed LOH in the precursor lesions, and the incidence of each histologic grade was 0 (0%) of 7 grade 1 epithelia, five (100%) of five grade 2 epithelia, 11 (100%) of 11 grade 3 epithelia, and 20 (100%) of 20 grade 4 epithelia (see Table 3).

DISCUSSION

It has been known that some carcinomas arise from their precursor lesions as a result of the mutational activation of oncogenes coupled with the inactivation of tumor suppressor genes.[7] Boland et al.[29] reported that allelic losses appeared to be clonal throughout extensively dissected adenomas and carcinomas in colorectal neoplasms. The histology of IPMT is a characteristic that it is frequently recognized to be a wide spectrum of intraductal epithelium in the same pancreas. The histologic variety observed within the same pancreas indicates to us that the "hyperplasia-dysplasia-carcinoma sequence" in the development of this tumor is just like the "adenoma-carcinoma sequence" of colorectal neoplasms. Previously, to investigate the carcinogenesis of IPMT, several studies on the basis of extensive multifocal microdissection analysis using some genetic marker, such as K-*ras* mutation, allelic losses of the tumor suppressor genes, and X-chromosome linked clonality analysis, have been reported.[15,16,18,19,21–23] However, the fixed view concerning the mechanism of IPMT has not been ascertained.

Table 2. Distribution of histologic findings and K-ras mutation in 23 patients with intraductal papillary mucinous tumors

Patient	WHO classification	Histologic grade					K-ras mutation	
		Normal	1	2	3	4	Codon	Sequence
1	Carcinoma	0/2	1/1 (2)	2/2	4/4	2/2	12	GAT
2	Carcinoma	0/1		1/1	3/3 (1)	2/2	12	GAT
3	Carcinoma	0/2	0/1	1/2	1/1	1/3 (1)	12	GAT
4	Carcinoma	0/5	0/3			0/5	wt	wt
5	Carcinoma	0/2			0/1	0/4 (1)	wt	wt
6	Carcinoma	0/1 (1)	0/2 (3)		1/1 (1)	1/1 (1)	12	GAT
7	Carcinoma	0/2	3/3	3/3	3/3		12	GAT
8	Carcinoma	0/2 (1)		1/1 (1)	5/5 (3)		13	GAC
9	Carcinoma	0/3	5/5 (1)	4/4	2/2		12	GTT
10	Borderline	0/2	2/4	2/3 (2)			12	GTT
11	Borderline	0/1	6/10	2/4			12	TGT
12	Borderline	0/1	3/4 (6)	1/1			12	CGT
13	Borderline	0/1	1/1 (1)	1/1			12	TGT
14	Borderline	0/2	0/7	0/4			wt	wt
15	Adenoma	0/2	0/2 (1)				wt	wt
16	Adenoma	0/2	2/3				12	GTT
17	Adenoma	0/2	3/3				12	GTT
18	Adenoma	0/1	3/3 (1)				12	GAT
19	Adenoma	0/1	2/3 (1)				12	GAT
20	Adenoma	0/1	0/12				wt	wt
21	Adenoma	0/1 (1)	0/2 (2)				wt	wt
22	Adenoma	0/1	0/3				wt	wt
23	Adenoma	0/1	0/2				wt	wt

No. of positive samples/No. of samples examined (not detectable); wt = wild type; shaded areas indicate mutation-positive site: (group 1 = hyperplasia-adenoma; group 2 = dysplasia; group 3 = noninvasive carcinoma; group 4 = invasive carcinoma).

K-*ras* mutation has been frequently sighted as a genetic marker because of the high incidence of the mutation in IPMTs, approximately 60% to 80%.[8–15] In the present study the distribution of K-*ras* mutation showed a single mutation in all cases, and multiple mutations were not seen in this study. In addition, it showed a homogeneous clonal pattern that is the same identical K-*ras* status that is seen in grade 1 and 2 epithelia that are considered as precursor lesions, which is compatible with previous reports.[15,23] However, some reports pointed out the presence of the multiple distinct mutations of K-*ras* in 20% to 64% of patients with IPMTs evaluated by PCR and restriction fragment length polymorphism (RFLP) analysis.[21,22] In our experience the use of an enzyme to enhance the mutated allele, restriction fragment length polymorphism, proved more difficult for obtaining reproducible results of the sequence of K-*ras* mutation (data not shown), which is also pointed out by Z'graggen et al.[15] In the present study the PCR following the direct sequence method was employed to detect K-*ras* point mutation because this method is considered to result in a naive genetic status in each sample that was obtained by microdissection. Although the high incidence of the mutation itself and

Table 3. Incidence of genetic alterations of each epithelium in cases with genetic alterations

Genetic alterations	Histologic grade			
	1	2	3	4
K-*ras* mutation	31/43 (72.1)	20/24 (83.3)	19/19 (100)	7/8 (87.5)
LOH in 9p21(*p16*)	8/10 (80)	10/12 (83.3)	15/17 (88.2)	14/18 (77.8)
LOH in 17p13(*p53*)	0/7 (0)	5/5 (100)	11/11 (100)	20/20 (100)

No. of positive samples/No. of samples examined (%); LOH = loss of heterozygosity.

Table 4. Distribution of histologic findings and loss of heterozygosity in 9p21(*p16*) in 23 patients with intraductal papillary mucinous tumors

Patient	WHO classification	Histologic grade				
		Normal	1	2	3	4
1	Carcinoma	0/2	2/2 (1)	2/2	3/3 (1)	1/2
2	Carcinoma	0/1		1/1	4/4	2/2
3	Carcinoma	0/1 (1)	0/1	1/2	1/1	4/4
4	Carcinoma	0/5	0/3			5/5
5	Carcinoma	0/2			1/1	2/5
6	Carcinoma	NI (2)	NI (5)		NI (2)	NI (2)
7	Carcinoma	0/2	0/3	0/3	0/3	
8	Carcinoma	0/3		1/2	6/8	
9	Carcinoma	0/3	0/6	0/4	0/2	
10	Borderline	0/2	4/4	5/5		
11	Borderline	0/1	0/10	0/4		
12	Borderline	0/1	0/10	0/1		
13	Borderline	0/1	0/2	0/3		
14	Borderline	0/2	0/7	0/4		
15	Adenoma	0/2	2/3			
16	Adenoma	0/2	0/3			
17	Adenoma	NI (2)	NI (3)			
18	Adenoma	0/1	0/4			
19	Adenoma	0/1	0/4			
20	Adenoma	0/1	0/12			
21	Adenoma	0/2	0/4			
22	Adenoma	0/1	0/3			
23	Adenoma	0/1	0/2			

No. of LOH samples/No. of samples (not detectable); NI = not informative; shaded area indicates LOH-positive site: group 1 = hyperplasia-adenoma; group 2 = dysplasia; group 3 = noninvasive carcinoma; group 4 = invasive carcinoma.

the homogeneous K-*ras* status with or without mutation in grade 1 and 2 epithelium indicate K-*ras* mutation would be an early genetic event in the development of IPMT, the role of this mutation remains unclear because it has been suggested that only a small fraction of hyperplastic lesions with mutated K-*ras* progress to carcinoma (<1%).[9,30] In our opinion, K-*ras* mutation would play only a limited role in the neoplastic transformation rather than carcinogenesis or malignant evolution in the development of IPMTs, because the incidence of K-*ras* mutations in grade 1 and 2 epithelia in cases of K-*ras* mutation already showed rates of 72.1% and 83.3%, respectively, which is almost equivalent to the incidence in grade 3 and 4 epithelia, 100% and 87.5%, respectively. Also, because all carcinomas and borderline cases did not always show K-*ras* mutation, the role of K-*ras* mutation might differ from one tumor to another. Nevertheless, K-*ras* mutation would be a key event leading to subsequent genetic alterations, including inactivation of the *p16* and *p53*, in the development of IPMTs.

The incidence of LOH in 9p21(*p16*) was increasingly seen according to the degree of histologic abnormality, from 12.5% in adenomas to 75% in carcinomas, which is compatible with other previous reports.[16,24] On the other hand, LOH in 17p13(*p53*) was seen only in invasive carcinomas at 100% incidence, and all cases with LOH in 17p13(*p53*) were concomitant with LOH in 9p21(*p16*). Sakai et al.[18] also reported that no LOH in the *p53* gene was detected in adenomas and borderline tumors or IPMTs, whereas it was frequently observed in carcinomas (3 of 5 cases), and other previous reports have shown similar results according to immunohistochemistry and mutation analysis.[12,19] In the present study the distribution of LOH in 9p21(*p16*) and 17p13(*p53*) was in a homogeneous and clonal pattern, findings that are similar to the distribution of K-*ras* mutation. However, the incidence of LOH in 9p21(*p16*) and 17p13(*p53*) in precursor lesions revealed different aspects for both. LOH in 9p21(*p16*) was seen in grade 1 epithelia with a high incidence (80% in grade 1 epithelia), which is similar to the K-*ras* mutation results, whereas the LOH of 17p13(*p53*) was not present in grade 1 epithelia but was present in grade 2 epithelia with a 100% incidence. These results suggest that LOH in 9p21(*p16*) is a candidate early genetic event in the development of IPMTs, whereas LOH in 17p13(*p53*) should be considered a later genetic event

Table 5. Distribution of histologic findings and loss of heterozygosity in 17p13(*p53*) in 23 patients with intraductal papillary mucinous tumors

Patient	WHO classification	Histologic grade				
		Normal	1	2	3	4
1	Carcinoma	0/2	0/1 (2)	2/2	4/4	2/2
2	Carcinoma	0/1		1/1	4/4	2/2
3	Carcinoma	0/1 (1)	0/0 (1)	2/2	1/1	4/4
4	Carcinoma	0/5	0/3			5/5
5	Carcinoma	0/2			1/1	5/5
6	Carcinoma	0/2	0/3 (2)		1/1 (1)	2/2
7	Carcinoma	0/2	0/3	0/3	0/2 (1)	
8	Carcinoma	0/3		0/2	0/8	
9	Carcinoma	0/2	0/8	0/3	0/2	
10	Borderline	0/2	0/4	0/5		
11	Borderline	0/1	0/9 (1)	0/4		
12	Borderline	0/1	0/10	0/1		
13	Borderline	0/1	0/2	0/3		
14	Borderline	0/2	0/7	0/4		
15	Adenoma	0/2	0/3			
16	Adenoma	0/1 (1)	0/3			
17	Adenoma	0/2	0/3			
18	Adenoma	NI (1)	NI (4)			
19	Adenoma	0/1	0/4			
20	Adenoma	0/1	0/12			
21	Adenoma	0/2	0/4			
22	Adenoma	0/1	0/1 (2)			
23	Adenoma	0/1	0/2			

No. of LOH samples/No. of samples (not detectable); NI = not informative; shaded area indicates LOH-positive site: group 1 = hyperplasia-adenoma; group 2 = dysplasia; group 3 = noninvasive carcinoma; group 4 = invasive carcinoma.

than K-*ras* mutation and LOH in 9p21(*p16*), and LOH in 17p13(*p53*) could very well be an important genetic event in the malignant evolution of IPMTs. This is very important in clinical applications because if it is possible to detect LOH in 17p13(*p53*) in the clinical materials, including pancreatic juice and biopsy samples, it would yield useful prognostic information such as diagnosis of tumor malignancy and allow for better decision making in choosing treatment procedures.

CONCLUSION

The present study of extensive multifocal microdissection analysis using three genetic markers, K-*ras* mutation and LOH in 9p21(*p16*) and 17p13(*p53*), clearly demonstrated the homogeneous genetic background and clonal expansion during the development from adenoma to carcinoma. These results are consistent with the hypothesis that clonal progression relates to the development of intraductal papillary mucinous tumors of the pancreas. However, the genetic background behind the actual tumor development remains unclear and it may well differ from one tumor to another.

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Introduction

Steven M. Strasberg, M.D., President, American Hepato-Pancreato-Biliary Association

Each year since 1994, the American Hepato-Pancreato-Biliary Association (AHPBA) has met in conjunction with the American Association for the Study of Liver Diseases (AASLD) at the Annual Meeting of the AASLD held in November. The first of these meetings took place in 1994 and this meeting took place on November 2, 2002, in Boston, Massachusetts.

The forum was held as a three mini-symposia. These have now been gathered into publications that follow. The first of these three papers deals with protection of the liver in hepatic surgery and was organized by Pierre Clavien of the University of Zurich, Switzerland. This important topic is explored in considerable detail and should be of great interest to readers of the Journal. The second symposium on live donor liver transplantation was lead by Myron Schwartz of the Mount Sinai Hospital in New York City. The manuscript that follows is a thorough analysis of important problems in this rapidly evolving technique. Theodore Pappas and Brian Clary of Duke University Medical Center in North Carolina were responsible for organizing the third section, which focused on cholangiocarcinoma. Their paper summarizes specific aspects of management of this interesting and often very curable tumor.

A listing of the individual participants is beyond the scope of this introduction. However, it is not an overstatement to say that the authors are an international "who's who" of liver and biliary tract surgeons. The conference was extremely well attended with over three-hundred fifty individuals focused in this area of surgery and the related area of medicine in the audience. Readers of the Journal will find all three manuscripts of great interest.

Presented at 2002 AHPBA/AASLD Surgical Forum, Boston, MA, November, 2002.

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Hilar Cholangiocarcinoma

Bryan Clary, M.D., William Jarnigan, M.D., Henry Pitt, M.D., Gregory Gores, M.D., Ronald Busuttil, M.D., Theodore Pappas, M.D.

Cancer of the biliary tree, including those occurring at the major biliary bifurcation (Klatskin's tumor), is an uncommon malignancy. Meaningful experience with these tumors has been limited to a few centers. Recent reports with increasing numbers of patients have allowed the construction of rational approaches to these patients. It is clear from these reports that complete resection with negative histologic margins is the only treatment that offers the possibility of long-term survival. Complete resection of hilar cholangiocarcinomas remains a technically demanding procedure requiring expertise in biliary and hepatic surgery. Patients with unresectable disease constitute a distinct majority and have traditionally been very difficult to successfully palliate and impossible to cure. A panel of hepatobiliary surgeons experienced in the management of hilar cholangiocarcinoma presented a symposium on issues relating to these patients at the recent joint American Hepato-Pancreato-Biliary Association/American Association for the Study of Liver Diseases (AHPBA-AASLD) forum in Boston, MA. The report below offers a summarization of the main points and comments raised by this panel. These summarizations are not meant as an exhaustive review and primarily reflect the opinions of the speakers based upon their experiences and interpretation of the existing literature. (J GASTROINTEST SURG 2004;8:298–302)

KEY WORDS: Cholangiocarcinoma, Klatskin's tumor

PREOPERATIVE IMAGING AND STAGING OF CHOLANGIOCARCINOMA

Discussion by William Jarnagin, M.D.

The identification and proper selection of patients with hilar cholangiocarcinoma for surgical therapy requires an understanding of several important anatomic and histologic features. Hilar cholangiocarcinomas represent approximately 50%–60% of cholangiocarcinomas. Over 90% are adenocarcinoma in histology and although most express CEA and CA19-9, serum levels are of limited clinical value. Submucosal spread extending from 1–2 cm beyond the radiographic abnormality is a common feature with implications on the site of duct transection of curative resection. The majority of hilar cholangiocarcinomas exhibit a nodular-sclerosing pattern with annular thickening of the duct and longitudinal and radial infiltration resulting in stricturing and contracture of the duct. A minority of these tumors are papillary and can reach enormous sizes, yet be attached to only a small portion of the wall. Given their growth pattern, papillary tumors expand rather than contract the duct. Despite their significant size, these can often be resected. The intimacy of the caudate lobe to the hilum is important to appreciate. The main duct draining the caudate lobe enters into the left hepatic duct and, as such, is commonly involved in cholangiocarcinomas involving the left duct. Drainage of the caudate process commonly occurs via a small duct draining into the main right hepatic duct. Extension of a hilar cholangiocarcinoma into the caudate ducts is common and has implications for its removal during curative attempts at resection. Extension beyond the primary bifurcation to the secondary hepatic radicles is common leading to the frequent need for concomitant hepatic resection for complete resection. Portal vein involvement is also a common finding in patients with hilar cholangiocarcinoma with unilateral encasement leading to ipsilateral atrophy.

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From the Department of Surgery, Duke University Medical Center, Durham, North Carolina (B.C., T.P.); Memorial Sloan-Kettering Cancer Center, New York, NY (W.J.); Medical College of Wisconsin, Milwaukee, Wisconsin (H.P.); Mayo Clinic, Rochester, Minnesota (G.G.); and University of California at Los Angeles, Los Angeles, California (R.B.).
Reprint requests: Bryan Clary, M.D., Box 3247, Duke University Medical Center, Durham, NC 27710. e-mail: clary001@mc.duke.edu

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As the likelihood of long-term survival is highly associated with a margin-negative resection, the preoperative imaging studies should be directed toward describing the extent of disease and those technical details as they relate to the planned operation. Classically described contraindications to resection aside from medical contraindications include extension into the secondary biliary radicles, ipsilateral secondary biliary radicle involvement with contralateral portal vein involvement and/or atrophy, encasement of the main portal vein and/or common hepatic artery, and distant metastases including nodal disease outside the field of a portal lymphadenectomy.

Preoperative imaging studies are thus directed to demonstrating these contraindications when possible. Alternative diagnoses should also be sought after in the preoperative imaging. Of 161 patients with presumed hilar cholangiocarcinoma evaluated at Memorial Sloan Kettering from 1996–2000, 28 patients ultimately had other diagnoses including gallbladder cancer (14 patients), benign stricture (9 patients), and metastatic disease from an alternative primary (2 patients). At Memorial Sloan Kettering, the preferred evaluation consists of magnetic resonance cholangiopancreateography (MRCP) and duplex ultrasound avoiding preoperative biliary instrumentation except in those patients with cholangitis or in those patients not likely to undergo an exploration in a timely fashion. Preoperative instrumentation of the biliary tree can lead to increased inflammation, biliary tree injury, pancreatitis, tumor seeding of the tract, and more frequent infectious complications in those patients undergoing curative resection. In institutions where magnetic resonance cholangiopancreatography (MRCP) is routinely performed, anatomic information equivalent to cholangiography is possible without instrumentation. Magnetic resonance imaging (MRI) is also useful in demonstrating atrophy/vascular involvement and intraabdominal metastases. Duplex ultrasonography is highly operator dependent, but in appropriate hands is capable of complementing the MRI in identifying the extent of biliary and vascular involvement. In centers where preoperative biliary drainage is routinely employed, percutaneous cholangiography (PTC) is excellent in defining the extent of biliary involvement. In these centers, computed tomography (CT) imaging readily compliments the PTC in the issues of metastases and vascular/atrophy. Arteriography is rarely indicated in assessing for possible vascular encasement given the quality of MRI and CT in the current era.

Despite excellent preoperative imaging, approximately 10%–20% of patients will be found at exploration to have metastatic disease that prohibits a curative resection. For this reason, laparoscopy is routinely employed at the time of intended curative resection. Recent data have suggested that fluorodeoxyglucose positron emission tomography (18FDG-PET) identifies otherwise metastatic disease in half of those patients harboring occult distant disease, but is relatively insensitive in demonstrating the primary lesion. Additionally, benign hilar strictures have been shown to be PET-avid.

The ability to predict the presence of occult metastatic disease on the basis of primary tumor extent and thereby allow a selective application of laparoscopy is well established. The American Joint Commission on Cancer (AJCC) system, which largely relies on histopathologic data, has limited clinical applicability to the preoperative evaluation. The Bismuth–Corlette staging system of biliary extent and, more recently, a staging system proposed by Blumgart and colleagues that incorporates biliary extent, vascular involvement, and atrophy are able to identify a subset of individuals at greater risk for occult metastatic disease. According to the Blumgart staging system, the yield of laparoscopy increases from 9% in T1 patients (tumor involving confluence, no atrophy or vascular involvement) to 36% in patients with T2 (unilateral secondary radicle involvement with ipsilateral vascular involvement or atrophy) and T3 (bilateral secondary radicle involvement, main portal vein involvement, or unilateral secondary radicle involvement with contralateral atrophy or vascular involvement).

SURGICAL RESECTION FOR HILAR CHOLANGIOCARCINOMA

Discussion by Bryan Clary, M.D.

The goals for surgical resection include a complete oncologic resection with preservation of a sufficient liver remnant and, in addition, the palliative relief of biliary obstruction. The contraindications to resection include medical comorbidities, distant metastatic disease, and a number of regional situations where complete resection is not possible whereas leaving an adequate liver remnant (bilateral extensive intrahepatic extension, a combination of extensive intrahepatic extension with contralateral vascular involvement or atrophy, main portal vein involvement).

An astute appreciation of the variants in biliary drainage is a prerequisite in the planning of a curative resection. Approximately two-thirds of patients harbor a variant of normal biliary anatomy whereby the right posterior sectoral duct enters into the left hepatic duct. Another common variant is an early takeoff of the posterior sectoral duct with the "bifurcation" occurring at the junction of the right anterior

sectoral and main left duct. In both of these anomalous situations, "bilateral secondary radicle involvement" may actually be resectable. If the secondary branching points are located very close to the bifurcation, resection may still be technically feasible even when taking into account the fact that tumor extension is typically 5–10 mm beyond the radiographic stricture. For example, involvement of an aberrant posterior sectoral duct arising from the left hepatic duct in conjunction with extensive disease with the left hepatic duct while technically "bilateral secondary radicle involvement" is often resectable as one can come across the anterior sectoral and posterior sectoral pedicles independently without extending deeply within the liver parenchyma. Given these issues, an excellent cholangiogram is a prerequisite to preoperative planning and to minimizing unnecessary explorations. Although some centers have been able to reliably identify these issues with MRCP, most rely upon either PTC or endoscopic retrograde cholangiopancreatography (ERCP) for this information. At Duke University Medical Center, PTC is routinely employed as a means of obtaining this information (as well as accomplishing preoperative biliary drainage).

The conduct of a curative operation involves a series of steps and begins with a thorough exploration of the peritoneal cavity. Laparoscopy is routinely employed as the first step although for patients without atrophy or vascular involvement (Blumgart T1) the yield is likely below 10%–15%. After assessing for possible distant peritoneal, hepatic, or nodal disease attention is then turned to the primary lesion. By palpation a general sense of the local extent is made. This manual assessment is not meant to supplant the preoperative cholangiography, but a recognition of advanced lesions that were not fully appreciated on the preoperative MRI or CT is often possible. If felt to be resectable on the basis of this exploration, the common bile duct is then isolated just above the pancreas and transected. A biopsy is then sent for frozen section to determine the presence or absence of tumor at this distal bile duct margin. As most patients are not appropriate for a combined pancreaticoduodenectomy/liver resection, a positive margin at this point precludes a curative operation and a palliative approach is then undertaken (see Dr. Pitt's discussion). In the event that this margin is negative, the common bile duct along with the lymphatic and adipose tissues of the duodenal hepatic ligament are then reflected superiorly and anteriorly, skeletonizing the portal vein and hepatic artery. As one proceeds in the plane superiorly along the anterior surface of the portal vein, identification of occult vascular involvement is sought. Ipsilateral vein involvement is not a contraindication to curative resection even when requiring resection of a short segment of the main portal vein, as this can be reconstructed primarily or in some instances with an interposition vein graft. Once the dissection reaches the level of the portal vein bifurcation, the contralateral main duct is transected and the margin is assessed by frozen section. In the event of a negative margin, the contralateral hemiliver and caudate are prepared for resection. The contralateral hemiliver is completely mobilized from the diaphragm and the small venous tributaries extending from the caudate directly into the inferior cava taken. The ipsilateral hepatic vein (right or common left/middle) is then isolated outside the liver. At this time the ipsilateral portal vein and hepatic artery are taken with a vascular stapler or suture ligature followed immediately thereafter by taking the ipsilateral hepatic vein. A parenchymal transection then ensues accomplished by a variety of different techniques. A Roux limb is then constructed and anastomosed to the open remaining hepatic duct(s). In a minority of cases, resection of the bile duct alone with or without the caudate lobe is sufficient for tumor clearance.

The role of preoperative stenting is controversial. It is generally accepted that preoperative biliary instrumentation is associated with an increase in the bile colonization rate and an increase in perioperative infectious complications, although mortality is not increased. Three randomized studies were conducted in the 1970s and 1980s on the topic of preoperative stenting. These studies have limited clinical applicability to the current era, as the morbidity rate of the drainage procedure and other technical advances have greatly improved the surgical outcomes of these patients. Most surgeons will agree that those patients with renal impairment, cholangitis, or significant pruritis (where an operation cannot be scheduled in a timely fashion) should undergo preoperative drainage. Although direct comparisons of endoscopic vs. percutaneous drainage do not readily exist, the standard approach at Duke University Medical Center is for percutaneous drainage, as the quality of the cholangiogram and drainage seem to be better for lesions at or above the bifurcation.

The mortality and morbidity rates after curative resection remain relatively high when compared with liver resections performed for other indications. Even in centers with great experience, mortality rates are approximately 5%–10%. The main determinant of survival across most reported series is the ability to achieve a margin-negative resection. There is a direct correlation in the literature between the frequency of hepatectomy and the margin-positivity rate. In most of these series, hepatectomy is not an independent predictor of survival when separated from a

margin-negative status and, as such, it is clearly the latter which is important. Five-year and median survivals in margin-positive patients are 0%–5% and 10–20 months respectively whereas in margin-negative patients these values are 30%–40% and 20–40 months. Nodal (N1) and vascular involvement are inconsistent predictors in the literature and represent relative but not absolute contraindications.

PALLIATIVE BYPASS FOR CHOLANGIOCARCINOMA

Discussion by Henry Pitt, M.D.

The ability to predict resectability in patients with hilar cholangiocarcinoma is less than perfect with current imaging modalities. It is not uncommon to find locoregional disease in the absence of distant metastatic disease that is too extensive thus precluding a curative resection. The median survival in these patients in the literature is approximately 9–15 months. As a substantial proportion of these patients live more than a few months, physicians treating these patients must be able to offer effective palliative strategies. Aside from the resective options, interventions appropriate in these patients may include biliary stenting (placed percutaneously, endoscopically, or surgically) or a intrahepatic bypass (i.e., segment III).

Most surgeons favor percutaneous drainage over endoscopic drainage for obstructions at or above the bifurcation. In the Johns Hopkins experience, operatively placed, bilateral, large silastic catheters (into a Roux limb of jejunum) seemed to lead to survival advantage when compared with percutaneous drains with equivalent qualities of life. There is no evidence either from the Johns Hopkins experience or elsewhere that adjuvant radiation therapy after operative palliation improves survival. Cholecystectomy as a component of the surgical palliation was emphasized given the propensity of stented patients to develop cholecystitis.

TRANSPLANTATION IN THE MANAGEMENT OF CHOLANGIOCARCINOMA

Discussion by Gregory Gores, M.D., and Ronald W. Busuttil, M.D.

Significant controversy exists over the role of liver transplantation in the management of hepatobiliary malignancies. These issues have become even more important in the era of living-related liver transplantation.

Historically, the outcome after liver transplantation for cholangiocarcinoma has been less than optimal with 3-year survival rates of approximately 15%–20%. At UCLA only 25 of the last 2727 liver transplantations over a 15-year period were performed for the management of this malignancy. Done with a backup recipient available, patients were excluded if nodal or vascular involvement was encountered. Eight of 25 patients arose in the setting of primary sclerosing cholangitis (PSC). Mortality was 12% and 3-year survival was 35%. In those patients with early stage cholangiocarcinomas arising in the setting of PSC, the 5-year survival was 80%. Given these results, transplantation of most patients with cholangiocarcinoma should, in general, be discouraged except within the context of investigational protocols including those patients with potential living donors.

Effective screening of patients with PSC remains an issue. Serum CA19-9 levels have been investigated and found to have a sensitivity and specificity of approximately 75% and 80% respectively when a level of greater than 100 IU/mL is used. Enhancing the accuracy of biliary brushings via digital image analysis (DIA), which is able to detect the ploidy state of a single cell or by fluorescent in-situ hybridization (FISH) analysis for chromosomal abnormalities, although promising, are not in widespread use. In a prospective study of 97 consecutive patients with biliary strictures, FISH and DIA increased the sensitivity of brush cytology from 15% to 40% to 50%. ^{18}FDG-PET scanning has recently been reported to be approximately 90% sensitive and specific in demonstrating

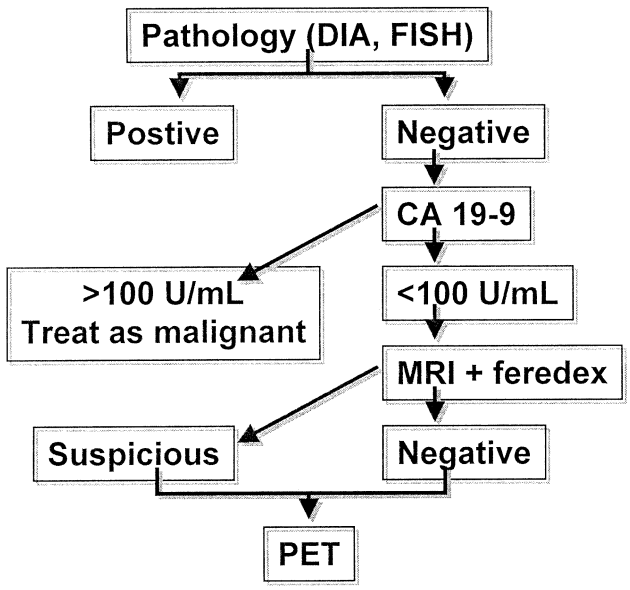

Fig 1. Algorithm for screening patients for cholangiocarcinoma. DIA = digital image analysis; FISH = fluorescent in-situ hybridization; MRI = magnetic resonance imaging; PET = positron emission tomography.

primary cholangiocarcinoma, yet the demonstration of metastatic disease remains very suboptimal. Given these considerations, the algorithm depicted in Fig 1 is used at the Mayo Clinic in the screening of patients with PSC. Patients with proven cholangiocarcinoma are then subjected to endoscopic ultrasound (EUS) for regional and distant (celiac) nodal involvement. In a recent Mayo Clinic review, a series of 30 patients with cholangiocarcinoma underwent EUS with nodal biopsy, which demonstrated nodal metastases in 17%.

Given the lack of effective treatment for patients with locally unresectable hilar cholangiocarcinoma, the Mayo Clinic recently embarked upon an investigational protocol whereby patients without extrahepatic or intrahepatic metastases who were deemed unresectable underwent neoadjuvant external beam irradiation plus bolus flourouracil (5-FU) followed by iridium brachytherapy and protracted infusional 5-FU or Xeloda until orthotropic liver transplantation (OLT). Patients without metastastic progression were explored within 3 months of cadaveric OLT or within 1 week of LDLT. At the time of the AASLD/AHPBA Forum, 41 patients had been enrolled of which 32 patients underwent exploration. Eleven of these 32 patients had occult metastatic disease precluding transplantation. Twenty patients have been transplanted to date with a 5-year 80% survival (vs. 0% in those enrolled patients selected out due to metastatic disease). Of the five deaths thus far, one was related to tumor recurrence, one to sudden death, one to another malignancy, and two as a result of complications after LDLT. Although these findings are encouraging, other groups to date have not repeated them. Transplantation of patients with cholangiocarcinoma undergoing neoadjuvant therapy, as such, remains a very selective process that should be reviewed by the regional United Network of Organ Sharing (UNOS) boards.

Adult–Adult Living Donor Liver Transplantation

Masatoshi Makuuchi, M.D., Charles M. Miller, M.D., Kim Olthoff, M.D., Myron Schwartz, M.D.

After the first report from Denver in 1998 of a successful liver transplant in an adult using the right lobe from a living donor, the procedure was rapidly adopted by many transplant centers as a potential solution to the critical shortage of donor livers. By the end of 2000, when the National Institutes of Health held a Consensus Conference on Adult–Adult Living Donor Transplantation (AALDT), a substantial body of literature had already developed and many of the associated technical and medical pitfalls had been defined. The exponential expansion of the procedure came to a dramatic halt in January 2002 when the death of a donor occurred at Mount Sinai Hospital—the busiest AALDT center in the United States. This led to a widespread reassessment of the risks inherent in right lobe donation. Yet, the problem that drove the development of this controversial technique—the dire shortage of organs for transplantation—still persists. After a 50% drop in the number of AALDT procedures performed in the United States in 2002 compared with 2001, centers are regrouping and approaching AALDT with renewed interest, albeit with heightened awareness of the attendant risks. On November 2, 2002, a state-of-the-art symposium on AALDT was held in Boston, MA, under the combined auspices of the American Hepatico-Pancreato-Biliary Association and the American Association for the Study of Liver Diseases. This article comprises the presentations at the symposium on three subjects of critical importance concerning AALDT. These include advances in surgical technique, candidate selection, and hepatic regeneration; each subject is acknowledged by an expert in the field. (J GASTROINTEST SURG 2004;8:303–312)

KEY WORDS: Living donor, liver transplantation, regeneration

APPLICATION OF ADVANCED HEPATOBILIARY SURGICAL TECHNIQUES TO LIVING DONOR TRANSPLANTATION

Discussion by Masatoshi Makuuchi, M.D

The number of adult patients undergoing living donor liver transplantation (LDLT) has recently increased.[1] It may be true that this recent breakthrough was mainly provided by the use of right liver graft. According to the Japanese Society for LDLT,[2] 322 out of 671 adult patients (48%) received a right liver graft. In Western countries[3] right liver grafts are now routinely used for adult patients. The reported rates[4–6] of survival after LDLT using right liver graft in these countries range from 86%–88%. These rates are equivalent to those occurring after cadaveric liver transplantation. However, there still remains some concern about right liver grafts regarding donor safety and technical controversies in middle hepatic vein (MHV) reconstruction.

The University of Tokyo Experience

Patients

One hundred twenty patients underwent LDLT procedures at the University of Tokyo from January 1996 to September 2002. They consisted of 60 males and 60 females with an average age of 47 years. The most common indication was cholestatic disease in 42, including primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis, followed by hepatocellular carcinoma in 28, viral hepatitis and cirrhosis in 18, fulminant hepatic failure in 10, metabolic diseases in 7, and biliary atresia in 5. The remaining 10 patients were operated on for cryptogenic cirrhosis. Preoperative serum total bilirubin levels and prothrombin times were 9.9 ± 7.4

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From the Artificial Organ and Transplantation Division, Department of Surgery, University of Tokyo, Tokyo, Japan (M.M.); The Recanati/Miller Transplantation Institute, Mount Sinai Hospital, New York, New York (C.M.M., M.S.); and Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania (K.O.).
Reprint requests: Myron Schwartz, M.D., 1 Gustave Levy Place, Box 1104, New York, NY 10029. e-mail: myron.schwartz@msnyuhealth.org

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mg/dl and 1.48 ± 0.43 (international normalized ratio), respectively (mean ± standard deviation). The United Network for Organ Sharing status of the patients was 1 in 11, 2A in 21, 2B in 47, and 3 in 41. The model for end-stage liver disease (MELD) score[7] was 12. The average graft weight was 536 ± 144 g, which corresponded to 47 ± 9% of the recipient's standard liver volume.[8] On average, the operation lasted 962 ± 238 minutes. Blood loss was 6011+ 5312 g corresponding to 104 ± 89 g per kg of body weight. The total transfusion averaged 8150 ± 4615 ml.

The rates of acute rejection and vascular and biliary complications were 30%, 6%, and 21%, respectively. Six patients died during hospitalization. Three of these deaths involved primary biliary cirrhosis in an advanced stage and the patients died from severe pneumonia or sepsis 26–58 days after LDLT. Two patients died from simultaneous thrombosis of the hepatic artery and portal vein. The other cause of death included rejection resistant to steroid pulse therapy. The postoperative hospital stay among the surviving patients was 58 ± 30 days.

Five patients experienced late death. Two patients died from virus-associated hemophagocytic syndrome (146 days and 370 days), 1 patient died from hepatocellular carcinoma recurrence (229 days), 1 patient died from cholestatic hepatitis C (351 days), and another patient died from heart failure due to amyloid polyneuropathy (441 days). The 3-year cumulative survival rate was 88% (Fig. 1). No retransplantation was performed.

Donors

All of the donors were related to the patients and consisted of 53 children, 23 siblings, 17 spouses, and 16 parents, and the 11 others were relatives. Donor selection criteria have been described previously.[9] In brief, the acceptance criteria for donors included an age between 20 and 65 years; familial relation to the recipient to within the third degree of consanguinity; ABO blood group compatibility; negative serology for hepatitis B and C viruses; normal hematology, liver, and kidney functions; and normal echocardiogram and chest x-ray. Computed tomography scan was used to measure graft volume. Hepatic angiography was performed to evaluate vessel anatomy. The donor's own blood and plasma were banked preoperatively. Signed informed consent was obtained before surgery.

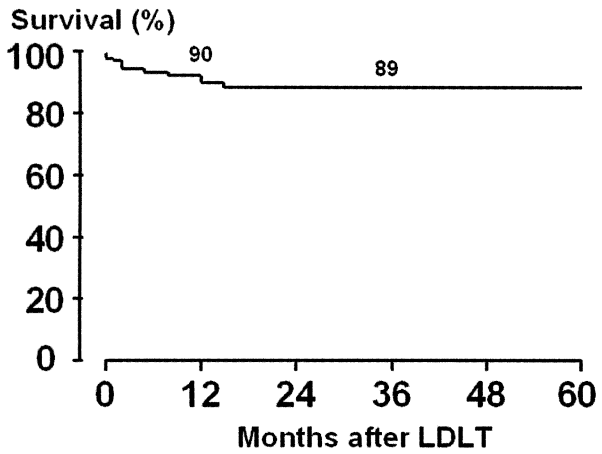

Fig. 1. Survival curve of the patients in University of Tokyo after living donor liver transplant (LDLT) (n = 120).

The most common procedure was left liver with or without caudate lobe resection (n = 60) followed by right liver resection (n = 49) and right lateral sectorectomy (n = 11). The average blood loss was 531 ± 302 g, which was replaced by 471 ± 339 ml of the donors' own fresh frozen plasma or whole blood. On average, the operation lasted 568 ± 168 minutes.

The most frequent complication was bile leakage from the dissection plane of the liver or stump of the bile duct. This occurred in 13 donors and 6 of these donors underwent reoperation for drainage. Other morbidities included gastrostasis and pleural effusion, which occurred in 7 donors. The average hospital stay was 15 ± 6 days. All of the donors did return to their normal daily lives.

Left Liver Graft

In the initial LDLT, only left liver grafts were used for adult patients. Shinshu University reported the first successful LDLT.[10] The patient had primary biliary cirrhosis. The Shinshu group devised the left liver with caudate lobe graft.[11] The caudate lobe corresponds to only 3%–4% of the whole liver volume. In conjunction with a left liver graft, however, the caudate lobe provides an 8%–12% gain in weight. Nishizaki and colleagues[12] performed left liver transplantation in 33 adult patients. They reported that all 5 patients who received grafts corresponding to less than 30% of the patients' standard liver volume survived the operation. The Shinshu group[13] has continued to perform left liver grafts in all adult patients with satisfactory results. At the University of Tokyo a left liver graft was used for good-risk patients with a MELD score of less than 15 after 2000.[14]

Right Liver Graft

It is clear that a right liver graft can help alleviate the problem of graft size disparity in adult patients. An"extended" right liver graft, which includes the trunk of the MHV, was devised by the Hong Kong group.[15] This method is beneficial with regard to venous drainage of the graft because the MHV is a

major draining vein of the right paramedian sector and its role in the left paramedian sector is limited. As the procedure was thought to increase the extent of the donor operation, a right liver graft[16] without the MHV trunk is now commonly used.

However, a right liver graft without the MHV trunk can cause severe congestion of the right paramedian sector (corresponding to segments V and VIII according to Couinaud's nomenclature for liver segmentation). Such congestion can lead to severe graft dysfunction and septic complications[17] because hepatic venous outflow of the right paramedian sector is drained mostly into the MHV.[18] MHV drainage into the recipient's venous system can be reconstructed using vein grafts. This provides a functioning liver mass comparable to an extended right liver graft.

We proposed MHV reconstruction criteria in right liver grafts.[19] Hepatic venous congestion in the right paramedian sector was investigated intraoperatively after parenchyma transection. First, liver surface discoloration in the right paramedian sector was observed after 5 minutes of simultaneous clamping of MHV tributaries and the right hepatic artery. Next, intraoperative Doppler ultrasonography was performed after declamping only the hepatic artery. If the portal flow of the paramedian sector was hepatofugal, the area was confirmed to be congested. All of the examinations for checking venous congestion can be finished in 10 minutes by an experienced surgeon.

If the congested area is dominant and reduced volume is estimated to be less than 40% of the recipients' standard liver volume, we have proceeded with bench reconstruction of MHV tributaries. The necessity of inferior right hepatic vein reconstruction was determined using the same criteria. MHV tributaries were reconstructed under these criteria in our series (Fig 2). MHV reconstruction was performed in 30 out of 49 grafts.[20] Of these, one vein graft was thrombosed 5 days after LDLT.

Right Lateral Sector Graft

A right lateral sector (segments VI and VII according to Couinaud's nomenclature for liver segmentation) graft was recently devised.[21] The details of the harvesting technique are as follows. Occlusion of the right paramedian and left branches of the portal veins and hepatic arteries reveal the demarcation line on the liver surface. The dissection plane is 5 mm to the left of the right portal fissure. Liver transection is performed using a Kelly clamp or an ultrasonic surgical aspirator under occlusion of the right paramedian branches of the portal vein and hepatic artery. The right lateral bile duct is then identified using intraoperative cholangiography before liver transection.

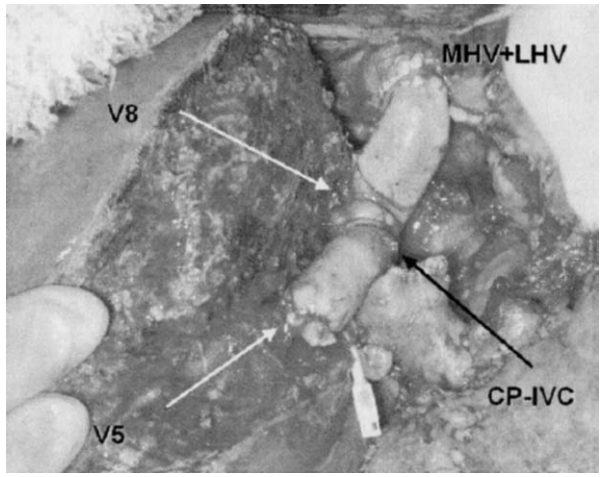

Fig. 2. A modified right liver graft. Middle hepatic vein was reconstructed with cyropreserved vena cava from cadavers (CP-IVC). MHV = middle hepatic vein; LHV = left hepatic vein; V5, V8 = stump of middle hepatic vein tributaries.

The procedure is indicated when the right liver is over 70% of the estimated volume of the whole donor liver and the estimated right lateral sector volume is greater than that of the left liver.[22] Recent volumetric analysis[23] of donors revealed that 84% had a larger right lateral sector than a left liver with caudate lobe when the volume of the right liver is estimated to be more than 70% of the whole. If the right lateral sector volume corresponds to more than 40% of the recipient's standard liver volume, it can be implanted also to these poor risk patients. If not, we have no strategies in LDLT for such patients. More meticulous hilum dissection is needed because the hepatic artery, portal vein, and bile duct are dissected at the second-order branch. Of these, most attention should be paid to bile duct dissection.[24] This option should be limited to expert surgeons.

Liver Graft for LDLT: Left or Right?

The greatest concern in donors after right liver donation is the risk of death. Eight deaths are now known in the world although the exact number of deaths may be larger because there is no worldwide registry of donor outcomes. Three of these deaths occurred in the Unites States and two of them occurred in right liver donors.[25] The safety of right hepatectomy varies depending mainly on the volume of the left liver. Fan and associates[26] warned that right hepatectomy imposes serious risks for the donor when the volume of the left liver is estimated to be less than 30% of the whole liver.

The graft type should also be determined by body size balance between donor and recipients. If the

donor body size is larger than that of the recipient, left liver of the donor will provide the recipient enough liver mass corresponding to more than 40% of the recipient's standard liver volume.[8] Other crucial points should include the fact that the minimal graft volume for successful LDLT might vary depending on the pretransplant condition and the disease of the recipient in each case. Ben-Haim and colleagues[27] commented that a small graft can be used safely in patients without cirrhosis or in Child's class A cirrhotic patients. Accordingly, it is crucial to determine whether the left liver provides enough liver mass to patients with fulminant hepatic failure. In Hong Kong and Japan, where organs from cadavers are scarce, LDLT is aggressively performed for United Network for Organ Sharing (UNOS) status I patients. Four adult patients with fulminant hepatic failure successfully underwent LDLT at Shinshu University.[28] Lo and associates[29] reported that a graft estimated to be 25% of the recipient's standard liver volume was transplanted in a patient with fulminant hepatic failure.

Conclusions

LDLT has recently emerged as one of the therapeutic modalities for end-stage liver disease in adults. Although right liver graft improved the surgical results of the patients, the procedure imposes greater surgical risk on living donors. Left liver or right lateral sector grafts should be considered as alternative options for good-risk patients.

LIVING DONOR LIVER TRANSPLANTATION IN ADULTS: WHEN IS IT BETTER? WHEN IS IT WORSE?

Discussion by Charles M. Miller, M.D.

The growth of adult–adult living donor liver transplantation (AALDLT) over the past 4 years has been rapid and explosive. Once this procedure had been pioneered at a few hospitals around the world, many liver transplant centers were motivated to initiate AALDLT to compensate for a scarcity of cadaveric donor organs, because of local competitive concerns, or both. In the United States, more than 40 programs have performed at least one AALDLT. Overall, in the United States more than 1000 of these procedures have been performed.

The strongest advocates for AALDLT have been the centers that find themselves in situations of severe organ scarcity. The starkest example of this is in Japan, where cadaveric donation is extraordinarily rare and still in its infancy. In the United States, however, the most rapid growth and innovation have occurred in New York, where a long history of organ scarcity exists. This relationship of cadaveric organ scarcity and AALDLT growth is natural and appropriate given that when cadaver organs are readily available, their use for adult transplant candidates is still considered the procedure of choice. Therefore, if we ask,"When is AALDLT preferred?", the first answer must be "When organ scarcity is resulting in excess waiting list morbidity and mortality."

Pediatric LDLT as a Model

Living liver donation for children was pioneered by Christoph Broelsch at the University of Chicago in 1989. It rapidly became widely accepted and adopted as an important option for children in need of liver transplantation and it has had a major impact in reducing both waiting list mortality and the size of the list itself. In fact, some transplant centers now consider living donor transplants to be the procedure of choice for pediatric patients as recipient and graft survival in single-center studies and large cohorts has been significantly better than that achieved with cadaveric organs.[30] In addition to improved recipient outcomes, donor morbidity and mortality rates are very low, approaching the rates obtained after living renal donation, a procedure with wide social acceptance. In addition, coercion is rarely a concern; the donor is most commonly a parent who presents with clear unconflicted motivation. There is little, if any, risk of inadequate graft size or poor donor status so that good initial liver function is the rule. Finally, the major indication in pediatric transplantation is biliary atresia. This disease does not recur in the recipient so the donor can be assured that his or her donation will have lasting benefit.

What Characteristics Make AALDLT Preferable?

Learning lessons from the pediatric model, the optimal circumstances for AALDLT should include a high likelihood for good recipient outcome as well as an extremely low risk of complications or death for the donor.[31] In addition, a clear and unambiguous motivation on the part of the donor that is well accepted not only by the recipient but also by the entire transplant team is crucial for success. These circumstances allow for the development of a strong therapeutic bond among the donor, recipient, and transplant team. Such a bond must remain intact to assure good long-term outcomes and avoid post-hoc recriminations should complications ensue in either the donor or recipient.

To maximize short-term outcomes, the provision of a graft with adequate functional mass is critical.

Both recipient and donor factors can impact on functional size.[32] The optimal situation is when the recipient has good functional status and minimal portal hypertension and the donor has a large parenchymal mass and uncomplicated venous outflow. This combination helps avoid small-for-size syndrome and many other associated complications.

To maximize long-term outcome, the recipient's disease should be one with minimal chance of recurrence. The fact that AALDLT is an elective procedure allows the transplant to be optimally timed. This is especially helpful in diseases with unpredictable courses such as some cases of hepatocellular carcinoma.

Preference According to Etiology

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

These two cholestatic diseases may represent the most preferred indications for AALDLT and in this respect are most similar to pediatric transplantation for biliary atresia. In general, these patients have excellent physiologic reserve, minimal or moderate portal hypertension, and excellent long-term prognosis with minimal risk of graft-threatening recurrent disease.[33] In addition, patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) have historically been disadvantaged by the UNOS allocation algorithm. It remains unclear whether the new MELD system initiated by UNOS in early 2002 will alleviate this bias. Both of these diseases allow for good prognostication that does not increase the need for LDLT but does improve the ability to prepare and schedule a transplant in a timely fashion.

Hepatitis B

Liver transplantation for hepatitis B has undergone a renaissance in the past decade. With better understanding of the need for prolonged and uninterrupted passive immunization and the emergence of new and effective antiviral agents, recurrence rates have been minimized and patient and graft survival have dramatically increased.[33,34] These improvements, combined with the fact that the course of cirrhosis in hepatitis B is prolonged and development of portal hypertension is gradual, gives strong support for the preferential use of AALDLT. The other positive factor is that these patients often harbor hepatocellular carcinoma rendering prognosis uncertain. The negative factor in this cohort is relative lack of need. For patients with hepatitis B, there is a pool of extended cadaveric donors who are hepatitis B core antibody positive ($HbCAb^+$); these organs are used almost exclusively for patients who are hepatitis B surface antigen positive ($HbSAg^+$).

Fulminant Hepatic Failure

Although the use of living donors for emergent transplantation in children has gained wide acceptance, there has been far more controversy and less experience in adults. Whereas adults with fulminant hepatic failure have a favorable profile from the perspective of physiologic reserve, lack of portal hypertension, and the low probability of disease recurrence, there are many factors that make LDLT an unnecessary or unfavorable choice.[35] The UNOS allocation system gives such strong priority to this group of patients that the identification of a suitable cadaveric graft and transplant can, on average, be accomplished within 48 hours. Therefore, the need for a living donor is minimal. Furthermore, whereas for pediatric patients the motivation of the parents is clear, with adult patients the emergent nature of the situation, the uncertain relationship between donor and recipient, and the inability of the recipient to participate fully in the complex decision makes LDLT in this situation highly coercive and problematic.

Hepatitis C

Patients with end-stage liver disease caused by hepatitis C make up the single largest patient cohort in need of liver transplantation. Because of this, many patients of all etiologies are forced to wait for cadaveric livers until their optimal window for transplantation has closed. In addition, hepatocellular carcinoma can be identified in more than 25% of candidates with hepatitis C. For these reasons, patients with hepatitis C must remain potential candidates for AALDLT despite the obvious and theoretical problems,[36] including the inevitability of disease recurrence. Preliminary reports have suggested that regeneration of the partial graft makes the liver more susceptible to graft-threatening recurrence.[37–39] These reports, however, remain unconfirmed and controversial. In contrast to patients with diseases that do not recur, the timing of transplant in patients with hepatitis C cannot be accelerated to take advantage of a less deteriorated physiologic reserve. The clock for recurrence starts ticking at the time of reperfusion.

Summary and Conclusions

LDLT for adults is an important and evolving technique for coping with the severe shortage of cadaveric organs throughout the world. Regions with the most severe shortage have spawned the programs with the greatest interest and productivity in AALDLT. Because of the inherent and specific risks to the donor, it is imperative that the recipient's chances for acceptable short- and long-term outcomes be

assured and discussed openly and freely with both the donor and recipient. The choice of the cadaveric or living donor option is complex and factors inherent to the donor, the recipient, and the transplant team, as well as the degree of risk each party is willing to accept, must be accounted for in each case. As technology evolves to the point at which donor risk is no greater than that of living renal donation and the survival of recipients is as good or better than with cadaveric grafting, LDLT will achieve the same preferred status in adults that it now has in children.

HEPATIC REGENERATION IN LIVING DONOR LIVER

Discussion by Kim Olthoff, M.D.

The ability of the liver to regenerate was recognized by the ancient Greeks in the myth of Prometheus, who had his liver eaten each night by an eagle as punishment for stealing fire from the gods, and each night it regenerated only to have it devoured again the next night. The gods can be vengeful.[40] Over the centuries much has been learned about what initiates liver regeneration, how it is sustained, and what inhibits it.[16,41] Today, hepatic resection is routinely and safely accomplished for malignant and benign disease because of the presumed ability of the liver to regain its functional mass in a matter of days to weeks. This assumed, yet essential, outcome has recently become even more important with the advent of adult–adult living donor liver transplantation (LDLT) and recent growth in this area.[3,42] By transplanting only a portion of what the expected liver volume in adults is, we must rely on the rapid regeneration of a hemiliver while it simultaneously maintains the basic metabolic functions required for the survival of both the donor and recipient.

Pathways of Liver Regeneration

In the liver, normally quiescent highly differentiated cells are capable of rapid proliferation after resection and tissue loss.[43] Early studies in rodent models demonstrated that after partial hepatectomy, hepatocytes begin to replicate within 24 hours with biliary epithelial cells and Kupffer cells not far behind.[44,45] On a molecular level, studies in the past decade have elucidated cytokine pathways, transcriptional regulation, and patterns of gene activation after partial hepatectomy in animal models.[46,47] It has become increasingly apparent that certain cytokines and growth factors, such as tumor necrosis factor (TNF-α) and interleukin (IL-6), play an important role in normal liver regeneration and recovery from injury.[48,49] These cytokines and other growth factors, released from Kupffer cells, "prime"the hepatocytes and initiate activation of transcription factors such as nuclear factor (NF-κB), signal transducer and activator of transcription 3 (STAT3), and activating protein-1 (AP-1), followed by selective upregulation of specific cell cycle genes, cyclins, and DNA replication.[50,51] Mice lacking IL-6 or the TNF receptor (TNFR) demonstrate impaired liver regeneration characterized by liver necrosis and failure and blunted DNA response in the hepatocytes.[52,53] More recently, an inhibiting factor, suppressor of cytokine signaling 3 (SOCS 3), has been described that may provide the key to how the liver knows when to stop regenerating.[54]

These cytokine mediated pathways also appear to play a role in the recovery from acute injury of the liver. In a model of acute carbon tetrachloride injury, IL-6-/- mice develop increased hepatocellular injury, defective regeneration, and increased apoptosis.[55] Similarly, in a model of Fas-mediated apoptosis, IL-6-/- mice develop severe apoptotic hepatitis and increased mortality.[56] In both of these models, pretreatment with IL-6 improved survival and reduced injury. Others have shown that IL-6 is protective after warm ischemic injury and partial hepatectomy in rodent models.[57,58] Thus, IL-6 is a significant survival and regenerative factor in multiple types of hepatic injury and important for initiation of cell cycle pathways in conditions that may require liver regeneration and repair such as liver transplantation.

Regeneration After Transplantation

Recent clinical observations in LDLT recipients show that a massive amount of regeneration occurs in the first 1–2 weeks after resection for donation.[59,60] However, it seems that most donors do not reach 100% of their starting volume even at 1-year follow-up. Recipients also have rapid proliferation of liver mass, the majority reaching a calculated standard liver volume by 1 month.[61]

It is important to remember that the transplant environment is unique in that the liver graft is simultaneously subjected to ischemic injury, metabolic stress, and the host immune response. Regeneration is required after transplantation to replace injured cells lost to ischemic injury and immune response and to restore volume in the setting of split livers and LDLTs. The molecular pathways leading to regeneration may be affected by both the inflammatory response of ischemic injury and the host immune response or our attempts to suppress it.

Factors Affecting the Regenerative Response

After volume loss, hepatocytes must rapidly adapt and seek a compromise between maintenance of continued differentiated function and cellular replication to permit survival.[62] Hepatocytes have to

maintain a certain balance and shift in energy economy in response to changing demands.[63] Numerous outside influences may interfere with this balance. Factors that have been shown to have a significant effect on liver regeneration include ischemia, liver mass, immunosuppression, steatosis, and age.

Animal studies have demonstrated impaired regeneration when massive hepatectomy is combined with warm ischemic injury.[58] Ischemic injury, both warm and cold, is an unavoidable component of transplantation. After prolonged cold ischemia of whole liver grafts, there is initiation of the cell cycle pathways with upregulation of markers of liver regeneration.[64] The more extensive the ischemic injury, the greater the expression and activation of cytokines, transcription factors, and immediate early genes and the greater the magnitude of hepatocellular replication.[65] However, the liver can only tolerate ischemic injury up to a "point of no return," after which the damage is too extensive and the graft is unable to maintain functional homeostasis and regenerative capabilities.[66]

The amount of liver mass transplanted is another important variable in the regenerative response after transplantation. Early experimental studies addressing regeneration after transplantation, and clinical observation, demonstrate that a small-for-size graft will adapt to its environment and achieve a size equal to the original native liver.[67] However, transplanted grafts display delays in DNA synthesis when compared with partial hepatectomy models.[68] In addition, it became apparent that graft size to recipient ratio was critical in that grafts that were too small had decreased survival.[69] These findings correlated with clinical experience in that small-for-size grafts regenerate to an appropriate size for the recipient, however, there was significant functional impairment of grafts that were less than 50% expected weight, demonstrated by prolonged cholestasis and histologic changes consistent with ischemic injury.[70] Liver grafts with a graft weight/standard liver volume of less than 40% have poor graft survival and prolonged hyperbilirubinemia.[71] Experimental models of partial grafts with significant ischemic injury demonstrate decreased survival.[72,73]

The question of the critical liver mass required for transplantation in living donation remains a matter of debate. Most centers have defined liver mass as graft-to-recipient body weight (GRBW) or as a percentage of the standard liver volume. Unfortunately, no uniform method of measuring or reporting graft volume in relation to the recipient has been established. Clinical experience with living donor and split grafts has led to an accepted lower limit of 0.8% GRBW or 40% of the standard liver volume.[29,71,74] Donor and recipient characteristics may significantly influence these minimal accepted standard volumes.

The state of the recipient is also an important component in determining appropriate liver volume. Patients with fulminant hepatic failure and those with significant metabolic stress may require more liver volume than stable patients transplanted under elective conditions.[8,29] Although it has been performed successfully, many centers are not performing LDLT in these patients because of the uncertainty of knowing if a partial graft is enough volume to support the recovery from fulminant liver failure.

Glucocorticoids, routinely used in immunosuppression protocols, have been shown to markedly inhibit cell cycle progression in both partial hepatectomy models and in transplant models with ischemic injury.[75–77] Cyclosporine has been shown to have differential effects on regeneration in a dose-dependent fashion.[78,79] Future studies involving the effect of sirolimus on regeneration are forthcoming and it will be interesting to see if the antiproliferative effects of sirolimus also interfere with the hepatocyte regenerative response.[80]

Hepatic steatosis is a potential risk factor for major hepatic resection.[81,82] Numerous animal studies have shown marked impairment of regeneration in steatotic livers as well as the inability to tolerate warm ischemic injury[83,84]—findings that correlate with the decreased survival of steatotic livers in the clinical transplant setting.[85] From clinical experience we know that steatotic liver grafts demonstrate a higher rate of primary nonfunction (PNF), higher transaminases, and poorer graft survival. There are no good clinical data of the effect of steatosis on regeneration in the transplant setting. Because donor steatosis affects both susceptibility to ischemic injury and regenerative capacity, some groups have empirically suggested increasing the necessary liver mass by 1% standard liver volume for each percentage of steatosis.[86] There are no studies looking at steatosis in the living donor setting, as most programs do not consider donors with steatosis or high body mass index (BMI).

Finally, age is a significant factor. Older livers do not regenerate as quickly as younger livers and they also demonstrate delayed regeneration after acute injury. Rodent models have demonstrated reduced and delayed thymidine kinase uptake in older animals after partial hepatectomy. In the transplant setting, older grafts have poorer long-term survival when combined with ischemic injury. Some early statistics out of the Scientific Registry of Transplant Recipients (SRTR) and UNOS demonstrate that the graft survival of older living donor grafts are inferior to

younger grafts.[87] Whether this is because of a decreased ability to regenerate alongside the other stresses of transplantation is yet to be shown. It must be emphasized that age may affect the regeneration and recovery of the living donor liver as well as the recipient. Many groups limit the upper age limit of the donor, although no definite age has been specified.

Regeneration and Other Post-transplant Processes

Although we may have learned a great deal about the molecular pathways of regeneration in recent years, we still know very little about how the rapid hepatocyte replication required in living donor grafts affects other processes. For example, it is not known if this vigorous regenerative response in the partial graft has significant effect upon the kinetics of viral replication in hepatitis C virus (HCV) positive individuals. There is evidence that more rapid progression occurs in patients with increased hepatocyte proliferation and early single center studies suggest that recipients of living donor liver transplants have an earlier and more severe recurrence of HCV when compared with recipients of whole cadaveric liver grafts.[88,89] There is also preliminary data that partial LD grafts have altered metabolism and pharmacokinetics with recipients requiring lower doses of tacrolimus in the early postoperative period than patients receiving whole grafts.[90,91] In addition, many of the cytokines, growth factors, and other cell cycle proteins that are upregulated in hepatocyte replication are also expressed in hepatomas and are also activated during periods of rejection. Will patients with hepatocellular carcinoma transplanted with living donor partial grafts have earlier recurrence? Do partial grafts induce a greater or lesser alloimmune response? We do not yet have these answers.

Only prospective comparative studies in living donation vs. cadaveric transplantation will provide enough data to answer questions related to regeneration in the clinical setting. Future avenues of exploration need to focus on dissecting the details of normal human liver regeneration in living donors and how these are altered after transplantation. Investigation should be directed into methods of enhancing regeneration in less than perfect partial grafts and in those with small-for-size syndrome and into methods of understanding the interrelationship between hepatocyte proliferation, viral kinetics, and the immune response.

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Protection of the Liver During Hepatic Surgery

Pierre-Alain Clavien, M.D., Ph.D., Jean Emond, M.D., Jean Nicolas Vauthey, M.D., Jacques Belghiti, M.D., Ravi S. Chari, M.D., Steven M. Strasberg, M.D.

Very few areas in medicine have seen as many controversies as the evaluation and treatment of patients with liver diseases. Many novel therapies, often marketed before conclusive demonstration of their efficacy, have been developed to enable selective destruction of liver tumors to minimize the risk of liver failure associated with major surgery. Whether these techniques are effective and result in lesser complications often remains speculative. Persisting challenges in selecting the optimal therapy are the evaluation of the risk of surgery in patients with normal or diseased liver and the preparation for surgery. A panel of hepato-biliary surgeons experienced in the management of complex cases convened at the annual meeting of the American Hepato-Pancreato-Biliary Association in Boston, MA, to address the rapidly evolving field of protective strategies for hepatic surgery. (J GASTROINTEST SURG 2004;8:313–327)

KEY WORDS: Hepatoprotection, liver volume, liver function

EVALUATION OF THE CIRRHOTIC AND DISEASED LIVER BEFORE HEPATIC SURGERY

Discussion by Jean Emond, M.D.

In addition to an indisputable role in the curative treatment of benign hepatic lesions, hepatectomy has traditionally been regarded as the most effective way to treat malignant hepatic tumors. The advantages are obvious; a complete extirpation of the disease focus is obtained and in patients with normal hepatic tissue complete regeneration and restoration of hepatic mass are expected. Over the last two decades progressive improvement in surgical techniques, anesthetic management, and technology to evaluate the liver, transect the parenchyma safely, and optimize hemostasis have greatly increased the safety of the procedure. However, as these advances have occurred so has our understanding of the biology of hepatobiliary malignancies and our ability to ablate lesions with minimally invasive techniques.

The balance between risk and benefit for hepatectomy has become more complex as the surgery has improved. In patients with benign liver tumors, there has been a trend toward nonoperative management of many lesions as well as an interest in the development of minimally invasive approaches to extirpation. Malignant tumors can occur in patients with normal livers (usually adenocarcinomas of the biliary epithelium) or metastases and may be optimally treated with resection. The key paradigm is that most primary liver cancers occur in patients with underlying liver disease, which impacts the prognosis independently of the cancer. Preoperative assessment of the patient for hepatectomy must, therefore, include assessment of the general medical, oncologic, and hepatologic status.

What Are the Goals of the Assessment?

A general health assessment is the first step in the evaluation of the patient with a liver tumor. Factors such as age, diabetes mellitus, or the presence of atherosclerotic disease may affect the prognosis of the patient, which a priori limits the therapeutic approach to the tumor.[1,2] The next step is the assessment of the

From the Department of Surgery, University Hospital Zurich, Zurich, Switzerland (P.A.C.); Center for Liver Disease, Columbia University College of Physicians and Surgeons, New York, New York (J.E.); Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas (J.N.V.); Department of HPB Surgery, Hopital Beaujon, Paris, France (J.B.); Departments of Surgery and Cancer Biology, Vanderbilt University Medical Center, Nashville, Tennessee (R.S.C.); and Division of HPB Surgery, Washington University School of Medicine, St. Louis, Missouri (S.M.S.).
Reprint requests: Pierre-Alain Clavien, M.D., Ph.D., F.A.C.S., F.R.C.S., Department of Visceral and Transplantation Surgery, University Hospital, Zurich, 100 Raemistrasse, 8091 Zurich, Switzerland. e-mail: clavien@chir.unizh.ch

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underlying liver disease and liver function, which might affect both perioperative risk as well as long-term prognosis in the setting of cirrhosis. In addition to affecting prognosis, the presence of cirrhosis portends the development of more cancers over time, which may affect the choice of therapy and even introduce evaluation for a transplant into the therapeutic algorithm. Finally, the extent and biology of the cancer needs to be assessed because partial hepatectomy is rarely helpful if there is multifocal or extrahepatic disease.

Ablation Menu

The therapeutic choices for the destruction of a local hepatic lesion are numerous and should be considered in an overall strategy for the treatment of a tumor, which is adjusted according to the patient's condition, liver disease, and extent of tumor. Most appealing, direct injection of the tumor with ethand or acetic acid[3,4] or radio frequency ablation[5] can be accomplished percutaneously, often as an outpatient procedure. These interventions require sophisticated imaging and may not fully destroy the lesion. Transarterial chemoembolization (TACE) permits selective treatment of a territory of liver and probably offers comparable effectiveness.[6] These approaches may be used in patients with serious medical illnesses who are not candidates for more definitive therapy such as resection or transplantation. Systemic chemotherapy has been of limited use in patients with cirrhosis because of the low response rates of hepatocellular carcinoma (HCC) and poor tolerance of the agents, though, recently, well-tolerated oral agents show some promise.[7]

Prognosis of Hepatectomy

Numerous authors have reported a range of outcomes of hepatectomy reflecting the difficulty of standardizing the reports because of varying patient populations. Obviously, the extent of hepatectomy ranges from the nonanatomic excision of a small lesion to an extended anatomic hepatectomy in which most of the parenchyma is removed. Several factors recur in these analyses: liver function as reflected by scoring systems such as the Child-Turcotte-Pugh score (CTP), the extent of resection, and the skill and experience of the surgical team with a mortality of resection in cirrhosis ranging from 1%–40%.[8–10]

The presence of obstructive jaundice greatly increases the risk of resection even in noncirrhotics and jaundice, perhaps as a surrogate for liver function, has been determined to portend a poor prognosis in a variety of hepatic interventions from transjugular intrahepatic portosystemic shunt (TIPS) to TACE.[11–13]

Preoperative Medical and Surgical Assessment

Our approach is sequential: the patient's overall condition is assessed, coexisting medical illnesses are excluded, and the liver disease is diagnosed and staged. Naturally, the diagnosis of underlying liver disease is essential and the detection of viral serologic markers and measurement of viral activity are important in patients with viral-induced liver disease in whom the formation of a hepatocellular cancer may be the first clinical complication. Standard liver function tests and a clinical evaluation are combined to generate an assessment summarized by the CTP score.[14]

We require that the CTP be normal or "A" to consider open resective surgery. Good liver function is necessary but not sufficient to predict a good result of resection. The patient must be free of significant portal hypertension; otherwise ascites and more ominous complications are the rule postoperatively. Portal hypertension is often asymptomatic and may be estimated by the platelet count, spleen size on three-dimensional (3D) imaging, or the presence of varices by endoscopy. These clinical evaluations may be supplemented by liver biopsy, not of the tumor, but of the rest of the parenchyma that is destined to become the remnant. Quantitative measurement of portal pressure by hepatic vein wedged pressure measurements has been championed by the Barcelona group as a reliable way to select patients who will tolerate hepatectomy with a high predictive value.[15]

Apart from cirrhosis, liver function is impaired and morbidity is increased in reversible states of liver injury such as steatosis and cholestasis. Steatosis of the donor liver has been widely studied as an adverse prognostic marker in liver transplantation.[16] The etiologies of hepatic steatosis are multiple and it is associated with a variety of states such as alcohol injury, obesity, postischemic states, or toxic injury including those from certain chemotherapeutics.[17] Although prediction is unreliable, steatosis is generally present when the liver is subjected to oxidative stress,[18] presumably increasing the risk of hepatectomy. Cholestasis, whether obstructive or hepatocellular, is a major risk factor for liver surgery and represents an absolute contraindication to hepatectomy. Liver cell failure manifested by cholestasis will be rapidly lethal unless the process is reversed or liver transplantation is indicated. In contrast, hepatectomy may be performed safely in patients with obstructive jaundice provided the biliary tree is drained preoperatively until liver function returns to normal. Though clinical experience is convincing, the practice of biliary drainage before hepatectomy has not been fully studied to determine the precise mode or duration for optimal results.

The morphologic assessment of the liver before resection is best accomplished with 3D imaging using either computed tomographic (CT) or magnetic resonance (MR) scanning. Current technology permits accurate evaluation of the lesion, its relation to vascular structures, and the parenchymal volume. In our practice, MR-based 3D reconstructions precisely define the vascular and biliary architecture of the liver. This test has become the single test needed to completely evaluate the patient anatomically for surgery. Predictions of adequacy of the remnant liver after hepatectomy are not completely reliable and have been the source of great interest in donor hepatectomy for living donor liver transplantation.[19] The use of preoperative portal embolization to drive the planned remnant toward regeneration and make extensive resections possible is discussed extensively elsewhere in this review.

Quantitative Liver Function Testing

The need for precise tests of metabolic capacity of the liver has long interested both hepatologists and surgeons. Standard liver chemistry tests, although surprisingly useful, do not discriminate subtle changes in function and may remain normal or minimally altered and fail to reflect limited functional reserve. Numerous tests have been developed that evaluate different components of metabolism and transformation of target substances thereby testing components of the liver's ability to take up, transform, and eliminate target substances that can be measured with transcutaneous detectors or sequential serum testing. Test compounds are typically defined as dependent upon either hepatic metabolism (aminopyrine, antipyrine, caffeine, erythromycin, lidocaine derivatives [monoethylglycylxylidide (MEGX)]) or hepatic blood flow (indocyanine green [ICG]).[20,21]

Despite the great variety of quantitative tests, they have been used very little in selecting patients for hepatectomy either because of the inconvenience of these procedures or the lack of predictive value in their use. Nonetheless, several investigators have championed the use of some assays, particularly the use of ICG clearance and reported correlation with postoperative events. Grazi and associates reported the use of MEGX clearance in a series of 157 patients with HCC who underwent liver resection with a mortality of 1.3%.[22,23]

In summary, hepatectomy is a powerful tool for the treatment of localized hepatic lesions. Its use is optimal if the patient is otherwise healthy, the disease is localized within the liver, and the liver is otherwise healthy. Under optimal circumstances, in a noncirrhotic, extensive resection, such as a right hepatectomy, can be performed with a mortality of well under 1% (the reported mortality in nearly 800 right hepatectomies for donation in the United States is .02% [unpublished UNOS review]). As the complexity of the procedure increases and the state of the liver is altered, the principles applied above are used to define an acceptable therapeutic strategy. Here, the role of less invasive ablative choices becomes relevant as does the possible need to replace the whole liver, either because of underlying cirrhosis or as an oncologic intervention to remove a precancerous tissue. Although the selection of patients for resection remains clinical in large measure, the introduction of quantitative function tests and the use of measurements of portal pressure prestage an era of increased accuracy of selection with the elimination of perioperative risk.

EVALUATION OF MINIMAL FUNCTIONAL LIVER MASS IN LIVER SURGERY

Discussion by Jean Nicolas Vauthey, M.D.

Resection remains an essential component of curative therapy for primary and metastatic liver cancer. Advancements in perioperative care and surgical technique have resulted in low mortality rates, but significant morbidity persists in patients with cirrhosis, compromised liver, or a small liver remnant after extended hepatic resection.[24–26] Despite recognition that the extent of resection is limited mainly by the size and function of the residual liver after resection, there is no consensus on what minimal volume of residual liver is sufficient to avoid postoperative liver failure. Figures ranging from 10%[27,28] to 40%[29,30] are difficult to compare because of different methods of measuring liver volume and variable degrees of underlying liver disease.

CT now provides an accurate reproducible method for measuring liver volume.[30,31] Total liver volume can be determined from a formula correlating total liver volume and body surface area (BSA).[32] A standardized method for application of these parameters to preoperative planning could improve patient selection for extended resection and potentially permit application of preoperative therapies designed to minimize postoperative complications after extended hepatic resection.

The traditional technique used to estimate preoperative volumes focuses on the liver to be resected. Using 3D volumetric CT reconstruction the entire volume of liver to be resected is calculated and the nonfunctional volume is subtracted: resected volume − tumor volume ÷ total liver volume − tumor volume.[29] Multiple tumors, lesions beyond the resolution of imaging, dilated bile ducts, and liver

compromised by cholestasis, cholangitis, or vascular obstruction contribute to error using this method.[29,33] Further, the functional significance of measured total liver volume in patients with chronic liver disease and atrophy or hypertrophy as a result of cirrhosis is also questionable.

Physiologic studies such as ICG dye clearance can be used to estimate hepatic reserve before and after liver resection. Though retention rate 15 minutes after intravenous injection of ICG (0.5 mg/kg) correlates with outcome in some series,[9,34,35] this information is best used as an adjunct to volumetry. Other physiologic-based volumetric tests are being developed to estimate the functional hepatic mass, such as single positron emission computed tomography (SPECT)[36] and, more recently, glycoprotein receptor measurements using radiocolloid liver scintigraphy with technetium-99m-galactosyl human serum albumin.[37] These tests are impractical for surgical planning, as they provide an overall measurement of function and do not differentiate between the liver to be resected and the anticipated liver remnant.

An alternative method of assessing liver volume avoids these pitfalls. Using this method, the anticipated remnant liver also called future liver remnant (FLR) is measured directly by 3D CT volumetry and the total liver volume is calculated using a formula.[32] The ratio of the measured FLR volume ÷ total estimated liver volume is determined using a formula which is derived from the association between total liver volume and BSA: total liver volume (cm^3) = $-794.41 + 1267.28 \times$ BSA (square meters).[32] Based on this method of FLR volume calculation, a correlation between FLR volume and operative outcome has been established.[33] The ratio of the CT measured FLR volume ÷ calculated total liver volume is defined as the standardized FLR.

Abdalla and associates[38] recently validated this method of systematic preoperative liver volume calculation using 3D CT volumetry. In 48 patients without chronic liver disease undergoing extended hepatectomy with and without preoperative portal vein embolization, the postoperative complication rate was significantly increased in patients with future liver remnant volume less than 20% of the total estimate liver volume. A correlation between liver volume and outcome has also been demonstrated using a standardized method of calculation based on BSA by Shirabe and associates in patients with chronic liver disease.[39] In this study all deaths from liver failure occurred in patients with FLR of less than 300 mL/m^2.

The standardized FLR measurement is useful in patients with anticipated small liver remnants who require extended resection because of multiple or centrally located tumors. In these patients, in contrast to some patients with large tumors, contralateral hypertrophy is not seen. The critical threshold for safe resection remains to be determined through further studies and likely varies depending on presence of underlying liver disease from cirrhosis, hepatitis, or prior chemotherapy. Considerable variability can occur in the lobar and segmental hepatic volumetric distribution. Therefore, systematic measurement is essential when extended resection is planned. Transient liver insufficiency measured by altered hepatic synthetic function (prothrombin time) and excretory function (bilirubin) are seen after extended resections with a small remnant liver volume ($\leqslant$ 25% of total liver volume).[33,39] Surrogate measures of the overall postoperative course (hospital stay) and intensive care unit stays seem to be increased as liver remnant size decreases.[33,40] Thus 20%–25% of the total liver volume seems to be the minimum safe volume that can be left after extended resection in patients with normal underlying liver. In diseased liver (cirrhosis or hepatitis) the safe minimal liver remnant seems to be 40% of the total liver volume.[29]

Similar methods of calculation using graft to recipient ratios have been used to estimate the appropriate graft size in living related liver transplantation (graft to recipient body weight ratio and graft to recipient estimated total liver volume based on BSA).[41] Using these ratios, liver transplantation has been determined to be safe with graft volume ÷ total estimated liver volume greater than 30%[42–44] and graft ÷ recipient body weight greater than 0.8%.[45] Because body weight and BSA provide similar correlations with total liver volume, the use of either BSA or body weight as denominator is appropriate.[32]

Planning extended hepatic resection must be individualized. Systematic preoperative measurement of the FLR volume is used for prediction of post-resection liver function. Further, as the limits of extended hepatic resection are expanded, such a standardized measurement technique permits comparison of outcome from patient to patient and institution to institution. In the future, systematic measurement should also assist in determining the patients who will require preoperative portal vein embolization before extended hepatectomies.

ARGUMENTS FOR A SELECTIVE APPROACH OF PREOPERATIVE PORTAL VEIN EMBOLIZATION BEFORE MAJOR HEPATIC RESECTION

Discussion by Jacques Belghiti, M.D.

Despite a dramatic improvement in the safety of liver surgery, there is theoretical evidence that an

insufficient hepatic functional reserve estimated by a small FLR volume after major liver resection can be considered as a risky situation.[2,8,29] Portal flow, which is the main factor for postoperative liver regeneration after liver resection, can drift preoperatively toward the FLR inducing parenchymal hypertrophy. Therefore, it could be assumed that portal vein embolization (PVE) can reduce the risk of postoperative complications by increasing the mass of the postresection functional liver.[46,47] However, the indications of PVE are still arbitrary regardless of the status of the nontumorous liver parenchyma including patients with either normal or chronic liver disease and whatever the exact quantification of sufficient minimal functional hepatic volume ranging from 25%–50% of the total liver volume is.[48–53] The aim of this paper was first to determine the incidence and impact of a small remnant liver volume after major liver resections in patients with normal liver and second to define the subgroup of patients who might benefit from PVE.

How Frequently Does a Major Hepatectomy Result in a Small Remnant Liver Volume?

In a large study evaluating the risk of liver resection, we have confirmed that the mortality rate was significantly higher in patients with a diseased liver including those with chronic liver disease, cholestasis, and steatosis.[8] The analysis of 662 liver resections in patients with a normal underlying liver illustrated that the overall mortality rate is 0.9%. The mortality rate of patients who underwent major resection was only 1.5%. Factors significantly associated with an increase in the mortality rate included an American Society of Anesthesiology (ASA) score greater than 1 and the association of an extrahepatic procedure. To investigate whether the volume of the remnant liver had an impact on the postoperative course, we studied a subgroup of 138 patients who underwent an elective solitary major liver resection (removal of three or more Couinaud's segments) with an ASA score of 1. None of these patients had a procedure aiming to hypertrophy the future remnant liver volume. The number of resected segments was respectively 3 in 18 patients (13% of the total number of patients), 4 in 88 patients (64%), 5 in 22 patients (16%), and 6 in 10 patients (7%). The remnant liver volume (RLV) was expressed as ratios with the preoperative FLV calculated by complete preoperative CT-scan volumetric assessments. Patients were divided into five groups based upon their RLV/FLV ratio from less than or equal to 30% to greater than or equal to 60%. As illustrated in Table 1, a small remnant liver, as restrictively defined by a RLV/FLV ratio of less than or equal to 30%, was only observed in 13 patients (9.4%), whereas 74 patients (53%) experienced a RLV/FLV ratio greater than 50%. Interestingly, there was not any linear correlation between the number of resected segments and the volume of the remaining liver. A possible explanation for these observations is that in patients with a large malignant tumor mass, the contralateral liver segments have undergone a progressive compensatory hypertrophy either because this tumor mass is not functional or because it impairs the adjacent portal blood flow. Therefore, our results confirmed that a major liver resection, in clinical practice, is rarely associated with a small remnant liver.[54]

Impact of the Remnant Liver Volume in the Postoperative Outcome

The analysis of postoperative liver function tests showed that all patients experienced a decrease of prothrombin time on postoperative day 1 without correlation with the RLV/FLV ratio that progressively normalized thereafter irrespective of remaining liver volume. In contrast, postoperative serum bilirubin was significantly correlated during the first week with the RLV/FLV ratio (data not shown). Therefore the most accurate postoperative marker of small RLV is serum bilirubin level.[55]

Sixty-four (47%) patients experienced one or more complications including pulmonary complications in 25 patients, abdominal infection, biliary leakage, or bilioma in 17 patients, ascites in 17 patients, liver failure in 7 patients, and postoperative hemorrhage in 6 patients. As shown in Fig. 1, the overall rate of complications was not statistically different between patients with a smaller or larger RLV. However, patients with RLV/FLV greater than or equal to 60% had the tendency to present more biliary complications (18%) probably because of tumor volume and technical difficulties. When excluding patients with RLV/FLV ratio greater than 60% the rate of complications, such as pulmonary, biliary, and ascites, both intensive care unit (ICU) and hospital stays seemed to increase linearly with RLV. Importantly, the ICU stay was twice as long and the hospital stay 60% longer in the group with the lowest RLV/FLV ratio (< 30%) compared with the group with a ratio of 51%–60%. Patients with RLV/FLV ratio less than 30% required more attention to their postoperative care, which manifested as longer stays in the ICU and longer hospital stays in general than patients with a larger liver remnant (Fig. 2). Thus, there is growing evidence that although mortality is low after extensive

Table 1. Relation between the RLV/FLV ratios and the number of segments resected

RLV/FLV ratio No. patients (%)	< 30% 13 (9%)	30%–40% 23 (17%)	40%–50% 29 (21%)	50%–60% 29 (21%)	> 60% 44 (32%)
No. of segments resected					
6 (n = 10)	2	0	2	3	3
5 (n = 22)	3	3	7	5	4
4 (n = 88)	8	19	18	18	25
3 (n = 18)	0	1	2	3	12

FLV = future liver remnant; RLV = remnant liver volume.

hepatic resection leaving a very small remnant in patients with normal liver, there is a clear trend toward slower recovery, greater need for critical care, and prolonged hospitalization. These are perhaps manifestations of the global physiological importance of a sufficient functioning liver in the postoperative patient.

Results of PVE Before Tight Hemi-Hepatectomy in Patients With Normal Liver

To assess the impact of liver hypertrophy of the future liver remnant volume induced by PVE on the immediate postoperative complications after a standardized major liver resection, we prospectively compared two groups of patients with normal liver who underwent an elective right hemi-hepatectomy.[56] Despite an increase of the left liver volume of 45% in the PVE group, a similar postoperative course was observed between patients with a RLV/FLV ratio of 31% when compared with patients having a RLV/FLV ratio of 47% after PVE. Intraoperative blood loss, incidence and type of postoperative complications, postoperative kinetics of liver function tests, and the duration of in-hospital stays were remarkably similar in patients undergoing right hepatectomy with or without preoperative PVE. Therefore, it seems that the significant hypertrophy of the left liver induced by PVE before a standardized right hemi-hepatectomy brought no measurable impact in terms of postoperative complications.[56]

Indications for Inducing Hypertrophy of the Future Liver Remnant (see Table 2)

Patients With Normal Liver. As shown previously, there are no indications for preoperative PVE when an elective standard hepatectomy up to four segments is planned in patients with a FLR greater than 30%. As suggested by Vauthey and associates, PVE is indicated when the percentage of future functional remnant volume is less than or equal to 25% or when an associated procedure is planned. However, some patients with liver metastasis and a FLR greater than 30% might receive benefit from a preoperative hypertrophy of the FLR. As shown in Table 2, these situations included patients with bilobar metastasis in whom a major hepatectomy is planned, patients in whom a major hepatectomy should be associated with gastrointestinal surgery, and patients

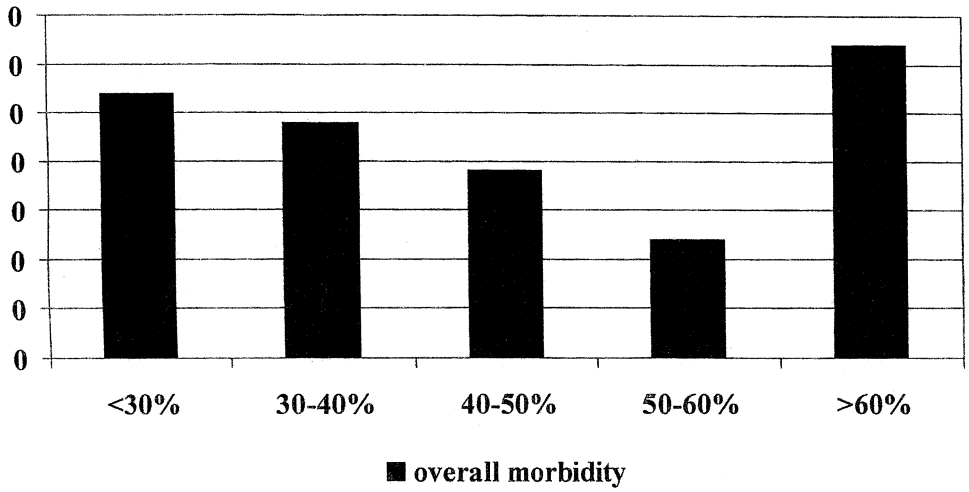

Fig. 1. Relationship between the rate of postoperative complications and the remnant liver volume in a subgroup of patients with normal underlying liver who underwent major liver resection.

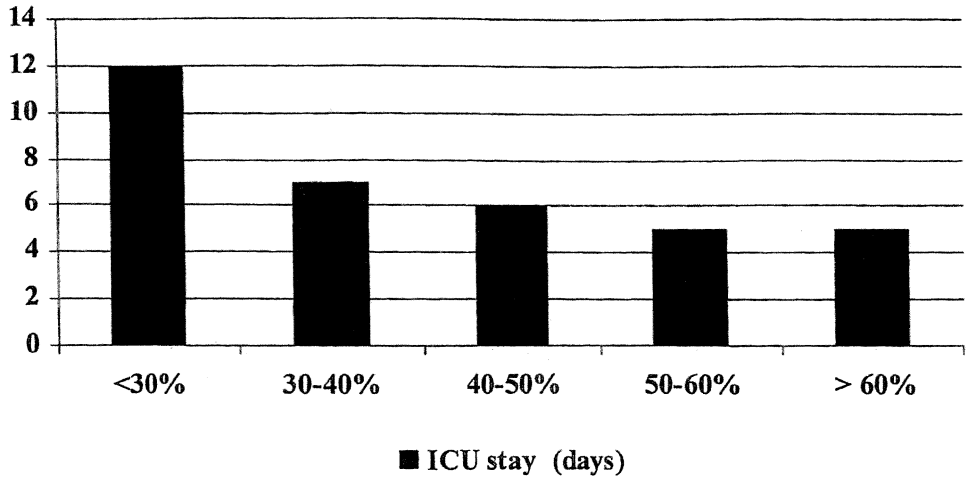

Fig. 2. Duration in the intensive care unit (ICU) according to the remnant liver volume in a subgroup of patients with normal underlying liver who underwent major liver resection.

who were recently treated by irinotecan and third-generation platinum agents. Those new compounds of chemotherapy can induce parenchymal injury of the nontumorous liver including steatosis, vascular injury, and mild fibrosis. Although the concept of postchemotherapy liver disease is not well defined and is unpredictable, some patients experienced delayed liver function recovery after major resection. To use the benefits of diversion of portal flow to the FLR, to avoid the risk of progression of liver disease, and to minimize the risk and number of procedures necessary to treat patients with gastrointestinal tumors with bilobar metastases, we developed a new planned two-step totally surgical approach to clear all primary and metastatic disease.[57] In the first step, the primary tumor and all left-sided liver metastases are resected using straightforward resection techniques. Simultaneously, right portal vein ligation is performed to induce hypertrophy in the left lobe, which has been cleared of all detectable disease.

Table 2. Indications for inducing preoperative hypertrophy of the future liver remnant before major hepatectomy

Patients with underlying normal liver:
● Future remnant liver volume < 30%
● Major hepatectomy associated with gastrointestinal procedure
● Resection of bilobar tumors including a major hepatectomy
Patients with diseased liver
● Cirrhosis
● Severe fibrosis
● Jaundice
● Steatosis > 30%
● Chemotherapy

Four to 8 weeks later, after hypertrophy of the disease-free remnant liver, a second step consisting of a right or extended right hepatectomy is planned to completely clear the remaining right-sided liver metastases.

Patients With Abnormal Liver. We strongly advocate the inclusion of PVE in the management of patients with chronic liver disease or with injured livers (i.e., major steatosis or cholestasis) before any major liver resection.[33,48,50,58] In these patients, the absence of hypertrophy of the nonembolized liver after successful PVE should be considered as an indicator of the absence of liver capacity to regenerate and therefore contraindicate major liver resection.[56]

ARGUMENTS AGAINST A SELECTIVE APPROACH OF PREOPERATIVE PORTAL VEIN EMBOLIZATION BEFORE MAJOR HEPATIC RESECTION

Discussion by Ravi S. Chari, M.D.

The overall hypothesis governing the implementation of portal vein embolization is that in cases when the post-resectional functional liver volume is anticipated to be small, preoperative portal vein embolization will result in increased volume of contralateral liver that is associated with improved function in that portion of the liver, resulting in improved postoperative patient survival. Causality between portal vein embolization, improved liver function, and improved outcome, however, has yet to be established.

From a physiological standpoint, disruption of portal vein venous flow results in increased flow to the contralateral liver resulting in congestion.[59] There is accumulation of periodic acid-Schiff (PAS) positive

material[60] and cell swelling, neither of which is associated with increased metabolic capacity.[61] Furthermore, portal vein embolization results in minimal loss of tissue or necrosis to the ipsilateral side of portal vein embolization. On balance, this induces a different mechanism of cell growth compared with compensatory hyperplasia of regeneration after partial hepatectomy.[62,63] When cells are examined after portal vein embolization, there is increased ploidy (DNA synthesis) but not necessarily an increase in number of cells.[64] As such, there is an extremely variable response to portal vein embolization when performed in the lab.[38] This is similar to clinical experience where the extent and time course after portal vein embolization is unclear. The observations to date suggest that the increase in contralateral liver size is neither predictable nor consistent.

From a radiologic standpoint, although both conventional and helical CT are equally precise in volumetric analyses, each has a standard error of mean of 15%.[65] In general, CT volumes can overestimate true displacement by as much as 10%.[66] This is especially true in a hypertrophying or enlarging liver.[67] Further confounding the issue is the fact that the presence of tumor results in inaccuracies in the calculation of liver volume[30] and that the physiology induced by portal vein embolization can also result in a falsely elevated liver volume.[67] Additionally, day-to-day observer variability of 6%–10% is present and intraobserver variability of 4%–8%[68] may alter or influence assessment of liver volumes. There is no recommended time after portal vein embolization to measure and observe for volume changes.

Overall, because the literature is a series of case reports, there are inconsistent inclusion criteria and the technique has not been well standardized. It is unclear on whom this procedure should be performed. There is a wide range of estimated functional residual volumes that range from 25%–45% of another number: total liver volume, which can be measured on CT scan, measured on CT scan with the tumor volume subtracted, or estimated based on formula.[69] Because of this, the indications are very poorly standardized. The embolization compound varies from absorbable and nonabsorbable and the interval after embolization that repeat imaging should be performed is not defined. Compounding this is the fact that not all individuals respond to this intervention, yet resection is still performed and these patients seemingly do well.[38] Within multiple reports, there are patients without hypertrophic response that are included in the group of "successes," yet the authors fail to establish a functional benefit from the intervention. Improvement of function has been attempted to be measured using methionine PET scanning, ICG excretion, and lidocaine extraction in dog models.[70] None of these have actually clearly demonstrated improved function. The procedure related complications are low.[69] A recent paper by Elias and associates has suggested that there may be an increase in the growth rate of tumors if the tumors are in the contralateral side of the embolization.[71]

A causal link between portal vein embolization and improved clinical outcome is hard to establish because of the inclusion of[59] patients who undergo resection and do well without portal vein embolization when the predicted post-resectional liver volume is less than other patients in whom portal vein embolization is deemed "essential" and[60] patients who do not respond to portal vein embolization and still undergo resection with comparable outcomes to those with a response.[72] These inclusion criteria variances are compounded by the fact that there is no comparative assessment of liver function in the cohorts and the fact that all the reported series are retrospective case reports.

Thus, it is evident that the data supporting port vein embolization to date is limited in scope and is biased. Because of this, it is difficult to establish a benefit for this intervention. There is, however, a defined albeit low complication rate; thus, it would seem that the established role of preoperative portal vein embolization is somewhat limited and it should be confined to a prospective trial where comparable groups of patients are treated with standard methods of embolization and liver volume measurements and the intervention correlated with predefined outcomes.

PROTECTIVE STRATEGIES DURING LIVER INJURY

Pierre-Alain Clavien, M.D.

Few areas in medicine have enjoyed similar success to liver transplantation. As a result the imbalance between organs available for transplantation and the number of patients awaiting an organ has grown dramatically over the past decade triggering an interest to maximize and optimize the use of potential organs. For example, marginal organs (i.e., organs not used previously or expected to be associated with increased risk of malfunction) and partial liver transplantation such as living-related and split liver transplantations are increasingly used in most transplant centers.[73,74] A common issue inherent to all strategies is the need to preserve the graft from the time of harvesting until implantation.[75] From cooling of the graft, initiated in the 1950s, and the introduction of the University of Wisconsin (UW) solution

for cold preservation in the mid-1980s,[76] many experimental studies have suggested novel protective strategies although very few have yet reached clinical practice. Similarly, the volume of liver surgery as part of the transplant process (e.g., living-related liver transplantation) or for resection of tumors has dramatically increased over the past years worldwide[77] and strategies to minimize the negative effects of ischemia are now in the forefront of clinical and experimental studies related to liver resection.

The liver can be subjected to three forms of ischemia, namely cold (or hypothermic), warm (or normothermic), and rewarming.[75] Cold ischemia occurs almost exclusively in the transplant setting where it is intentionally applied to reduce the metabolic activity of the graft while the organ awaits implantation. Warm ischemia occurs in a variety of situations including transplantation, trauma, shock, and liver surgery where hepatic inflow occlusion (Pringle maneuver) or inflow and outflow (total vascular exclusion) are induced to minimize blood loss while dividing the liver parenchyma. Rewarming ischemia typically occurs during manipulation of the graft (e.g., ex situ split liver preparation) or during the period of implantation of the graft when the cold liver is subjected to room or body temperature while performing the vascular reconstruction. Of note, injury to the liver cells after any type of ischemia is mainly detected after reperfusion when oxygen supply and blood elements are restored. Morphological studies in various animal models have shown major differences in the pattern of cold and warm injury. In the 1980s, it was demonstrated that cold ischemia specifically causes injury to the sinusoidal endothelial cell (SEC),[78–80] a finding supported by many subsequent studies.[81–84] Despite structural changes[79,81,85] most SECs remain alive during the period of ischemia,[75] but rapidly die upon reperfusion. The morphological changes typically identified in the endothelial cells result from active processes involving the cytoskeleton and extracellular matrix.[86,87] Adhesion of platelets to the sinusoid lining induces sinusoid endothelial cell apoptosis upon reperfusion of the cold ischemic liver.[88] Models using the isolated perfused rat liver revealed that leukocytes and platelets synergistically exacerbate SEC injury by induction of apoptosis and that Kupffer cells are involved in the mechanism of injury mediated by these cells.[89]

In contrast to cold ischemia, warm (normothermic) ischemia is poorly tolerated and rapidly leads to the death of hepatocytes.[90,91] This severe injury of the hepatocytes is probably preceded by massive death of endothelial cells.[92] The role of Kupffer cells, the resident hepatic macrophages, and adherent leukocytes and platelets remains an area of active investigation. Upon reperfusion, Kupffer cells are activated.[93,94] This is evidenced by structural changes,[93] formation of oxygen free radicals,[95,96] increased phagocytosis and release of lysosomal enzymes,[93] and various cytokines including tumor necrosis factor α (TNF-α).[97,98] Further binding of these cytokines to their respective receptor or release of oxygen free radicals during early stages of reperfusion initiates the complex apoptotic machinery leading to the death of hepatocytes.[98] Leukocyte recruitment into sinusoids during the early phase of reperfusion is mediated through activation of the complement cascade. Complement components can directly cause cell injury by assemblage and deposition on membranes.[99]

The impact of rewarming on the structural integrity of the liver and the mechanism of this type of injury is poorly understood. It probably reflects a combination of cold and warm injury. Many protective strategies have been proposed that can be divided into three different categories: (1) surgical interventions, (2) the use of pharmacological agents, and (3) gene therapy. Strategies aiming at a preemptive induction of tolerance against ischemic injury can be covered by the concept of preconditioning and strategies aiming directly at interfering with the pathways of injury either by inhibiting deleterious molecules or enhancing protective pathways can be covered by the term direct protection.

Two powerful surgical strategies are in clinical use: ischemic preconditioning and intermittent clamping. Other protocols that have demonstrated protection in animal models include preconditioning by hyperthermia[100–105] and application of a portosystemic shunt during the hepatic inflow occlusion,[106] but these approaches never made the transition into clinical practice outside of case reports.

Ischemic preconditioning consists of a brief period of ischemia followed by a short interval of reperfusion before the actual operative procedure with a prolonged ischemic stress.[107] During the operation, hepatic inflow is occluded by placing a vascular clamp or a loop around the portal triad rendering the whole organ ischemic. After an ischemic interval of 10–15 minutes, the clamp is removed and the liver is reperfused for 10–15 minutes before the prolonged ischemic insult. Our current understanding of the underlying biological principle is that cells primed by various kinds of subinjurious stress trigger defense mechanisms against subsequent lethal injury of the same or different type.[108]

The first attempts to minimize ischemic injury were undertaken by interrupting long ischemic periods with multiple short intervals of reperfusion ("intermittent clamping").[109] Although the protective

mechanisms of this concept still remain elusive, intermittent clamping is currently used in practice by many centers. It is assumed that the protective mechanisms are similar to those described in ischemic preconditioning, mainly by reduction of apoptosis.[110] In a prospective randomized study Belghiti and associates demonstrated that cycles of short intervals of ischemia (15 minutes) and reperfusion (5 minutes) provide a high degree of protection in patients undergoing major liver resection.[111]

A number of animal studies indicate that the liver can be preconditioned by temporary exposure of the organ or the whole body to hyperthermia.[101–105,112] The heat stress response is associated with the induction of an intracellular stress protein named heat shock proteins (Hsp). They belong to a class of proteins called chaperones that are involved in protein folding during synthesis and represent cellular mechanisms of protection from protein degradation.

Extracorporeal machine perfusion systems have been proposed as a tool to provide superior tissue preservation and viable nonheart beating donor organs. The aim of such systems is to stop the process of biodegradation.[113,114] By continuously providing the graft with essential substrates (e.g., glucose, amino acids, nucleotides, oxygen) combined with permanent disposal of toxic metabolites,[115] it is expected that organ viability can be better maintained.

A large number of pharmacological agents were shown to confer protection against ischemic injury in the liver. They either block the injurious pathways directly or they subject the liver to preconditioning, that is, they induce a low level of stress to the liver cells, which initiates cellular defense mechanisms against a subsequent stronger insult. Pharmacological strategies target various pathways: antioxidants, inhibitors of intracellular proteases, adenosine agonists and nitric oxide donors, prostaglandins, matrix metalloprotease inhibitors, and inhibitors of TNF-α action have been used with some success. In many cases the mechanism of action is not understood and the specificity of the pharmacological agent is too broad, bearing the danger of systemic side effects.

An example of such a potential pathway is the reactive oxygen species released by activated Kupffer cells after ischemia.[116,117] In hepatocytes, proinflammatory cytokines can induce the formation of reactive oxygen species, for example, TNF-α, interleukin-1, or interferon-γ.[118] Moreover, ischemic cell damage can lead to an intracellular oxidant stress during reoxygenation.[119] Because of the central role of oxidative stress in the setting of ischemia reperfusion, a large number of studies attempted to identify methods to either prevent or neutralize oxidative stress. It has been furthermore demonstrated that strategies aiming at overexpressing antioxidant proteins (e.g., superoxide dismutase[120–122]) may confer protection against extended ischemic injury.

A second example of such a pharmacological target are protease inhibitors and antiapoptotic agents. In a rat model of warm ischemia, Cursio and associates demonstrated maximal caspase activation 3 hours after reperfusion, which preceded morphologic indicators of apoptosis.[123] Pretreatment of the animals with the caspase inhibitor Z-Asp-2,6-dichlorobenzoyloxymethylketone (Z-Asp-cmk) 2 minutes before ischemia efficiently protected rats from lethal liver injury that normally occurred 24–48 hours after surgery.[123,124] Other proteases such as calpain have been reported as mediators of preservation-reperfusion injury through modulation of apoptosis[125] and necrosis.[126] The protective effects of calpain inhibition has been reported in cold and warm ischemic injury.[91,127–129]

Finally, attempts have been made to provide protection using gene therapy approaches. Genes that have been focused on are mainly targeting enzymes involved in the removal of reactive oxygen species, for example, heme oxygenase I[130,131] and superoxide dismutase[120] (SOD) by adenoviral gene therapy. Using a model of partial hepatic ischemia and reperfusion injuries, a beneficial effect of the treatment with SOD was demonstrated. Subsequent studies by others showed that the introduction of genes coding for cytosolic as well as mitochondrial SOD were successfully reducing warm ischemia reperfusion injury.[122] Other gene targets, that is, antiapoptotic proteins such as B-cell lymphocytic-leukemia proto-oncogene-2 binding athanogene-1 (Bcl-2 Bag-1), have been successfully used in animal models. Thus, experimental approaches are demonstrating promising new strategies that will have to be carefully evaluated and await clinical trials.

NEW "BLOODLESS" TECHNIQUES OF LIVER TRANSECTION/AVOIDING INFLOW OCCLUSION: TWO NEW DEVICES FOR TRANSECTION OF THE LIVER

Steven M. Strasberg, M.D.

Most blood loss during liver resection occurs during parenchymal transection. Three strategies have evolved to limit blood loss during transection: (1) temporary occlusion of hepatic blood inflow with or without occlusion of outflow vessels, (2) reduction of pressure in hepatic veins, and (3) prevention of blood loss along the plane of resection. The techniques for limiting blood flow into or out of the liver,

as well as those to lower hepatic pressure, have been standard techniques in liver resection for a number of years. Methods to reduce blood loss while going through the liver include vessel isolation by the classical finger fracture technique, isolation by dissection with surgical instruments, and, more recently, the ultrasonic dissector. Once vessels are isolated, occlusion has been achieved with ligatures, clips, or cautery, either monopolar or bipolar. Additional methods to limit blood loss during resection are the use of deep sutures along the line of resection, liver clamps, and manual compression. The harmonic scalpel can seal blood vessels within the liver, but current models are limited by the size of blood vessels that they can occlude. Therefore, its use is generally limited to the first centimeter or two of hepatic parenchyma. All of the preceding techniques have usually been used in conjunction with intermittent inflow occlusion.

Recently, two devices have been introduced that have the potential for transection of the liver without inflow occlusion. These include a computer-controlled bipolar vessel device marketed as LigaSure by Valleylab, Inc. (Valleylab, Inc., Boulder, CO) and a saline-linked radio frequency (RF) ablation device marketed as the 3.0 dissector-sealer by TissueLink Medical, Inc. (TissueLink Medical, Inc., Dover, NH). To understand why these devices are capable of improved control by cautery, it is necessary to understand why cautery fails to normally be an efficient method for going through the liver.

The purpose of medical electrocautery is to cause heating that itself is produced by to-and-fro movement of charged molecules in an alternating current circuit. If current is dampened by any means, then heating is reduced. The problem with standard electrocautery is that it creates very superficial coagulation secondary to rapid dampening of the current for the following reasons. Medical electrical generators are constructed to increase voltage to maintain current as resistance rises. However, for reasons of safety, there is a maximum allowed voltage. Therefore, if resistance rises too high, voltage will attain a maximum and current will decrease resulting in ineffective heating. Most tissues, including the liver, have low tissue resistance (impedance). If the tissue becomes carbonized, then impedance will rise to a very high level. Only a very thin layer of char is needed to stop electrical current and then there will be no electrical heating. Unfortunately, the older cautery devices rapidly cause surface charring that limits the depth of coagulation. This is immediately visible to any surgeon who has used standard electrocautery on the surface of the liver. The firm black char may be effective in causing coagulation and the cessation of superficial bleeding, but the depth of coagulation is only a few millimeters and the price that is paid for doing this is that current is stopped.

The computer-controlled bipolar vessel-sealing device LigaSure provides currents in bursts. It does so as a result of being able to sense rising impedance. As a result, the temperatures that would reduce current before the tissue was "cooked through" do not occur and there is complete coagulation of the tissue between the blades of the clamp. The saline-linked RF ablator is unipolar equipment. It prevents unwanted high temperatures and charring by maintaining the contact point cool by the infusion of saline. As a result, there is a much greater depth of coagulation possible than with standard cautery.

We have recently published our experience with the bipolar vessels sealing device for parenchymal transection during liver surgery.[132] The first portion of our experience consisted of developing a method of dividing the liver with this equipment without having adhesion of coagulated liver to the clamp. The method basically consists of creating an opening in the liver with a bluntly tapering clamp. The opening so created acts as a tunnel for one blade of the bipolar clamp to be inserted into the liver. The liver is then crushed and power is applied to the crushed tissue that is subsequently cut after removing the clamp.[132]

Our experience with the equipment in the study cited consisted of 27 patients who had a variety of diagnoses. The most common diagnosis consisting of 50% of the patients was metastatic colorectal cancer. Approximately one-half of the resections were major liver resections and a few were enucleations. Inflow occlusion was used only if bleeding became a problem. Our experience showed that the instrument seals vessels and bile ducts effectively in normal parenchyma and that when bleeding occurred, it was because of mechanical injury during dissection rather than failure of vessel sealing. Vascular inflow occlusion was used in only 9% of the patients and the median blood loss in the study was 500 ml. The amount of blood loss and the percent amount of blood transfused compare favorably to other modern series in which inflow occlusion was routine. The device was much less effective on pathological vessels, such as those around cysts, which were to be enucleated.

We have also had considerable experience using the saline-linked cautery device (3.0 dissector sealer). We have studied this device in animals and found that with inflow occlusion it is capable of causing a depth of ablation of greater than 20 mm. Without inflow occlusion the depth of ablation is approximately 15 mm. The time to create a 15 mm depth of ablation is approximately 7 or 8 minutes. Therefore,

using this device one can "precoagulate" along the plane of resection to a depth of over 1 cm. The device is used by coagulating over a linear section of liver to be divided and then coming through the liver with blunt or sharp dissection to the depth of coagulation. The device itself may be used for separating the liver or a sucker or scissors may also be used. Vessels greater than 2 or 3 mm are generally clipped or tied before division. The advantage of the device is that it allows clear isolation of all vascular structures without bleeding. We have now used this device in more than 30 liver resections. Inflow occlusion is distinctly rare and is related to bleeding caused by providing insufficient time to transect the liver. Procedural blood loss has also been low and unrelated to transection of the liver. The current transection time for a major liver resection using this device is between 60 and 90 minutes in our hands and is somewhat slower than the bipolar clamp technique.

It is essential to be aware of the depth of burn and the position of normal structures with this device. Normal structures can be damaged with the saline-linked cautery device just as they can with other forms of RF ablation. Most susceptible to this type of injury are bile ducts. Blood vessels are generally protected by the cooling "heat sink" effect of high blood flow in the vessels. However, veins and arteries can be injured with this device and it is inadvisable to isolate veins and arteries that are subsequently to be used in a vascular anastomosis, for example, donor liver veins from segment VIII and segment V that are to be used for anastomosis in the living related donor operation. The device also has the potential for surface ablation of tumors.

In comparing the two devices for hepatic transection, we have made the following observations. The bipolar clamp is somewhat faster than the saline-linked device but the saline-linked device can probably be used with a lower rate of inflow occlusion and transfusion. The bipolar clamp is not a cancer treatment device but the saline-linked device can be used for ablation of the cut surface of the liver so that it has the capacity to extend resection margins. Both devices will probably find an important place in intraabdominal surgery. The saline-linked cautery device will probably have a particularly important role in hepatic surgery.

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Preoperative Lower Esophageal Sphincter Pressure Affects Outcome of Laparoscopic Esophageal Myotomy for Achalasia

Mustafa A. Arain, M.D., Jeffrey H. Peters, M.D., Anan P. Tambankar, M.D., Giuseppe Portale, M.D., Gideon Almogy, M.D., Steven R. DeMeester, M.D., Peter F. Crookes, M.D., Jeffrey A. Hagen, M.D., Cedric G. Bremner, M.D., Tom R. DeMeester, M.D.

The primary aim of this study was to identify factors that influence outcome of the surgical treatment of achalasia. A secondary aim was to compare outcomes after laparoscopic Heller myotomy and partial fundoplication using either a Dor or Toupet hemifundoplication. Between 1994 and 2002, a total of 78 patients underwent laparoscopic Heller myotomy and partial fundoplication. Preoperative investigations included esophageal manometry, a videoesophogram, and upper gastrointestinal endoscopy with biopsy. In 64 patients (35 males and 29 females), telephone contact was possible at a median 24 months (IQR 14-34). A Dor fundoplication was performed in 41 patients and a Toupet fundoplication in 23. Symptoms were assessed prior to surgery and at follow-up by an independent physician using standardized definitions to grade the severity of dysphagia, regurgitation, and chest pain. To assess outcome, dysphagia was categorized as *persistent* or *resolved*. Persistent was defined as dysphagia that occurred on a weekly or daily basis. Resolved was defined as dysphagia that occurred occasionally or not at all. At follow-up, patients were asked to make a personal evaluation of their outcome as to whether (1) their swallowing was improved by the procedure, (2) they were satisfied with the outcome, and (3) they would undergo surgery again under the same circumstances. There was a significant improvement in dysphagia and regurgitation scores after surgery ($P < 0.05$). The scores for chest pain/heartburn remained unchanged. By physician assessment, dysphagia was resolved in 49 patients (77%) and persisted in 15 (33%). By patient assessment, 62 patients (97%) reported an improvement in the symptom of dysphagia, and 60 (94%) stated that they were satisfied with their improvement and would undergo surgery if they had to make the choice again. On univariate analysis, patients who had resolution of their dysphagia had a significantly higher resting lower esophageal sphincter (LES) pressure prior to myotomy ($P = 0.01$) and on multivariate analysis only a high resting LES pressure prior to surgery was a predictor of resolution of dysphagia ($P = 0.015$). Outcome comparison of patients with Dor and Toupet fundoplications showed no significant differences in physician assessment of postoperative symptom scores and resolution of dysphagia, patient assessment of outcome, or postoperative use of proton pump inhibitors. Ninety-four percent of patients are satisfied with their surgical myotomy for achalasia. By physician assessment dysphagia was resolved in 77% of patients. A high LES resting pressure before surgery predicted resolution of dysphagia. (J GASTROINTEST SURG 2004;8:328–334)

KEY WORDS: Achalasia, laparoscopy, LES, esophagus, myotomy

From the Department of Surgery, Division of Thoracic and Foregut Surgery, Keck School of Medicine, University of Southern California, Los Angeles, California.
Reprint requests: Jeffrey H. Peters, M.D., Professor of Surgery, 1510 San Pablo St., Suite 514, Los Angeles, CA 90033. e-mail: jhpeters@surgery.usc.edu

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The long-term success and safety of laparoscopic myotomy have shifted the balance in favor of surgery as the primary therapeutic option for patients with achalasia.[1] Historical concerns about the morbidity associated with open surgical techniques have essentially disappeared and the morbidity and mortality of both surgical and nonsurgical options are now nearly identical.[2] These changes have focused clinical investigations on improvements in surgical technique and the identification of factors that affect outcome after a myotomy such as (1) prior nonoperative treatment, (2) the degree of dilation and anatomic distortion of the esophageal body, (3) the magnitude of the resting and residual pressures of the lower esophageal sphincter (LES) prior to myotomy, and (4) the addition of and type of antireflux procedure added as an adjunct to myotomy.[3–12]

The primary aim of this study was to identify factors that influence outcome of the surgical treatment of achalasia. A secondary aim was to compare outcomes after laparoscopic Heller myotomy and partial fundoplication using either a Dor or Toupet hemifundoplication.

PATIENTS AND METHODS

Study Population

The study population consisted of 78 consecutive patients with achalasia who underwent a laparoscopic myotomy and partial fundoplication between July 1994 and May 2002. Follow-up was complete in 64 patients (84%) at a median of 24 months. There were 35 males and 29 females whose median age was 50 years (range 13 to 78 years).

Symptomatic and physiologic characteristics of the study population are summarized in Tables 1 and 2, respectively. At the time of the initial presentation, achalasia had been diagnosed or was suspected in 52 (81%)of the 64 patients. A delay in diagnosis was most commonly caused by attributing the symptoms to gastroesophageal reflux disease.

Prior to the correct diagnosis of achalasia, proton pump inhibitors were prescribed in 31 (48%) of 64 of patients, a cholecystectomy was performed in one, and surgery for suspected sleep apnea was performed in another.

Table 1. Clinical characteristics of the study population (n = 64)

Clinical characteristics	No. of patients	%
Symptoms		
Dysphagia	64	100
Regurgitation	63	98
Chest pain	39	66
Weight loss	31	48
Previous therapy		
PPI use	31	48
Pneumatic dilation	10	15.6
Botox	8	12.5
Botox and pneumatic dilation	4	6.3

PPI = Proton pump inhibitor.

Table 2. Clinical studies prior to surgery

Study	No. of patients	Median ± IQR	%
Manometry (n = 59)			
LES pressure (mm Hg)	—	33.6 (range 24.7–41.2)	—
No previous treatment	42	34.1 (range 25.4–40.0)	—
Dilation or Botox	17	33.2 (range 23.6–41.2)	—
LES overall length (cm)	—	3.1 (range 2.6–3.6)	—
LES abdominal length (cm)	—	2.0 (range 1.4–2.4)	—
24-hour pH (n = 10)			
Increased acid exposure	0	—	0
Endoscopy (n = 64)			
Erosive esophagitis	15	—	25
Barrett's epithelium	2	—	3.1
Intestinal metaplasia on biopsy	3	—	4.7
Barium swallow (n = 64)			
Hiatal hernia	6	—	9
Epiphrenic diverticulum	1	—	1.5

Preoperative Investigations

Preoperative investigations included esophageal manometry, a videoesophogram, and upper gastrointestinal endoscopy with biopsy in all patients. Twenty-four-hour esophageal pH monitoring was performed selectively.

Standard esophageal motility studies were performed after an overnight fast using a nine-hole catheter and a water perfusion technique as previously described.[13] LES resting pressure was measured at

the respiratory inversion point and the resting pressure, overall length, and abdominal length were calculated from the mean of five recordings. LES relaxation was measured using four channels placed within the LES at the same level.[14] A total of five wet swallows were analyzed and the residual pressure in the LES channels was recoded at the onset of the esophageal contraction wave in the esophageal channel 5 cm proximal to the LES channels. The mean residual pressure for each channel was calculated. LESr relaxation was considered to be complete if the mean residual pressure in all four channels fell to less than the 7.5 mm Hg (ninety-fifth percentile of normal), incomplete if the residual pressure remained above 7.5 mm Hg in one or more channels, and absent if there was no change in residual pressures. Manometric LES parameters could not be obtained in five patients because of difficulty in passage of the catheter or patient intolerance. Esophageal body motility was assessed by placing the first port 1 cm below the cricopharyngeus with the remaining four ports trailing at 5 cm intervals.[15] A total of 10 wet swallows of 5 ml of distilled water with a 20-second interval between each swallow were analyzed. Achalasia was diagnosed by the presence of incomplete relaxation of the LES and aperistalsis of the esophageal body. A hypertensive LES and pressurization of the esophageal body when present were recorded but were not required for the diagnosis. Vigorous achalasia, that is, the presence of nonperistaltic esophageal contractions greater than 38 mm Hg, was also recorded.

Esophageal pH monitoring was performed using a standard electrode (Medtronic Functional Diagnostics, Minneapolis, MN) placed 5 cm above the upper border of the manometrically defined LES. Patients with an esophageal pH <4 for more than 4.4% of the recording time were classified as having abnormal esophageal acid exposure.[16] The pattern of the pH tracing was analyzed to differentiate true gastroesophageal reflux from pH changes secondary to fermentation of ingested food within the esophageal body.[17]

A barium videoesophogram was obtained to assess the vertical axis of the esophagus, the degree of dilatation of the esophageal lumen, and the presence of a "bird-beak" deformity at the gastroesophageal junction.

Upper gastrointestinal endoscopy with biopsies was performed prior to surgery to exclude pseudoachalasia and to obtain histologic evidence of esophagitis and Barrett's esophagus.

Operative Technique

A surgical myotomy was performed laparoscopically in all patients. Briefly, the procedure began by mobilization of the fundus off the left lateral crus and dividing the proximal short gastric vessels. The fat pad was removed form the gastroesophageal junction exposing the distal esophagus and cardia. An 8 to 10 cm myotomy of the esophageal body was performed and extended 1 to 2 cm onto the stomach.[18] The myotomy was accompanied by an antireflux procedure in all patients. A Toupet fundoplication was fashioned in 23 patients and a Dor fundoplication in 41.[19,20]

Measurement of Outcome

Symptoms were assessed prior to surgery and at follow-up by an independent physician other than the operating Treatment surgeon by using standardized definitions to grade the severity of dysphagia, regurgitation, and chest pain (Table 3). Patients' assessment of the outcome of their surgery was done at the last follow-up evaluation.

An emphasis was placed on the symptom of dysphagia and was categorized as follows: *none*, when no dysphagia symptoms were present; *occasional* when dysphagia symptoms occurred less than once a month; *weekly*, when dysphagia symptoms occurred more than once a month but not on a daily basis; and *daily* when dysphagia symptoms occurred on a daily basis. To assess outcome, dysphagia was categorized as *persistent* or *resolved*. Persistent was defined as dysphagia that occurred on a weekly or daily basis. Resolved was defined as dysphagia that occurred occasionally or not at all.

The etiology of the symptoms of chest pain and heartburn in patients with achalasia is an enigma.[17,21]

Table 3. Scoring system

Score	Dysphagia	Regurgitation	Chest pain/ heartburn
0	None	None	None
1	Monthly	Monthly	Not requiring regular PPI medication
2	Weekly	Weekly	Requiring regular PPI medication
3	Daily	Daily	Disabling
4	Food impaction, self-induced regurgitation, inability to maintain weight, requiring TPN	Aspiration, pneumonia, having to sleep upright	—

PPI = proton pump inhibitor; TPN = total parenteral nutrition.

The correlation between esophageal body contractions with chest pain and the correlation of heartburn to distal esophageal acid exposure are poor. Further, it has been suggested that in patients with achalasia, chest pain may be misinterpreted as heartburn.[21] For these reasons we made no distinction between the symptoms of heartburn and chest pain. To quantify the symptoms of chest pain/heartburn, patients were graded according to the effect and frequency of proton pump inhibitor medications (see Table 3).

Patient assessment was done by asking each patient to make a personal evaluation of his or her outcome as to whether (1) their swallowing was improved by the procedure, (2) they were satisfied with the outcome, and (3) they would undergo surgery again under the same circumstances.

Statistical Analysis

Fisher's exact test was used to compare proportions between individual groups, the Wilcoxon matched-pairs test was used to compare paired observations, and the Mann-Whitney U test was used to compare continuous data between individual groups. Multivariate analysis was used to identify indepent predictors for resolution of dysphagia. $P < 0$ .05 was accepted as significant. The software packages GraphPad Prism version 3.02 (GraphPad Software, Inc., San Diego, CA) and SPSS 10.0.1 standard version for Windows (SPSS Inc., Chicago, IL) were used for statistical analyses.

RESULTS

Effect of Myotomy on Preoperative Symptoms

Symptomatic assessment of myotomy was made at a median of 24 months after surgery (range 6 to 99.8 months). By physician assessment, dysphagia was resolved in 49 patients (77%) and persisted in 15 (33%) (Table 4). Of the 15 who had persistent dysphagia, six had it once per week and nine had it daily. Overall, the median dysphagia score decreased from 3 to 1 ($P < 0.05$) after surgery. By patient assessment, 62 patients (97%) reported an improvement in the symptom of dysphagia, and 60 (94%) stated that they were satisfied with their improvement and would undergo surgery if they had to make the choice again.

Table 4. Physician assessment of dysphagia after surgery (n = 64)

Dysphagia	No. of patients	%
Resolved	49	77
None	21	33
Occasional	28	44
Persistent	15	23
Weekly	6	9
Daily	9	14

The most marked improvement occurred for the symptom of regurgitation. The number of patients who complained of regurgitation decreased from 63 to 15 after surgery (74% improvement). Of the 15 who had postoperative regurgitation, all but one had regurgitation less than once per month. Overall, the median regurgitation score decreased from 3.5 to 0 ($P < 0.05$) after surgery.

The symptom of chest pain/heartburn showed the least improvement. The number of patients with chest pain/heartburn decreased from 45 to 37 after surgery (18% improvement). Of the 37 who had chest pain/heartburn, 11 took regularly took proton pump inhibitors and 3 of these 11 had symptoms despite the medication. Twenty-four-hour esophageal pH monitoring was performed in two of these three patients, and acid exposure time was normal for both. Four other patients were suspected of having acid-induced chest pain/heartburn and also underwent 24-hour esophageal pH monitoring. It was positive in only one of the four. Overall, the median chest pain/heartburn score of 1 prior to surgery remained unchanged after surgery.

Factors Associated With Persistent Dysphagia

The characteristics prior to surgery of patients whose dysphagia resolved or persisted after myotomy are compared in Table 5. On univariate analysis, patients who had resolution of their dysphagia had a significantly higher LES resting pressure prior to myotomy ($P = 0.01$) (Fig. 1). On multivariate analysis of the characteristics in Table 5, only a high resting LES pressure prior to surgery was a predictor of resolution of dysphagia ($P = 0.015$). The relationship of resolved or persistent dysphagia to 10 mm Hg increments in LES resting pressure is shown in Fig. 2.

Comparison of Outcome to the Type of Fundoplication

The median follow-up for the Toupet and Dor fundoplication was 39.4 and 16.0 months, respectively ($P < 0.05$). Outcome comparisons at this time interval showed no significant differences in physician assessment of postoperative symptom scores and resolution of dysphagia, postoperative use of proton pump inhibitors, or patient assessment of outcome (Table 6).

DISCUSSION

Recently published studies in achalasia patients treated with laparoscopic Heller myotomy have shown

Table 5. Comparison of patients with resolution or persistence of dysphagia

Characteristics	Resolved (n = 49)	Persistent (n = 15)	Difference
Age (yr)	46.7	50.4	NS
Males/females	25/24	10/5	NS
BMI (kg/m^2)	23.7	25.4	NS
Duration of symptoms (mo)	61.8	123	NS
Botox/dilation	17	5	NS
LES			
Resting pressure (mm Hg)	35.9*	24.5†	$P = 0.01$
Overall length (cm)	3.3*	2.7†	NS
Abdominal length (cm)	2.0*	1.9†	NS
Hiatal hernia	4	2	NS
Dor/Toupet fundoplication	31/18	10/5	NS
Duration of follow-up (mo)	25	28.4	NS

BMI = body mass index; NS = not significant.
*Number of patients = 46.
†Number of patients = 12.

an 85% to 95% relief in dysphagia.[22–26] These studies often rely on the patient's own assessment of his or her symptoms. Using similar criteria 96% of our patients have reported relief of their dysphagia. There are two problems with this approach. First, patients with achalasia often modify their diet to avoid the symptom of dysphagia. Second, persistent outflow resistance of the esophagus coupled with esophageal dilatation results in the equivalent of a functional forestomach allowing the patient to comfortably ingest

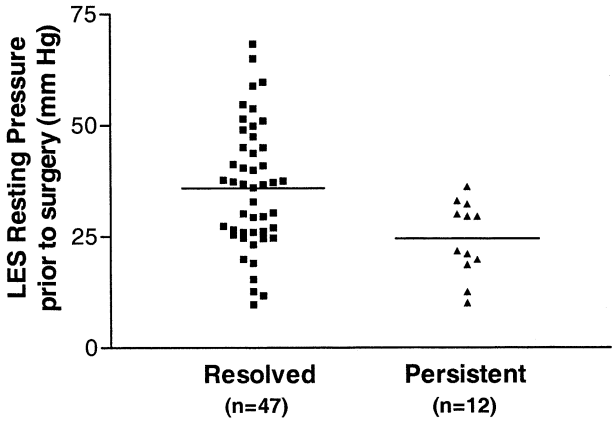

Fig. 1. Comparison of lower esophageal sphincter (*LES*) resting pressure prior to surgery in patients with resolution or persistence of dysphagia after surgery ($P < 0.05$).

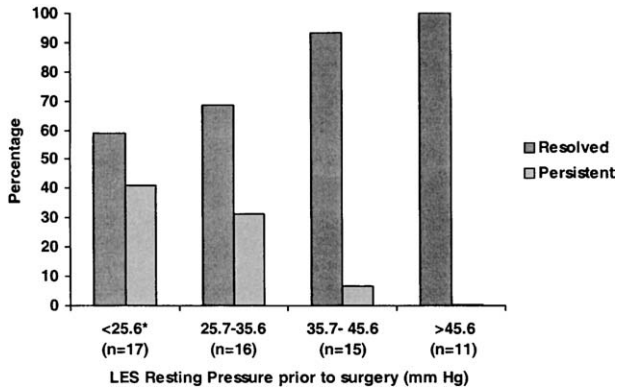

Fig. 2. Relationship of 10 mm Hg increments in lower esophageal sphincter (*LES*) resting pressure prior to surgery to resolution or persistence of dysphagia. Chi-square test for trend $P < 0.01$. * = Ninety-fifth percentile of LES resting pressure in 50 healthy volunteers studied at our institution.

an increased volume of food. Both factors may overestimate the therapeutic effectiveness of the myotomy.

A more critical analysis of the results of therapy requires an objective measurement of esophageal

Table 6. Comparison of outcome with Dor and Toupet fundoplication

Assessment after surgery	Dor (n = 41)	Toupet (n = 23)	Difference
Median follow-up (mo)	16	39.4	$P < 0.05$
Dysphagia*			
Resolved	31 (76%)	20 (78%)	NS
Persistent	10 (24%)	5 (22%)	NS
Frequency of dysphagia*			
None	13 (32%)	8 (35%)	NS
Occasional	18 (44%)	10 (43%)	NS
Weekly	4 (10%)	2 (9%)	NS
Daily	6 (14%)	3 (13%)	NS
Median symptom score*			
Dysphagia	1	1	NS
Regurgitation	0	0	NS
Chest pain/ heartburn	1	1	NS
PPI use	6 (14%)	5 (22%)	NS
Patient assessment			
Swallowing improved	40 (97%)	22 (96%)	NS
Satisfied with swallowing	38 (93%)	22 (96%)	NS
Would have surgery again	38 (93%)	22 (96%)	NS

PPI = proton pump inhibitor.
*Physician assessment.

emptying such as a timed barium esophagram. Our own experience and that of others is that patients who are satisfied with their outcome are reluctant to have even simple studies done, and the cost of performing the studies has become problematic. We had an independent physician grade the symptom of dysphagia and regurgitation in order to evaluate the patients more objectively. Standardized definitions were used based on the frequency with which these symptoms occurred. We found that 77% of patients (49 of 64) had resolution of their dysphagia. This degree of resolution is lower than other published results for myotomy but in our minds more realistic.

The primary aim of our study was to identify factors that influence the outcome of surgery in patients with achalasia. We found that patients who had a good outcome had a high LES resting pressure before surgery (see Fig. 1). Further there was a trend showing that the higher the resting LES pressure was before surgery, the better the outcome of a myotomy (see Fig. 2). An important observation was that patients with a LES resting pressure greater than 36 mm Hg before surgery all had resolution of their dysphagia. Multivariate analysis of major factors influencing the results of myotomy showed that LES resting pressure before surgery was statistically the only predictor of outcome, emphasizing that sphincter pressure is a key component in the disease. The concept of using resting LES pressure as a predictor of outcome adds to the established convenience, safety, and therapeutic benefit of laparoscopic Heller myotomy. Providing a dependable predictor of treatment outcome will encourage continuation of the trend for patients with achalasia to pursue surgical therapy. In fact, most physicians would agree that laparoscopic Heller myotomy should now be considered the therapy of choice for achalasia.

The need to add an antireflux procedure to a myotomy has been controversial.[10,27–29] Opponents argue that the addition of a fundoplication to a myotomy adds outflow resistance to an already compromised esophageal body and is counterproductive. They state that with meticulous dissection an adequate myotomy can be achieved without disruption of the natural antireflux mechanisms of the gastroesophageal junction. Proponents argue that disruption of the normal reflux mechanisms during surgery and extension of the myotomy on to the gastric cardia increase the risk of gastroesophageal reflux after surgery. They state that an antireflux procedure is essential in order to protect against long-term complications associated with gastroesophageal reflux. Because we agree with the latter, our second aim was to determine whether there was difference in the degree of fundoplication by comparing the outcomes of two commonly performed antireflux procedures: the 180-degree Dor fundoplication and the 270-degree Toupet partial fundoplication. There was no difference between the procedures with regard to the relief of dysphagia, regurgitation, or chest pain/heartburn. Furthermore, the need for proton pump inhibitor therapy after surgery was similar in both. We recognize however, that the number of patients in each group was small creating the possibility of a type II error (i.e,. too small of a sample size to detect a small difference in outcome). A large multicenter prospective randomized study to address this question is currently underway. Donahue et al.[30] reported similar results in a series of 48 patients (25 Toupet, 23 Dor). In contrast, Raiser et al.[31] compared outcomes in 10 patients with Dor fundoplication to outcomes in 29 with Toupet fundoplication and found that the latter group had less dysphagia and heartburn after surgery; however, the difference lost statistical significance in long-term follow-up. Proponents of the Toupet fundoplication propose that the procedure has the advantage of holding the cut edges of the myotomized muscle open. Opponents argue that a posterior partial fundoplication may actually cause dysphagia by anterior angulation of the esophagus.[32] Surgeons who favor the Dor partial fundoplication state that it is much easier to perform, requires minimal mobilization of the distal esophagus and stomach, and places a fundic patch over the myotomy site to protect the mucosa and prevent rehealing of the myotomy. Opponents state that the size of the fundoplication is insufficient to protect against reflux. We have shown that there is no difference in outcomes between the two types of fundoplications with regard to the relief dysphagia or the use of proton pump inhibitors. This, plus the ease and limited dissection necessary to perform the Dor partial fundoplication, makes it the antireflux procedure of choice to be used with a myotomy in the treatment of achalasia. The Toupet procedure should be reserved for situations where there has been extensive dissection of the hiatus during the repair of an associated hiatal hernia or excision of an associate epiphrenic diverticulum.

CONCLUSION

Ninety-four percent of patients were satisfied with their surgical myotomies for achalasia. By physician assessment dysphagia was resolved in 77% of patients. A high LES resting pressure prior to surgery predicted resolution of dysphagia. The type of partial fundoplication, Dor or Toupet, did not significantly change outcome after surgery.

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Effects of Manometrically Discovered Nonspecific Motility Disorders of the Esophagus on the Outcomes of Antireflux Surgery

Vic Velanovich, M.D., Arvind Mahatme, M.D.

Nonspecific motility disorders (NMDs) of the esophagus are common manometric findings in patients evaluated for gastroesophageal reflux disease (GERD). However, it is unclear how these disorders affect the outcomes of antireflux surgery. The purpose of this study was to assess symptomatic outcomes of patients with and without NMDs undergoing surgical treatment for GERD. A prospectively gathered database of all patients undergoing antireflux surgery was retrospectively reviewed for preoperative symptoms, symptom severity using the GERD-HRQL (best score 0, worst score 50), esophageal manometry measurements, presence of NMD, type of operation, any transient or permanent postoperative dysphagia, severity of postoperative dysphagia (best score 0, worst score 5), and postoperative symptom severity. A total of 239 patients were studied; 24% had a NMD identified by preoperative esophageal manometry, and 17% of this +NMD group had preoperative dysphagia or atypical chest/epigastric pain compared to 28% of those without a NMD (−NMD group) (P = NS). Preoperative symptom scores were +NMD 33 vs. −NMD 27 (P = 0.01). Postoperative symptom scores were +NMD 5 vs. −NMD 3 (P = NS). There were no differences in preoperative or postoperative dysphagia scores. Transient postoperative dysphagia was 15.8% in the +NMD group vs. 16.4% in the −NMD group (P = NS). Postoperative dilation was 0% in the +NMD group vs. 2% in the −NMD group (P = NS). Manometrically discovered NMDs do not appear to affect preoperative symptoms or symptomatic outcomes of patients surgically treated for GERD. These findings my reflect the severity of GERD and may improve with antireflux surgery. (J GASTROINTEST SURG 2004;8:335–341)

KEY WORDS: Esophageal motility disorders, gastroesophageal reflux disease, antireflux surgery, Nissen fundoplication

Esophageal manometry is a frequently used diagnostic tool in the evaluation of patients with symptoms from a presumed esophageal source. Indications for its use include dysphagia, gastroesophageal reflux, noncardiac chest pain, exclusion of generalized gastrointestinal disease (e.g., scleroderma or chronic idiopathic pseudoobstruction), and exclusion of an esophageal etiology for anorexia nervosa.[1] This has led to the characterization of a number of disorders of esophageal motility. These abnormalities of esophageal motility have been categorized into four basic groups as follows: (1) inadequate lower esophageal sphincter (LES) relaxation (e.g., achalasia); (2) uncoordinated contraction (e.g., diffuse esophageal spasm); (3) hypercontraction (e.g., nutcracker esophagus); and (4) hypocontraction (e.g., ineffective esophageal motility).[2,3] However, motility abnormalities are identified by esophageal manometry, which does not fit nicely into any one of these categories. These have been called *nonspecific esophageal motility disorders*.[2,4]

Esophageal motility disorders can be associated with a variety of symptoms and may be primary or secondary phenomena. Gastroesophageal reflux disease (GERD) and esophageal motility disorders can potentiate each other. Prolonged GERD has been shown to cause a deterioration of esophageal motor function.[5,6] Patients with ineffective esophageal motility seem to have worse GERD as a result of poor esophageal clearance.[7] In addition, motility disorders are found more frequently in patients with noncardiac

From the Division of General Surgery, Henry Ford Hospital, Detroit, Michigan.
Reprint requests: Vic Velanovich, M.D., Division of General Surgery, K-8, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202-2689. e-mail: vvelano1@hfhs.org

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chest pain and nonobstructive dysphagia.[2–4,8] Although the effects of ineffective esophageal motility and poor esophageal peristalsis on the outcomes of antireflux surgery have been studied,[7,9] whether these unnamed nonspecific motility disorders (NMDs) affect postoperative symptoms is less clear. The hypothesis of this study is that minor motor disorders of the esophagus do not affect the symptomatic results of antireflux surgery.

MATERIAL AND METHODS

Patients

A database is maintained by the senior author (V.V.) on all patients who undergo any type of antireflux surgery. This database contains information on patient's age, sex, symptoms and their severity (as measured by the GERD-HRQL[10]), preoperative physiologic testing (esophageal manometry, 24-hour esophageal pH monitoring, esophagography, endoscopy, and gastric emptying scintigraphy), operation performed, complications, and symptomatic outcome. Histologic analysis of biopsy specimens is not kept in the database. The database was retrospectively reviewed for all patients who have had an antireflux procedure, excluding those who underwent surgery for a paraesophageal hernia but including redo operations. Data collected included preoperative symptoms, symptom severity (defined by the GERD-HRQL scores), esophageal manometry results (i.e., LES pressure, esophageal body peristaltic amplitude, presence of minor motor disorders), type of operation performed, any transient or permanent postoperative dysphagia, and postoperative symptom severity. The database was reviewed for patients undergoing antireflux surgery from July 1996 to December 2001, inclusive.

The GERD-HRQL instrument is a 10-item Likert-type questionnaire that has been previously described.[10] Each question is scored by the patient from 0 to 5 based on anchors for each score (e.g., 0 is asymptomatic, 5 is incapacitating—unable to do daily activities). The total GERD-HRQL score is the sum of the scores for each of the 10 questions; therefore, the best possible score is 0 (asymptomatic in all 10 items) and the worst possible score is 50 (incapacitating—unable to do daily activities in all 10 items). One particular question (No. 7) asks, "Do you have difficulty swallowing?" This is the dysphagia question, and this will be analyzed separately.

Esophageal Manometry

All esophageal manometry studies were performed in the Henry Ford Hospital Gastroenterology Laboratory by trained gastroenterologic nurses and read by staff gastroenterologists (see acknowledgments). Equipment used was the Polygraf 98 Manometry program, Mui Scientific Manometric pump, and Medtronic Zinetics Quad lumen 5 cm staggered water perfusion catheter (Medtronic, Minneapolis, MN).

The patient is given nothing by mouth for 6 hours and has not taken muscle relaxants for 24 hours prior to the test. The catheter is placed 70 cm into the stomach. The patient is placed in a supine position or the head of the bed may be slightly elevated. The manometric pump is turned on to begin the water infusion. Tracings are begun and the catheter is zeroed in the stomach. The catheter is withdrawn in 1 cm increments using the "slow pull-through" method, and the patient is asked to take a deep breath in and out to check the tracings. As the proximal lumen approaches the LES, a rise in pressure is noted. The patient is given a 5 cc sip of water and asked to swallow. As the patient swallows, a tracing is recorded. The catheter is then withdrawn another 1 cm, and if the pressure is maintained, another swallow is recorded. This is repeated until the lumen is out of the LES. In the LES, at least two tracings of the maximum pressure and two swallows are recorded. The catheter is then withdrawn in the same manner, and in 5 cm the LES pressure will again be apparent as the catheter has 5 cm spacings between the lumens. The maximum LES pressure tracings and wet swallows are recorded for the four lumens. When the distal lumen exists, the LES and the pressure drops, and the catheter is withdrawn 3 cm into the body of the esophagus. The LES length is not measured.

With the catheter in the body of the esophagus, it will be apparent that the distal lumen is no longer in the LES. Therefore peristaltic amplitudes are measured in the distal esophagus. A series of 10 wet swallows are performed in the stationary site. There is a 20-second delay between the swallows. The upper esophageal sphincter is measured after the catheter is pulled back and an increase in pressure is noted. The patient is then asked to perform two dry swallows, and the maximum pressure for the upper esophageal sphincter is recorded.

The manometric records of all patients with NMDs were reviewed to confirm abnormal findings.

Definition of Nonspecific Motility Disorders

NMDs for the purposes of this study are defined as abnormal contractions of the esophagus identified by manometry, which are otherwise unnamed.[2–4] Specifically, all named esophageal motility disorders (e.g., achalasia, nutcracker esophagus, hypertensive LES, and diffuse esophageal spasm) were excluded. In addition, hypocontractile esophageal peristalsis (i.e.,

esophageal body peristaltic amplitudes of <50 mm Hg) and specifically ineffective esophageal motility[11] (defined as the sum total of low-amplitude peristaltic contractions [<30 mm Hg] and nontransmitted contractions ⩾30% of the total number of wet swallows) without abnormal contractions were excluded from this definition. The contractions presented in Table 1 are all the abnormal contractions we are identifying as NMDs. In defining NMDs in this manner we are aiming to study the manometric findings that seem not to have clear clinical significance.

Operations

All operations were performed by or under the direct supervision of the senior author (V.V.). The operation of choice was a laparoscopic Nissen fundoplication. Initially patients with hypocontractile esophageal peristalsis were treated with a partial fundoplication (i.e., a Toupet fundoplication), but with the publication of studies demonstrating a high rate of recurrent reflux with this operation,[12] all patients are now offered a Nissen fundoplication. Some patients were offered an open (through a midline laparotomy) Nissen or Toupet fundoplication based on prior abdominal surgery, whereas others requested the open operations. Patients with foreshortened esophagi were offered Collis-Nissen fundoplications, all of which were done through a midline laparotomy. All redo operations were done as open procedures.

Follow-up was with the senior author (V.V.) routinely for 6 weeks or longer if the situation warranted. For the purposes of this study, patients were contacted by telephone to assess symptoms. The median follow-up in this study was 30 months (range 2 to 72 months).

Table 1. Nonspecific motility disorders identified by esophageal manometry in 57 patients

Minor motor disorder	Number identified*	% of patients†
Spontaneous contractions	16	28%
Simultaneous contractions	12	21%
Nonpropagating contractions	15	26%
Double-peaked contractions	12	21%
Wide-body contractions	7	12%
Repetitive/secondary contractions	5	9%
"Abnormal"/nonspecified contractions	7	12%

*Total number of abnormal contractions larger than number of patients because many patients had more than one abnormality noted on esophageal manometry.
†Percentage greater than 100% because many patients had more than one abnormality noted on esophageal manometry.

Statistical Analysis

Nominal data were analyzed by means of Fisher's exact test. Continuous data were first analyzed using the Wilk-Shapario test. The data for the GERD-HRQL scores were found not to follow a gaussian distribution. Therefore these data are presented as medians with ranges and were analyzed nonparametrically using the Mann-Whitney U test. The data for the esophageal manometry measurements were found to follow a gaussian distribution. These data are presented as means ± standard deviations and analyzed using Students' t test. A value of $P \leqslant 0.05$ was considered significant.

RESULTS

Demographics

A total of 239 patients were included in this study. One hundred eighty-two did not have nonspecific motility disorders of the esophagus (−NMD), whereas 57 did (+NMD). In the −NMD group, 57% were male, with an average age of 45 ± 13 years; 131 (72%) underwent laparoscopic Nissen fundoplications, 24 (13%) had open Nissen fundoplications, 13 (7%) had laparoscopic Toupet fundoplications, seven (4%) had open Toupet fundoplications, four (2%) had Collis-Nissen fundoplications, and three (2%) had redo Nissen fundoplications. In the +NMD group, 61% were male, with an average age of 50 ± 14 years; 48 (84%) underwent laparoscopic Nissen fundoplications, seven (12%) had open Nissen procedures, and two (4%) had laparoscopic Toupet fundoplications. Twenty-six percent of patients undergoing a Nissen fundoplication had an NMD compared to 14% of patients undergoing a Toupet fundoplication. Table 1 shows the type and number of NMDs identified. All of these were contractions that were either not part of the propagating peristaltic wave or otherwise not of normal morphology.

Preoperative Comparisons

Seventeen percent of patients in the +NMD group had preoperative dysphagia and/or chest pain compared to 28% of the −NMD group, although this difference was not statistically significant. When analyzed by type of operation, in the −NMD group 29% of the Nissen patients and 28% of the Toupet patients had preoperative dysphagia/chest pain, whereas in the +NMD group 17% of the Nissen patients had preoperative dysphagia/chest pain. Because there were only two +NMD patients who underwent Toupet fundoplication, meaningful analysis could not be done in this group.

The median total GERD-HRQL preoperative score for the +NMD group was 33 (range 24) compared to 27 (range 32) for the –NMD group ($P = 0.01$). This implies that overall, the +NMD group had more severe symptoms. Fig. 1 shows the groups when analyzed by type of operation. There was no difference between operation groups for the −NMD patients. Once again, the +NMD/Toupet group was too small to provide meaningful analysis. However, both groups had similar dysphagia scores: +NMD 2 (range 4) vs. −NMD 2 (range 5), (P = NS).

Fig. 2 compares the esophageal manometry measurements for each group. Both groups had similar LES pressures (+NMD 10.5 ± 4.8 mm Hg vs. −NMD 10.6 ± 5.5 mm Hg, P = NS). All patients had greater than 80% relaxation of the LES. However, +NMD patients had an average lower esophageal body peristaltic amplitude (+NMD 51.3 ± 20.8 mm Hg vs. −NMD 68.4 ± 28.3, $P < 0.0001$). The average preoperative DeMeester scores as determined by 24-hour esophageal pH monitoring were similar (+NMD 55.8 ± 30.6 vs. −NMD 56.1 ± 40.4, P = NS).

Postoperative Comparisons

Fig. 3 presents postoperative symptom severity. For both the +NMD and −NMD groups there was a statistically significant improvement in total and dysphagia-specific GERD-HRQL median scores. For the +NMD group the improvement was from 33 (range 24) to 5 (range 20) ($P < 0.0001$). For the −NMD group the improvement was from 27 (range 32) to 3 (range 32), $P < 0.0001$. There was no statistically significant difference between these groups with respect to postoperative total GERD-HRQL score. Similarly, both groups had statistically significant improvement in dysphagia scores. For the +NMD group the improvement was from 2 (range 4) to 0.5 (range 4) ($P = 0.03$), whereas for the −NMD group, the improvement was from 2 (range 5) to 0 (range 5) ($P < 0.0001$). There was no statistically significant difference between the groups with respect to postoperative dysphagia scores. Postoperatively 6.6% of −NMD patients complained of persistent or recurrent heartburn, whereas 8.8% of +NMD patients had heartburn (P = NS).

Transient dysphagia occurred in 16.4% of −NMD patients compared to 15.8% of +NMD patients (P = NS). Three −NMD patients (2%) ultimately required esophageal dilation to relieve their dysphagia as compared to none of the +NMD patients (P = NS).

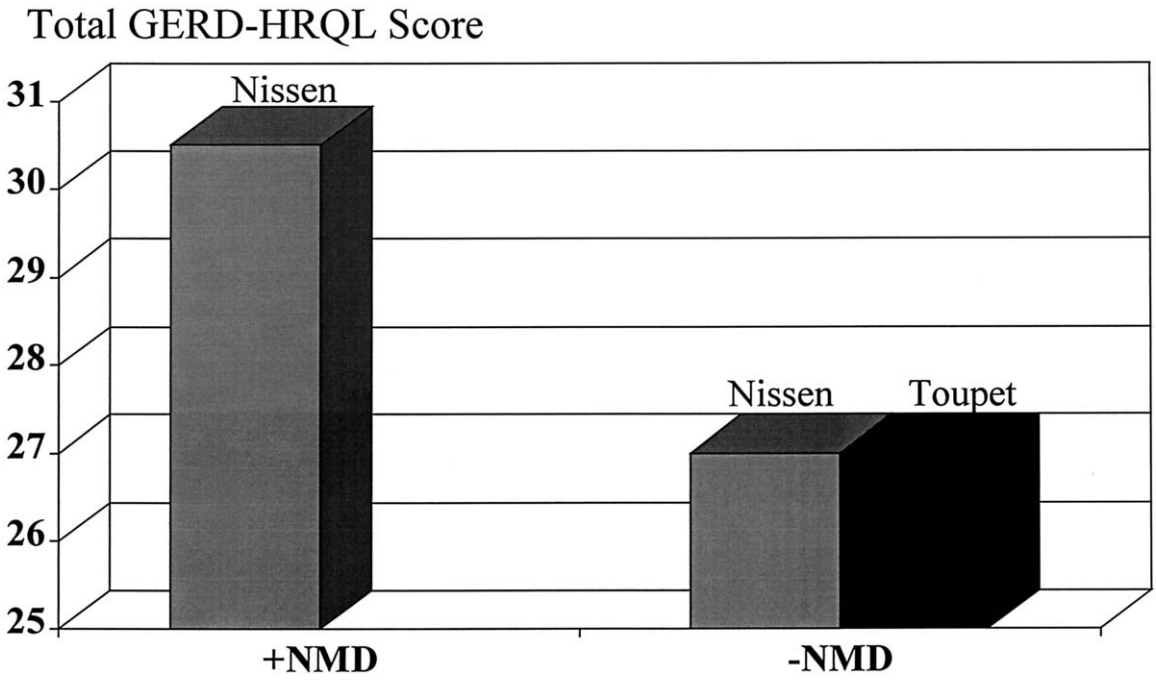

Fig. 1. Median preoperative total GERD-HRQL scores for patients with and without NMDs, $P = 0.01$. *Gray bars* indicate patients who ultimately underwent Nissen fundoplications; *black bars* indicate patients who underwent Toupet fundoplications. Because there were only two patients in the +NMD/Toupet group, they were excluded. NMD = non specific motor disorders; GERD = gastroesophageal reflux disease; HRQL = quality of life scale.

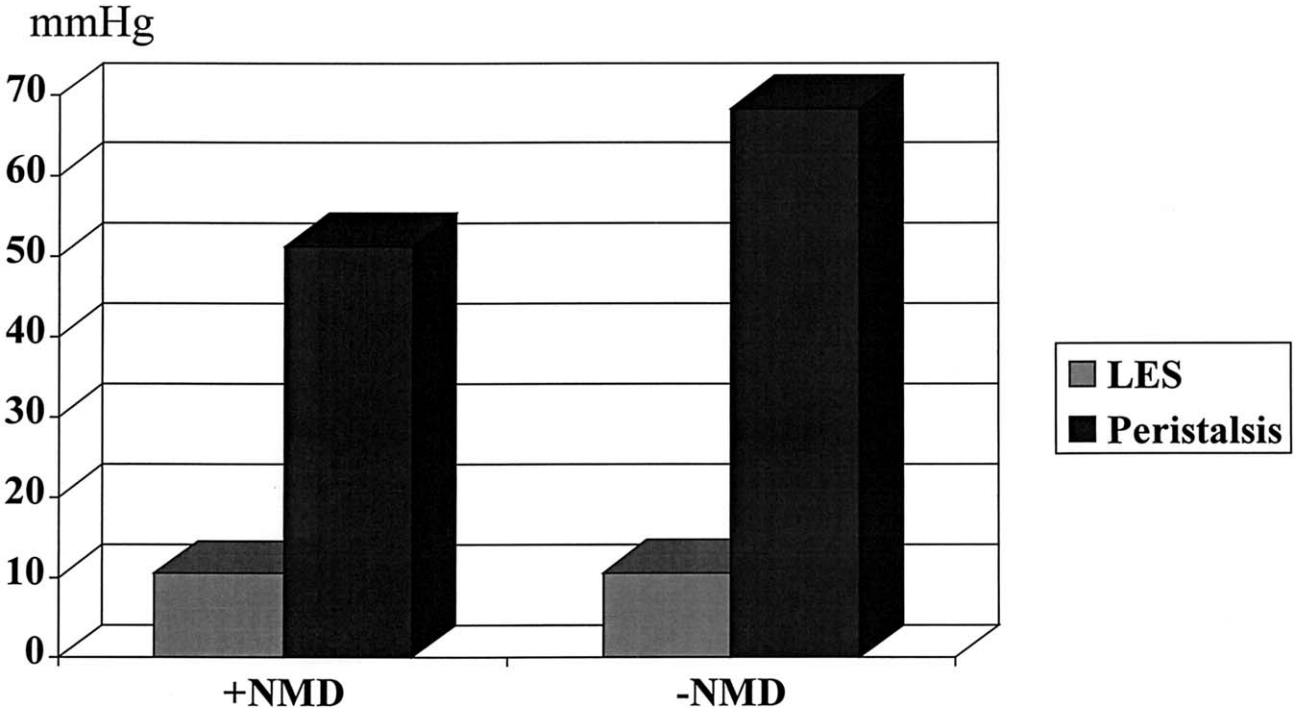

Fig. 2. Comparison of average lower esophageal sphincter (*LES*) pressures (mm Hg) and esophageal body peristaltic amplitudes for patients with and without NMDs. LES, P = NS; peristalsis, $P < 0.0001$. NMD = non specific motor disorders.

DISCUSSION

Esophageal motility disorders can be either primary or secondary phenomena.[2–4] There are well-characterized primary esophageal motility disorders, such as achalasia, whereas secondary esophageal dysmotility may be caused by GERD. It is also known that patients with noncardiac chest pain and nonobstructive dysphagia also have a higher incidence of motor abnormalities found by esophageal manometry.[2–4] However, it is unclear whether this represents autonomic dysfunction,[13] hyperalgesia, or primary muscular dysfunction.[14,15] Nonspecific motility disorders are particular vexing, because they are more common than the named motility disorders and proven treatments are lacking.[16]

Motility disorders are common in patients with GERD. In our series, 24% of patients had NMD. It appears that motility disorders are both caused by and potentiate the symptoms of GERD.[5–7] Initially, it was thought that hypocontractile esophageal body peristalsis would affect antireflux surgery; and, therefore, partial fundoplications, such as a Toupet fundoplication, were recommended over a total fundoplication, such as Nissen fundoplication.[17–19] However, other reports have concluded that esophageal dysmotility does not affect the results of a Nissen fundoplication.[20–22] In fact, antireflux surgery has been shown to improve esophageal motility.[23] Therefore, it seems that lower pressure amplitudes of esophageal body peristalsis do not affect symptomatic outcomes of antireflux surgery.

Nevertheless, as it is known that patients with noncardiac chest pain and nonobstructive dysphagia have a higher incidence of esophageal motor disorders, it is reasonable to hypothesize that patients with these disorders will have more postoperative symptoms. However, in our series, patients without NMD had a higher rate of preoperative dysphagia and chest pain compared to those with NMD (see Fig. 1). Yet, when measuring symptom severity using the GERD-HRQL, the +NMD group had statistically significantly worse median scores (see Fig. 2), implying that these patients were more symptomatic overall. On the other hand, dysphagia scores were similar. We would like to emphasize that patients with hypocontractile esophageal peristalsis or ineffective esophageal motility without abnormal contractions were not included in our group of patients with NMD. In fact, the +NMD group of patients had a lower average esophageal body peristaltic amplitude compared to the −NMD group (see Fig. 3), implying that a higher proportion of these patients had poor esophageal peristalsis. Nevertheless, this did not translate into a higher rate of postoperative dysphagia, nor worse postoperative symptom scores.

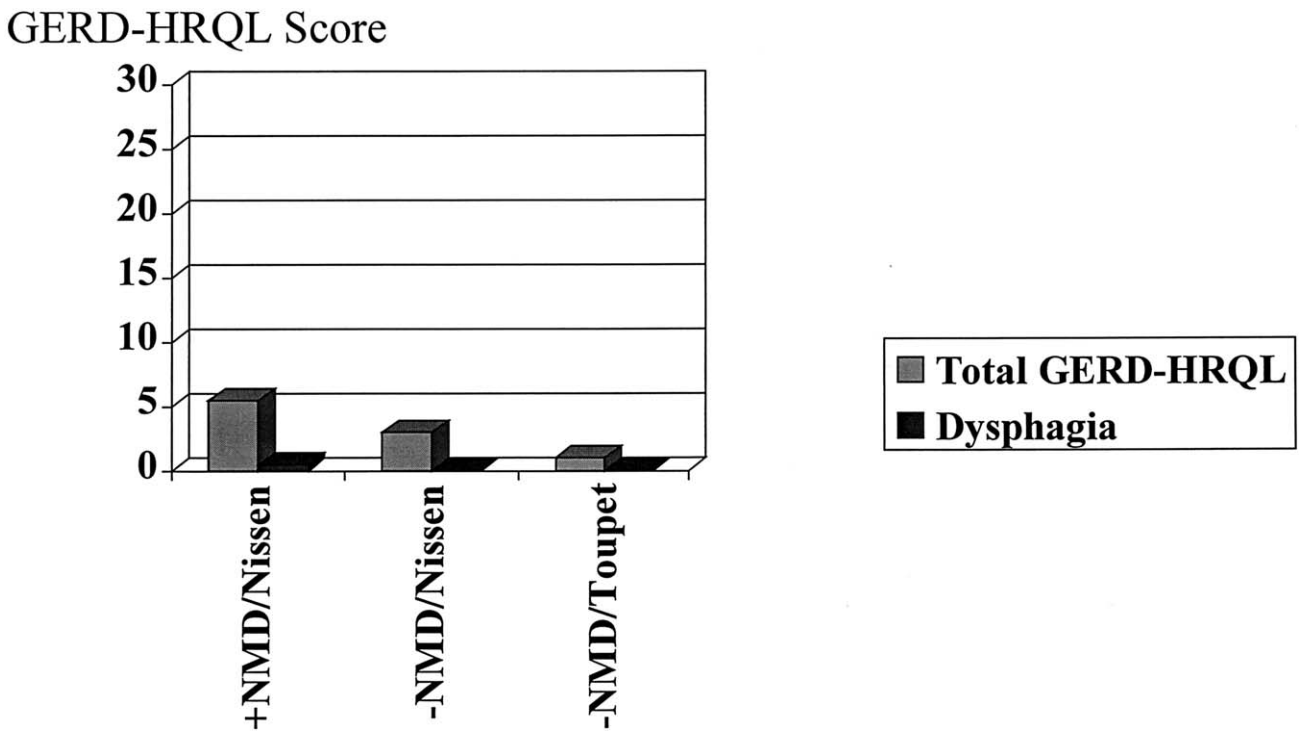

Fig. 3. Comparison of median postoperative total GERD-HRQL scores and median dysphagia scores (question No. 7) for patients with and without NMDs, P = NS, both comparisons. NMD = non specific motor disorders; GERD = gastroesophageal reflux disease; HRQL = quality of life scale.

Why would NMDs not affect symptomatic outcomes of antireflux surgery? First, NMDs may not be disorders at all, but rather random occurrences that happen more frequently in normal individuals than suggested in the literature pertaining to esophageal manometry. Approximately 5% of "normal" individuals will have nonpropulsive, simultaneous contractions with wet swallows by manometry.[24] Esophageal manometry measures esophageal motility as a "snapshot," that is, a one-time event, on a particular day and time. Perhaps if esophageal manometry were done more frequently on the same individual, more of these "abnormal contractions" would be identified. Second, physiologic measurements may not correlate to patient-perceived symptoms. We have previously shown that symptom severity for GERD is not related to esophageal manometry and 24-hour pH monitoring, but it does seem to be related to the endoscopically determined grade of esophagitis.[25] Third, postoperative dysphagia may also be due to issues not related to esophageal physiology, such as personality issues and maladaptive eating patterns.[26,27] Therefore, in this milieu, it may not be possible to isolate one cause of dysphagia, or, for that matter, other postoperative symptoms.

CONCLUSION

NMDs of the esophagus are common in patients seen for surgical treatment of GERD. These findings do not appear to result in a higher incidence of preoperative symptoms generally considered referable to NMDs (specifically, noncardiac chest pain and nonobstructive dysphagia). These disorders do not appear to affect symptomatic outcomes of antireflux surgery. In fact, median dysphagia symptom scores improved for both groups of patients, implying that this symptom is improved with correction of the GERD. No tailoring of surgical treatment is required.

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Lymphoepithelial Cysts of the Pancreas: Case Report and Review of the Literature

Pablo Capitanich, M.D., Mario L. Iovaldi, M.D., Mario Medrano, M.D., Patricio Malizia, M.D., Javier Herrera, M.D., Francisco Celeste, M.D., Luis A.R. Boerr, M.D., Carlos Moran Obiol, M.D., Norberto A. Mezzadri, M.D.

The aim of this report was to describe the clinical and pathologic features of lymphoepithelial cysts of the pancreas, establish the differential diagnosis of other pancreatic cysts, and review the literature. A 53-year-old man was incidentally diagnosed with a pancreatic lesion after an abdominal CT scan. This study showed a solid mass in the tail of the pancreas not enhanced by helical CT. Endoscopic ultrasound examination revealed a low-density tissue mass on the surface of the pancreas, less echogenic than the surrounding parenchyma. Distal pancreatectomy and splenectomy were performed with a suspected diagnosis of mucinous cystic tumor. The patient has had an uneventful postoperative period, and the pathologic finding was a lymphoepithelial cyst of the pancreas. Lymphoepithelial cyst of the pancreas is an unusual and benign entity that must be taken into consideration when evaluating a cystic lesion of the pancreas because a different therapeutic approach may be required. (J GASTROINTEST SURG 2004;8: 342–345)

KEY WORDS: Pancreas, lymphoepithelial cyst, pancreatic cyst

Pancreatic cysts are divided into two main categories: true pancreatic cysts and pseudopancreatic cysts. The latter, without an epithelial lining, represent 75% of all pancreatic lesions, and the remaining 25% are true pancreatic cysts. These in turn can be classified into neoplastic, congenital, parasitic, and peripancreatic cysts.[1] Neoplasms are the most commonly found true cysts, representing 10% to 15% of the total.

Lymphoepithelial cysts of the pancreas constitute a rare and benign entity. They were first described in 1985 by Luchtrath and Schriefers.[2] In 1987 Truong et al.[3] reported a second case, which they named "lymphoepithelial cyst of the pancreas." Only 64 cases have been reported in the English language literature.[4] Because lymphoepithelial cyst (LEC) is an uncommon lesion, which has various imaging presentations, a differential diagnosis may be difficult. The main objective of this report is to describe a recent case and review the existing bibliography on the topic.

CASE REPORT

A 53-year-old male patient was found to have a lesion in the tail of the pancreas after undergoing an abdominal computed tomography (CT) scan. The patient reported sporadic abdominal pain in the right upper quadrant apparently associated with eating fatty foods. Abdominal ultrasound imaging was performed revealing gallbladder adenomyosis and multiple lithiasis. The patient also had a history of smoking and had received medical treatment for chronic pulmonary obstructive disease.

An enhanced abdominal CT scan with oral and intravenous contrast disclosed a 4×2.5 cm mass with a soft tissue component in the tail of the pancreas, located anterior to the pancreatic parenchyma (Fig. 1). Endoscopic ultrasonography performed with a radial system (Olympus GF UM20; Olympus America, Inc., Melville, NY) showed a 35×50 mm ovoid image with a smooth lining protruding from the gland, with an isohypoechoic structure and finely granular tissue (Fig. 2).

From the Departments of Surgery (P.C., M.L.I., P.M., J.H., N.A.M.), Gastroenterology (M.M., L.A.R.B., C.M.O.), and Pathology (F.C.), Hospital Alemán, Buenos Aires, Argentina.
Reprint requests: Pablo Capitanich, M.D., Department of Surgery, Hospital Alemán, Av. Pueyrredon 1640, C1118AAT Buenos Aires, Argentina. e-mail: pcapitanich@hospitalaleman.com.ar

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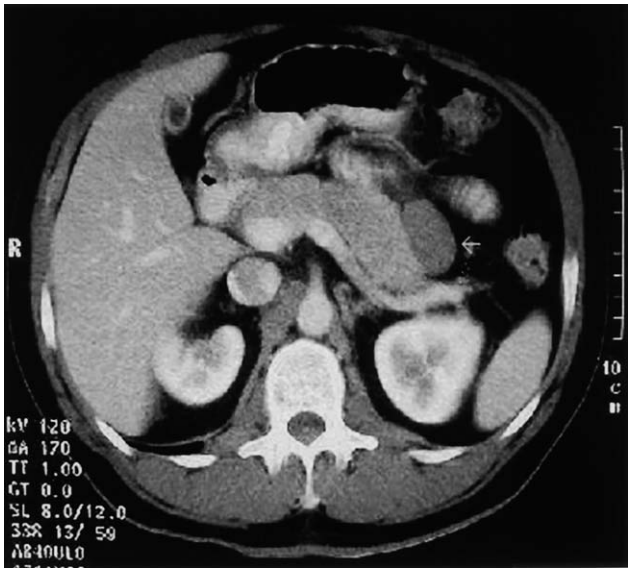

Fig. 1. Helical CT scan showing a 4 × 2.5 cm mass with a soft tissue component in the tail of the pancreas (*arrow*) without enhancement after intravenous contrast injection.

The patient underwent a cholecystectomy with transcystic cholangiography. There were no abnormalities in the bile duct or in the Wirsung duct. Because of the cystic lesion in the tail of the pancreas, distal pancreatectomy and splenectomy were performed with a tentative diagnosis of mucinous cystic tumor. Pathologic examination revealed a mass measuring 4 cm in diameter located in the tail of the pancreas. The cyst was lined by a thin wall, had a rough whitish inner surface, and was filled with sebaceous-looking gray material. Microscopy evidenced a cyst wall lined by squamous epithelium and surrounded by abundant mature lymphoid tissue with follicles and germinal centers. These findings were diagnostic of a benign LEC of the pancreas (Fig. 3). Pathologic findings in the gallbladder confirmed adenomyosis and chronic cholecystitis. After the cyst was removed, the postoperative course was uneventful. The patient was released after 4 days and remained asymptomatic.

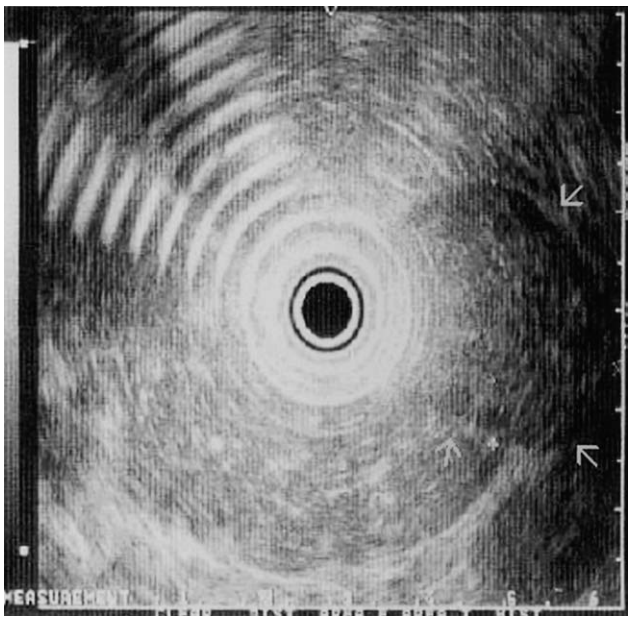

Fig. 2. Endoscopic ultrasound imaging defined a 35 × 50 mm ovoid image with an isohypoechoic structure (*arrows*) protruding from the tail of the pancreas.

DISCUSSION

Although it was originally believed that LECs occurred predominantly in middle-aged men (mean age 54 years; range 26 to 82 years), several cases have been reported in women, for a male:female rate of 4 to 1.[4,5] Eighty percent of the reported cases are in adults over the age of 40. In 50% of patients the findings were incidental.[1] The remaining 50% were evidenced by abdominal pain, nausea, vomiting, diarrhea,[1] and less frequent symptoms such as fever, weight loss, and fatigue.[6]

LECs may be located in any area of the pancreas and are characterized by a superficial lesion surrounded partially by normal pancreatic tissue.[7] LECs of the pancreas may be multilocular (60%) or unilocular (40%)[7]; they are frequently lined by a well-defined wall and are filled with a "cheesy" yellowish viscous

Fig. 3. Microscopic evidence of a cyst wall lined with squamous epithelium and surrounded by abundant mature lymphoid tissue with follicles and germinal centers confirming the diagnosis of lymphoepithelial cyst of the pancreas.

material.[6] The size of these lesions varies from 1.2 to 17 cm (mean 4. 6 cm).[4]

Among their histologic features, LECs present a wall lined by stratified keratinized squamous epithelium completely surrounded by lymphoid tissue, generally presenting germinal centers.[7,8] The cysts are filled with a dense material, composed mainly of debris, keratin, and cholesterol crystals.[9] The deepest portion of the cyst in contact with pancreatic tissue is separated by a fibrous lining.[6] The adjacent parenchyma is normal, and in instances of a ruptured cyst, there is evidence of an intense desmoplastic reaction in the surrounding tissues.[6]

The pathogenesis of LECs of the pancreas is uncertain. Several hypothesis have been formulated:

1. Squamous metaplasia of an obstructed and dilated pancreatic duct. This theory does not explain the presence of the lymphoid tissue characteristic in this lesion.[6,7]
2. Because of the similarity between LECs of the pancreas and brachial cysts observed in lateral areas of the neck, these lesions would derive from remnants of a brachial cleft misplaced in the pancreas during embryogenesis. However, such a brachial remnant has never been effectively demonstrated to contain pancreatic parenchyma.[6,7]
3. LECs might originate in an intrapancreatic accessory spleen. This theory explains the presence of lymphoid tissue. However, it does not account for the existence of stratified epithelium covering the cyst.[6]
4. Despite the fact that LECs of the parotid gland are frequently related to Epstein-Barr virus, research in our patient using in situ hybridization techniques has not revealed Epstein-Barr virus in LECs of the pancreas, as confirmed by other investigators.[10]
5. One hypothesis speculated that these lesions may by driven by lymphoid cells with an affinity for ductal epithelia and the capacity to induce their growth by the factors they mediate (Rosai J, personal communication, May 1995). The type of the lining epithelium then may be a factor of antigens present in different types of ductal tissue to which these lymphocytes are attracted.[7]
6. The most widely accepted theory states that LECs of the pancreas might develop from ectopic pancreatic tissue included in a peripancreatic lymph node.[6,7] This hypothesis might explain the extrinsic localization of the lesion and the fact that the cysts are covered with pancreatic tissue only in their deepest area. Another fact that supports this hypothesis is the reported finding of pancreatic tissue in lymph nodes.[11]

The preoperative diagnosis is difficult because very little is known about this uncommon lesion. Sometimes it is difficult to make a differential diagnosis between these pancreatic lesions and more frequent ones such as mucinous cysts or other neoplasms. The clinical and pathologic features of each entity provide sufficient information to differentiate squamous-lined cysts of the pancreas.[7]

Ultrasonography has proved effective to assess these lesions. However, it may be misleading because they are occasionally diagnosed as solid, or solid cystic.[3,12,13] In the case reported here, endoscopic ultrasonography revealed a solid-apppearing lesion. This image, slightly hypoechogenic with respect to the rest of the pancreatic parenchyma, appeared to be partially protruding from a lobulated gland. The dense semisolid cyst, filled with debris and keratinous material, would explain the solid feature observed by endoscopic ultrasound imaging in our patient and in several other cases in the literature.

The CT findings vary from those of typical uniloc-ular or multilocular cystic lesions with a low Hounsfield unit (HU) cystic content[13,14] to an isodense mass.[12] Koga et al.[13] have described two lesions, a cystic mass with solid components and a CT low-attenuation solid-looking hypoechoic mass with an enhancing rim. CT findings in our patient revealed a nonenhanced low-density tissue mass.

Magnetic resonance imaging (MRI) on the basis of the lipid cystic component perceived a lesion with a high signal in T1 and a low signal in T2, being the keratin content of the cyst, a recognized characteristic feature LECs of the pancreas.[15] Therefore MRI should be helpful in making a correct diagnosis, especially when a fat-suppressed T1-weighted image is used.

Fine-needle aspiration (FNA) biopsy has been proposed for biochemical and cytologic studies in the differential diagnosis of LEC .[9,16,17,18] The published articles dealing with biochemical studies of FNA biopsy material obtained from LECs of the pancreas have shown a high level of tumor markers (carcinoembryonic antigen, CA 19-9) in the range of malignant lesion, as well as variable levels of amylase. Therefore biochemical study of such lesions might lead to an incorrect diagnosis if not followed by further examinations.[9,14,19] The cytology of FNA biopsy based on the presence of squamous cells, keratinous debris, and lymphoid tissue provides certainty in diagnosing a LEC. We believe that FNA presents several limitations in the differential diagnosis of LEC, and its use should be considered separately in each individual

patient. If a neoplastic lesion is suspected after CT scan and endoscopic ultrasound imaging, we feel that a tranparietal FNA biopsy should not be performed because the risk of tumoral dissemination has been clearly assessed in the literature; in addition, there is a lack of appropriate equipment to perform a reliable endoscopic ultrasound-guided FNA to minimize that potential risk. We rely on MRI and endoscopic ultrasound–guided FNA as the most suitable studies to reach a diagnosis.

Several types of surgical treatments have been used in patients with LECs; these range from simple excision of the lesion to more radical procedures such as distal pancreatectomy with or without splenectomy[6,20,21] or cephalic pancreatoduodenectomy.[13,22] The latter might be useful when the diagnosis is not definite or when the lesion is firmly adhered to the pancreas by fibrous tissue.[6] In asymptomatic patients with a high surgical risk and an FNA biopsy suggesting LEC, some authors recommend observation of the lesion.[23]

CONCLUSION

In light of the recent findings, we strongly believe that the differential diagnosis of this entity is of the utmost importance and should be given serious consideration. Preoperative diagnosis of this benign lesion would eliminate unnecessary radical surgical treatments such as pancreaticoduodenectomy or distal pancreatectomy with splenectomy.

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The Role and Interactions of Nitric Oxide (NO), Carbon Monoxide (CO), and Prostanoids in the Pathogenesis of Postoperative Ileus in Rats[1]

R.P. Korolkiewicz, M.D., Ph.D., J. Sein-Anand, M.D., Ph.D., J. Ruczyński, M.Sc., P. Rekowski, Ph.D., L. Bieniaszewski, M.D., Ph.D., Z. Chodorowski, M.D., Ph.D., J. Petrusewicz, Ph.D., M. Ujda, M.D., J. Dąbkowski, M.D., M. Bitel, M.D., S. Kato, Ph.D., K. Takeuchi, Ph.D.

The effects of heme oxygenase (HO) inhibitors, zinc-protoporphyrin-IX (ZnPP-IX), and tin protoporphyrin-IX (SnPP-IX) and their interactions with L-arginine/nitric oxide synthase (NOS) and cyclooxygenase (COX) pathways were investigated in postoperative ileus in rats. Intestinal transit was measured as Evans blue migration after skin incision, laparotomy or laparotomy plus gut evisceration and handling. Laparotomy and small intestinal manipulations increased blood plasma nitrites/nitrates level 1.88-fold. N^{ω}-nitro-L-arginine methyl ester, indomethacin, a selective COX-1 blocker (resveratrol) and COX-2 antagonists (nimesulide, DuP-697, NS-398) reversed the additional inhibitory effects of gut manipulation subsequent to laparotomy. In contrast, N-(3-(aminomethyl)benzyl)acetamidine or S-methylisothiourea, highly selective inducible NOS blockers, remained ineffective. ZnPP-IX and SnPP-IX overturned the effects of laparotomy on dye propulsion, but were only partially effective after laparotomy and gut handling attenuating the additional inhibitory influences of gut manipulation, the intestinal transit reaching 89.21%, 92.87%, 53.46%, and 48.56% of respective controls transit. Salutary effects of L-NAME, ZnPP-IX, and SnPP-IX were dose-dependent, L-arginine or hemin (HO substrate) sensitive. Administration of indomethacin and resveratrol subsequent to SnPP-IX reversed the inhibitory effects of laparotomy and manipulation, amounting to 93.91% and 87.43% of controls. On the other hand, L-NAME injected after SnPP-IX abolished the salutary effects of the latter, study dye migration reached 25.18% of control rat. Therefore we demonstrated that nitric oxide, carbon monoxide, and prostanoids play a role in the pathogenesis of postoperative ileus albeit in different mechanisms. Laparotomy stimulated HO activity, whereas gut manipulation led to an excessive constitutive NOS stimulation accompanied by augmented prostanoid synthesis by COX-1. Unaffected synthesis of either NO or CO enables a return of gastrointestinal transit during postoperative period, whereas a pharmacological blockade of two complementary metabolic pathways provides a most effective measure against postoperative ileus development. (J GASTROINTEST SURG 2004;8:346–357)

KEY WORDS: Ileus, rats, carbon monoxide, nitric oxde, prostanoids

INTRODUCTION

Intra- and extra-abdominal surgery attenuates aboral propulsive gut movements resulting in postoperative ileus (PI).[1] Primary importance in the pathogenesis of PI has been ascribed to neural reflexes, the afferent stimuli conducted by capsaicin-sensitive unmyelinated fibers, and the efferent limb of the reflex arc comprised of adrenergic and nitrergic neuromuscular activity.[2–3] Consequently, thoracic epidural anaesthesia improved PI treatment in humans,

From the Departments of Pharmacology (R.P.K., J.P., M.B.), Internal Medicine and Toxicology (J.S.-A., Z.C.), and Hypertension and Diabetology (L.B.), Medical University of Gdańsk, Gdańsk, Poland; Department of Chemistry (J.R., P.R.), University of Gdańsk, Gdańsk, Poland; Department of Cardiology (M.U., J.D.), Voivodeship Hospital, Stalowa Wola, Poland; and Department of Pharmacology and Experimental Therapeutics (S.K., K.T.), Kyoto Pharmaceutical University, Kyoto, Japan.

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Reprint requests: R. Korolkiewicz, M.D., Ph.D., Department of Pharmacology, Medical University of Gdańsk, Do Studzienki 38, 80-227 Gdańsk, Poland. e-mail: rokor@amedec.amg.gda.pl

[1]Results were presented in part as an oral communication at the Brain-Gut Axis in Gastrointestinal Protection and Damage Symposium, Cracow, Poland, September 2001, and published as an abstract in J Physiol Pharmacol 2001.

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whereas NOS inhibition reversed the small bowel transit blockade in rodents.[3–4]

VIP, NO, and CO inhibit intestinal propulsion, whereas the effect of prostaglandins on gut motility depend on their profile, prostanoid receptor profile, and other mediators acting at target sites.[5–8]

Gastrointestinal (GI) tract contains two enzyme systems linked to guanylate cyclase stimulation: NOS and HO.[9–10] Much parallelism exists between CO and NO and PGs generating systems, as for example multiple isoforms of those three enzymes occur, including constitutive forms: COX-1, cNOS, HO-2, HO-3 and their inducible counterparts: COX-2, iNOS, and HO-1.[9–13] cNOS, HO-2, and COX-1 are widely expressed and contribute toward tissue homeostasis,[9–10] whereas COX-2, iNOS, and HO-1 are inducible enzymes, their activity being triggered by bacterial lipopolysaccharide, interleukin-1β, and tumor necrosis factor-α.[9–10,12]

COX-1 and COX-2 products affect NOS expression and iNOS regulates COX-2 activity and expression.[14] Similarly, the exogenously supplied or iNOS-derived NO reciprocally influence HO-1 expression in mesangial cells.[15] Based on the pharmacological activity and colocalization of HO-2 with neuronal NOS in rabbit, opossum, and human GI tracts, speculations were made concerning the regulation of NOS pathway by HO.[16–17] The involvement of PGs in the development of PI is well known[18] and this observation has been extended by providing evidence that laparotomy stimulated COX-2 activity, whereas additional surgical gut manipulation led to an excessive PGs synthesis by COX-1.[19] Based on our previously published results and taking into consideration the findings of Moore et al., that low concentrations of inhaled CO attenuated PI in mice by interacting with inflammatory cascade elements,[20] new experiments were designed to prove a hypothesis that a modulation of endogenous CO production by HO inhibitors influences PI development. Moreover, based on the analogies between CO, NO, and PG generating systems and the preventive effects of COX blockers and NOS inhibitors, we aimed to confirm the dose-dependence nature of the salutary effects of the latter and further examine NO, CO, and PG interactions.[3,19,21–22]

MATERIAL AND METHODS

Surgical Protocol

Experimental procedures were approved by the Bioethics Committee of the Medical University of Gdańsk, Poland. Male albino Wistar rats (180-250 g) were fasted for 48 hours maintaining a free access to tap water. Animals were randomly divided into 3 groups before undergoing abdominal surgery under diethyl ether anaesthesia as described in details elsewhere.[19] Briefly, rats underwent skin incision, laparotomy, or laparotomy and subsequent gut evisceration followed by mechanical stimulation of caecum and small intestine. After the operation, the rats recovered for 1 h.[23] Subsequently, all animals received 0.15 ml of Evans blue via an orogastric tube and 30 minutes later animals were sacrificed by cardiotomy under anaesthesia. The small intestines were excised and gently, in order to avoid tissue stretching, laid on the corkboard for measurements, which consisted of establishing the most distal point of dye migration from the pylorus. Measurements were performed by a blinded observer unaware of the treatment the animals were receiving.

Experimental Design

The experimental protocol and the dosage of experimental compounds is depicted in detail in Fig. 1. Subsequent to a pilot series of experiments involving conscious (untreated) rats and ether-anaesthetized animals, intestinal Evans blue migration was measured after skin incision, laparotomy, or laparotomy and gut manipulation.

NOS and HO Inhibitors

The effects of intravenously (i.v.) injected N^{ω}-nitro-L-arginine methyl ester (L-NAME), zinc-protoporphyrin IX (ZnPP-IX), tin-protoporphrin-IX (SnPP-IX), subcutaneously (s.c.) administered N-(3-(aminomethyl)benzyl)acetamidine (1400W) or S-methylisothiourea (SMT), and intraperitoneally (i.p.) injected L-arginine or hemin were investigated after various types of surgical intervention. Respective controls in each experimental group received an equal volume of saline (0.9% NaCl) instead of the study drug. In the third series of experiments NO production was measured indirectly as stable NO metabolites: NOx (nitrites and nitrates) in blood plasma of control (untreated) or rats injected with L-NAME, 1400W, or SMT after skin incision, laparotomy, or laparotomy and gut manipulation.[24] Blood samples for NOx level measurements were collected under light ether anesthesia immediately before sacrifice.

Finally we investigated the results of combination therapy with NOS, HO, and COX inhibitors employing their most effective doses.[19] The animals were divided in two groups. The first group served as a control and received 0.9% NaCl instead of study drugs before and after skin incision or laparotomy plus

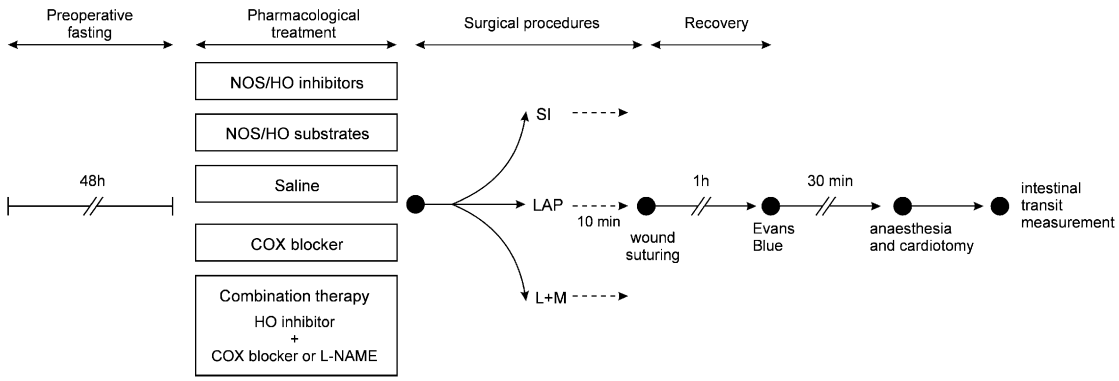

Fig. 1. The effects of NOS, HO, or COX inhibitors administered separately or in combination were tested on the intestinal transit of Evans blue, after surgical intervention in rats subjected to different nociceptive stimuli: skin incision (SI), laparotomy (LAP), or laparotomy followed by gut handling (L + M). L-NAME (1-30 mg/kg, 0. 5 h before operation), ZnPPP-IX (10-100 μM/kg, 2 h before operation), SnPP-IX (10-50 μM/kg, 2 h before surgery) were injected intravenously. Contrastingly 1400W, SMT (10 mg/kg) were given subcutaneously, whereas L-arginine (600 mg/kg, 2 h before operation) or hemin (50 μM/kg, 24 h before surgery), were administered intraperitoneally.

gut manipulation. Rats in the second group were injected with the highest effective dose of SnPP-IX (50 μM/kg, 1.5 hours before surgery) and were divided into two subgroups. In the first subgroup rats were injected with indomethacin (30 mg/kg, s.c.), resveratrol, nimesulide, DuP-697, NS-398 (10 mg/kg, s.c.) 1 hour before surgical intervention consisting of skin incision or laparotomy plus gut handling. Animals in the second subgroup received i.v. L-NAME (30 mg/kg), 30 minutes before an operation.

Experimental Drugs

L-NAME hydrochloride, SMT hemisulfate, L-arginine hydrochloride, and resveratrol were dissolved in saline. Indomethacin, nimesulide, NS-398, and DuP-697 were dissolved in a small volume of 70% ethanol and the solution was made up to the desired concentration with saline. ZnPP-IX and SnPP-IX and hemin were freshly dissolved in 0.1 ml of 0.5 M NaOH, adjusted to pH 7.4 with 0.1 M HCl and diluted to required volume with saline; the solutions were kept in the dark to prevent photodegradation. Evans blue solution was prepared by dissolving 100 mg of the pigment in 2 ml of saline. L-NAME, L-arginine, NS-398, NADPH, and indomethacin were purchased from RBI (Natick, MA). SMT, resveratrol, nimesulide, FAD, hemin, ZnPP-IX, and Evans blue were obtained from Sigma-Aldrich Sp. z o.o. (Poznań, Poland). 1400W was purchased from Biochemicals.net, a division of A. G. Scientific, Inc. (San Diego, CA). SnPP-IX was obtained from Porphyrin Products (Logan, UT). Saline and diethyl ether were bought from Fresenius Kabi (Kutno, Poland) and Lachemia (Neratovice, Czech Republic), respectively. Other reagents were obtained from P.P.H. Polskie Odczynniki Chemiczne (Gliwice, Poland).

Statistical Analysis of the Acquired Data

No significant differences in small intestine length were discovered between animals in different experimental groups and hence the distance covered by Evans blue was expressed in cm and the results were presented in the text as a mean value ± standard error of the mean (SEM) for the number of rats mentioned in each group. Results were compared using one-way analysis of variance (ANOVA) plus Bonferroni post-ANOVA test. Two-tailed p values of less than 0.05 were taken to indicate significant difference.

RESULTS

The Effects of Ether Anesthesia and Surgical Intervention Upon the Intestinal Transit

Evans blue migrated over a distance of 57.0 ± 5.74 cm out of a total length of 115 ± 2.10 cm of the small intestine in the untretated conscious rats (n = 6). Ether anesthesia and skin incision have not influenced the intestinal transit of Evans blue reaching 56.88 ± 2.94 cm of 115 ± 3.83 cm and 62.67 ± 3.00 cm of 112 ± 3.08 cm, respectively (n = 8 and 6). Contrastingly, both laparotomy and laparotomy followed by gut manipulation have significantly reduced intestinal motility, the dye migrating 23.75 ± 1.40 cm out of 106 ± 3.67 cm in the former group (n = 8) and 11.28 ± 1.85 cm out of 118 ± 2.10 cm in the latter group (n = 9). The length of small intestine between

all experimental groups was not statistically different in all experiments (Fig. 2).

The Effects of L-NAME or L-arginine on the Intestinal Transit After Different Types of Surgical Intervention

L-NAME reversed the additional inhibitory effects of gut handling after laparotomy on gastrointestinal transit in a dose-dependent manner and thus Evans blue migrated over a distance of 10.64 ± 1.29 cm out of the total 96.71 ± 14.40 cm length of the small intestine in controls (n = 7), whereas it covered 18.17 ± 1.67 cm out of 113 ± 2.46 cm, 24.17 ± 1.30 cm out of 107 ± 3.71 cm and 31.0 ± 1.73 cm out of 114 ± 3.08 cm in rats treated with 3 (n = 6), 10 (n = 6), and 30 mg/kg (n = 8) of L-NAME, respectively (Fig. 3). L-arginine notably overturned the action of the most effective L-NAME dose in experimental animals (n = 6), the dye transit returning to 11.33 ± 1.52 cm out of 105 ± 5.07 cm, a value not different from controls. The length of the small intestine was not different between any of the treatment groups.

L-NAME, 1400W, SMT, and L-arginine have not demonstrated any marked influence on the intestinal transportation of Evans blue after skin incision or laparotomy. L-NAME significantly reversed the additional inhibitory effects of gut manipulation following laparotomy increasing the dye forward motion from 11.07 ± 1.77 cm in control animals (n = 7) to 32.50 ± 1.95 cm in L-NAME treated rats (n = 6). Contrastingly, 1400W (n = 5) and SMT (n = 6) remained ineffective, Evans blue covering the distance of 11.60 ± 2.29 cm and 11.33 ± 0.88 cm. On the other hand L-arginine augmented the degree of peristaltic inhibition so that the distance covered by Evans blue equaled 4.88 ± 0.85 cm in this particular group (n = 7). The length of the small intestine was not different between any of the experimental groups (data not shown), whereas the marked differences between the transit after skin incision and that after laparotomy with or without mechanical gut stimulation were

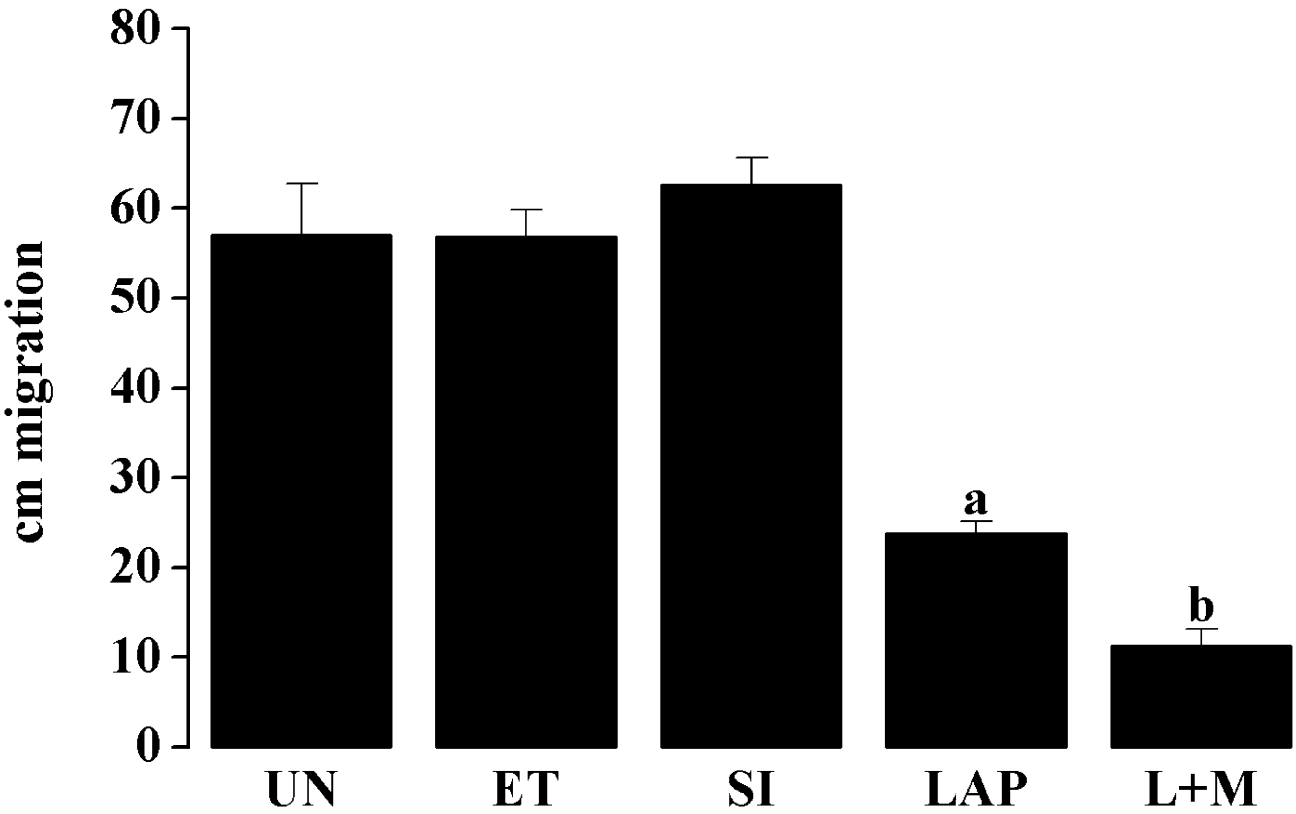

Fig. 2. Small intestinal Evans blue transit in rats: untreated (UN), undergoing ether anesthesia (ET), skin incision (SI), laparotomy (LAP), and laparotomy followed by gut manipulation (L + M). Results are shown as cm migration of the dye and are presented as a mean result ± SEM of a number of experiments performed in different animals (n = 6-9). Statistical significance was calculated using one-way ANOVA followed by Bonferroni post-ANOVA test: [a]UN, ET, SI vs. LAP or L + M ($p < 0.001$); [b]LAP vs. L + M ($p < 0.05$).

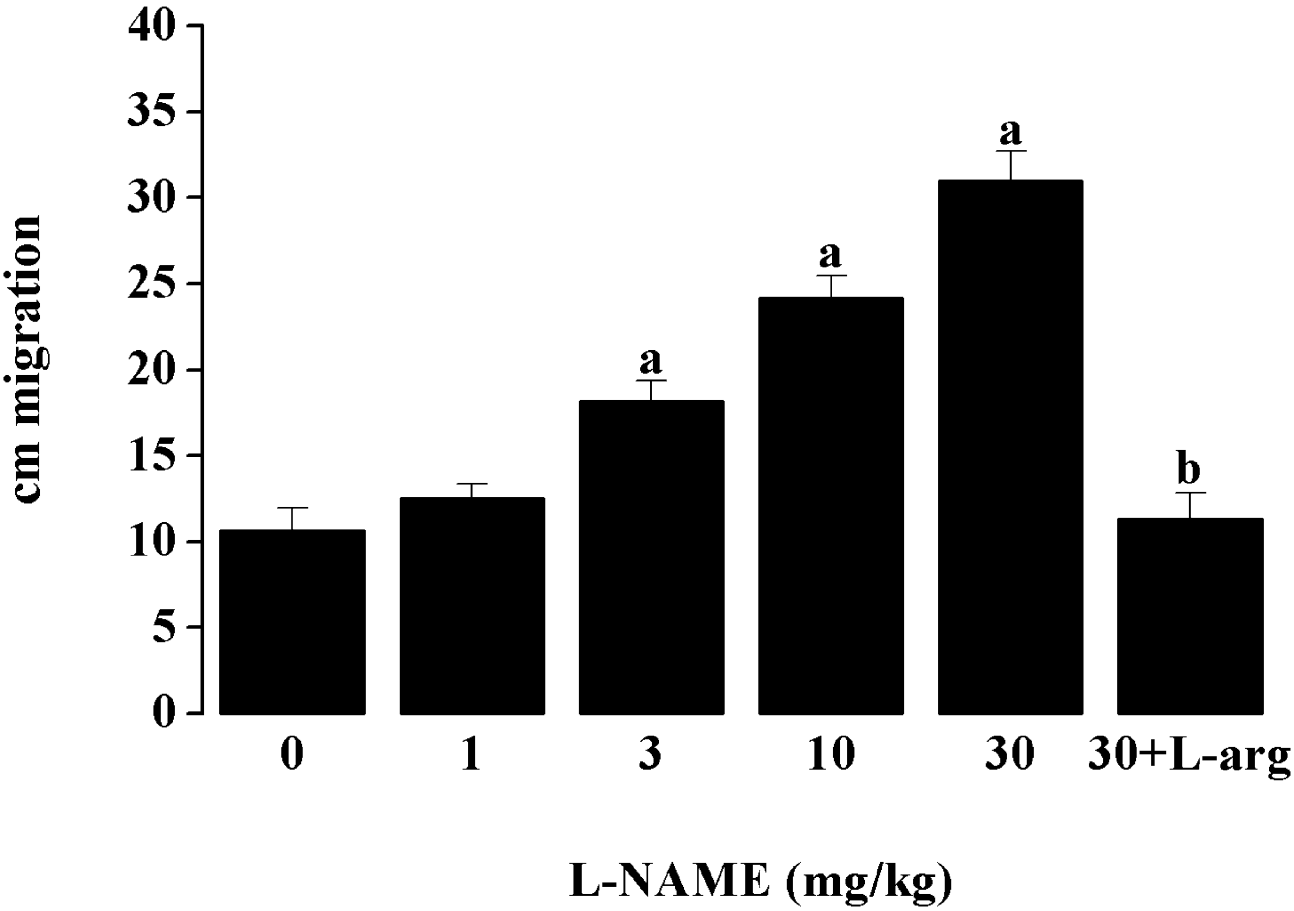

Fig. 3. The effects of increasing L-NAME doses on the small intestinal transit of Evans blue following laparotomy and gut manipulation. Results are shown as cm migration of Evans blue and are presented as a mean result ± SEM of experiments performed in different animals (n = 6-7). Statistical significance was calculated using one-way ANOVA followed by Bonferroni post-ANOVA test: [a]untreated rats (controls) vs. animals pretreated with L-NAME (3 mg/kg, $p < 0.05$), 10 mg/kg and 30 mg/kg ($p < 0.001$); [b]animals pretreated with L-NAME (30 mg/kg) vs. L-NAME (30 mg/kg) + L-arginine (L-arg, 600 mg/kg, $p < 0.001$).

notable in the three experimental groups. Much alike, the differences between propulsion after laparotomy and that following laparotomy and gut manipulation remained significantly different in particular treatment groups (Fig. 4).

Laparatomy with a subsequent handling of small intestine evoked a significant enhancement of blood plasma NOx levels, which amounted to 73.27 ± 5.17 μM/l (n = 8) in comparison to untreated animals 45.27 ± 5.69 μM/l (n = 5), skin incision 38.91 ± 3.68 μM/l (n = 8), or laparotomy 27.44 ± 6.76 μM/l (n = 7). The increased NO synthesis has been markedly reduced by L-NAME, reaching 36.78 ± 4.03 μM/l (n = 8), but not by 1400W (n = 7) or SMT (n = 6). In the former case NOx concentrations equaled 84.43 ± 4.61 μM/l, whereas in the latter it reached 80.41 ± 6.46 μM/l (Fig. 5).

ZnPP-IX and SnPP-IX exerted no discernible effect on GI transit of Evans blue of rats undergoing skin incision in comparison to untreated animals. The dye passage was equal to 60.0 ± 4.18 cm or 62.20 ± 2.06 cm in the former (n = 5) and 62.40 ± 1.75 cm or 58.33 ± 3.97 cm in the latter groups (n = 5 or 6). Contrastingly, both agents totally attenuated the inhibitory influences of laparotomy on the GI transit in a dose-dependent manner and thus the values of Evans blue propulsion amounting to 21.44 ± 1.10 cm or 24.29 ± 1.76 cm in untreated laparotomized animals (n = 8 or 7), 20.20 ± 1.46 cm or 33.171.72 cm, 30.60 ± 2.34 or 42.83 ± 2.43 cm and 55.67 ± 3.54 cm or 54.17 ± 3.00 cm in rats injected correspondingly with 10 (n = 5 or 6), 30 (n = 5 or 6) and 100 or 50 μg/kg (n = 6) of ZnPP-IX or SNPP-IX, correspondingly. Similarly ZnPP-IX and

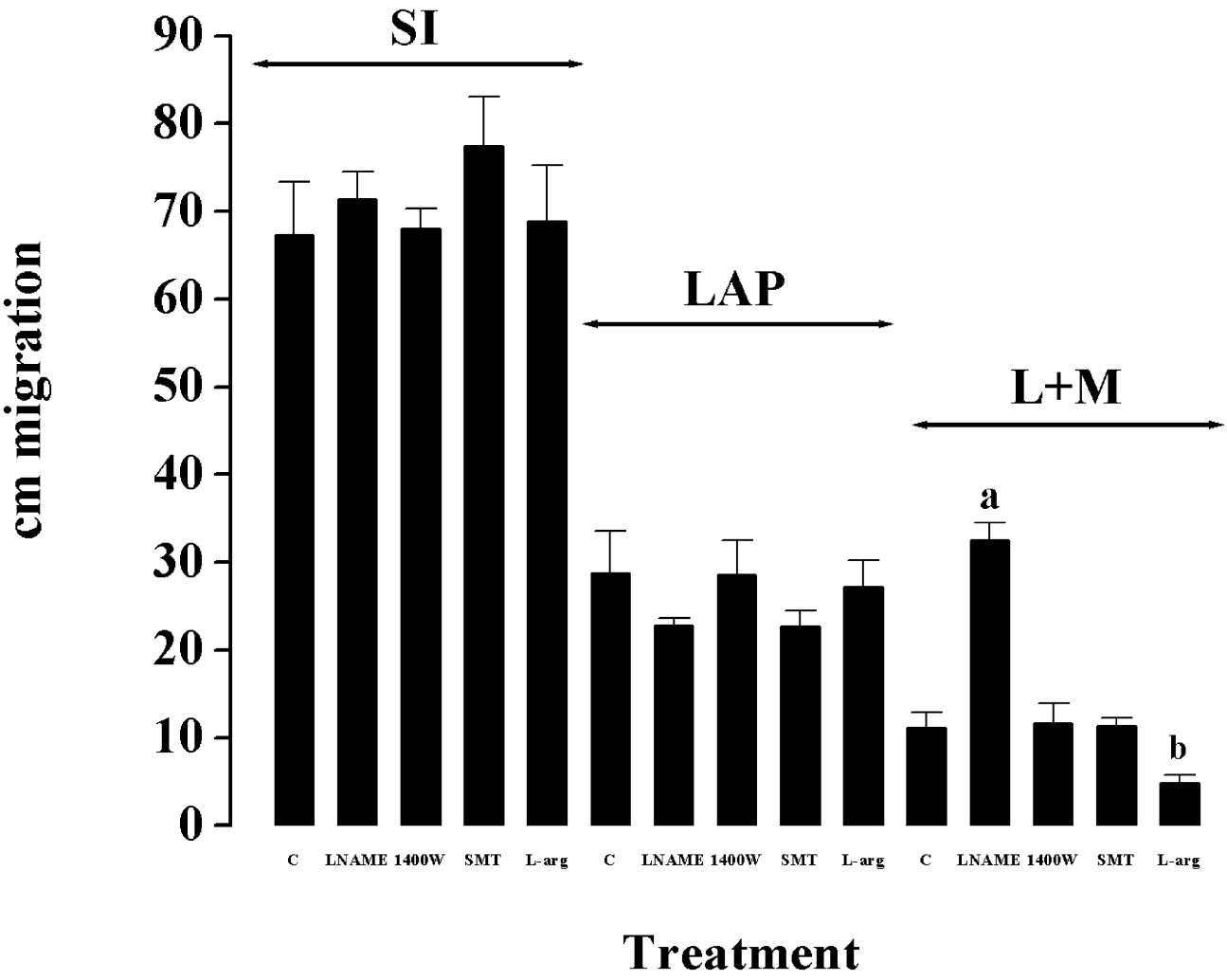

Fig. 4. The effects of L-NAME (30 mg/kg), SMT or 1400W (10 mg/kg) and L-arginine (L-arg, 600 mg/kg) on the small intestinal transit of Evans blue following skin incison (SI), laparotomy (LAP) or laparotomy followed by gut manipulation (L + M). Results are shown as cm migration of Evans blue and are presented as a mean result ± SEM of experiments performed on different animals (n = 5-7). Statistical significance was calculated using one-way ANOVA followed by Bonferroni test: [a]rats pretreated with L-NAME before L + M vs. untreated rats undergoing the same type of operation (C) or rats injected with 1400W, SMT and L-arg ($p < 0.001$). [b]rats receiving L-arg prior to L + M vs. respective controls undergoing the same type of operation (C) ($p < 0.01$).

SnPP-IX significantly attenuated the additional inhibitory effects of gut manipulation after laparotomy in a dose-dependent manner. Therefore Evans blue moved 9.71 ± 1.02 cm or 12.14 ± 1.65 cm in controls (n = 7) and 14.40 ± 0.51 cm or 14.40 ± 1.12 cm, 19.86 ± 1.07 cm or 21.67 ± 1.17 cm and 33.36 ± 1.27 cm or 28.33 ± 1.31 cm in rats injected with 10 (n = 5), 30 (n = 14 or 6) and 100 (n = 11) or 50 μg/kg (n = 6) of ZnPP-IX or SnPP-IX, respectively (Figs. 6 and 7). Hemin remained without any notable effect on the intestinal transit of Evans blue in rats undergoing skin incision (n = 5), so that the dye passage equalled 51.60 ± 2.91 cm. However, the HO substrate attenuated the salutary effects of ZnPP-IX (n = 5 or 6) and SnPP-IX (n = 6 or 7), both after laparotomy and after laparotomy followed by gut handling. Thus in the former group Evans blue transit amounted to 13.20 ± 1.46 cm and 11.80 ± 2.58cm, whereas in the latter group the dye translocation was 25.17 ± 1.51 cm and 11.57 ± 1.25 cm. These results were not different from the respective controls (Figs. 6 and 7). Moreover hemin severely potentiated the degree of intestinal transit inhibition evoked by laparotomy and gut manipulation subsequent to laparotomy (n = 6) and therefore Evans blue motility amounted to 10.50 ± 1.08 cm and

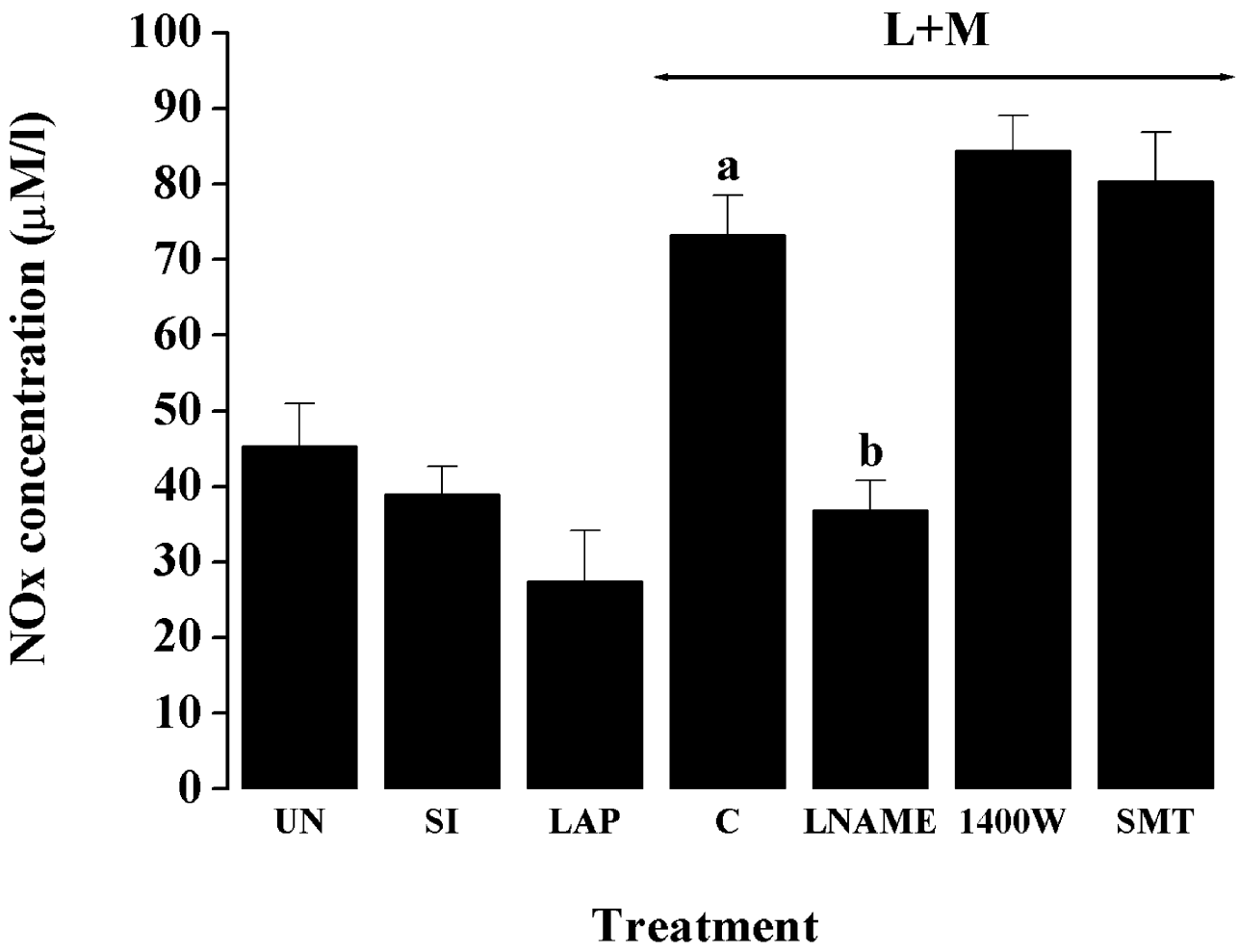

Fig. 5. Nitrite and nitrate (NOx) blood plasma concentration (μM/l) in untreated rats (UN) and animals undergoing skin incision (SI), laparotomy (LAP), or laparotomy and subsequent gut manipulation (L + M) or rats pretreated with L-NAME (30 mg/kg), SMT, or 1400W (10 mg/kg). NOx levels were estimated using the method described by Green et al. [24]. Each blood sample was collected from a separate animal and each column represents a mean value of NOx concentration ± SEM from several measurements (n = 7-8). C-stands for controls. Statistical significance was calculated using one-way ANOVA followed by Bonferroni test: [a]L + M(C) vs. UN ($p < 0.05$) or SI ($p < 0.01$) or LAP ($p < 0.001$); [b]L + M + NAME vs. L + M(C) or L + M + 1400 W or L + M + SMT ($p < 0.001$).

3.83 ± 0.87 cm in those groups (Fig. 7). Additionally, the length of the small intestine was not different between any of the experimental groups (data not shown), whereas the marked differences between the transit after skin incision and that after laparotomy with or without mechanical gut stimulation remained significant in all experimental groups. Much alike, the differences between propulsion after laparotomy and that following laparotomy and gut manipulation remained significantly different in the treatment groups.

Interactions Between NO, CO, and Prostanoids

As anticipated the administration of indomethacin, resveratrol, nimesulide (n = 5), DuP-697, NS-398 (n = 6), or L-NAME (n = 5) subsequent to SnPP-IX exhibited no marked effect on the intestinal transit after skin incision (data not shown). Indomethacin (n = 7), nimesulide (n = 6), resveratrol (n = 5), NS-398 (n = 5), and DuP-697 (n = 6) attenuated the additional inhibitory effects of gut manipulation following laparotomy. The distance covered by the migrating dye equaled: 40.86 ± 2.70 cm (n = 7), 33.50 ± 1.28 cm (n = 6), 25.0 ± 1.58 cm, 28.60 ± 2.32 cm (n = 5), or 27.50 ± 1.06 cm (n = 6) in comparison to untreated animals 11.67 ± 0.89 (n = 6). Furthermore the pretreatment with SnPP-IX strikingly potentiated the salutary effects of indomethacin (n = 6) and resveratrol (n = 7), but not those of nimesulide (n = 5), NS-398, and DuP-697 (n = 5),

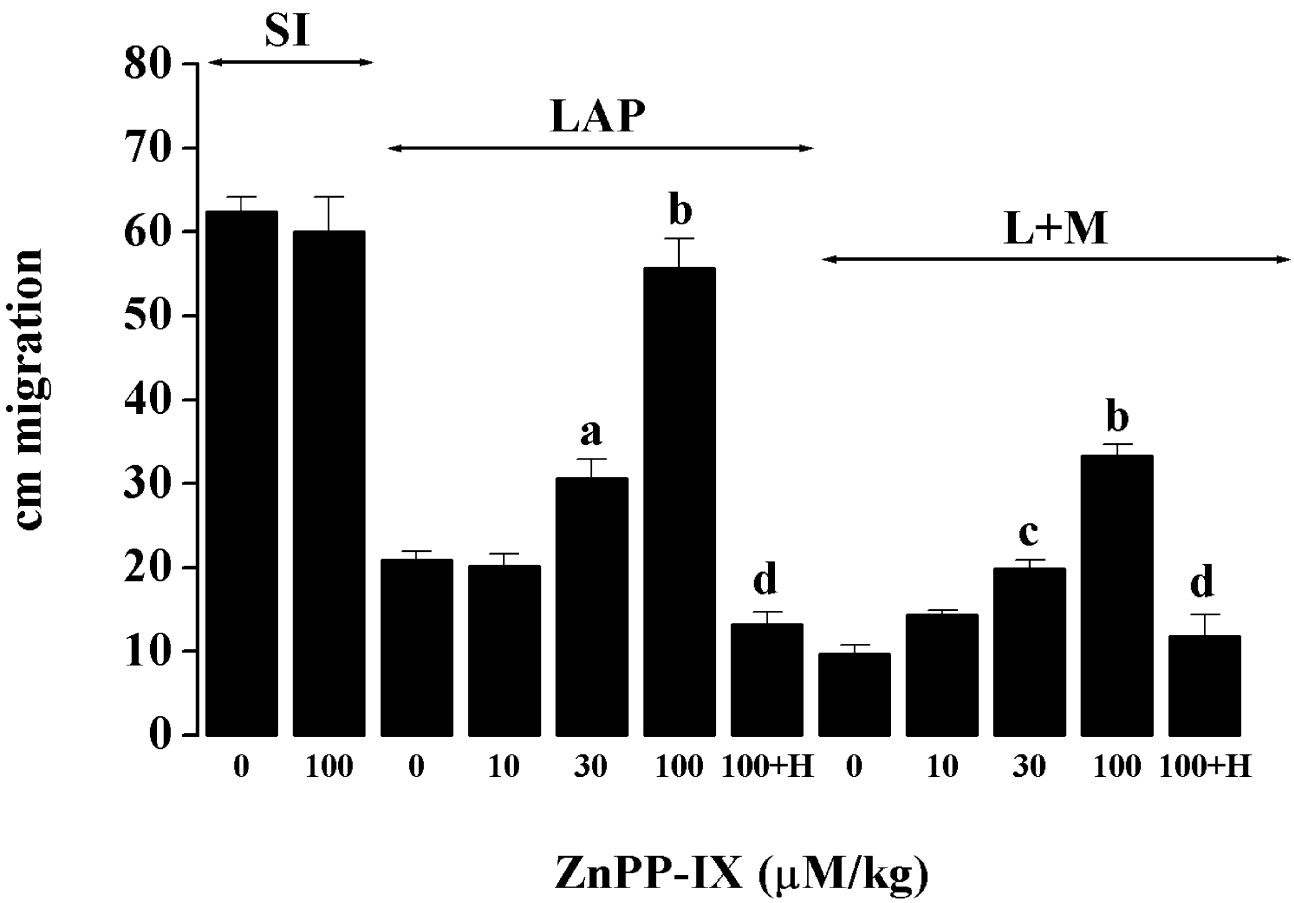

Fig. 6. The effects of ZnPP-IX on the small intestinal transit of Evans blue following skin incision (SI), laparotomy (LAP), or laparotomy and gut manipulation (L + M). Results are shown as cm migration of Evans blue and are presented as a mean result ± SEM of several experiments performed in different animals (n = 5-14). Statistical significance was calculated using one-way ANOVA followed by Bonferroni test: [a]pretreatment with ZnPP-IX (30 μM/kg) vs. respective controls undergong laparotomy ($p < 0.05$); [b]pretreatment with ZnPP-IX (100 μM/kg) vs. controls with the same type of operation ($p < 0.001$); [c]pretreatment with ZnPP-IX (30 μM/kg) vs. controls with the same type of operation ($p < 0.01$); [d]pretreatment with hemin (50 μM/kg) prior to ZnPP-IX (50 μM/kg) vs. pretreatment with Zn PP-IX only (50 μM/kg, $p < 0.001$).

completely reversing the inhibition of the intestinal transit evoked by laparotomy and gut manipulation so that results were not statistically different from those obtained after skin incision. Therefore the movement of Evans blue in the small intestine amounted to: 55.50 ± 3.55 cm (n = 6), 51.67 ± 2.14 cm (n = 5), 37.60 ± 3.26 cm (n = 5), 32.0 ± 2.39 cm, and 33.80 ± 1.85 cm (n = 5). These observations remain in contrast to the effects SnPP-IX alone, the dye migrating over the route of 28.33 ± 2.35 cm (n = 6). Noticeably L-NAME eliminated the beneficial effects of SnPP-IX on the reversal of gut motility inhibition evoked by laparotomy and intestinal manipulation, 14.88 ± 2.29 cm (n = 7) (Fig. 8).

DISCUSSION

We have demonstrated that apart from NO and prostanoids, the endogenously produced CO is an important factor in the pathogenesis of PI in rats and that HO blockade influences gut motility inhibition evoked by laparotomy and laprotomy plus intestinal handling in a different way.

This study has confirmed that mechanical gut stimulation triggers enhanced NO synthesis by cNOS, as highly selective iNOS blockers; 1400W and SMT, remained ineffective in doses inhibiting iNOS activity in vivo.[26–27] Moreover, a period of roughly 1.5 hours is too short to significantly increase iNOS expression in GI smooth muscle cells, as proved by Kalff

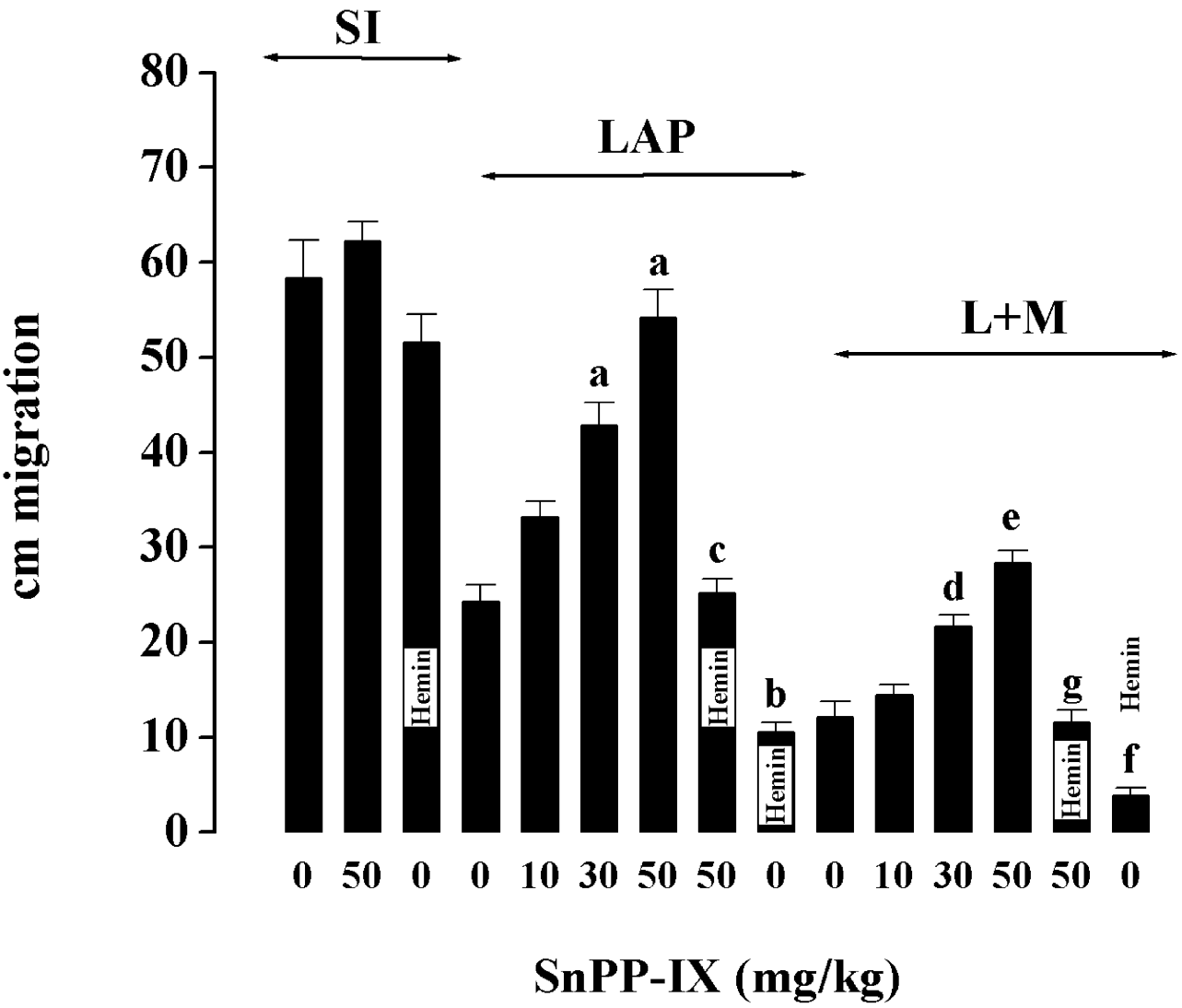

Fig. 7. The effects of SnPP-IX on the small intestinal transit of Evans blue following skin incision (SI), laparotomy (LAP), or laparotomy and gut manipulation (L + M). Results are shown as cm migration of Evans blue and are presented as a mean result ± SEM of several experiments performed in different animals (n = 5-7). Statistical significance was calculated using one-way ANOVA followed by Bonferroni test: [a]pretreatment with SnPP-IX (30 or 50 μM/kg) vs. untreated control rats undergoing laparotomy ($p < 0.001$); [b]pretreatment with hemin (50 μM/kg) vs. untreated control rats undergoing laparotomy ($p < 0.001$); [c]pretreatment with hemin (50 μM/kg) prior to SnPP-IX (50 μM/kg) vs. pretreatment with Sn PP-IX (50 μM/kg) only ($p < 0.001$); [d]pretreatment with SnPP-IX (30 μM/kg) vs. untreated control rats undergoing laparotomy and gut manipulation ($p < 0.05$); [e]pretreatment with SnPP-IX (50 μM/kg) vs. untreated control rats undergoing laparotomy and gut manipulation ($p < 0.001$); [f]pretreatment with hemin (50 μM/kg) vs. untreated control rats undergoing laparotomy and gut manipulation ($p < 0.001$); [g]pretreatment with hemin (50 μM/kg) prior to SnPP-IX (50 μM/kg) vs. pretreatment with Sn PP-IX (50 μM/kg) only ($p < 0.001$).

et al.[21] Although the harmful effects of NO are usually associated with copious amounts of the molecule produced by iNOS, it is diffcult to precisely estimate the actual amount of NO generated by smooth muscle cells of the small intestine as NO is being rapidly converted to NOx products or other metabolites, which are transferred to the circulation. Enhanced NO synthesis, evidenced by elevated urinary nitrate secretion, has been observed after laparotomy or extra-abdominal surgical procedures in humans.[25]

SnPP-IX and ZnPP-IX reversed, in a dose-dependent manner, the inhibition of intestinal transit

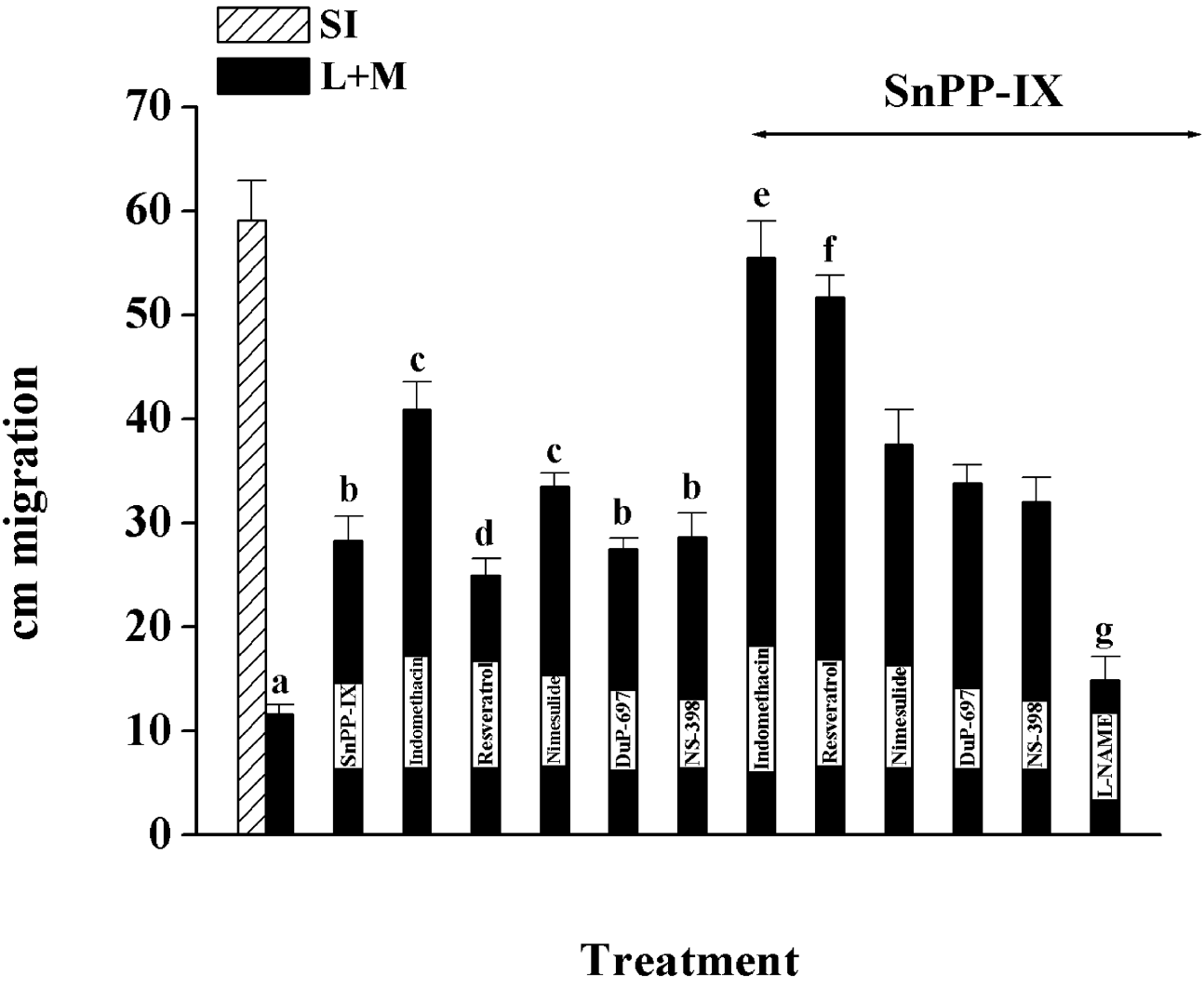

Fig. 8. The effects of combined treatment with NOS, HO, and COX inhibitors on the small intestinal transit of Evans blue following skin incision (SI), or laparotomy and gut manipulation (L + M). Results are shown as cm migration of Evans blue and are presented as a mean result ± SEM of several experiments performed in different animals (n = 5-7). Statistical significance was calculated using one-way ANOVA followed by Bonferroni test: [a]SI vs L + M ($p < 0.001$); [b]pretreatment with SnPP-IX (50 μM/kg), DuP-697 or NS-398 (10 mg/kg) vs. controls undergoing the same type of operation ($p < 0.01$); [c]pretreatment with indomethacin (IND 30 mg/kg), nimesulide (10 mg/kg) vs. controls undergoing the same type of operation ($p < 0.001$); [d]pretreatment with resveratrol (10 mg/kg) vs. controls undergoing the same type of operation ($p < 0.05$); [e]rat pretreated with combination of SnPP-IX plus IND (50 μg/kg + 30 mg/kg) vs. animals undergoing the same type of operation preoperatively injected with SnPP-IX ($p < 0.001$) or indomethacin only ($p < 0.01$); [f]pretreatment with combination of SnPP-IX and resveratrol vs. animals undergoing the same type of operation, preoperatively injected with SnPP-IX or resveratrol only ($p < 0.001$); [g]pretreatment with combination of SnPP-IX and L-NAME (30 mg/kg) vs. animals undergoing the same type of operation, preoperatively injected with SnPP-IX only ($p < 0.05$).

evoked by laparotomy and attenuated the additional blockade of intestinal motility induced by mechanical gut stimulation. Even though the use of metalloporphrins to examine the physiological role of HO has been criticized,[28] Appleton et al.[29] have demonstrated that low concentrations of some metalloporphyrins selectively block HO. Besides, two arguments favor the hypothesis that the beneficial effects of metalloporphyrins in PI may at least be partly related to HO blockade. Firstly, ZnPP-IX and SnPP-IX were used in doses depressing HO activity and CO synthesis in rat.[30] Secondly, L-NAME was

unable to affect the intestinal transit after laparotomy[3,18–19] and the pharmacological activities of SnPP-IX and ZnPP-IX were hemin-sensitive, which by itself aggravated the degree of intestinal transit inhibition induced by laparotomy or laparotomy plus gut manipulation. Thus our results imply that laparotomy triggers enhanced CO synthesis and the antiperistaltic effects of CO could probably result from direct myorelaxant effects of CO. What is more, enhanced endogenous CO production has been demonstrated after lumbar surgery or laparoscopic cholecystectomy.[5,16,31–33] Based on the temporal profile of HO expression in GI tract, one can speculate that HO-2 appears to play a role of a likely candidate in the amplified CO synthesis following surgical intervention, contrasting with an increase of HO-1 expression in intestinal muscualris 3 hours and a peak 6 hours following intestinal manipulation.[20]

The combination of SnPP-IX and indomethacin or resveratrol completely reversed the inhibitory action of gut manipulation following laparotomy on the intestinal transit of the study dye, so that the results were not notably different from controls. On the other hand the results of the administration of nimesulide, DuP-697, and NS-398 subsequent to SnPP-IX were not any better than the pretreatment with a single agent, suggesting that the differential effects of COX inhibitors may at least partially correlate to a different selectivity toward COX isoforms.

L-NAME counteracted the beneficial effect of SnPP-IX on gut motility after laparotomy followed by intestinal evisceration and surgical handling. As the combined treatment remained without any marked effect on the GI transit of Evans blue after skin incision and taking into account that L-NAME showed no noticeable action on gut motility after laparotomy, it seems that the synthesis of either NO or CO must remain unaffected to enable a partial return of GI transit postoperatively. Summarizing the results discussed above, the endogenous NO, CO, and prostanoids do not affect small bowel propulsive motility under normal circumstances, a contradictory hypothesis to results published by some groups,[5,8,32,34] but staying in partial agreement with De Winter et al.[3] and Pairet and Ruckebush.[35]

The determiantion of the exact source of the released NO, CO, and PG cannot be determined based on our experiments alone, as different cell types could synthesize and release those mediators under a plethora of physiological and pathological conditions.[9–15] However, the putative explation of the beneficial activities of COX and HO inhibitors could have resulted from a direct or indirect interaction of COX blockers with NOS, enteric nervous system[14,36–37] or their analgesic action, preventing the activation of inhibitory spinal reflexes.[38–39] In order to study those interactions and pinpoint more precisely the exact action locus, the direct measurements of prostanoid and their metabolite concentrations in tissues are in progress at the moment.

Putting the acquired data in clinical context, one must realize that although the currently used model is relatively simple and well established,[3,18–19] it possesses some drawbacks. For example, the effective duration of PI in humans may primarily depend on the return of colonic motility return[40] and this model provides a mixture of gastric emptying and small intestinal propulsion (a relation of both to each other is not definable) but contributes to PI pathogenesis. In contrast to the salutary effects of low concentrations of inhaled CO,[20] we have demonstrated that the enhanced synthesis of endogenous CO may be detrimental. These differences seem to be at least partially dependent on the temporal frame of the experiment and the model of the disease used.

Summarizing, laparotomy stimulates HO and COX-2 activities, whereas additional gut handling leads to NO release accompanied by COX-1 regulated prostanoid synthesis.[19] The combination of indomethacin or resveratrol with SnPP-IX turned out most effective in the reversal of intestinal propulsion subsequent to laparotomy, implying that the pharmacological blockade of two different but complementary metabolic pathways provided an effective measure against PI development. On the other hand, the observation that administration of L-NAME counteracted the beneficial effect of HO blockers indicates that at least synthesis of either NO or CO must remain unaffected to enable a partial return of GI transit during the postoperative period.

The authors are indebted to Dr. Zdzislaw Konstański without whose invaluable technical expertise and patience the development and application of the current experimental model would not have been possible.

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Successful Perioperative Management of Factor X Deficiency Associated With Primary Amyloidosis

Kazuaki Takabe, M.D., Ph.D., Peter R. Holman, M.D., Kenneth D. Herbst, M.D., Catherine A. Glass, R.N., Michael Bouvet, M.D.

Acquired bleeding abnormalities are common in patients with primary amyloid light-chain amyloidosis. Factor X deficiency is the most common coagulopathy associated with life-threatening hemorrhagic complications when surgery is indicated. Fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs) are the most frequently used blood products in this disease; however, FFP is often ineffective in controlling bleeding and PCCs have a significant risk of thrombosis when used intraoperatively. This report describes a patient with primary amyloidosis and factor X deficiency who underwent hemicolectomy with preoperative and intraoperative administration of recombinant human factor VIIa and postoperative administration of Bebulin (a PCC that contains the highest concentration of factor X). The management was successful with no signs of bleeding postoperatively. To our knowledge, few reports of successful perioperative management of factor X deficiency have been published to date. This is the first case report using recombinant human factor VIIa and Bebulin in the perioperative management of factor X deficiency associated with primary amyloidosis. Recombinant human factor VIIa and Bebulin may allow for successful perioperative management of bleeding disorders in patients with primary amyloidosis. (J GASTROINTEST SURG 2004;8:358–362)

KEY WORDS: Amyloidosis, factor X, operation, hemorrhage, coagulopathy

The prognosis for primary amyloidosis, an intractable and incurable metabolic disease, has recently been improved as a result of new clinical data and treatments.[1–3] However, abnormal bleeding is frequently observed in the management of patients with primary amyloid light-chain amyloidosis,[2] and severe life-threatening bleeding can occur.[4–6] Acquired deficiency of factor X (Stuart factor) is the most common coagulation factor deficiency that has been identified and is reported to occur in 8.7% to 14% of patients with primary amyloid light-chain amyloidosis[1,2] because of the adsorption of factor X to amyloid fibrils exposed to circulating blood.[7] Replacement therapy using either fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCCs) is typically used. However, FFP is often ineffective because of the rapid removal of factor X from the circulation,[8] and PCCs have significant risk of thromboembolic complications.[9–13] Recently, recombinant human factor VIIa (rhF-VIIa) was reported to be effective in controlling the bleeding of factor X deficiency.[14] We report herein the first case in the English literature of acquired factor X deficiency that was managed successfully during right hemicolectomy using rhF-VIIa and Bebulin without any perioperative bleeding episodes.

CASE REPORT

A 52-year-old man was in excellent health until he experienced persistent and heavy bleeding after a tooth extraction. Three months later, he was evaluated for bruising of the legs, fatigue, and anemia. Urinalysis demonstrated the presence of kappa light chains. Bone marrow evaluation demonstrated 60% hypercellularity with 11% well-differentiated plasma cells, and Congo red stain was positive for focal amyloid deposition. Flow cytometry demonstrated kappa light-chain restriction. Results of cytogenetic studies were normal. MRI of the abdomen and pelvis demonstrated hepatosplenomegaly, with the liver measuring 24 cm and the spleen measuring 12 cm and hematomas of the bilateral paraspinous musculature and right

From the Departments of Surgery (K.T., M.B.) and Hematology/Oncology (P.R.H., K.H., C.G.), University of California San Diego School of Medicine, San Diego, California.
Reprint requests: Michael Bouvet, M.D., Department of Surgery, University of California San Diego School of Medicine, 3350 La Jolla Village Dr. (112E), San Diego, CA 92161. e-mail: mbouvet@ucsd.edu

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buttock. Results of coagulation studies are shown in Fig. 1, which demonstrated a significant decrease of factor X at 25%. The patient was diagnosed with factor X deficiency associated with primary amyloid light-chain amyloidosis. The patient received five monthly cycles of chemotherapy with melphalan and prednisone. The patient tolerated the chemotherapy well, but the bone marrow biopsy remained unchanged with stable amyloid deposition.

The patient then underwent colonoscopic evaluation for fecal occult blood and was subsequently diagnosed with a large villous adenoma in the right colon. A severe coagulopathy persisted (see Fig. 1). The beta 2 microglobulin was elevated at 3.19 (normal range 0.8 to 3.0 mg/L), and abdominal fat aspiration was positive for amyloid deposition. Cardiology evaluation demonstrated concentric left ventricular thickening together with right ventricular thickening, but the ejection fraction was normal. The interventricular septal wall thickness was 17 mm (normal range 7 to 11 mm) and had remained stable from a prior study 6 months earlier. Results of pulmonary function testing were normal, and a skeletal survey showed no lytic lesions. These results suggested that the patient was a reasonable candidate for high-dose chemotherapy and stem cell transplantation to palliate his amyloidosis; however, the large colon polyp required removal for diagnostic purposes prior to transplant. Subsequently the patient underwent a colonoscopy in an attempt to remove the polyp. In preparation for the possible polypectomy, the patient was given 4 units of FFP, 10 units of cryoprecipitate, and DDAVP (Desmopressin; 1-desamino-8-d-arginine); however, this treatment failed to correct the prothrombin time. A therapeutic colonoscope was used, which demonstrated a very large sessile right colon polyp measuring 3 to 4 cm with a very broad base without a thin stalk. Active oozing from the edges was also observed. A jumbo (30 mm) snare was not able to pass over the top of the polyp because of the large size. At this point it was decided that the polyp was best removed surgically because of both the risk of perforation and the risk of either immediate or delayed bleeding.

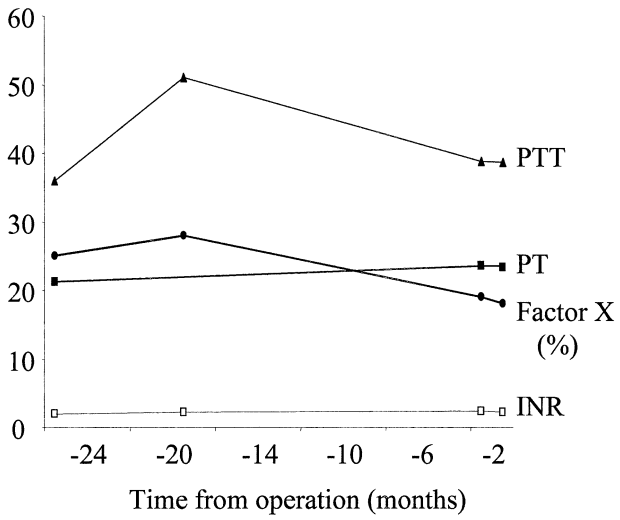

Fig. 1. Preoperative changes in coagulation parameters. The patient demonstrated worsening of coagulopathy preoperatively. Closed circles = factor X; closed squares = prothrombin time (*PT*); open squares = international normalized ration (*INR*), and closed triangles = partial thromboplastin time (*PTT*).

Preoperatively the patient was coagulopathic with factor X of 18%. First, Bebulin, a plasma-derived PCC that contains relatively greater ratios of factor X than the other available PCCs, was given at a dosage of 60 units/kg intravenously to evaluate its effect on prothrombin time/international normalized ratio (Fig. 2, *A*). Although Bebulin successfully corrected the plasma factor X level, we were not able to use it intraoperatively because it is known to have procoagulant potential and may cause disseminated intravascular coagulation. Therefore rhF-VIIa (Novoseven), at a dosage of 90 μg/kg, was given intravenously over 5 minutes at 9 hours prior to surgery (Fig. 2, *B*) and a right hemicolectomy was performed. RhF-VIIa, 90 μg/kg, was given again immediately before surgery was begun and every 2 hours for the next 20 hours because of the very short half-life of factor VIIa (Fig. 3). During the operation, massive hepatomegaly overlying the spleen and stomach was observed. Initially, a splenectomy combined with hemicolectomy was planned to help improve the factor X–related coagulopathy[14] for the treatment of amyloidosis. However, intraoperatively it was thought that the risks of splenectomy would outweigh the benefits. The rhF-VIIa was followed by the administration of Bebulin at a dosage of 100 units/kg intravenously every 12 hours for 3 days and then daily for 2 days. Estimated blood loss from surgery was 200 ml. The hematocrit was maintained between 26.9% and 31.9% throughout the hospital course and was improved from 24.3% preoperatively with 4 units of packed red blood cells transfused only once before surgery. Pathologic diagnosis of the resected specimen was villoglandular adenoma measuring 2.9 × 2.6 × 2.5 cm. The patient's postoperative course was free of any complications, and he was discharged on postoperative day 8, without any complaints or signs of bleeding.

DISCUSSION

Primary amyloidosis is a serious systemic disease with an incidence of 8 patients per 1 million persons

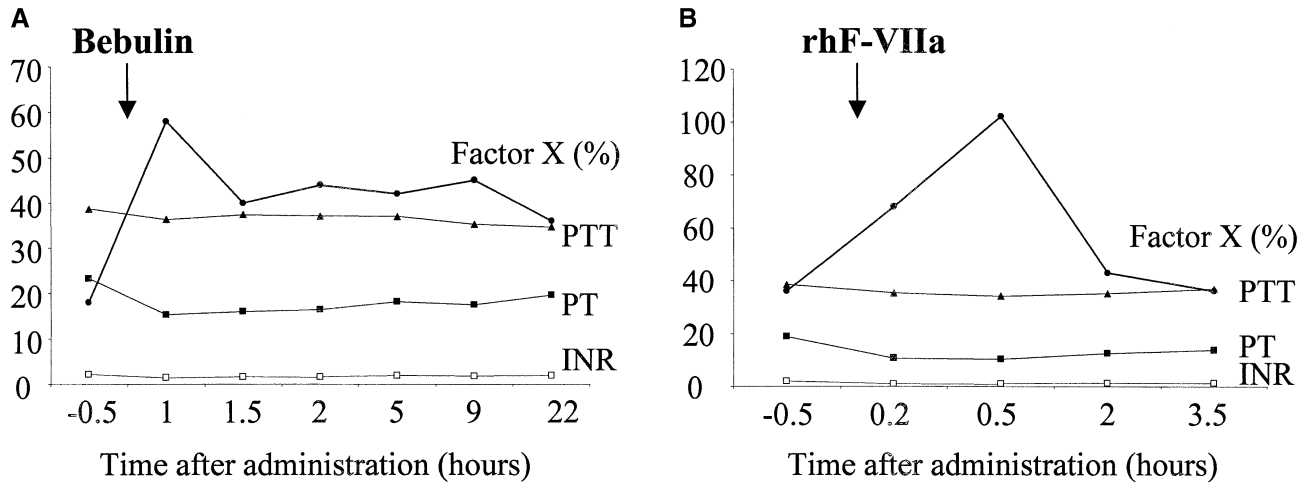

Fig. 2. Preoperative effects of Bebulin (**A**) and rhF-VIIa (**B**) on coagulation parameters. Time course of factor X (*closed circles*), prothrombin time (*PT*) (*closed squares*), international normalized ratio (*INR*) (*open squares*), and partial thromboplastin time (*PTT*) (*closed triangles*) after infusion of Bebulin, 60 U/kg (**A**) and rhF-VIIa, 90 μg/kg (**B**).

per year.[15] Median survival of untreated patients is 13 months from the time of diagnosis.[16] Recently, however, with the introduction of chemotherapy with stem cell transplantation, life expectancy appears to have improved dramatically with a 4-year survival rate of 60% in carefully selected patients.[3] Abnormal bleeding is frequently observed in patients with primary amyloid light-chain amyloidosis,[2] and severe life-threatening bleeding can occur.[4–6] In addition, some cases require surgical intervention for gastrointestinal bleeding,[17–19] and providing adequate hemostasis for surgical procedures can be challenging.[20] It has been previously reported that less than 5% of primary amyloidosis is associated with factor X deficiency,[15] but recent larger series of 368 and 337 patients demonstrated that the incidence is higher (8.7 %[1] and 14 %,[2] respectively).

Factor X is an indispensable coagulation factor, important in both the intrinsic and extrinsic coagulation pathways where they merge into the common pathway with the activation of factor X. In its activated form, factor X converts prothrombin to thrombin. Thrombin then cleaves fibrinogen to fibrin, allowing clots formation to occur. It is believed that acquired factor X deficiency in amyloidosis is caused by adsorption of factor X to amyloid fibrils exposed to circulating blood.[7] This is based on the observation that factor X is cleared rapidly from the circulation with immobilization of the protein in the vasculature.[8] Therefore replacement therapy of factor X often cannot meet the demand, and splenectomy to remove the reservoir of amyloid fibrils has been reported to improve the coagulation abnormality.[21] Together with the fact that splenectomy may be an effective management strategy for patients with amyloidosis-associated factor X deficiency, along with the prolonged life expectancy due to improved treatment modalities, the likelihood that such patients will require surgical intervention appears to be increasing.

To our knowledge, perioperative management of factor X deficiency associated with amyloidosis has rarely been described. FFP and PCCs are most commonly used as replacement therapy because no purified factor X concentrate is available.[22,23] However, administration of FFP only rarely improves clinical bleeding[24,25] or factor X levels.[26] The biologic half-life of exogenous factor X is 20 to 40 hours, so although administration of PCC was reported to improve clinical bleeding only poorly and transiently,[4] an adequate factor X level can be built up with repeated infusions. Intermediate-purity factor IX PCCs, such as Bebulin, contain significant amounts of factor X. However, use of PCCs in bleeding as a result of factor X deficiency involves a significant risk of thromboembolic complications such as disseminated intravascular coagulation and myocardial infarction,[9–13] which is probably related to the presence of activated coagulation factors.[22] Therefore we believe that using PCCs to obtain high levels of factor X intraoperatively poses too great a risk.

Recently use of rhF-VIIa was reported to be effective in treating congenital factor X deficiency.[14,27] The mechanism of factor VIIa treatment is very complex and unclear. It has been postulated that rhF-VIIa binds to tissue factor exposed on activated cells, and the tissue factor VIIa complex activates factor X and factor Xa greatly enhances thrombin generation

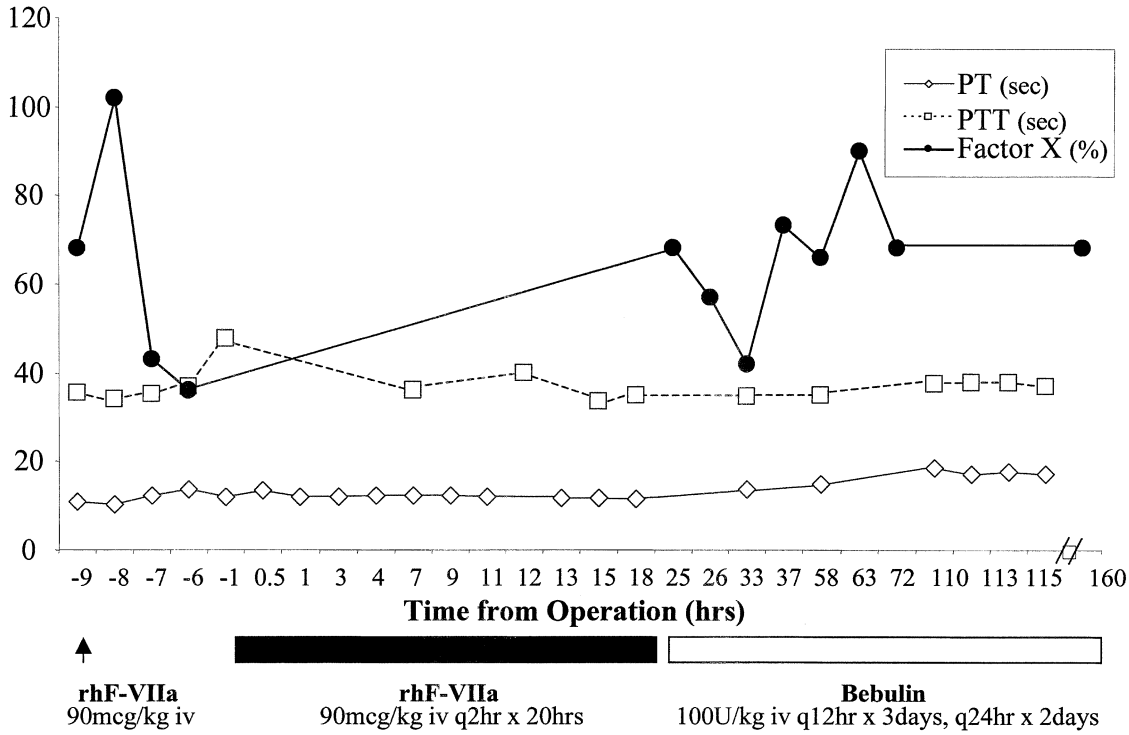

Fig. 3. Perioperative regimen and changes in coagulation parameters. Perioperative time course of factor X (*closed circles*), prothrombin time (*PT*) (*open squares*), and partial thromboplastin time (*PTT*) (*open diamonds*) during perioperative regimen of rhF-VIIa and Bebulin.

on the platelet surface.[27] In addition, high concentrations of factor VIIa may bind to activated platelets and enhance local thrombin formation.[28] Our patient was treated with 4 units of FFP, 10 units of cryoprecipitate, and DDAVP prior to polypectomy, with failure to correct the prothrombin time. On the other hand, rhF-VIIa followed by Bebulin treatment demonstrated the correction of both prothrombin time and factor X level (see Fig. 2). It is known that rhF-VIIa can activate coagulation factor X when combined with tissue factor.[14] Bebulin is an intermediate-purity factor IX PCC that contains more factor X than any other available PCCs. Therefore it was clear in our patient that rhF-VIIa/Bebulin treatment was superior in terms of correcting coagulopathy compared with FFP/cryoprecipitate/DDAVP treatment.

As a definitive treatment for amyloidosis, chemotherapy and autologous stem cell transplantation can improve life expectancy in selected patients. However, gastrointestinal bleeding does occur, even with stem cell transplantation.[29] Therefore we believe that our experience will provide very useful information, even in the era of stem cell transplantation. It is obvious that drawing conclusions from a single case is always tenuous, and experience with this management in additional patients is clearly needed to confirm its benefits. However, we believe that rhF-VIIa/Bebulin treatment was useful in our patient, and we suggest that it be considered as one option for perioperative management of factor X deficiency in patients with primary amyloid light-chain amyloidosis.

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These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians utilize procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2004;8:363–364)

Treatment of Gallstone and Gallbladder Disease

Introduction

Gallstone disease represents a national health care problem, resulting in more than 600,000 cholecystectomies per year. The majority of these operations are for symptomatic gallstone disease. Nearly 90% of cholecystectomies are performed laparoscopically. Alternative forms of treatment are palliative rather than curative.

Symptoms and Diagnosis

Most patients with gallstones do not have symptoms. Natural history studies show that patients with asymptomatic gallstones incidentally discovered will develop symptoms at a rate of approximately 1.5% to 2.0% of patients per year. Typical biliary pain due to gallstones is a temporary (ranging from 30 minutes to 24 hours) epigastric or right upper abdominal pain after meals. The pain may at times radiate to the right flank, back, or shoulder. In some patients, the symptoms are mild and consist of vague indigestion or dyspepsia. The diagnosis of gallstones is usually established by ultrasonography. Ultrasound findings of a thickened gallbladder wall and fluid around the gallbladder suggest the presence of acute cholecystitis. Radionuclide scanning is not a useful test for the diagnosis of gallstones, but it is useful in diagnosing acute cholecystitis.

Treatment

A surgeon should see the patient within a few weeks of an attack if the acute episode has resolved or symptoms are mild. Patients with significant right upper quadrant tenderness, fever, or elevated white blood cell count should see a surgeon the same day. The presence of gallstones without abdominal symptoms is not an indication for cholecystectomy unless there is a predisposition for malignancy—that is, the gallbladder wall is calcified or there is a family history of gallbladder cancer. Once a patient with gallstones becomes symptomatic, elective cholecystectomy is indicated. The primary indication for urgent cholecystectomy is acute cholecystitis. Gallstone pancreatitis, choledocholithiasis (common duct stones), and cholangitis require surgical consultation. Patients with recurrent symptoms typical of biliary pain, but without gallstones on ultrasound imaging, should be referred for surgical consultation.

Cholecystectomy may be performed by laparoscopic techniques or by laparotomy. The advantages of the laparoscopic approach are less pain, shorter hospital stay, faster return to normal activity, and less abdominal scarring. Alternative nonstandard forms of treatment include dissolution of gallstones with oral agents, extracorporeal shock wave lithotripsy, and instilling solvents directly into the gallbladder. Oral dissolution therapy has limited efficacy and is costly. Shock wave lithotripsy and contact dissolution are not approved by the FDA for definitive treatment of gallstones.

Risks

The risks are low in patients undergoing elective cholecystectomy and include the following: injury to the bile ducts, retained stones in the bile ducts, or injury to surrounding organs. The bile duct injury rate is approximately 0.5% of operated patients for

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laparoscopic cholecystectomy. The presence of anatomic variations and inflammation contribute to an increased risk of complications including bile duct injury. The mortality rate in a good-risk patient undergoing elective operation is less than 0.1%. Operative risks usually arise from comorbid conditions such as cardiac or pulmonary disease.

Conversion of Laparoscopic Cholecystectomy to an Open Procedure

A laparoscopic approach is feasible in most patients. Conversion to an open procedure may be required because of the presence of adhesions, difficulty in delineating the anatomy, or a suspected complication. Conversion is more often necessary in elderly patients and those with prior upper abdominal operations, a thickened gallbladder wall, or acute cholecystitis. The incidence of conversion to an open procedure is approximately 5%, depending on the patient population.

Expected Outcomes

The majority of good-risk patients undergoing elective laparoscopic cholecystectomy can usually be discharged from the hospital the same or the next day. High-risk patients and those undergoing emergency operations may require longer hospital stays. When open cholecystectomy is performed, patients are usually discharged after two or three nights in the hospital. Hospitalization may be prolonged in patients requiring placement of abdominal drains, exploration of the bile duct, or those with complicated biliary tract disease. Nearly 95% of patients experience relief of biliary pain after cholecystectomy. The remaining 5% may have a cause of pain other than gallstones. Patients with dyspepsia or diarrhea before surgery may find that these symptoms persist after operation.

Treatment of Common Duct Stones

Common duct stones may be removed either endoscopically or surgically. The endoscopic approach may be indicated for patients with cholangitis, obstructive jaundice, and in selected patients with gallstone pancreatitis. Endoscopic clearance of common duct stones is an effective treatment but may be complicated by pancreatitis, bleeding, or perforation in up to 5% of cases. Surgical removal of common duct stones can be performed by means of open or laparoscopic techniques with appropriate equipment and surgical expertise. Open cholecystectomy with common bile duct exploration is a safe and effective treatment, especially in acutely ill patients. Because most common duct stones arise from the gallbladder, cholecystectomy is also indicated unless the patient is a poor operative risk.

Costs

Cholecystectomy is cost-effective compared to alternative treatments. It definitively treats the disease and reliably alleviates the symptoms.

Qualifications for Performing Surgery on the Gallbladder

At a minimum, surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent should perform laparoscopic and open cholecystectomy. In addition to the standard residency training, qualifications should be based on training, experience, and outcomes.

SUGGESTED READINGS

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KEY WORDS: Gallstones, choledocholithiasis, cholecystitis, cholelithiasis, cholecystectomy, gallbladder disease, acute disease, acalculous cholecystitis, common bile duct stones, guideline, patient

Surgical Repair of Groin Hernias

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians utilize procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2004;8:365–366)

Introduction

Groin hernias include inguinal and femoral hernias. Repair of groin hernias is one of the most commonly performed outpatient surgical procedures. They are most commonly seen in men. Although these hernias afflict persons of all ages, this guideline will consider only the adult patient.

A groin hernia is not a "rupture," per se, but rather a groin bulge or mass that develops as a result of weakened layers of the abdominal wall and protrusion of intra-abdominal contents through a defect in the wall. Direct inguinal hernias develop when the posterior portion of the inguinal canal attenuates, allowing the nearby contents of the abdominal cavity to protrude, whereas an indirect inguinal hernia occurs along the spermatic cord or round ligament in the inguinal canal. A femoral hernia passes behind the area of a direct hernia and follows the femoral vessels. These hernias are uncommon and occur mostly in women.

Symptoms and Diagnosis

Patients with inguinal hernias typically present with vague groin pain. However, inguinal hernias may be asymptomatic, discovered incidentally during physical examination, or present as a bulge discovered by the patient. Because most hernias should be repaired, the patient should be referred to a surgeon for evaluation and possible operative treatment. Sophisticated tests are not required because the diagnosis can usually be made on physical examination, which is best performed with the patient standing and straining against a held breath (Valsalva maneuver). Ultrasound and diagnostic x-rays also are not usually necessary.

More difficult to diagnose is the occasional patient with groin pain but no history of groin bulge and without physical findings of a hernia by the primary physician or surgeon. Such a patient may not have a hernia but rather a groin muscle strain. In contrast, if a hernia is not found on physical examination, but the patient describes a groin bulge, a hernia is likely present. Femoral hernias often present as pain below the groin crease, rather than a bulge, and are particularly difficult to diagnose in elderly or obese patients with sudden groin pain but no physical findings of groin hernia of any type.

The majority of groin hernias are readily reducible, have minimal or no tenderness, and can be electively referred to a surgeon within a period of weeks. However, if the hernia is tender and not reducible, the patient should be referred immediately because the patient may have strangulated bowel or other viscera trapped in the hernia. Aggressive attempts to reduce a groin hernia with sedation, ice packs, or sustained weight or pressure should not be pursued. Symptoms such as nausea and vomiting suggest bowel obstruction, which mandates immediate referral to a surgeon.

Treatment

Because patients with groin hernias are usually offered and receive elective repair, the incidence of emergent incarcerated (nonreducible) hernias is relatively low. Urgent repair is required for a sudden, nonreducible hernia or a chronically incarcerated hernia that becomes acutely painful or tender, as this indicates impending strangulation. Although severe morbidity and mortality can be avoided by prompt diagnosis and operation, this clinical emergency causes the death of more than 2000 patients per year in North America.

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Most inguinal hernias that should be repaired are symptomatic or are enlarging over time. Hernia belts should be discouraged and should be limited to patients who are not candidates for elective operation. Their use can lead to a more difficult repair and a higher risk of complications or recurrence. Femoral hernias should almost always be repaired because of the high incidence of bowel strangulation. Patients with groin hernias should undergo surgical evaluation within a month after detection. Urgent repair is required for all painful, nonreducible hernias, whereas asymptomatic hernias can be repaired electively. Elderly patients with minor comorbid conditions will easily tolerate an outpatient elective hernia repair, thus avoiding emergent repair of an incarcerated hernia. The timing of repair is determined by the symptoms.

The objective of any inguinal or femoral hernia operation is to repair the defect in the abdominal wall. The three basic approaches are as follows: (1) open repair (the traditional repair, which uses the patient's own tissues); (2) open, tension-free repair (in which mesh is used to bridge or cover the defect); and (3) laparoscopic repair, a tension-free repair that also uses mesh. Open techniques of hernia repair can be performed under local, regional, or general anesthesia, whereas laparoscopic hernia repair requires general anesthesia.

Because of the presently higher cost and complexity of laparoscopic repair, open repair is more frequently performed.

Risks

The risk of infection or a significant hematoma after operation is approximately 1%. Hernias recur in 5% to 10% of patients and these recurrences require another repair.

Expected Outcomes

Short-term outcome studies suggest that a quick return to normal activities can be achieved after both open and laparoscopic hernia repair. Usual daily activities can be resumed within a few days after surgery, depending on the patient's comfort level. Oral pain medications are needed for only a few days.

Qualifications for Performing Inguinal and Femoral Hernia Repairs

Surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent should perform both elective and emergent inguinal hernia repair. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform open inguinal hernia repair, with and without tension-free techniques. Advanced laparoscopic training is required for laparoscopic groin hernia repair. The qualifications of the surgeon should be based on training (education), experience, and outcomes.

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KEY WORDS: Patient, guideline, groin hernia, inguinal hernia, femoral hernia, open repair, tension-free repair, laparoscopic repair, recurrence, groin pain, complications, mesh, incarcerated

Esophageal Achalasia

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians utilize procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2004;8:367–368)

Introduction

Esophageal achalasia is a primary esophageal motility disorder of unknown etiology. It is characterized by absence of esophageal peristalsis and increased or normal resting pressure of the lower esophageal sphincter (LES), which fails to relax completely in response to swallowing.

Clinical Presentation

Dysphagia is the most common symptom and is experienced by virtually all patients. Regurgitation is the second most common symptom and is present in approximately 60% of patients. It occurs more often in the supine position and exposes the patients to the risk of aspiration of undigested food. Chest pain occurs in approximately 40% of patients and is usually experienced at the time of a meal. Heartburn occurs in approximately 40% of patients. In untreated patients, this symptom is usually due to stasis and fermentation of food in the esophagus or esophageal distention.

Diagnosis

In addition to careful symptomatic evaluation, a number of tests should be routinely performed. Barium swallow usually shows narrowing at the level of the gastroesophageal junction and various degrees of esophageal dilatation. Endoscopy with biopsy, if indicated, is important to rule out the presence of a peptic stricture or cancer and gastroduodenal pathology. Esophageal manometry is the key test for establishing the diagnosis. The classic manometric findings are absence of esophageal peristalsis and a hypertensive or normotensive LES, which fails to relax completely in response to swallowing.

Prolonged pH monitoring may be helpful preoperatively in patients who have previously failed treatment with pneumatic dilatation, botulinum toxin (Botox), or surgical myotomy, for whom a myotomy is planned. Demonstration of reflux clearly indicates the need for a gastric fundoplication in addition to the myotomy.

In patients over the age of 60 years, with recent onset of dysphagia and excessive weight loss, secondary or pseudoachalasia should be ruled out. Because cancer of the gastroesophageal junction is the most common cause of pseudoachalasia, endoscopic ultrasound imaging or a CT scan of the gastroesophageal junction can help to establish the diagnosis.

Treatment

Treatment is palliative, and it is directed toward elimination of the outflow resistance at the level of the gastroesophageal junction. Several treatment modalities are available to achieve this goal.

Pneumatic dilatation has a success rate between 70% and 80%. Gastroesophageal reflux occurs after dilatation in 25% to 35% of patients. Up to 5% of patients may sustain a perforation at the time of a dilatation. These patients may require open surgery to close the perforation and perform a myotomy.

Intrasphincteric injection of botulinum toxin results in initial relief of symptoms in approximately 60% of patients, but this is transitory and symptoms will return in the majority of patients within a year. Subsequent injections are less effective and the benefit is of briefer duration. In addition, this treatment may cause an inflammatory reaction at the level of the gastroesophageal junction, which obliterates the anatomic planes. Consequently a subsequent myotomy is more difficult, is followed by a mucosal perforation more frequently, and the relief of dysphagia

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is less predictable. Because of these shortcomings, botulinum toxin should be reserved for elderly or high-risk patients who are poor candidates for dilatation or surgery.

Traditionally, pneumatic dilatation has been the first line of treatment for esophageal achalasia, whereas surgery was reserved for patients who had persistent dysphagia after multiple dilatations or who had suffered a perforation during dilatation.

Today, minimally invasive surgery has completely changed this treatment algorithm, and a laparoscopic Heller myotomy and partial fundoplication are preferred by most gastroenterologists and surgeons as the primary treatment modality. Critical details of the operation include a 7 cm myotomy of the lower esophagus, extending 2 cm onto the gastric wall. Because of the lack of esophageal peristalsis, a partial (Dor or Toupet) rather than a total fundoplication is frequently added to prevent reflux. Patients are usually able to eat on the morning of the first postoperative day, and can be discharged home after one or two days.

The need for esophagectomy for achalasia is uncommon, even in the presence of a dilated esophagus, and should be reserved for failures after myotomy.

All patients undergoing treatment for achalasia should be followed by surveillance endoscopy, because they are at increased risk for development of both squamous carcinoma and adenocarcinoma.

Risk

Aspiration of retained food in the esophagus at the time of induction of anesthesia and perforation of the esophageal mucosa are the most common operative complications. Persistent or recurrent dysphagia occurs in 5% to 10% of patients. A complete workup is necessary to evaluate the cause of the dysphagia in these patients. Either pneumatic dilatation or a second operation can often correct the problem. Up to 15% of patients may experience gastroesophageal reflux after myotomy, as measured by 24-hour pH monitoring. In patients undergoing elective myotomy, the mortality rate is less than 1%.

Expected Outcomes

Approximately 90% of patients have long-term relief of dysphagia after a myotomy, with a low incidence of symptomatic acid reflux. Patients should undergo 24-hour pH testing routinely after surgery, as reflux is often asymptomatic. The patient should be treated with proton pump inhibitors if acid reflux is present.

Qualifications for Performing Operations for Achalasia

At a minimum, surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent should perform operations for achalasia. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform Heller myotomy and fundoplication procedures. The level of training in advanced laparoscopic techniques necessary to conduct minimally invasive surgery of the esophagus is important to assess. The qualifications of a surgeon performing any operative procedure should be based on training, experience, and outcomes.

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KEY WORDS: Achalasia, esophageal motility disorders, dysphagia, pneumatic dilatation, Heller myotomy, partial fundoplication, botulinum toxin, patient, guideline

Surgical Repair of Incisional Hernias

These Guidelines have been written by the Patient Care Committee of The Society for Surgery of the Alimentary Tract (SSAT). Their goal is to guide physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs. They are based on a critical review of the literature and expert opinion. Together these sources of information result in a consensus that is recorded in the form of these Guidelines. The consensus addresses the *range* of acceptable clinical practice and should not be construed as a standard of care. These Guidelines will require periodic revision to ensure that clinicians utilize procedures appropriately, but the reader must realize that clinical judgment may justify a course of action outside of the recommendations contained herein. If you would like to ask a medical question, please use the SSAT Directory to find an SSAT physician in your area. (J GASTROINTEST SURG 2004;8:369–370)

Introduction

Surgery in the abdomen requires creation and subsequent closure of an abdominal incision that is never as strong as the original abdominal wall. Weakening of surgical closures over time may result in the development of an incisional hernia, which is estimated to occur in 3% to 13% of primary abdominal incisions. Recurrence rates after incisional hernia repair are markedly higher and are estimated to range from 25% to 50%. Factors that contribute to the development of incisional hernias include wound infections, obesity, diabetes, and smoking. Reasons for repairing incisional hernias are as follows: (1) to relieve symptoms; (2) to prevent gradual enlargement over time; and (3) to avoid incarceration and strangulation of bowel.

Symptoms and Diagnosis

Incisional hernias can present in a variety of different ways, but the most frequent complaint is pain. The pain is usually located over the hernia and is greatest at the fascial margins. It is usually dull in nature and typically does not radiate. Straining maneuvers may exacerbate pain or demonstrate a previously unnoticed defect. Patients may describe changes in bowel habits that can result from incarceration of abdominal viscera. The presence of an irreducible hernia should prompt surgical referral. Sharp pain or peritoneal signs suggest the possible diagnosis of strangulation; urgent surgical referral is then necessary.

The diagnosis is made by physical examination. Findings may include a visible bulge or palpable fascial edges. The size and number of fascial defects are often difficult to determine preoperatively. Usually the clinical examination represents the "tip of the iceberg"; additional fascial defects not appreciated preoperatively are often identified at operation. A palpable mass in a suspected incisional hernia should not be aspirated because this mass may contain bowel.

Treatment

There are many ways to surgically repair incisional hernias. Smaller incisional hernias (<3 cm.) can be repaired with primary tissue approximation with sutures. Repair of larger defects generally requires the use of prosthetic materials, which allows for a tension-free repair. Laparoscopic techniques may be used for repair of incisional hernias in selected patients. Potential benefits of the laparoscopic approach include good visualization of all fascial defects and smaller incisions with less pain and quicker recovery.

Risks

The risks of incisional hernia repair include "seroma," wound infection, injury to intra-abdominal structures, and recurrent hernia. Major complications such as a mesh infection or enterocutaneous fistula may result in prolonged morbidity and require reoperation.

Expected Outcomes

Successful repair can be expected in the majority of cases. The risk of recurrence increases markedly in patients who have had previous failed repairs, in patients with very large hernias, and in cases where one or more margins of the hernia defect is bone or cartilage. There are no studies yet published that provide good evidence comparing laparoscopic and open repairs.

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After surgery, patients are instructed to limit activity for varying lengths of time according to surgeon preference. Limitations on lifting and straining are generally recommended for several weeks after surgery. Limitations on activity after the laparoscopic approach are generally of shorter duration than following traditional open repairs.

Qualifications for Performing Incisional Hernia Repairs

Surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent should perform both elective and emergent incisional hernia repair. These surgeons have completed at least 5 years of surgical training after medical school graduation and are qualified to perform open incisional hernia repair with and without tension-free techniques. The level of training in advanced laparoscopic techniques necessary to conduct minimally invasive incisional herniorrhaphy has not been formally determined, but surgeons with advanced laparoscopic experience are qualified to perform this procedure.

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KEY WORDS: Hernia, incisions, laparoscopy, mesh, patient, guideline, prosthetic material

DiO-Labeled CC531s Colon Carcinoma Cells Traverse the Hepatic Sinusoidal Endothelium via the Fas/FasL Pathway

To the Editor:

We have read with great interest the article by Haier et al.[1] in the May-June 2003 JOURNAL OF GASTROINTESTINAL SURGERY issue, titled: "An Intravital Model to Monitor Steps of Metastatic Tumor Cell Adhesion Within the Hepatic Microcirculation." Recently, our group discussed a similar method to trace labeled CC531s cells.[2] Haier et al. used Calcein AM, whereas in our study DiO, a stable lipophilic fluorescent probe, was used. This DiO-labeling method was applied in combination with confocal laser scanning microscopy (CLSM) after perfusion fixation of the liver. In this way, labeled tumor cells could be traced over a depth of more than 100 μm.[2] This method has been reviewed in *Biophotonics International*.[3] Furthermore, in order to visualize liver macrophages, latex beads were injected into the penile vein prior to perfusion-fixation. This enabled us to visualize early interactions of Kupffer cells (KC) and CC531s tumor cells. Our observations clearly demonstrate phagocytosis of CC531s by KC. After 1 hour of circulation of the CC531s, the KC form protrusions around the CC531s. After 8 hours the CC531s are inside the cell, resulting in double-labeled KC with TRITC-latex beads and DiO-CC531s remnants.[2] The cells, however, were still present in the sinusoids. Haier et al., in contrast, visualized that the majority of the adherent colon carcinoma cells were found outside the sinusoids. Also Mook et al.[4] recently discussed a comparable model using eGFP-labeled CC531s cells in combination with intravital microscopy. However, Mook et al.[3] did not observe adherence of the CC531s to the endothelium. In contrast, based on their observations, they postulate that CC531s become trapped in the sinusoids and proliferate from there on.

Based on the observations by Haier et al.,[1] it is unclear how the CC531s cells pass the hepatic sinusoidal endothelial lining. In the August 2003 issue of *Liver International*, we showed that when Fas on liver sinusoidal endothelial cells (LSECs) binds to its ligand on CC531s cells, apoptosis is induced.[5] By this means a gateway is made through the endothelial lining and CC531s can pass through to the liver parenchyma. In our study CC531s cells induced apoptosis in LSECs in vitro after 18 hours; however, after 3 hours no apoptosis could be measured. When a CC531s cell is trapped in the liver sinusoid, the sinusoidal lining is disrupted as visualized with scanning electron microscopy at 18 hours (Fig. 1.). Interestingly, Haier et al.[1] visualized extravasation of the CC531s after 30 minutes.

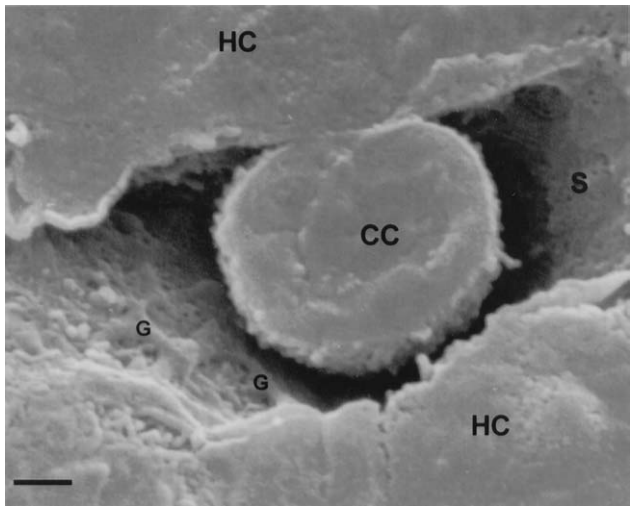

Fig. 1. Scanning electron microscopic image of a hepatic Sinusoid (S) with a CC531s cell (CC). Note the hepatocytes (*HC*), which border the sinusoid (*S*); CC531s cell is arrested in the sinusoid 18 hours after injection. The endothelial lining shows severe damage in the form of Gaps (*G*). Scale bar = 1 μm.

Therefore, we postulate that CC531s cells open the endothelial lining by inducing apoptosis in the LSECs. The access to the parenchyma is free. Once the colon cancer cells are inside the parenchyma, they can not be accessed by the local immune system, hepatic natural killer cells and Kupffer cells.

Katrien Vekemans, Filip Braet, and Eddie Wisse*
Laboratory for Cell Biology and Histology
Free University Brussels (VUB)
Brussels-Jette, Belgium

**Current address: Flanders Institute for Biotechnology (VIB)*
Department for Molecular Biomedical Research
Molecular Cell Biology Unit
Ghent University (UGent)
Ghent, Belgium

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Reply

Based on their results, Vekemans et al. postulate that successful tumor cell adhesion within the liver sinusoids can induce endothelial cell apoptosis with subsequent exposure of the underlying parenchyma—a process that starts later than 3 hours but was visualized after 18 hours. They report that the Fas-ligand binding appears to be responsible for the ability of colon carcinoma cells to invade the liver parenchyma mediated by the resulting gaps within the endothelial cell lining. Once the tumor cells reached the liver parenchyma, they were no longer accessible for immune responses. Their figure provides evidence from electron microscopy that (1) the endothelial lining of the liver sinusoids has gaps in the direct neighborhood of the adherent tumor cells, and (2) a remaining vessel lumen surrounds the adherent tumor cell.

In their comments, Vekemans et al. discuss potential controversies between the time course of endothelial cell apoptosis in their experiments and the tumor cell migration into the liver parenchyma found in our study. However, under physiologic conditions the endothelial layer within liver sinusoids is incomplete and contains gaps leaving extracellular matrix proteins, such as fibronectin and vitronectin, directly accessible for circulating cells in the space of, Disse. Therefore, circulating tumor cells can use integrins and selectins to specifically bind to microvascular structures within the hepatic sinusoids (Haier et al., unpublished results). Furthermore, although induction of endothelial cell apoptosis may enhance the ability of adherent tumor cells to migrate into the liver parenchyma, the resulting damage within the endothelial layer appears not to be a prerequisite for the extravasation.

Using a similar technique to the one used in our study, Mook et al.[1] did not observe specific cell adhesion but noted size-restricted cell entrapment within the sinusoids. This group, however, injected very high numbers of cells (5×10^6 in 0.5 ml) directly into the portal vein. In our study we found that this procedure results in severe disturbances of the hepatic microcirculation with subsequent occlusion of sinusoids with cell clusters. In our opinion, these findings do not reflect the physiologic conditions during metastasis formation. Therefore we used injection of lower numbers of tumor cells (1×10^6 in 1 ml) into the systemic circulation. As described in our report, we compared this approach with other routes of cell application and found that cellular adhesive interactions were independent whether the cells were injected intracardially (left or right heart) or into the portal vein. Furthermore, circulating tumor cells that were able to pass the liver microcirculation were still observed 30 minutes after injection; during this time the cells had to pass different capillary beds several times without mechanical cell arrest.

In summary, the data provided by Vekeman et al. are not in contrast to the early extravasation of colon carcinoma cells in our study. The induction of the Fas/FasL-mediated endothelial cell apoptosis may improve the accessibility of extracellular matrix proteins for the tumor cells resulting in enhanced migration into the parenchyma at later time points, as described by Koop et al.[2]

Dr. Jorg Haier
Head, Molecular Biology Laboratory
Department of General Surgery
Muenster University Hospital
Muenster, Germany

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In summary, the data provided by Vekeman et al. are not in contrast to the early extravasation of colon carcinoma cells in our study. The induction of the Fas/FasL-mediated endothelial cell apoptosis may improve the accessibility of extracellular matrix proteins for the tumor cells resulting in enhanced migration into the parenchyma at later time points, as described by Koop et al.[2]

Dr. Jorg Haier
Head, Molecular Biology Laboratory
Department of General Surgery
Muenster University Hospital
Muenster, Germany

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