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Metabolic Characterization of Nondiabetic Severely Obese Patients Undergoing Roux-en-Y Gastric Bypass: Preoperative Classification Predicts the Effects of Gastric Bypass on Insulin–Glucose Homeostasis

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Abstract
Introduction Obese individuals may have normal insulin–glucose homeostasis, insulin resistance, or diabetes mellitus. Whereas gastric bypass cures insulin resistance and diabetes mellitus, its effects on normal physiology have not been described. We studied insulin resistance and β-cell function for patients undergoing gastric bypass.
Methods One hundred thirty-eight patients undergoing gastric bypass had fasting insulin and glucose levels drawn on days 0, 12, 40, 180, and 365. Thirty-one (22%) patients with diabetes mellitus were excluded from this analysis. Homeostatic model of assessment was used to estimate insulin resistance, insulin sensitivity, and β-cell function. Based on this model, patients were categorized as high insulin resistance if their insulin resistance was >2.3.
Results Body mass index did not correlate with insulin resistance. Forty-seven (34%) patients were categorized as high insulin resistance. Correction of insulin resistance for this group occurred by 12 days postoperatively. Sixty (43%) patients were categorized as low insulin resistance. They demonstrated an increase of β-cell function by 12 days postoperatively, which returned to baseline by 6 months. At 1 year postoperatively, the low insulin resistance group had significantly higher β-cell function per degree of insulin sensitivity.
Conclusions Adipose mass alone cannot explain insulin resistance. Severely obese individuals can be categorized by degree of insulin resistance, and the effect of gastric bypass depends upon this preoperative physiology.

Keywords Severe obesity · Insulin resistance · Insulin sensitivity · β-cell function · Laparoscopic Roux-en-Y gastric bypass

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Introduction

Severe obesity is recognized as a major public health concern in the United States at this time. Obesity is associated with comorbid conditions, such as hypertension, type 2 diabetes mellitus, dyslipidemia, biliary tract disease, osteoarthritis, and sleep apnea.[1] Estimates for annual mortality due strictly to obesity range between 280,000 and 325,000.[2]

The most plausible explanation for the morbidity and mortality because of obesity involves its relationship with the insulin resistance (IR) syndrome (metabolic syndrome, syndrome X). The IR syndrome is a cluster of clinical abnormalities that includes obesity, hyperglycemia or hyperinsulinemia, dyslipidemia, and hypertension,[3] and is a major predictor for cardiovascular morbidity.[4,5] Gastric bypass cures diabetes mellitus,[6] with an associated reduction in per annum mortality from 4.5 to 1.0% in severely obese diabetic patients.[7] Several

studies have documented improvement in IR after gastric bypass.[6,8–12] Although it has not yet been demonstrated, it would be logical to presume that resolution of IR in nondiabetic severely obese individuals would also lead to a reduction in morbidity.

There exists, however, a population of severely obese individuals with normal insulin and glucose homeostasis, and low risk for cardiovascular morbidity. Approximately 50 years ago, Vague[13] proposed the idea that individuals with fat in predominantly subcutaneous and hip distributions had lower risk for diabetes and cardiovascular morbidity than individuals with central obesity. NIH consensus criteria for bariatric surgery do not discriminate between severely obese individuals based on metabolic health, or distribution of adiposity. As a result, a subset of patients undergoing bariatric surgery are metabolically healthy; Lee et al.[12] noted that only 52.2% of all patients undergoing bariatric surgery in their series could be categorized with the metabolic syndrome by Adult Treatment Panel III guidelines, defined as the presence of greater than three of the following: waist circumference >102 cm in men and 88 cm in women; serum triglyceride level greater than 150 mg/dl; high density lipoprotein cholesterol level less than 40 mg/dl in men and 50 mg/dl in women; blood pressure of at least 130/85 mmHg; and serum glucose level of greater than 110 mg/dl. Whereas gastric bypass is a powerful tool to cure problems with insulin and glucose homeostasis, there is no data published regarding its effects in metabolically normal, but severely obese individuals. Furthermore, there are now reports of potentially deleterious metabolic consequences of gastric bypass, such as hyperinsulinemic hypoglycemia with nesidioblastosis.[14]

Glycemic control is dependent on the relationship between insulin sensitivity of peripheral tissues and β-cell function. *Insulin sensitivity* is the ability of peripheral tissues to dispose of glucose in response to insulin. *Insulin resistance* is the inverse of insulin sensitivity, and signifies the need for increasing levels of insulin to dispose of similar quantities of glucose. *β-Cell function* is the ability of the β-cell to secrete insulin in response to a given concentration of glucose. Kahn et al.[15] first described a hyperbolic relationship between insulin sensitivity and β-cell function. It is now understood that these variables need to be evaluated together.[16] We studied IR and β-cell function in a series of nondiabetic patients undergoing gastric bypass. We sought to characterize patients preoperatively based on degree of IR, and to follow the effects of gastric bypass on IR and β-cell function during the year after surgery.

Methods

This is a series from a tertiary care academic hospital in a metropolitan setting. All subjects qualified for surgery under published NIH consensus guidelines for treatment of the morbidly obese patient.[17] Patients were evaluated and cleared for surgery by specialists in behavioral medicine and nutrition. Demographic data, including sex, age, weight, body mass index (BMI), comorbidities as determined by diagnosis made before entering our program, postoperative *duration* of stay, complications, readmissions, and postoperative weight were recorded. Subjects' charts were reviewed with their permission and in accordance with the Institutional Review Board at the University of Massachusetts Medical School. Patients with diabetes mellitus were excluded from this study. We defined patients as diabetic if they either used oral hypoglycemic medications or insulin, or were found in our preoperative evaluation to have a glycosylated hemoglobin level greater than 7.5 mg/dl and were subsequently started on medications to improve glycemic control before their operation.

After an overnight fast, levels of insulin and of glucose were determined. A solid phase chemiluminescent immunoassay was used to determine insulin (IMMULITE 2000 Insulin), whereas glucose was determined by an oxygen rate method employing a Beckman Oxygen electrode (SYNCHRON LX Systems).[18] These blood draws were performed preoperatively and again approximately 12, 40, 180, and 365 days postoperatively. The homeostatic model of assessment[19,20] was used to estimate IR (HOMA-IR), insulin sensitivity (%S), and β-cell function (HOMA-B); we utilized the computer program available via the world wide web at http://www.dtu.ox.ac.uk, as the authors of this model assert it is a better estimate of absolute IR and β-cell function than the linear equations, which have been developed from it.[21]

We performed a laparoscopic Roux-en-Y gastric bypass, with a gastric pouch of approximately 30 ml, an antecolic, antegastric Roux limb of jejunum, and a gastrojejunostomy performed with a 25-mm end-to-end anastomotic circular stapling device. The jejunojejunostomy was performed with a linear stapling device and was positioned 100 to 120 cm distal to the gastrojejunostomy.

Statistical Methods

Differences between groups at baseline were evaluated using the Student's *t* test for continuous variables with normally distributed errors, the Mann–Whitney U test when errors are not normally distributed, and Fisher's exact test for categorical variables. The effects of the intervention across time and between HOMA-IR groups were evaluated by analysis of variance using general linear mixed models (GLMM)[22–24] by restricted estimation with maximum likelihood.[25] The significance of effects from GLMM were evaluated using the likelihood ratio chi-square statistic.[26] In the presence of significant main or interaction effects involving pairwise comparisons between three or more

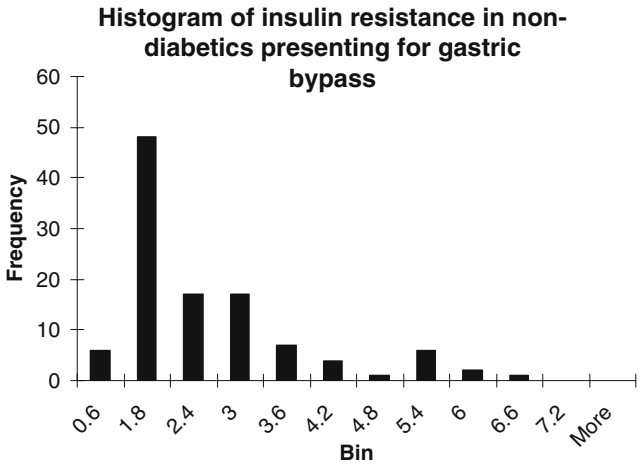

Figure 1 Frequency histogram for IR of this population of nondiabetic patients undergoing laparoscopic Roux-en-Y gastric bypass. The bin number for IR, as estimated by HOMA-IR, is on the *x*-axis. The total number of patients within each particular bin is on the *y*-axis. HOMA-IR of 1 is normal, indicating no IR. We selected a cutpoint of 2.3 to define patients as less insulin-resistant or more insulin-resistant. This histogram demonstrates the wide range of IR in this population. HOMA-IR = Insulin resistance as estimated by the homeostatic model of assessment.

means, multiple comparisons were performed using the Tukey's honestly significant difference multiple comparisons procedure using the estimated variance–covariance matrix from the ANOVA. The relationship between insulin sensitivity and β-cell function was modeled using growth curves[27,28] fitted by GLMM and with the significance of model parameters when comparing the two groups evaluated by likelihood ratio chi-square tests[24] on nested models. Statistical significance was determined to be present when p values were less than or equal to 0.05. If p values were between 0.10 and 0.05, the result was reported as "approaching significance." All calculations were performed using the SPSS Statistical Software Package version 12[29] and the SAS Statistical Software System[30] with SAS Proc MIXED.[21,31,32]

Results

Figure 1 demonstrates that there is a wide spectrum of IR among the population of nondiabetic individuals undergoing gastric bypass for severe obesity; HOMA-IR ranged from 0.4 to 6.3. Of note, BMI was not correlated with HOMA-IR (Fig. 2, R^2=0.05, NS).

We divided this series of patients into those with high HOMA-IR (HOMA-IR > 2.3) and those with lower HOMA-IR. This cutpoint was chosen because of the findings of Stern et al.[33] who suggest that it selects an insulin-resistant population with a sensitivity of 84.9% and specificity of 78.7%. Table 1 lists the demographics of these two populations. Age, gender, and the prevalence of the comorbid illnesses such as hypertension, hypercholesterolemia, asthma, gastroesophageal reflux disease, and sleep apnea, are similar. The high IR group had a higher weight, BMI, and excess body weight (EBW).

The high IR group had, as expected, higher fasting insulin, HOMA-IR, and HOMA-B preoperatively (Table 2b). Along with a higher degree of IR, this group had higher β-cell function. After gastric bypass, there was an early correction of HOMA-IR, visible as early as 12 days, which persisted throughout the study period of 1 year (Table 2b and Fig. 3). By 180 days, HOMA-B also began to decrease (Table 2b and Fig. 3). At 1-year follow-up, this group had a significantly lower degree of IR and of β-cell function than preoperatively.

In contrast, the low IR group had normal fasting glucose and normal insulin preoperatively, with a normal calculated HOMA-IR (1.3±0.5) and HOMA-B (101±37) (Table 2a). Postoperatively, the fasting glucose decreased from 96±18

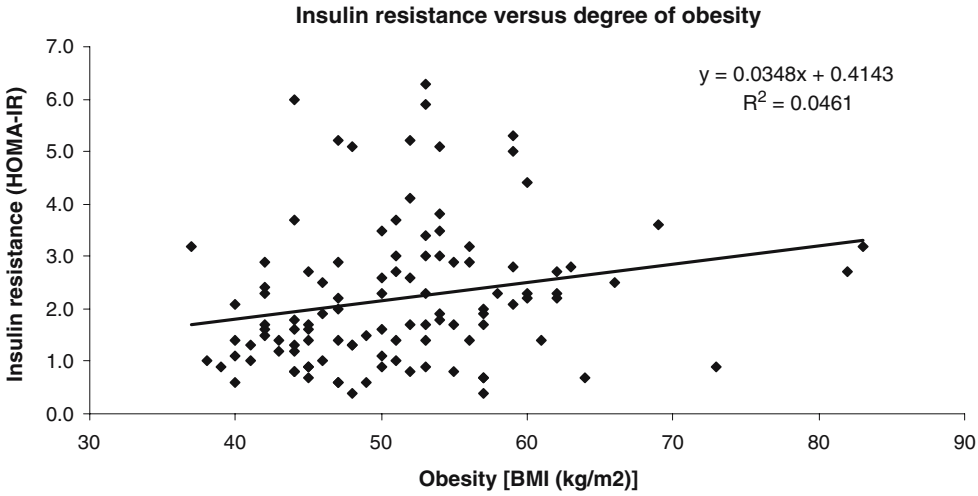

Figure 2 The lack of correlation between degree of obesity and IR. Degree of obesity, as estimated by BMI, is on the *x*-axis. Insulin resistance, as estimated by HOMA-IR, is on the *y*-axis. There is no correlation between IR and degree of obesity in our population of severely obese, nondiabetic patients undergoing laparoscopic Roux-en-Y gastric bypass (R^2=0.05, NS). BMI = Body to mass index, HOMA-IR = IR as estimated by homeostatic model of assessment.

Table 1 The Demographics of Low IR vs High IR Severely Obese, Nondiabetic Patients Undergoing Laparoscopic Roux-En-Y Gastric Bypass

	HOMA-IR < 2.3 (n=60)	HOMA IR ≥ 2.3 (n=47)	p value
Age (years)	39 (8)	39 (10)	NS
% Male	10	13	NS
Weight (lb)	299 (52)	331 (73)	0.01*
BMI (kg/m^2)	49 (7)	54 (9)	0.001*
EBW (lb)	169 (43)	201 (63)	0.002*
Hypertension (%)	35	43	NS
GERD (%)	8	18	NS
Sleep apnea (%)	33	40	NS
Asthma (%)	15	17	NS
Hypercholesterolemia (%)	20	21	NS

Numbers are expressed as mean (standard deviation) or as percentages. There is no difference in age, gender, or the presence of hypertension, GERD, sleep apnea, asthma, and hypercholesterolemia between these two populations. The high IR patients have significantly higher weight, BMI, and calculated EBW.

GERD = Gastroesophageal reflux disease

*p<0.05

to 90±16 mg/dl (p=0.11) at 12 days and to 87±11 mg/dl (p=0.04) at 40 days. This was accompanied by an early increase in fasting insulin from 8±3 μIU/ml preoperatively to 12±6 μIU/ml (p=0.0004) at 12 days. Reduction of fasting glucose level with an increase in fasting insulin signifies an increase in β-cell function, as estimated by HOMA-B in the early postoperative period (Fig. 3b). By 40 days, HOMA-B and HOMA-IR returned to their baseline levels, where they remained at 1 year follow-up.

This series confirms that the hyperbolic *relationship* between insulin sensitivity and β-cell function, as described by Kahn et al.,[15] is true for nondiabetic severely obese individuals presenting for bariatric surgery (Fig. 4). This graph also demonstrates the effect of gastric bypass on this relationship. One year after the operation, the curve is shifted to the right; thus, there is a higher degree of insulin secretion by β-cells in relation to insulin sensitivity.

The curve, however, does not shift symmetrically. At the lower range of insulin sensitivity, this shift is most evident, whereas at higher range of insulin sensitivity, the preoperative and postoperative curves overlap. This suggests that this population of patients is not uniform, with regard to the effect of gastric bypass.

Because of this asymmetric shift, we analyzed the high IR and low IR groups independently to ascertain whether they responded to laparoscopic Roux-en-Y gastric bypass differently. To compare the preoperative curves to the postoperative curves, we graphed the logarithm of insulin sensitivity [ln (%S)] against the logarithm of β-cell function [ln (%B)]. In patients with poor insulin sensitivity/high IR (i.e., HOMA-IR>2.3), there is a shift to higher insulin sensitivity and lower β-cell function (Fig. 5b). However,

Table 2 Fasting Glucose, Fasting Insulin, Calculated HOMA-IR, and Calculated HOMA-B

	Preoperative	12 days	40 days	180 days	365 days
a. Good insulin sensitivity (HOMA-IR < 2.3)					
Fasting glucose (mg/dl)	96 (18)	90 (16)	87 (11)	91 (6)	90 (11)
Fasting insulin (μIU/ml)	8 (3)	12 (6)[a]	9 (4)	8 (5)	7 (5)
HOMA-IR	1.3 (0.5)	1.8 (0.8)*	1.3 (0.5)	1.2 (0.8)	0.9 (0.7)
HOMA-B	101 (37)	147 (51)[a]	126 (44)	104 (43)	104 (107)
b. Poor insulin sensitivity (HOMA-IR > 2.3)					
Fasting glucose (mg/dl)	103 (18)	91 (15)[a]	88 (8)[a]	89 (9)[a]	92 (6)[a]
Fasting Insulin (μIU/ml)	26 (16)[b]	17 (8)[a]	13 (6)[a]	11 (6)[a]	11 (7)[a]
HOMA-IR	3.6 (1.3)[b]	2.5 (1.2)[a,b]	1.9 (0.9)[a]	1.5 (0.8)[a]	1.7 (1.0)[a,b]
HOMA-B	185 (54)[b]	180 (52)[b]	159 (47)	135 (46)[a]	127 (49)[a,b]

Data are expressed as mean (standard deviation).

The high IR group has significantly higher fasting insulin, HOMA-IR, and HOMA-B preoperatively. These correct quickly postoperatively, and are not distinguishable from the values of the low IR group by 40 days postoperatively. The low IR group demonstrates a significant rise in fasting insulin, HOMA-IR, and HOMA-B at 12 days postoperatively, which corrects by 40 days postoperatively. At 1 year follow-up, the high IR group has a reduction in fasting insulin, HOMA-IR, and HOMA-B from baseline level, whereas the low IR group has no significant change in these parameters from baseline level.

IR = Insulin resistance, HOMA-IR = insulin resistance as estimated by homeostatic model of assessment, HOMA-B = β-cell function as estimated by homeostatic model of assessment

[a] Significantly different than preoperative value (p<0.05)

[b] Significantly different than group with good insulin sensitivity (p<0.05) at similar follow-up point

*p=0.06.

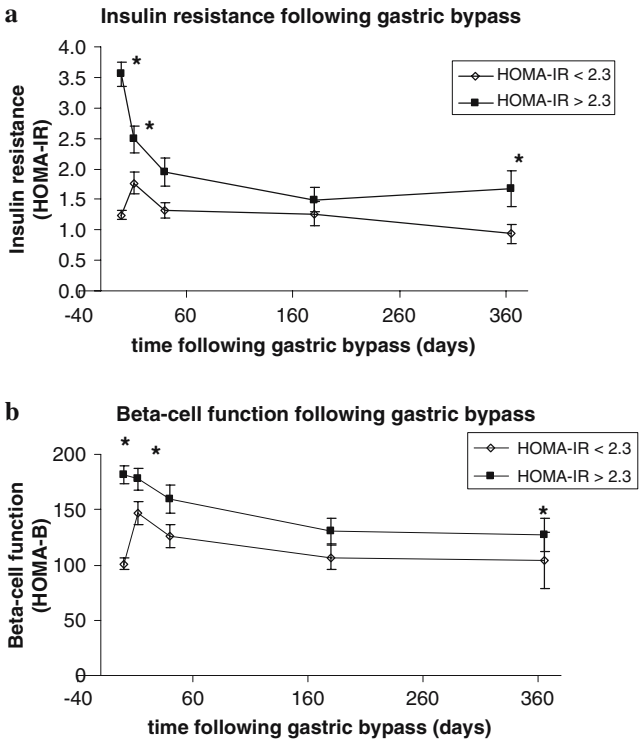

Figure 3 **a, b** Fasting glucose, fasting insulin, calculated HOMA-IR, and calculated HOMA-B. Time after laparoscopic Roux-en-Y gastric bypass is on the *x*-axis. Insulin resistance, as estimated by HOMA-IR, is on the *y*-axis of subpanel **a**. β-Cell function, as estimated by HOMA-B, is on the *y*-axis of subpanel **b**. Asterisk indicates significant difference between the low IR and the high IR group. There is a rapid reduction in IR in the high IR group, which is followed temporally by a reduction in numbers, which are expressed as mean (standard deviation) or as percentages. There is no difference in age, gender, or the presence of hypertension, gastroesophageal reflux disease (GERD), sleep apnea, asthma, and hypercholesterolemia between these two populations. The high IR patients have significantly higher weight, BMI, and calculated EBW. By 40 days postoperatively, the groups do not differ in these parameters. IR = Insulin resistance, HOMA-IR = insulin resistance as estimated by homeostatic model of assessment, HOMA-B = β-cell function as estimated by homeostatic model of assessment.

the slope and *y*-intercept for the curves preoperatively and at 1 year postoperatively are identical (Table 3b). This implies the mechanism responsible for communication between insulin sensitivity and β-cell function has not been altered, and that glycemic control is not likely to be affected.

In contrast, the patients who had good insulin sensitivity/low IR (HOMA-IR<2.3) demonstrate an alteration in the relationship between insulin sensitivity and β-cell function 1 year after gastric bypass (Fig. 5a). The secretion of insulin per degree of insulin sensitivity is markedly increased, as demonstrated by an increase in the slope and *y*-intercept of the curve relating these two variables (Table 3a). The mechanism responsible for correlating β-cell function and insulin sensitivity has been altered. This finding suggests that this group may be predisposed to hypoglycemia.

Discussion

We demonstrate that the population undergoing bariatric surgery can be categorized by the degree of abnormality in insulin glucose homeostasis. We use HOMA-IR for several reasons. It has a good correlation to the insulin glucose clamp technique in terms of categorizing subjects based on insulin sensitivity.[34] It is far less costly, from both time and monetary standpoint. Finally, epidemiologic studies that suggest IR is a predictor for cardiovascular morbidity utilize fasting insulin, or formulas/computer programs that estimate IR based on fasting levels of insulin and glucose for the same pragmatic reasons. Thus, if one wishes to predict cardiovascular morbidity, HOMA-IR may be a more relevant assessment of IR than the insulin glucose clamp.

Our findings reiterate the observation first made by Vague[13] more than 50 years ago that the obese population should not be regarded as homogenous with regard to metabolic health and, as a result, risk of cardiovascular morbidity. Individuals interested in bariatric surgery present a wide spectrum with regard to insulin glucose homeostasis from no identifiable abnormality to a high degree of IR. Obesity, as estimated by BMI, is not at all a predictor for degree of metabolic impairment. This fact has major implications for the criteria we use to assess candidacy for bariatric surgery. As Flum et al.[35] have recently demonstrated, gastric bypass is not an intervention without risk; all cause mortality at 1 year was 4.6%, with male gender and age greater than 65 predicting higher rates of mortality. Whereas this particular study was performed on Medicare

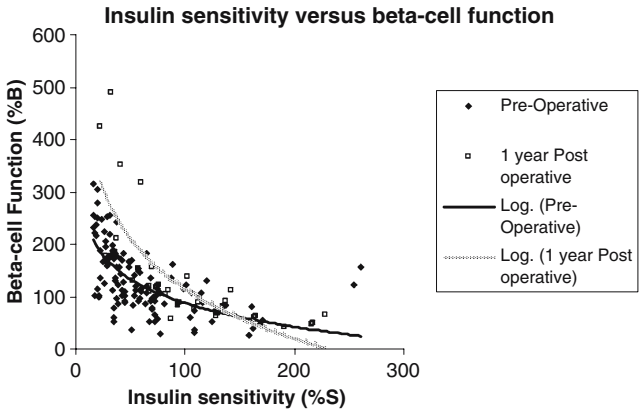

Figure 4 The relationship between insulin sensitivity and β-cell function. Insulin sensitivity, as estimated by percent sensitivity, is on the *x*-axis. β-Cell function, as estimated by percent β-cell function or HOMA-B, is on the *y*-axis. There is a hyperbolic relationship between insulin sensitivity and β-cell function. At 1 year postoperatively from laparoscopic Roux-en-Y gastric bypass, the curve is shifted to the right. This shift is most apparent with the parts of the curves representing low insulin sensitivity. At higher insulin sensitivity, the curves nearly overlap. (%S = insulin sensitivity as estimated by homeostatic model of assessment, %B = β-cell function as estimated by homeostatic model of assessment.

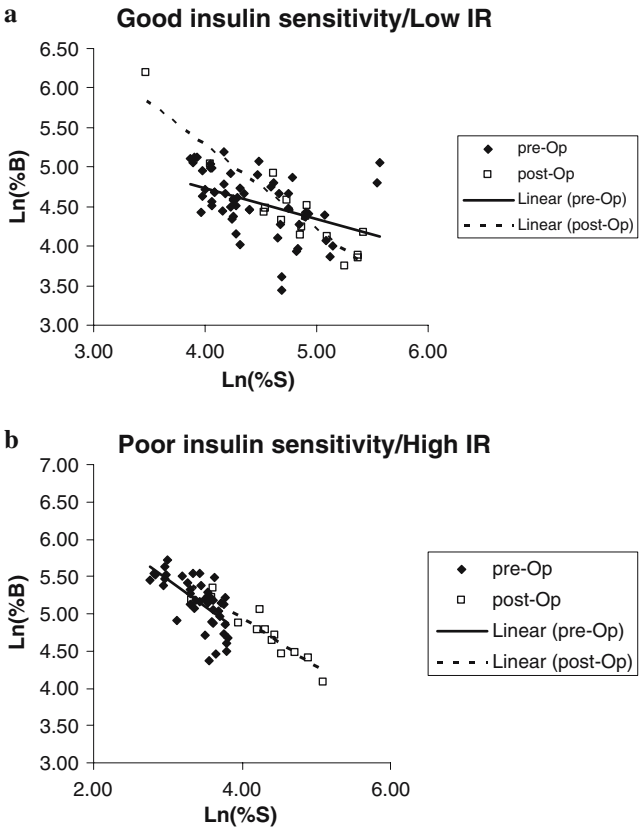

Figure 5 The relationship between the logarithm of insulin sensitivity [ln (%S)] and the logarithm of β-cell function [ln (%B)] in severely obese, nondiabetic patients before and 1 year after laparoscopic Roux-en-Y gastric bypass. The group with poor insulin sensitivity/high IR manifest higher insulin sensitivity and lower β-cell function postoperatively, but the relationship between these two parameters, indicated by the slope and *y*-intercept of the trendline, remains unchanged. In contrast, the group with good insulin sensitivity/low IR preoperatively demonstrates a shift to a steeper curve postoperatively. ln (%S) = natural logarithm of insulin sensitivity, as estimated by homeostatic model of assessment, ln (%B) = natural logarithm of β-cell function, as estimated by homeostatic model of assessment.

patients, and thus biased toward an older population, the all cause mortality rates at 1 year postoperatively for 35- to 44-year-old individuals was 3.4%. Mortality increased to 4.1% for 45- to 54-year-old individuals and 5.2% for 55- to 64-year-old individuals. For severely obese individuals with type 2 diabetes mellitus and nondiabetic patients with IR syndrome, this risk is likely worthwhile.

However, there exists a population of severely obese individuals that have no abnormality in insulin glucose homeostasis; in our series, *43%* of all patients undergoing gastric bypass were classified as low IR or less insulin-resistant. This population may not be at increased risk for cardiovascular morbidity because of their obesity. The medical community needs to scrutinize the risks of gastric bypass vs the potential benefits for this group closely. This point is extremely topical as investigators have noted major increases in the utilization of gastric bypass for severe obesity, with disproportionate increases among women, who have a greater likelihood of being metabolically healthy, those with private insurance, and those in wealthier zip codes.[36]

Many studies have correlated increasing severity of obesity with development of the IR syndrome.[37] This effect was visible even when investigators studied individuals with normal BMIs.[38] Our findings suggest that simply increasing the amount of adipose tissue in humans does not, in and of itself, explain the development of IR. We identify one population with increased adipose stores with no identifiable abnormality in insulin–glucose homeostasis. We also identify a population of severely obese individuals with IR, and who experience major improvements in IR with postoperative weight loss. In neither of these two groups is IR correlated with degree of obesity, as measured by BMI. This suggests that the adipose stores, in and of themselves, do not cause IR.

We hypothesize that adipose tissue is a marker for excess intake of energy. A population of individuals exists that can deal with excess energy intake by forming appropriate subcutaneous adipose stores. A separate population exists, which, when confronted with intake of excess energy, cannot form appropriate adipose stores. Recent studies have identified families with mutations in the peroxisome proliferator-activated receptor-γ, predisposing members to the metabolic syndrome.[39,40] In addition, these individuals have lipodystrophy, with excessive central and intraabdominal obesity, but with lacking hip and gluteal adipose stores. Further evidence for the disordered storage of excess energy is the accumulation of triglyceride in tissue never meant to serve as adipose depots, such as skeletal muscle and liver, in individuals with metabolic syndrome.

We demonstrate that insulin sensitivity and β-cell function are correlated; their relationship can be defined by a hyperbolic function. This relationship has long been ac-

Table 3 Comparison of Relationship Between Insulin Sensitivity and β-Cell Function Preoperatively vs that at 1 Year Postoperatively

	Preoperative	1 Year postoperative	*p* value
Good insulin sensitivity/Low IR			
B (slope)	−0.38	−1.06	0.002
Y-intercept	6.26	9.51	0.001
Poor insulin sensitivity/High IR			
B (slope)	−0.68	−0.65	NS
Y-intercept	7.50	7.54	NS

The group of patients with poor insulin sensitivity/high IR have no alteration in the slope nor in the *y*-intercept of the trendline. In contrast, the group with good insulin sensitivity/low IR have a steeper slope ($p=0.002$) and an altered *y*-intercept ($p=0.001$). This indicates a significantly increased degree of β-cell function per degree of insulin sensitivity. This may suggest a predisposition to hyperinsulinism.

knowledged.[41] As insulin sensitivity decreases, and conversely IR increases, β-cell function also increases so that the glycemic control *remains* constant. In our series, patients with high IR had an average HOMA-B of 185, indicating a β-cell function of 185% of normal, preoperatively. In these insulin-resistant patients, gastric bypass may not effect an increase in β-cell production of insulin in response to glucose, as this may already be maximal. Reduction of β-cell function in this population lags behind reduction in IR, and can be interpreted as a response to this improved insulin sensitivity. The mechanism that correlates insulin sensitivity and β-cell function remains unchanged; this population has simply moved to an equilibrium with higher insulin sensitivity and lower β-cell function.

In contrast, in noninsulin-resistant individuals (i.e., the low IR group) the average preoperative HOMA-B was 101, which is effectively normal. This population likely has abundant reserve in β-cell function, allowing an early postoperative surge in this parameter. This early surge in β-cell function is no longer visible at 6 months. In addition, at 1 year postoperatively, this population exhibits an increased β-cell function per degree of insulin sensitivity. It must be remembered that this population had normal glycemic control preoperatively. This relative increase in β-cell function suggests that this group is at risk for hypoglycemia postoperatively. This idea demands further investigation, with corroboration by other centers.

In summary, we present data that elucidates the metabolic heterogeneity of the severely obese population. The impact of gastric bypass on insulin–glucose homeostasis is dependent on preoperative characteristics. We cannot simply presume that all severely obese individuals have similar abnormalities in insulin–glucose homeostasis and will reap metabolic benefits after gastric bypass. These findings, if corroborated, mandate a reworking of the guidelines by which we offer gastric bypass to include preoperative metabolic characterization of patients.

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DISCUSSION

Dr. M. Sarr (Rochester, MN): Dr. Perugini and I have discussed this paper beforehand, and I will have to admit I have had a very, very difficult time understanding several of the concepts of this work.

First, I will remind the audience, these are nondiabetics, some of whom have insulin resistance and some of whom might be considered as having the metabolic X syndrome even though they are not hyperglycemic. That is a new concept for many of us.

Second, the derivation of the HOMA-IR score—that is, the score that defines insulin resistance—is not well-defined. Rich, I think you should tell us how that was done, because you take the fasting insulin concentration in the blood – and, again, these are fasting studies – and the blood glucose concentration and from those two parameters estimate the insulin resistance.

Third, the hypothesis being proposed is that once the nondiabetics that do not have insulin resistance lose weight, they might be the group that has a higher relative amount of insulin secreted than normal for a certain fasting blood glucose, and they may actually be the patients who develop noninsulinoma hyperinsulinemic hypoglycemia postoperatively.

There are, however, several assumptions. One is that postprandial insulin metabolism and homeostasis is the same as what you are estimating from your fasting studies. Maybe you could discuss this point.

Second, just out of interest, were you able to correlate body fat distribution in these nondiabetics with their insulin resistance, according to whether they had central obesity or peripheral obesity?

Dr. Perugini: The homeostasis model of assessment is a computer model generated at Oxford University and first published in the mid-'80s. The problem is that the gold standard for studying insulin sensitivity and beta cell function is with the insulin and glucose clamp. This particular procedure requires a patient to be on bedrest for up to seven hours and requires two peripheral lines to be started, one of which infuses glucose, and one of which infuses insulin. It is not useful in the clinical setting because it is so cumbersome. Researchers at Oxford performed insulin and glucose clamps on a large body of patients; they then developed a computer program to model the outcomes based on the fasting insulin and the fasting glucose level.

Now, there are a bunch of theoretical presumptions that they made. Suffice it to say, when you compare the results from the HOMA to the results from an insulin and glucose clamp, the correlation coefficient is actually very high; the R is about .7.

Whenever big, broad-based epidemiologic studies examine whether insulin resistance has any impact on cardiovascular morbidity, nobody can use a clamp, for the same pragmatic reasons I just mentioned. These studies typically use calculations to estimate insulin sensitivity; the most common of these is the HOMA.

It is a very simple computer model. You need only plug in is glucose and insulin. It is an on-line, Web-based computer program that anybody has access to.

Dr. Sarr: Was that done in fat people or in others?

Dr. Perugini: There were no restrictions. Indeed, the patient population that I showed you from Europe, where Stern tried to correlate the results of an insulin and glucose clamp with the HOMA, was done on a broad spectrum of the population in Europe. Does it apply to this severely obese patient population? It is not very clear. It probably does.

The final question had to do with whether these patients had central obesity versus peripheral obesity. We don't measure that, as it is quite difficult to do reproducibly in this patient population. So, no, I have no data to correlate this with waist-to-hip circumference or central versus peripheral obesity.

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Preliminary Experience by A Thoracic Service with Endoscopic Transoral Stapling of Cervical (Zenker's) Diverticulum

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Abstract
Recently endoscopic transoral stapling (ES) of cervical (Zenker's) diverticulum (ZD) has been reported. In a 10-year retrospective review, we identified 47 patients undergoing ES or open surgery (OS) for ZD. ES was attempted in 28 patients and OS in 19. Using an intention to treat analysis, outcomes examined included operative time, length of stay, and dysphagia severity using a scale from 1 (no dysphagia) to 5 (severe dysphagia). ES was completed in 24/28 patients with four conversions to OS. The mean age was 75 years for the ES group and 70 years for the OS group ($p=0.079$). Mean operative time (1.57 versus 2.35 h.) was less ($p<0.03$) in the ES group. Length of stay (2.12 versus 2.44 days) was shorter for ES but not significant ($P=0.49$). Mean follow up was 17 (1–103) months for both groups. Dysphagia scores were comparable between the two groups preoperatively (2.78 ES versus 2.79 OS; $p=0.98$) and improved significantly ($p=0.001$) to 1.1 after ES and 1.0 after OS. The time to oral intake was 1.38 days in the ES group and 1.29 days in the OS group ($p=0.80$). We conclude that ES is feasible and can be performed with shorter operative times and comparable short-term results to OS.

Keywords Cervical (Zenker's) diverticulum · Transoral stapling · Cricopharyngeal myotomy

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Introduction

Zenker's diverticula (ZD) are thought to be a form of pulsion diverticulum that occur in an area of muscular weakness (Killian's triangle) located between the inferior constrictor and cricopharyngeus (CP) muscles. More recent observations suggest that the primary problem may be dysfunction of the lower esophageal sphincter and gastroesophageal reflux, with a consequent hypertonic upper esophageal sphincter leading to a pulsion diverticulum just above the cricopharyngeus. This condition was first described by Ludlow in 1764.[1] Subsequently, Zenker published a series of 23 cases in 1877.[2] Typically, elderly people, especially males, are affected. Symptoms include dysphagia, regurgitation of undigested food, globus sensation, halitosis, and aspiration pneumonia. Surgical intervention has been recognized as the only effective treatment and shown to result in improvement of symptoms and quality of life with little morbidity, despite the advanced age of many affected patients.[3]

Recently, endoscopic repair of ZD has been described and is gaining popularity.[4] However, the majority of reports

of endoscopic repair have been from otolaryngologists, many from European centers.[5,6] A recent study from Gutschow et al. compared open surgical (OS) intervention to endoscopic repair by either endoscopic stapling (ES) or endoscopic laser division.[7] They demonstrated better symptomatic relief with open surgical techniques compared to ES, particularly with ZD less than 3 cm.[7] In the larger diverticulum (3 cm or larger), there was no difference between the endoscopic and open procedures when looking at patients who were either asymptomatic or who had mild occasional symptoms. Furthermore, when looking specifically at the endoscopic group, ES was found to be safer than laser division with several patients developing mediastinitis after the use of the laser.

This report summarizes the preliminary experience from our group with endoscopic stapling (ES) for ZD. Results are compared to patients treated by open surgery (OS).

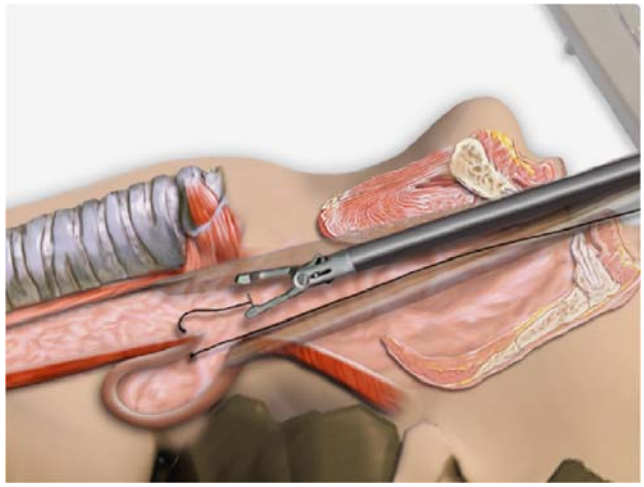

Figure 2 Placement of stay suture in the common wall between the esophagus and the diverticulum.

Materials and Methods

After obtaining IRB approval, a retrospective review was performed over a 10-year period from 1995 to 2005 of patients undergoing operation for ZD at the University of Pittsburgh. Outcomes examined included operative time, length of stay, and preoperative and postoperative dysphagia scores using a scale from 1 (no dysphagia) to 5 (severe dysphagia).

The evaluation and operative technique for ES is as follows. The main criterion for considering ES is the presence of a diverticulum of at least 3 cm in size. Other major concerns are limitations in the ability to open the mouth widely and the presence of a prominent overbite of the upper teeth. All procedures are performed under general anesthesia. Flexible esophagoscopy is first performed to assess the diverticulum and also to suction any retained material from the diverticulum. We then perform rigid esophagoscopy using the Weerda laryngoscope (Karl Storz, Tuttlingen, Germany). This scope has two jaws (Fig. 1). One jaw is placed in the esophagus and the second is placed in the diverticulum. The jaws are then expanded, which allows clear visualization of the diverticulum and the common septum formed by the CP. As our experience has evolved, we have modified our technique by placing a traction suture (US Surgical Endostitch-Norwalk, Connecticut) in the common septum (Fig. 2). Using the suture to provide traction on the common septum, a modified Endo-GIA 30 stapler is placed across the septum and fired (Fig. 3). Further firings of the stapler as needed are performed to ensure the common septum is divided to the base of the diverticulum. The stapler is modified by shortening the tip of the anvil (Fig. 4). This is necessary so that the stapler will both cut and staple to the end of the stapler tip and consequently cut and staple to the base of the diverticulum. The modified

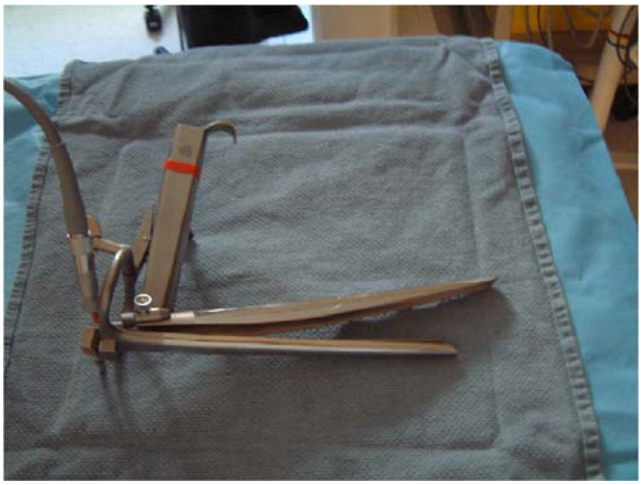

Figure 1 Weerda laryngoscope.

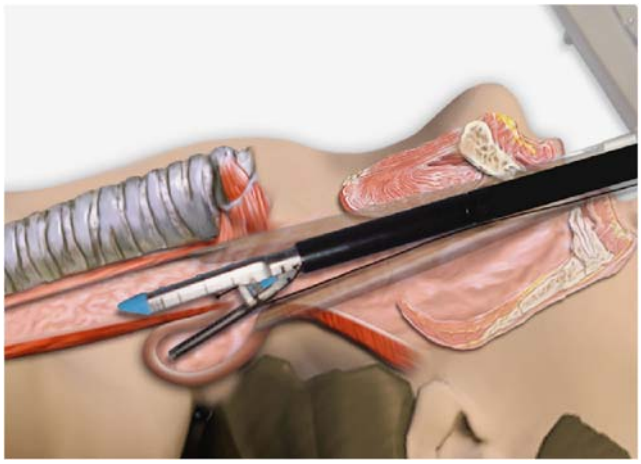

Figure 3 Stapling of diverticulum using modified Endo-GIA 30.

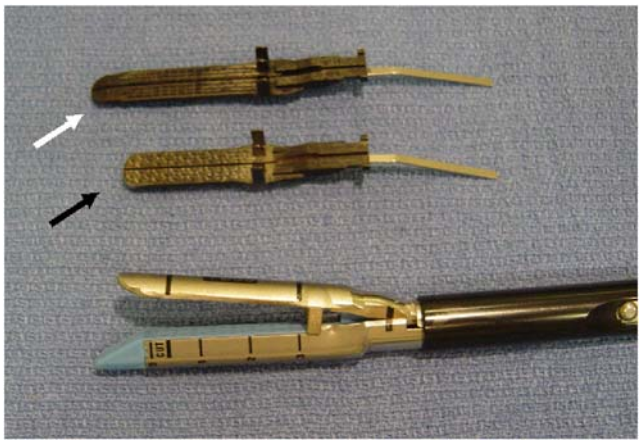

Figure 4 Endo-GIA 30 stapler with the black arrow demonstrating an unmodified anvil and the white arrow indicating an anvil modified by removing the tapered tip and allowing the stapler to both cut and staple to the end of the jaws.

anvil is placed within the diverticulum and the disposable cartridge within the esophageal lumen (Fig. 3). We do not place a nasogastric tube postoperatively. A barium swallow is obtained on the first postoperative day and a liquid diet initiated if satisfactory.

Standard OS techniques employ a left neck incision along the anterior border of the sternocleidomastoid muscle, reflection of the carotid sheath laterally, and exposure of the esophagus, attempting to avoid injury to the recurrent laryngeal nerve. In all cases, a cricopharyngeal myotomy was performed and, depending on the anatomic findings and surgeon preference, a diverticulectomy or diverticulopexy performed.

Statistical Analysis

All data were entered into an SPSS (version 11.0 for Windows) file. Statistical analysis included independent-samples *t*-test analysis of mean values and paired samples *t*-test analysis of pre and postoperative scores. A value of $p<0.05$ was considered significant.

Results

In the series, there were 47 total patients and included 28 (59.6%) men and 19 (40.4%) women. ES was attempted in 28 patients and successfully performed in 24 patients. Of the four conversions, two were a result of difficulty placing the laryngoscope secondary to oropharyngeal anatomy. In both cases, flexible endoscopy identified a ZD of greater than 4 cm in size. However, because of difficulty visualizing both the esophagus and diverticulum with placement of the Weerda laryngoscope, both cases were converted to OS. An ES in a third patient was aborted after perforation of the diverticulum occurred with placement of the operating laryngoscope. Although the ZD was noted to be greater than 3 cm in size, multiple attempts at placement of the laryngoscope led to a mucosal tear at the base of the diverticulum. The procedure was converted to OS and a diverticulectomy and cricopharyngeal myotomy was performed. Drains were placed as well as a laparoscopic feeding jejunostomy. The patient required a single dilatation of the esophagus and was discharged from the hospital tolerating a diet. The fourth case converted to OS was secondary to a small diverticulum of approximately 2 cm in size, which did not allow entrance of the stapler. Three of the four conversions had outcomes similar to standard OS, with the perforation requiring a longer hospitalization and slower advancement of oral intake.

Using an intention to treat analysis, there were 28 patients in the ES group with four conversions. Nineteen patients underwent intentional OS. The mean age of the ES group was 75 and 70 years for the OS group ($p=0.079$). The median ASA score was 2.1 for the ES group and 2.1 for the OS group ($p=0.992$). Traction sutures on the common septum were used in the last 20 ES cases. Of the 19 open procedures, one was a CP myotomy alone and the remaining 18 were a CP myotomy in conjunction with diverticulopexy ($n=14$) or diverticulectomy ($n=4$). Three of the patients in the series had undergone prior OS by other surgeons. Two of these patients underwent ES and one underwent OS on their reoperations by our group.

There were no operative mortalities and a single complication in each group. In the OS group, a patient developed clostridium-difficile colitis postoperatively. In the ES group, one patient required a single dilatation 4 days after the initial procedure. Mean operative times were less ($p<0.03$) in the ES patients (1.57 versus 2.35 h). Length of stay was shorter in ES patients than the OS group but not significant (2.12 versus 2.44 days; $p=0.49$) days. Time to oral intake was similar for ES (1.38 days) and OS (1.29 days) patients ($p=0.80$).

Median follow-up was 17 (1–103) months. Preoperatively, the dysphagia scores were comparable between the two groups (2.78 ES versus 2.79 OS; $p=0.98$). The postoperative dysphagia scores significantly improved after operation for both groups. In the ES patients the postoperative dysphagia score improved to 1.1 ($p=0.001$) and in the OS patients the postoperative score improved to 1.0 ($p=0.001$).

Discussion

The goals of surgical treatment for ZD are: 1) release of the upper esophageal sphincter by CP division or myotomy and 2) elimination of the reservoir trapping food particles and secretions. The most important aspect of operation is

division or myotomy of the CP.[8] Approaches to the diverticulum include diverticulectomy, diverticulopexy (by suspending the diverticulum sac to the prevertebral fascia), or imbrication of the diverticulum (by dissecting the diverticulum and inverting it into the lumen of the esophagus with a "purse-string" suture).[9] The most common open approach performed by our group was CP myotomy with diverticulopexy, which was performed in 74% of the OS patients. The advantage of diverticulopexy over diverticulectomy is that the esophageal mucosa is not violated, minimizing the chances of infection and fistula formation.

Because many of ZD patients are elderly, often with significant comorbid disease, an endoscopic approach, avoiding the need for a neck incision, offers potential advantages. The first report of an endoscopic approach was by Mosher in 1917, where a knife blade was used to divide the common wall.[10] Because of complications, little attention was paid to endoscopic approaches until Dohlman and Mattsson in 1960 reported endoscopic division of the common septum using a diathermy knife.[11] Other subsequent reports have involved the use of a laser to divide the common septum.[12] A disadvantage of the above endoscopic methods is that mucosal closure is not performed, so there is the possibility of contamination and infection of the adjacent cervical space.[12] Collard[4] revolutionized the endoscopic treatment of ZD by the introduction of the endoscopic stapler. The advantage of the stapler is that in addition to a more rapid division of the common septum, the three rows of staples on each side of the section line provide excellent closure and hemostasis of the mucosal edges.

There is certainly a learning curve with the ES, and as we became more comfortable with the procedure, we began to incorporate ES more frequently into our practice. Some technical points need to be emphasized. It is important to divide the CP muscle completely. If the diverticulum is too small, this will lead to difficulties in placing the stapler and an inadequate division of the CP. For this reason, we recommend that ES be reserved for ZD of at least 3 cm or more in size. Other factors that make ES technically difficult include the presence of prominent upper incisors, limited mouth opening, and inability to adequately extend the neck. As noted, two of our conversions were secondary to limited mouth opening and difficulty placing the operating laryngoscope. A third conversion was because of a diverticulum that would not accept the stapler, and a fourth conversion was caused by perforation of the esophagus with the laryngoscope. However, our conversions were not limited to our initial ES patients, but occurred throughout our ES experience.

The use of a traction suture greatly facilitates exposure and stapling of the ZD. The advantage of the Endostitch is that it easily passes through the Weerdoscope orifice. In addition, the suture needle is passed from one arm of the driver to the other by toggling the handle. This again greatly simplifies passage of the needle through the common septum. On postoperative barium swallow evaluations, a small residual pouch was occasionally seen in the ES group, but did not affect outcomes as dysphagia scores were similarly improved in both the ES and OS groups.

In conclusion, we have demonstrated that ES is feasible and was successfully completed in 85% of the initial 28 cases performed by our thoracic group. As our experience has grown, the number of conversions has decreased. One minor complication occurred after ES, and there appears to be advantages with reduced operating time and length of stay in this retrospective series. Furthermore, preoperative and postoperative dysphagia scores are equivalent between the two groups, demonstrating similar symptomatic relief. Although long-term follow-up is lacking, ES of ZD appears to be a safe, viable alternative to OS.

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Towards the Molecular Characterization of Disease: Comparison of Molecular and Histological Analysis of Esophageal Epithelia

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Abstract Reliable quantification of gene expression offers the possibility of more accurate and prognostically relevant characterization of tissues than potentially subjective interpretations of histopathologists. We measured the expression of 18 selected genes and compared them to histological features in a spectrum of esophageal disease to evaluate the feasibility of molecular characterization of normal and pathologic esophageal epithelia. Esophageal tissue biopsies from 82 patients with foregut symptoms were laser capture microdissected, and the expression levels of 18 selected genes were measured by quantitative real-time polymerase chain reaction. Linear discriminant analysis, which uses combinations of genes to distinguish between histological groups, was performed to compare gene expression and the following five histological groups: (1) normal squamous epithelium (n=35), (2) reflux esophagitis (n=13), (3) non-dysplastic Barrett's (n=33), (4) dysplastic Barrett's (n=16), (5) adenocarcinoma (n=31). A panel of seven genes had 90–94% predictive power to distinguish non-dysplastic and dysplastic Barrett's esophagus. Clustering analysis revealed structure in gene expression values even in the absence of histology. Expression levels in 17 genes differed significantly across histological groups. Classification based on gene expression agreed with histopathological assessment in the following percentage of cases: normal squamous epithelium=53%, reflux esophagitis=31%, non-dysplastic Barrett's= 76%, dysplastic Barrett's=40%, and adenocarcinoma=59%. Interestingly, predictive power improved markedly when inflammatory and dysplastic tissues were removed (77–94%). Gene expression classification agrees well with histopathological examination. When differences occur, it is unclear whether this effect is due to intraobserver variability in pathological diagnosis or to a genuine difference between gene expression and histopathology.

Daniel Vallböhmer and Paul Marjoram contributed equally to the paper.

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Keywords Quantitative real-time PCR · Esophageal epithelia · Molecular classification

Introduction

For hundreds of years, the appearance of tissues viewed by the human eye under a microscope has been the primary mechanism to classify pathology and thus human disease. Histopathology has served us well and continues to do so, but has many limitations and drawbacks. Modern technology, via high-throughput genetic analysis, provides a new and possibly better approach: the molecular characterization of tissues, both normal and abnormal. Molecular tissue signatures have been most avidly pursued in oncology, although in theory, the principle applies equally to any tissue.

The molecular characterization of normal and abnormal esophageal tissues is as needed and holds as much promise as anywhere in medicine. Histopathologic analysis of esophageal disease often falls short; exemplified by the poor correlation of histologic inflammation with objective measures of gastroesophageal reflux and the high interobserver variability in the classification of esophageal metaplasia, and dysplasia.[1–3] Furthermore, the phenotypic appearance of standard histopathology often fails to provide prognostic significance. In a recent study aimed at evaluating pathologic interpretation by general pathologists in community practice, specialized columnar epithelium with no dysplasia was identified as such by 35%, called low-grade dysplasia by 35%, moderate dysplasia by 15%, indeterminate for dysplasia by 10%, and invasive adenocarcinoma by 5%; gastric metaplasia without specialized columnar epithelium was identified as Barrett's esophagus in 38% of cases.[1] In recent years, several biotechnological developments have given us a greatly enhanced ability to characterize molecular biomarkers. This is particularly true for the analysis of gene expression data, where real-time polymerase chain reaction (RT-PCR) and especially microarray technology have been described as nothing short of a scientific revolution.[4,5] However, in spite of (or perhaps because of) a vast wealth of information that can potentially be obtained, microarray analysis has encountered problems in the stability and reproducibility of the data sets that are supposed to differentiate one tissue type from another.[6,7] Small sample sizes used to generate training sets of genes, coupled with limited numbers of independent cross-validation sets, difficulty in sorting out important genes from irrelevant genes, as well as variability associated with the user and the platform, have been cited as contributing factors.[6,8] For these reasons, for this study, we chose to use the real-time PCR technique, which generates a range of numerical values that allow the precise and accurate quantification of specific mRNAs. Instead of having to determine de novo an empirical training set of genes and then perform validations as would be done in microarray analysis, our plan was to use genes that had already been shown in previous studies to play roles in carcinogenesis as our classifier set with which to characterize tissues at different stages in the development of Barrett's associated adenocarcinoma.[9–23] We selected 18 different genes, all thought to perform a vital cellular function, and used RT-PCR to quantitatively analyze their expression over a wide range of normal and abnormal epithelia of the human foregut.

Materials and Methods

Patients

Eighty-two patients, including 28 women and 54 men, with a median age of 57 years (21–86), with various degrees of esophageal mucosal injury were included in the study. One hundred twenty eight tissue samples ($n=128$) were obtained from either endoscopic biopsy or surgical specimens and were immediately snap-frozen in liquid nitrogen. Twelve patients were classified into separate groups depending on whether their tissue samples showed metaplasia next to dysplasia or adenocarcinoma. A single specimen was analyzed from 62 patients, and multiple specimens were analyzed from 20 patients. In those cases where multiple samples from one patient were analyzed, the average value was used in the statistical analysis. Tissue samples were evaluated histologically and classified into five groups:

(1) Thirty-five samples of normal squamous epithelium of the lower esophagus, 3 cm above the squamocolumnar junction, from 32 patients (NE group)
(2) Thirteen samples of reflux esophagitis from 13 patients (REF group)
(3) Thirty-three samples containing specialized intestinal metaplasia without dysplasia on biopsy from 17 patients (BE group)
(4) Sixteen samples containing specialized intestinal metaplasia and either low- or high-grade dysplasia from ten patients (dysplasia group)
5) Thirty-one samples with confirmed adenocarcinoma of the esophagus from 22 patients (carcinoma group).

Approval for this study was obtained from the Institutional Review Board of the University Of Southern California Keck School Of Medicine, and written informed consent was obtained from participating patients.

Histologic Analysis

All pathological examinations for this study were performed by a single pathologist (P.T.C.) with specialized expertise in

gastrointestinal and esophageal pathology. The following criteria were used to define each tissue type we analyzed:

(1) *Squamous epithelium* was defined as normal when it did not satisfy the criteria given below and when there was no other pathologic lesion such as infection, dysplasia, or malignancy.
(2) *Reflux esophagitis* was defined in the squamous epithelium-lined mucosa by the presence either of intraepithelial eosinophils and/or the presence of maturation abnormalities including basal cell hyperplasia and papillary elongation.
3) *Intestinal metaplasia* was defined by the presence of a columnar epithelium that contained well-defined goblet cells on a hematoxylin-and-eosin-stained section.
4) *Dysplasia* was defined by the presence of cytologic abnormalities of dysplasia in the columnar epithelium involving both surface and foveolar/glandular regions associated with either gland complexity of loss of nuclear polarity.
5) *Adenocarcinoma* was defined by the presence of invasive malignant glands.

Genetic Analysis

Laser Capture Microdissection For laser capture microdissection (LCM), tissue samples were prepared as previously described.[23] After the evaluation of a pathologist, normal esophageal samples or reflux esophagitis samples were

Table 1 Primers and Probes Sequences

Gene	GenBank accession	Forward primer (5′–3′)	Reverse primer (5′–3′)	TaqMan probe (5′–3′)
β-actin	NM_001101	GAGCGCGGCTACAGCTT	TCCTTAATGTCACGC ACGATTT	ACCACCACGGCCG AGCGG
Bax alpha	NM_138761	TGGCAGACCGTGAC CATCTT	GGCCTCAGCCCATCTTCTTC	AGTGCTCACCGCCTC ACTCACCATCTG
Bcl-2	NM_000657	CCTGTGGATGACTGA GTACCTGAA	CACCTACCCAGCCTCCGTTA	CGGCACCTGCACACC TGGATCC
Cdx-2	NM_001265	ACCAGGACGAAAGAC AAATATCGA	TGTAGCGACTGTAGTGAA ACTCCTTCT	TGTACACGGACCACCA GCGGCTG
Cox-1	NM_000962	CGCTGGTTCTGGGA GTTTGTC	GGGACTGGGGATAA GGTTGGA	CGAGAGATGCTCATGC GCCTGG
Cox-2	NM_000963	GCTCAAACATGATGT TTGCATTC	GCTGGCCCTCGCTTATGA	TGCCCAGCACTTCAC GCATCAGTT
β-Catenin	NM_001904	CCCTGAACTGACAAA ACTGCTAAATG	TTTAGAAAGCTGATGGAC CATAACTG	AGCCTTATTAACCACCAC CTGGTCCTCG
Dr-5	NM_0038423	GACCCTTGTGCTCG TTGTC	AGGTCTTGTTGGGT GATCAGA	TCAGCTGAGACCAAC AGCAGGACC
EGFR	NM_005228	TGCGTCTCTTGCCG GAAT	GGCTCACCCTCCAGAAGCTT	ACGCATTCCCTGCCT CGGCTG
Her2/neu	NM_004448	CTGAACTGGTGTATG CAGATTGC	TTCCGAGCGGCCAAGTC	TGTGTACGAGCCGC ACATCCTCCA
hTERT	NM_003219	CGTACAGGTTTCACG CATGTG	ATGACGCGCAGGAAAAATG	CAGCTCCCATTTCAT CAGCAAGTTTGGA
MMP-2	NM_004530	ATTTTGATGACGATGA GCTATGGA	CCATCGGCGTTGCCATAC	TCACACGGACCACTT GGCCTTCTCC
Survivin	NM_001168	TGCCCCGACGTTGCC	CAGTTCTTGAATGTAGA GATGCGGT	CCTGGCAGCCCTTTCT CAAGGACC
SPARC	NM_003118	TCTTCCCTGTACACT GGCAGTTC	AGCTCGGTGTGGG AGAGGTA	CAGCTGGACCAGCAC CCCATTGAC
TIMP-1	NM_003254	AGACGGCCTTCTGC AATTCC	GTATAAGGTGGTCTGGTT GACTTC	CCTCGTCATCAGGGCC AAGTTCGT
TS	NM_001071	GCCTCGGTGTGCCTTTCA	CCCGTGATGTGCGCAAT	TCGCCAGCTACGCCCT GCTCA
TSP-1	NM_003246	GCAAGGACTGCGT TGGTGAT	GGGATTGGACAGGCATCCAT	CCAGATCTGCAACAAG CAGGACTGTCCA
TSPAN-1	NM_005727	ACCACAATGGCTGAG CACTTC	TCCTGGGAACCATAATCTT TCTTG	TGGCAGGCACTACCAG CAACGTCA
VEGF	NM_003376	AGTGGTCCCAGGCTGCAC	TCCATGAACTTCACCACTTCGT	ATGGCAGAAGGAGG AGGGCAGAATCA

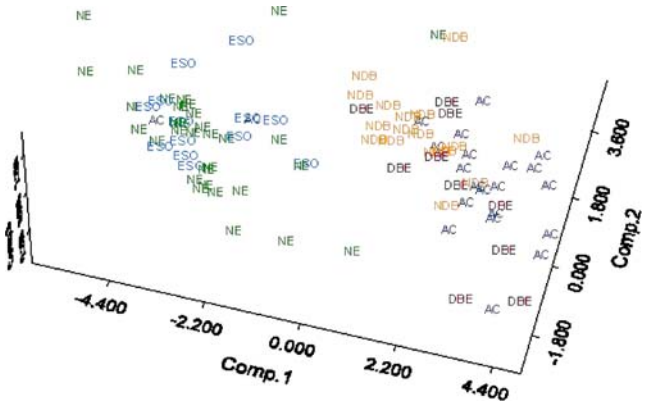

Figure 1 Samples plotted according to first three principal components.

dissected from the slides using a scalpel if the histology of the samples was homogeneous and contained more than 90% tissue of interest. All other sections were selectively isolated by LCM (P.A.L.M. Microsystem, Leica, Wetzlar, Germany) according to the standard procedure.[24] The dissected flakes of tissue were transferred to a reaction tube containing 400 µl of RNA lysis buffer.

RNA Isolation and cDNA Synthesis RNA isolation from optimal cutting temperature compound (OCT)-embedded samples was performed according to a proprietary procedure of Response Genetics (Los Angeles, CA; US patent number 6,248,535). Afterwards, cDNA was prepared as previously described.[25]

RT-PCR Quantification of mRNA Expression Quantitation of Bax, Bcl-2, Cdx-2, Cox-1, Cox-2, β-Catenin, Dr-5, epidermal growth factor receptor (EGFR), Her2/neu, hTERT, MMP-2, survivin, secreted protein acidic and rich in cysteine (SPARC), TIMP-1, TS, TSP-1, TSPAN-1, vascular endothelial growth factor (VEGF), and an internal reference gene (β-actin) was performed using a fluorescence-based real-time detection method [ABI PRISM 7900 Sequence Detection System (TaqMan®) Perkin-Elmer (PE) Applied Biosystem, Foster City, CA, USA], according to a procedure previously described.[4] The primers and probes used are listed in Table 1.

Statistical Analysis

Statistical analysis was done in consultation with a dedicated statistician (PM) expert in the computational methods of microarrays and multiple genetic analyses. These analyses included: tests to find genes with significantly changed expression across disease stage; linear discriminant analysis (LDA) to find combinations of genes that can predict histologic group; cross-validation tests to provide accurate estimates of error rates in the statistical assignment of sample to histologic group; a cluster analysis; and a principal components analysis to facilitate effective visualization of results. The reader can find a more lengthy description of these analyses in the Appendix.

Table 2 Gene Expression of 18 Genes in Different Histologic Groups

Gene ×100/-actin mRNA expression median (range)

Gene	Normal squamous epithelium	Reflux esophagitis	Non-dysplastic Barrett's	Dysplasia	Adenocarcinoma
Bax	2.30 (0.46–11.06)	2.21 (1.18–8.14)	8.65 (4.08–19.61)	9.42 (2.07–19.19)	12.64 (1.60–28.65)
Bcl-2	0. 8 (0.20–4.24)	0.66 (0.16–1.95)	1.81 (0.42–5.11)	2.04 (0.39–5.84)	3.01 (0.72–16.35)
Cdx-2	0.02 (0.01–15.20)	0.03 (0.01–2.59)	4.25 (0.2–10.66)	10.52 (0.29–33.03)	4.42 (0.01–60.37)
Cox-1	3.89 (0.01–19.42)	3.94 (0.45–6.93)	0.81 (0.19–2.22)	0.79 (0.35–2.09)	0.94 (0.31–4.04)
Cox-2	0.13 (0.01–3.33)	0.16 (0.01–3.86)	0.74 (0.22–3.83)	1.19 (0.30–3.03)	1.72 (0.10–13.10)
β-Catenin	1.54 (0.16–3.52)	1.33 (0.84–2.65)	2.96 (1.00–5.37)	3.59 (2.12–9.15)	2.71 (0.95–7.89)
Dr-5	1.22 (0.20–13.92)	1.41 (0.59–3.27)	9.34 (3.99–26.03)	11.09 (6.41–40.20)	9.26 (0.72–39.23)
EGFR	5.32 (0.44–14.96)	5.62 (3.06–8.46)	5.91 (0.91–24.18)	5.91 (2.44–18.61)	5.68 (2.01–63.59)
Her2/neu	0.54 (0.07–1.53)	0.5 (0.17–0.71)	0.6 (0.09–3.00)	0.78 (0.27–15.39)	0.65 (0.14–15.52)
hTERT	0.08 (0.01–7.43)	0.07 (0.01–3.83)	0.25 (0.01–1.29)	0.59 (0.05–1.42)	0.79 (0.01–23.49)
MMP-2	0.16 (0.01–0.75)	0.12 (0.03–0.27)	3.99 (0.66–23.11)	4.27 (0.90–11.54)	6.97 (0.06–76.77)
Survivin	5.24 (1.20–12.96)	3.93 (2.59–7.89)	4.46 (1.48–14.70)	10.6 (1.19–19.18)	12.67 (1.68–37.94)
SPARC	1.00 (0.13–2.86)	0.92 (0.28–1.32)	2.26 (0.41–26.05)	5.0 (0.41–13.31)	4.68 (0.46–72.75)
TIMP-1	0.74 (0.04–11.69)	0.6 (0.22–2.46)	5.67 (2.54–36.77)	7.48 (2.77–16.92)	10.21 (0.45–31.29)
TS	3.15 (0.30–10.00)	3.14 (1.33–5.43)	3.46 (2.61–14.8)	7.87 (3.43–14.34)	7.92 (2.54–22.25)
TSP-1	0.79 (0.17–6.08)	0.85 (0.21–2.73)	2.14 (0.70–109.6)	7.42 (0.59–23.93)	11.05 (0.45–100.55)
TSPAN-1	0.10 (0.01–112.5)	0.1 (0.03–0.84)	97.93 (22.4–205.7)	51.17 (12.7–184.2)	25.5 (0.06–137.37)
VEGF	4.95 (0.07–20.47)	5.32 (2.02–11.29)	10.84 (4.51–20.07)	18.8 (9.36–53.36)	17.73 (2.81–64.55)

Table 3 LDA for All Histological Groups Using the Full Panel of Genes

		Genetic prediction group					
		Normal squamous	Reflux esophagitis	Non-dysplastic Barrett's	Dysplastic Barrett's	Adenocarcinoma	Error rate
Actual histologic group	Normal squamous	17	14	0	1	0	0.47
	Reflux esophagitis	9	4	0	0	0	0.69
	Non-dysplastic Barrett's	0	0	13	2	2	0.24
	Dysplastic Barrett's	0	0	3	4	3	0.60
	Adenocarcinoma	1	1	4	3	13	0.41

Results

First, the genetic data were examined visually without regard to histopathology to determine any intrinsic structure. Figure 1 shows a plot in which each sample is plotted according to its coordinates on the first three principal component axes. The data divide very clearly into two groups containing on the one hand normal squamous epithelium and reflux esophagitis and on the other hand non-dysplastic Barrett's, dysplasia, and adenocarcinoma. Furthermore, in the latter group, there is a reasonably clear distinction between non-dysplastic Barrett's and adenocarcinoma, whereas dysplasia is mixed over these two groups.

The median values and ranges of gene expression determined by quantitative RT-PCR for 18 genes in 5 epithelial groups are listed in Table 2. Significance analysis of microarrays testing (SAM) showed that the expression levels in 17 of the 18 genes differed significantly across the histological groups (the exception being EGFR). This result was confirmed by both *t* tests and Wilcoxon Rank Sum tests. We therefore only considered these 17 genes in all further analyses reported in this paper.

Table 4 LDA for the Three Histological Groups Normal Squamous Epithelium, Non-dysplastic Barrett's, and Esophageal Adenocarcinoma Using the Full Panel of Genes

		Genetic prediction group			
		NE	NDB	AC	Error rate
Actual histologic group	Normal squamous	30	1	1	0.06
	Non-dysplastic Barrett's	0	15	2	0.12
	Adenocarcinoma	2	3	17	0.23

LDA for the Detection of Combinations of Genes Able to Distinguish Histologic Groups

The results of the LDA to distinguish the five different histological groups using the panel of 17 genes are shown in Table 3. The best-predicted histological groups were non-dysplastic Barrett's, with a cross-validation error rate of 0.24, and adenocarcinoma of the esophagus, with an error rate of 0.41. Compared to these results, the error rates for dysplasia and reflux esophagitis were much higher at 0.6 and 0.69, respectively. Reflux esophagitis is mainly misclassified as normal squamous epithelium (9 out of 13 tissue samples). Additionally, dysplastic tissue is misclassified as non-dysplastic Barrett's and adenocarcinoma tissue (six out of ten tissue samples). The estimated error rate for this analysis (provided by a cross-validation analysis—see Appendix) was 0.48.

The results show that patterns of gene expression in inflamed and dysplastic tissues differ considerably from histologic assessment. Table 4 shows that predictive power improves markedly when the inflammatory and dysplastic tissues are removed (error rates of 6–23%, overall error rate=0.14). Also, an LDA was performed to attempt to distinguish just the non-dysplastic Barrett's and dysplasia group, i.e., the step at which the change from metaplastic to dysplastic tissue occurs. Results are shown in Table 5 (overall error rate=0.38).

Table 5 LDA for Just Two Histologies, Non-dysplastic Barrett's, and Dysplasia, Using the Full Panel of Genes

		Genetic prediction group		
		NDB	DBE	Error rate
Actual histologic group	Non-dysplastic Barrett's	11	6	0.40
	Dysplastic Barrett's	6	4	0.35

Table 6 LDA for All Histological Groups Using the Most Informative Genes (Bax, Bcl-2, Cdx-2, Cox-2, β-Catenin, Dr-5, MMP-2, Survivin, SPARC, TSPAN, and VEGF)

		Genetic prediction group					
		NE	REF	NDB	DBE	AC	Error rate
Actual histologic group	Normal squamous	18	13	1	0	0	0.44
	Reflux esophagitis	5	8	0	0	0	0.38
	Non-dysplastic Barrett's	0	0	14	1	2	0.18
	Dysplastic Barrett's	0	0	3	6	1	0.40
	Adenocarcinoma	1	1	2	2	16	0.27

It is possible that some of the genes do not play an important role in the development of Barrett's associated adenocarcinoma and therefore add only noise to the results. An R-script was used to exhaustively explore all possible models and find those that had highest predictive power. This was separately done for each of the analyses reported in Tables 3, 4, and 5. The models with the lowest overall estimated error rates in each case were examined. For the analysis in which there were five histologic groups (cf. Table 3), there was a single best model containing the genes Bax, Bcl-2, Cdx-2, Cox-2, β-Catenin, Dr-5, MMP-2, Survivin, SPARC, TSPAN, and VEGF with an error rate of 33%. The results for this model are shown in Table 6. For the analysis of just three histologies (cf. Table 4), there were four models with an equal lowest error rate of 0.056. The following genes appeared in all four models: Cox-2, TS, hTERT, Bcl-2, SPARC, TSPAN, VEGF, Her2/neu, and MMP2. For the analysis in which there are just two histologic groups (cf. Table 5), there is a single best model containing Bax, β-Catenin, TIMP1, Her2/neu, TS, SPARC, and VEGF with an error rate of 0.08. MMP-2 can be added to or excluded from this model without affecting fit. Results for this analysis, with MMP-2 excluded from the model, are shown in Table 7.

Unsupervised Clustering Analysis

Finally, a K-means clustering analysis was performed (see Appendix). In Table 8, the results for analyses with five groups (i.e., $K=5$) are shown. If the clusters to histological groups, in the way that maximizes the correlation between the two (assignments are indicated in parentheses in the column headings), are assigned, an overall error rate of 43% is obtained. This compares to a raw error rate of 29% in the LDA (before cross-validation). This shows that the data exhibit a good degree of structure even in the absence of histologic information.

Table 7 LDA for the Two Histological Groups Non-dysplastic Barrett's and Dysplasia Using the Most Informative Genes (Bax, β-Catenin, TIMP1, Her2/neu, TS, SPARC, and VEGF)

		Genetic prediction group		
		NDB	DBE	Error rate
Actual histologic group	Non-dysplastic Barrett's	16	1	0.06
	Dysplastic Barrett's	1	9	0.1

Discussion

We analyzed the quantitative expression levels of 18 genes thought to be associated with gastrointestinal carcinogenesis in five epithelia in the progression from normal squamous mucosa to Barrett's associated adenocarcinoma. This study was aimed mainly at determining whether differences in the expression profiles of these genes among the classical histological groups are sufficient to be able to successfully discriminate between samples by correctly assigning them to their known histological groups. A meaningful evaluation of a supervised predictive model depends on a correct predetermination of the histologic classification of the samples, but of course, there is a level of uncertainty inherent in pathologic interpretation, which may result in histologic misclassification in some cases. For the present study, we tried to minimize this concern as much as possible by having the evaluations done by an expert pathologist whose specialty is esophageal histology (PTC). Although we believe that each sample has been assigned to its proper histology, still there cannot be complete certainty in this regard, especially in the case of difficult-to-classify histologies such as dysplasia.

The expression levels in 17 of the 18 genes differed significantly across these histological groups. Some genes showed a pattern of up-regulation in the development of esophageal adenocarcinoma, whereas others were down-regulated. The sole exception was EGFR, which had a remarkably constant expression among the different types of tissues. In contrast, EGFR protein overexpression and gene amplification have been reported in squamous cell carcinomas of the esophagus.[26]

Table 8 K-means Clustering Analysis with K=5 Clusters (Optimal Assignment of K-means Clusters to Actual Histologic Group Indicated in Parentheses)

		K-means clusters				
		1 (DBE)	2 (NDB)	3 (REF)	4 (NE)	5 (AC)
Actual histologic group	Normal squamous	2	1	7	22	0
	Reflux esophagitis	1	0	4	8	0
	Non-dysplastic Barrett's	0	13	0	0	4
	Dysplastic Barrett's	0	5	0	0	5
	Adenocarcinoma	1	4	1	1	15

The results of the study show that, through appropriate data analysis, the selected gene set can distinguish normal from neoplastic tissue with a high degree of accuracy and distinguish normal Dysplastic Barrett's (DBE) and adenocarcinoma (AC) with *acceptable* accuracy. Examination of the data via a principal components analysis, which is an unsupervised clustering method for visualization of data, showed that the samples fell into two widely separated groups, one containing normal squamous epithelium and inflamed esophageal mucosa, the other containing metaplastic, dysplastic, and malignant tissue samples. Analysis of the full panel of genes (Tables 3 and 9) showed that 1 of the 48 normal tissues was mistaken for a neoplastic tissue by the genetic analysis, whereas 2 of the 49 neoplastic tissues were mistaken for normal tissue, corresponding to a misclassification rate of only about 3%. Interestingly, both of the samples identified as normal tissue were adenocarcinomas (Table 3); none of the non-Dysplastic Barrett's (NDB) or the DBE was misclassified as normal tissue.

At the other extreme, the full set of genes had limited ability to discriminate between the reflux esophagitis tissues and the normal squamous epithelium groups (misclassification rate=0.61). This result is not surprising considering the similar ranges and medians of expression of most of the genes in these two tissues (Table 3) and probably reflects the fact that the gene set chosen for this study was mainly oriented toward factors involved in carcinogenesis rather than inflammation. However, the better performance of the "test to identify the best-fitting models" (see Appendix) reduces the error for the prediction of reflux esophagitis to a rate of 0.38 (Table 6), which suggests that some of the genes of the set may be involved in inflammation to some extent.

Tissues classified as dysplastic by histopathology were also misclassified at a high rate of 0.6 by LDA using the full panel of 17 genes (Table 3). The distribution of these tissues almost evenly into the NDB and AC as well as DBE categories suggests considerable genetic diversity among tissues categorized as "dysplasia." This distribution is also seen in the principal component analysis (Fig. 1), which separates the AC from the NDB with only a small overlap, but the DBE is spread widely across these two clusters (Fig. 1). The question of whether there is prognostic significance to this variability in gene expression profiles of dysplasia or whether it will be possible to identify the low-grade and high-grade subclassifications of dysplasia will require additional studies with well-characterized specimens. Positive identification of these histologies is difficult but is an important issue because clinical decisions are made on this basis.[27] As with the normal and inflamed tissues, the process of finding and using the best-fitting model substantially decreased the mismatch rate (Table 6), and interestingly, LDA of just the NDB and DBE groups using the most informative genes (i.e., Bax, β-Catenin, TIMP1, Her2/neu, TS, SPARC, and VEGF; Table 7) had a discrepancy rate of only 0.08 with just one sample of each group "misidentified." In our opinion, the transition from metasplastic to dysplastic tissue is a critical step in the development of Barrett's associated adenocarcinoma with considerable clinical significance.[28] Thus, the ability to definitively distinguish metaplasia from dysplasia using a

Table 9 LDA for All Histological Groups, Excluding AC, Using the Full Panel of Genes

		Genetic prediction group				
		Normal squamous	Reflux esophagitis	Non-dysplastic Barrett's	Dysplastic Barrett's	Error rate
Actual histologic group	Normal squamous	16	15	0	1	0.50
	Reflux esophagitis	8	5	0	0	0.62
	Non-dysplastic Barrett's	0	0	14	3	0.18
	Dysplastic Barrett's	0	0	4	6	0.40

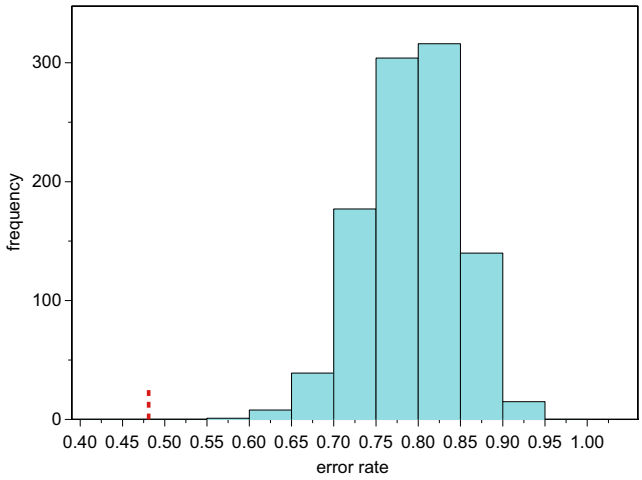

Figure 2 Histogram of frequency of cross-validated error rates in 1,000 permuted data sets (error rate for fit of observed data shown in *red*).

panel of genes may provide an important decision factor for recommending either surveillance, ablation, endoscopic mucosal resection, or resection.

Similar results were observed in classification of DBE and AC. Using the full panel of genes to classify the five tissue histologies, DBE and AC had misclassification rates of 0.24 and 0.41, respectively, with some samples going into both the DBE and AC categories. However, the misclassification rates of DBE and AC declined dramatically when the dysplasias and inflammatory tissues were removed, and the full set of genes was "asked" to discriminate only among NDB, AC, and normal esophagus (Table 4), or if only the most informative genes were used (Table 6).

The technique of K-means clustering is an unsupervised method, which identifies groups of similar gene expression profiles without any prior designation of relationships between genes or groups of samples. Thus, the fact that with a pre-set number of five clusters, the K-means technique provides a clustering structure that fits well with that of the classical histologies (Table 8) and provides an independent verification of a natural grouping of each of the stages in accord with characteristic gene expression profiles.

In conclusion, we have shown that a gene set selected for progression-related genes can classify a high percentage of samples in accord with classical histological designations. It may be possible to identify all of the histologies correctly by gene expression profiling if additional genes are found that more narrowly characterize each histology, especially the morphological appearance. However, it can be debated whether the goal of developing a genetic test should be merely to provide a better way to assign samples to the classical histological designations. Expression profiling of the appropriate genes, whether it matches the histologies or not, may provide its own prognostic value. For example, if indeed tissues that appear to be dysplasia but resemble both NDB and AC genetically have different rates of progression to cancer, a predictive ability would be lost if only the morphological appearance were taken into account. Determining the prognostic significance of genetic variations within the histologic groups will require further studies, but these results do suggest the possibility that there may not be one "gold standard" that best reflects the true status of the disease, but rather that both pathological examination as well as gene expression profiling may have to be used for optimal disease classification.

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Appendix

A more lengthy discussion of the statistical techniques used in this analysis is provided in the following.

SAM/t test The analysis was begun by identifying genes that have significantly changed expression for one or more stages of the disease. After log-transforming the data, three methods to do this were used: *t* tests, Wilcoxon rank sum tests, and SAM.[29] SAM is a package that uses a function of the change in gene expression, related to the standard deviation, and then tests the significance of the calculated value via permutation tests.[29]

LDA An LDA attempts to find vectors, consisting of linear combinations of gene expression values, which are able to successfully discriminate between samples by correctly assigning them to their known histological groups. This is an example of a "supervised clustering" method. Other examples include neural nets and multinomial regression. In previous work, an LDA was found to perform as well as, or better than, these other methods.[30]

In a context such as in this study, in which there are relatively many genes, one has to be aware of the issue of overfitting; that is, given enough genes, it might be expected to explain any classification, even for data that represent nothing but noise. Two schemes were employed to guard against this. Firstly, when fitting the LDA, the cross-validation error rate as an assessment of goodness-of-fit was used. Secondly, the results were compared to those obtained from analyzing data sets in which the histologies were randomly permuted (Fig. 2). These approaches are briefly explained in the following.

Cross-validation In a cross-validation test for a given model, one sample is left out of the data set and fit an

LDA for the remaining samples. Then the omitted sample is reintroduced and checked whether the fitted LDA can correctly predict the type of this sample. For a sample of size *n*, this procedure is repeated *n* times, leaving out a different sample each time. Then the overall error rate (the proportion of samples that have their histology incorrectly predicted) for all *n* cases, as well as reporting a breakdown of this error rate by histological grouping, is reported.

Permutation Test In the permutation test, the data set is taken and then randomly permuted the histologic labeling of the samples. Thus, a new data set is created in which the frequency of each histologic group is the same as for the original data, but for which the relationship between histology and gene expression is no longer likely to hold. Therefore, these permuted data sets are considered to represent noise. One thousand permuted data sets are generated using this scheme, and then an LDA on each data set is performed. The error rates for these data are reported, and the results to the error rate obtained on the original data are compared. This gives a measure of significance for our LDA fit.

Principal Components Principal components analysis is a standard statistical technique that finds linear combinations of gene expression values that capture as much of the variation in the data as possible. It is analogous to an LDA in which the histological information is not used. The principal components can then be used as a means of data reduction to represent multivariate data in plots involving fewer (in our case 3) dimensions.

Test to Identify "Best Models of Genes" As well as being interested in the fit obtained from an LDA using all genes, it is also interesting to know which subset of genes is most accurate in predicting histologic group. Somewhat counter-intuitively, it is not likely to be the case that the model containing all genes will predict histology most accurately.[31] The reason for this is that if, for example, five genes are sufficient to characterize the data, extra genes that are added to the analysis will merely model the remaining noise and will thus decrease the accuracy when they are also used to predict the type of future samples. Given that there were just 17 potentially useful genes, it was possible to exhaustively explore all two[17] possible LDA models and determine those that were best-fitting. This was performed using an R-script (available from the authors).

An important note regarding estimated error rates in such an exhaustive analysis should be noted. For a single LDA, the cross-validation error rate gives an accurate and unbiased estimate of the expected predictive error of the fitted model. However, when many such models are compared and those with the lowest error rates are selected, these error rates are now expected to underestimate the future predictive error rate of the given models. Thus, the analysis should be interpreted as a way of finding the models that best predict the data, and a ranking of models in terms of their predictive power, rather than as an unbiased estimate of the exact error rates of those models. For a discussion of these issues, see Ambroise and McLachlan.[31]

K-means Clustering To compare the study results with those that might be obtained by an analysis that does not use the histologic information, a further (so-called 'unsupervised') analysis was conducted. For this, K-means clustering was used, a method that clusters data based upon correlations between gene expression without knowledge of the true histology and that has been widely used to analyze microarray data.[32] When using K-means clustering, one has to pre-specify the number of groups (*K*) into which the data is clustered. Informally speaking, the method then constructs *K* "centers" and clusters each sample to its closest center. In the context of our study, these centers are vectors of gene expression values. The algorithm will report the clustering corresponding to the optimal set of centers.

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COX-2 mRNA Expression is Significantly Increased in Acid-exposed Compared to Nonexposed Squamous Epithelium in Gastroesophageal Reflux Disease

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Abstract
Background Little is known about the role of cyclooxygenase (COX)-2 in gastroesophageal reflux disease (GERD) and the development of Barrett's metaplasia. The objectives of this study were to further analyze COX-2 mRNA expression in patients with GERD compared to Barrett's esophagus (BE) and Barrett's cancer (BC).
Methods Tissue samples from 110 patients with GERD (n=43), BE (n=20), and BC (n=47) were obtained in routine upper GI endoscopy. Expression levels of COX-2 were measured by quantitative real-time reverse trancriptase polymerase chain reaction (RT-PCR). Also, 24-h pH monitoring was performed in all patients of the GERD study group and the DeMeester composite score was used to match COX-2 mRNA expression with the severity of acid exposure in the lower esophagus.
Results COX-2 mRNA is progressively upregulated within the metaplasia–dysplasia–adenocarcinoma (MDA) sequence (p=0.001). COX-2 levels of the squamous epithelium in the distal esophagus from patients with GERD and a pathologic mean DeMeester score (>14.72) were significantly higher than in patients with normal DeMeester scores (p=0.01).
Conclusion In summary our findings suggest that alterations in COX-2 mRNA expression occur independently of endoscopic or histologic signs of GERD in the acid-exposed squamous epithelium of the distal esophagus. However, this early COX-2 increase in GERD is further upregulated within the MDA sequence for yet unknown reasons.

Keywords GERD · COX-2 · Esophageal cancer · Chemoprevention

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Introduction

Gastroesophageal reflux disease (GERD) is a common disease that affects up to 30% of the Western population.[1] It is associated with esophageal adenocarcinoma, a rapidly increasing cancer in the Western world.[2–4] Cancer development is a multistep process that starts with the mucosal injury of the squamous epithelium of the distal esophagus by GERD and progresses through intestinal metaplasia and dysplasia to invasive adenocarcinoma.[3] Molecular events associated with the pathogenesis of esophageal adenocarcinoma have recently been identified.[5] Whereas most efforts have been directed at the metaplasia–dysplasia–adenocarcinoma (MDA) sequence, little is known about the molecular changes that occur in the early progression of disease, i.e., the transformation of squamous epithelium in the distal esophagus to metaplastic Barrett's epithelium.

Cyclooxygenase (COX) is the rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins. The isoform COX-1 is thought to be constitutively expressed in a variety of tissues, whereas COX-2 is induced by cytokines, growth factors, mitogens, and oncoproteins. COX-2 is involved in the regulation of a broad range of cellular processes, including angiogenesis, apoptosis, and cell proliferation. Recently, overexpression of COX-2 has been reported in various types of tumors, including esophageal adenocarcinoma.[6–8] Several studies revealed an increased COX-2 expression in the MDA sequence, suggesting COX-2 to be involved Barrett's cancer (BC) development.[9–11]

Less is known about the role of COX-2 in the initial phase, the conversion of squamous epithelium to Barrett's metaplasia. Whereas studies dealing with severe reflux in rodents confirmed that inhibition of COX-2 with selective inhibitors resulted in a reduced incidence of intestinal metaplasia and cancer development, further insights in the process of COX-2 upregulation at the earliest stages of esophageal carcinogenesis might lead to new therapeutic strategies for patients with GERD.

To further elucidate the role of COX-2 in GERD and Barrett's development, we analyzed the mRNA expression in biopsy specimens of GERD patients with and without the presence of Barrett's metaplasia.

Material and Methods

Patients

Tissue samples of 110 consecutive patients with GERD, Barrett's esophagus (BE), and BC were obtained at upper GI endoscopy between June 1997 and November 2002. For normal tissue controls, for each study group paired biopsies from the proximal esophagus were obtained. Biopsy specimens were immediately bisected and snap-frozen in liquid nitrogen and stored at −70°C until further processing. One biopsy half was routinely fixed in 4% buffered formalin and paraffin-embedded overnight. Representative sections (beginning, middle, and end of sectioning) were stained with hematoxylin and eosin by a standard method and were examined by two experienced staff pathologists. For total RNA extraction and reverse trancriptase polymerase chain reaction (RT-PCR), fresh frozen biopsy halves were used without performing laser-captured microdissection.

Detailed clinicopathologic data of the GERD, BE, and BC group are shown in Tables 1, 3, and 4.

(1) *GERD group*: Patients were considered to have gastroesophageal reflux based on the presence of typical reflux symptoms, which included heartburn, regurgitation, and epigastric pain. None of the GERD study patients showed atypical symptoms of GERD, such as new-onset bronchial asthma, chronic cough, and symptomatology from ear, nose, and throat regions. Tissue samples from 43 patients of squamous epithelium from the distal and proximal esophagus were taken. Twenty (47.5%) patients had positive 24-h pH studies, 35 (81.4%) had evidence of histologic esophagitis, and 33 (76.8%) had endoscopic signs of esophagitis (Tables 1 and 2).

(2) *Barrett's esophagus group*: Samples were from 20 patients with histologically confirmed BE. Squamous epithelium from the proximal esophagus was collected as paired control tissue. Fifteen (75%) patients had no dysplasia, 4 (20%) had low grade dysplasia, and 1

Table 1 Clinicopathologic Parameters of GERD Patients

Parameters	
Patients (*n*)	
Total	43
Male	15 (34.9%)
Female	28 (65.1%)
Median age in years (min–max)	52.9 (17.7–82.5)
DeMeester Score (pH)[14]	
<14.72	23 (52.5%)
>14.72	20 (47.5%)
Histology[13]	
Grade 0	8 (18.6%)
Grade 1	26 (60.5%)
Grade 2	6 (13.9%)
Grade 3	3 (7.0%)
Endoscopy[24]	
Grade 0	10 (23.2%)
Grade 1	23 (53.5%)
Grade 2	6 (14.0%)
Grade 3	4 (9.3%)

Table 2 Distribution of the DeMeester Score with Histologic and Endoscopic Signs of Reflux

DeMeester score	Histology (*n*)[13]				Endoscopy (*n*)[24]			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
<14.72 (*n*=23)	6[a]	14	2	1	8[a]	12	3	0
>14.72 (*n*=20)	2	12	4	2	2	11	3	4

[a] No patient was negative for histology and endoscopy at the same time.

(5%) patient had high-grade dysplasia. Patients with evidence of dysplasia were not included in the statistical analysis because of low patient numbers (Table 3).

(3) *Barrett's cancer group*: Samples were from 47 patients showing esophageal adenocarcinoma in BE. Normal squamous epithelium was taken from the proximal esophagus as paired control tissue (Table 4).

Informed consent was obtained from each patient in accordance to the requirements of our institution's board of ethics.

Definition of Reflux Esophagitis by Endoscopy and Histopathology

The criteria by Savary and Miller[12] were used to define endoscopic GERD into grades I–IV. Morphologic criteria reported by Elster[13] were applied for histopathologic classification of reflux esophagitis into grades 0–3 (Tables 1 and 2).

All tissue specimens were evaluated by two experienced staff pathologists (S.E.B. and U.D.).

PH Monitoring

Twenty-four-hour pH monitoring was performed by positioning a glass pH electrode (Medtronic Inc., Minneapolis, MN, USA) 5 cm above the manometrically measured upper border of the lower esophageal sphincter. The electrode was connected to a digital recording device (Medtronic Inc./Synectics Medical, EsopHogram Reflux Analysis, version 2.01, Minneapolis, MN, USA) and the pH was continuously monitored for 24 h. The following parameters were measured: total percentage of time with pH less than 4, percentage of time the pH was less than 4 when subject was upright, percentage of time the pH was less than 4 when subject was supine, total number of GERD episodes longer than 5 min, time of the longest GERD episode, and composite score based on these parameters.[14]

Table 3 Clinicopathologic Parameters of Barrett's Patients

Parameters	
Patients (*n*)	
Total	20
Male	17 (85%)
Female	3 (15%)
Median Age (min–max)	58.9 (20.6–81.3)
Barrett's length (*n*)	
<1 cm (ultrashort)	5 (25%)
1–3 cm (short)	7 (35%)
>3 cm (long)	8 (40%)
Dysplasia (*n*)	
No dysplasia	15 (75%)
Low-grade dysplasia	4 (20%)
High grade dysplasia	1 (5%)

Table 4 Clinicopathologic Parameters of BC Patients

Parameters	
Patients (*n*)	
Total	47 (85.1%)
Male	45 (95.7%)
Female	2 (4.3%)
Median Age (min./max.)	60.9 (41.4–81.2)
Residual tumor category	
R0	40 (85.1%)
R1	0 (0%)
R2	1 (2.1%)
not resected	6 (12.8%)
c/pT category	
T1	20 (42.6%)
T2	12 (25.5%)
T3	14 (29.8%)
T4	1 (2.1%)
c/pN category	
N0	29 (61.7%)
N1	18 (38.3%)
c/pM category	
M0	38 (80.9%)
M1a	5 (10.6%)
M1b	4 (8.5%)
Grading	
G1	3 (6.4%)
G2	33 (70.2%)
G3	11 (23.4%)

Tumor–Node–Metastasis (pTNM) Pathological Classification: c/pT = primary tumor, c/pN = regional lymph node metastasis, c/pM = distant metastasis, G = grade of differentiation, R = residual tumor category

RNA Isolation and cDNA Synthesis

Biopsy specimens were bisected and snap-frozen in liquid nitrogen. Representative sections (beginning, middle, and end of sectioning) were stained with hematoxylin and eosin by a standard method and examined by two experienced staff pathologists.

Total RNA was isolated from fresh frozen biopsy halves using the Trizol-Kit (Life Technologies/GIBCO, Grand Island, NY, USA) according to the manufacturer's instructions. After the generation of cDNA using oligo (dT)18 primers and Moloney murine leukemia virus reverse transcriptase (Clontech Advantage™ Kit, Clontech Lab. Inc., Palo Alto, CA, USA), direct quantitative real-time RT-PCR (*Taq*Man™, ABI PRISM 7900HT Sequence Detection System Applied Biosystems, Darmstadt, Germany) assays were performed in triplicates to determine COX-2 mRNA expression levels.

Quantitative Real-time RT-PCR

The primers and probes for COX-2 used in the study were previously reported.[15] Thermal cycling conditions for COX-2 were 120 s at 50°C and 10 min at 95°C for initial denaturation followed by 40 cycles at 95°C for 15 s and 60°C for 60 s. We used serial dilutions of standard cDNA synthesized from human placenta total cellular RNA (Clontech Lab. Inc.). Triplicates of the tissue samples were assayed in each run. COX-2 levels were standardized with β-actin (ratio COX-2/β-actin) to account for loading differences. Gene expression levels (mRNA) were reported using the median as point estimator and the range of values.

Statistical Analysis

COX-2 mRNA levels and endoscopic and histopathological data were analyzed by nonparametric testing (Wilcoxon rank test, Mann–Whitney test, Kruskal–Wallis test, and Friedmann test). The level of significance was set to $p < 0.05$ and p values are given for two-sided testing. All statistical tests were performed using the software package SPSS for Windows, version 11.0, Chicago, IL, USA.

Results

COX-2 Expression in Different Study Groups

COX-2 mRNA expression was detectable by quantitative real-time RT-PCR in all 110 tissue samples. According to the histopathologic group, median COX-2 mRNA expression was lowest in normal squamous epithelium of the distal esophagus (median 0.35, range 0.08–7.8), intermediate in BE (median 0.86, range 0.08–9.61), and highest in esophageal adenocarcinoma (median 1.62, range 0.001–99.21) ($p=0.001$). The median value and range of expression levels of COX-2 mRNA in the three study groups are listed in Table 5.

In patients with BE without dysplasia, COX-2 expression was significantly higher in metaplastic tissue compared to paired normal squamous epithelium ($p=0.03$).

Esophageal cancer patients had higher COX-2 mRNA expression levels in cancer tissues compared to paired normal squamous epithelium and BE ($p=0.001$).

The mean COX-2 mRNA expression of squamous epithelium in all three study groups did not show any significant difference ($p=0.10$). Furthermore, COX-2 mRNA expression in biopsy specimens obtained from histologically and endoscopically classified GERD did not show a significant difference in distal acid-exposed tissues and paired squamous epithelium control tissues ($p=0.63$). No significant difference in COX-2 mRNA expression of metaplastic Barrett's epithelium in patients with BE and patients with BC was detected ($p=0.29$).

COX-2 Expression and Clinicopathological Factors of Patients with GERD

Biopsy specimens obtained from patients with a mean DeMeester score >14.72 showed significantly upregulated median COX-2 mRNA levels in the distal acid-exposed ($p=0.01$) esophagus compared with patients having a

Table 5 COX-2 mRNA Expression in Study Groups

		Median	Min	Max	*p* value
GERD[a] ($n=43$)	Proximal ($n=39$)	0.3835	0.1058	5.9145	0.63
	Distal ($n=43$)	0.3562	0.0853	7.8081	
BE ($n=15$)	Squamous epithelium ($n=10$)	0.4412	0.0754	2.0350	0.03
	Intestinal metaplasia ($n=15$)	0.8600	0.0838	9.6151	
Barrett's adenocarcinoma ($n=47$)	Squamous epithelium ($n=38$)	0.2824	0.0001	3.0755	0.001
	Intestinal metaplasia ($n=15$)	1.2295	0.2689	8.8384	
	Barrett's carcinoma ($n=45$)	1.6210	0.0001	99.218	

[a] Defined by clinical reflux symptoms and positive histology and/or endoscopy

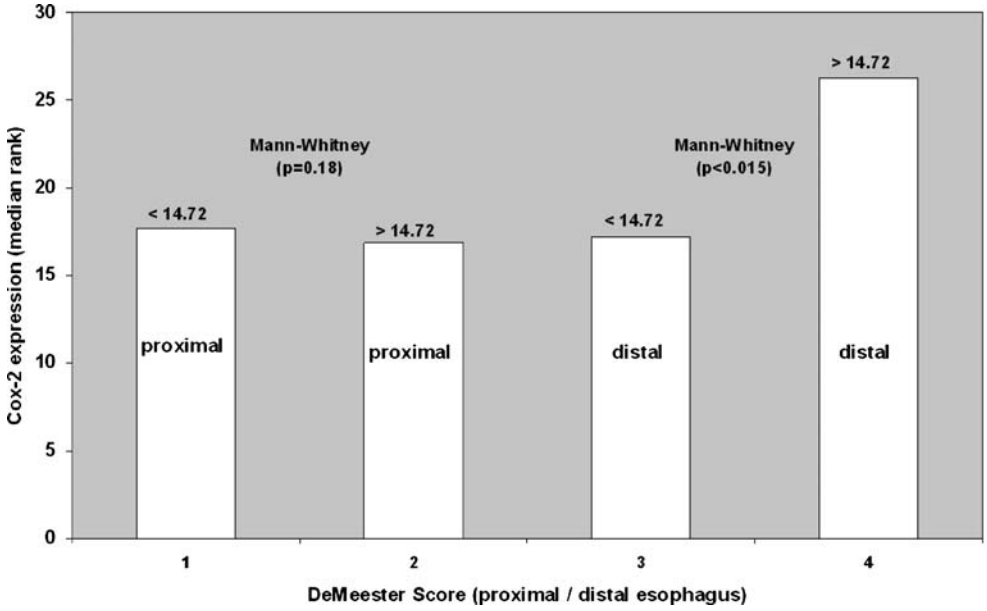

Figure 1 COX-2 mRNA in GERD associated to DeMeester score.

negative DeMeester score (Fig. 1). No significant correlation was detected between COX-2 expression and endoscopic or histologic findings (p=0.63) (Table 5).

COX-2 Expression and Clinicopathological Factors of Patients with Barrett's Adenocarcinoma

Overexpression of COX-2 mRNA in patients with Barrett's adenocarcinoma was not associated with grading (p=0.58), T category (p=0.95), N category (p=1.0), or patients' survival (log-rank test, p=0.70).

Discussion

We present a study on mRNA expression of COX-2 in the reflux MDA sequence. We could reconfirm that progression of BE to esophageal adenocarcinoma is accompanied by an increase in COX-2 expression as reported by other groups.[10,11] As previously described by Hamoui et al., we could demonstrate that COX-2 expression was significantly correlated with exposure of the distal esophagus to acid reflux, suggesting alteration of COX-2 expression to be one of the earliest specific changes in the reflux MDA sequence.

Epidemiologic studies revealed that the use of COX-2 inhibitors was associated with a decreased risk for esophageal cancer. Much interest was focused on the potential role of COX-2 in esophageal carcinogenesis.[7,8] Previous studies analyzed the expression pattern of COX-2 in the MDA sequence. Our group recently demonstrated that COX-2 protein expression by immunohistochemistry was progressively increased in metaplastic, dysplastic, and cancer tissue with the most significant differences between squamous epithelium and metaplasia and from low-grade to high-grade dysplasia.[16] Kuramochi et al.[9] measured the gene expression of COX-2 by real-time quantitative polymerase chain reaction in the pathogenesis of Barrett's adenocarcinoma and also showed a stepwise increase of COX-2 mRNA expression at the different stages. Our results are in agreement with these findings, showing that median COX-2 mRNA expression is stepwise upregulated in Barrett's metaplasia and adenocarcinoma.

The development of esophageal adenocarcinoma is a multistep process that starts with the mucosal injury of the squamous epithelium of the distal esophagus by GERD and progresses through intestinal metaplasia, dysplasia, to cancer.[2,3] Whereas several molecular events associated with the progression from metaplastic to cancer tissue have been identified in recent years, little is known about the molecular changes that occur in the beginning of disease.[5] This first step, conversion of squamous mucosa to columnar mucosa, is perhaps the most critical because adenocarcinoma cannot develop within squamous mucosa.[3] Therefore, we additionally examined COX-2 mRNA expression in esophageal biopsies from patients with GERD. We were able to show that COX-2 expression in biopsies obtained from patients with a positive DeMeester score >14.72 was significantly upregulated compared to patients with a negative DeMeester score. These findings are in agreement with a recent study by Hamoui et al.[17] In their study, expression levels of several known genes were compared with the degree of acid exposure in the lower esophagus found on 24-h esophageal pH monitoring of 61 patients with GERD. They demonstrated that the expression levels of COX-2 correlated positively with the 24-h pH score, whereas there was no correlation between the expression of other tested genes and esophageal acid

exposure. Therefore, acid reflux disease alters gene expression in esophageal mucosa, and leads to overexpression of COX-2, representing one of the earliest changes associated with gastroesophageal reflux, because in our study the increase in COX-2 expression was independent of the endoscopic or histologic findings in the squamous mucosa. To examine the specificity of this observation, we additionally examined COX-2 mRNA expression in paired specimens derived from proximal esophageal tissue samples, which appeared "normal" on endoscopy and histopathology, although cervical 24-h pH monitoring was not performed. Our GERD study patients showed no clinical symptoms of cervical or extra esophageal reflux disease, suggesting that the proximal esophageal epithelium was not exposed to acid reflux. Although dual channel 24-h pH monitoring was not performed, our data suggest that COX-2 mRNA expression was significantly upregulated only in the acid-exposed squamous epithelium of the distal esophagus. A field effect as shown for other genes[18] could not be detected in our study, thus indicating that COX-2 upregulation is probably an immediate response to acid exposure in the distal esophagus rather than a genetic variation of the entire esophagus.

Chemoprevention strategies might therefore be applied earlier in the neoplastic process because the use of selective COX-2 inhibitors might prevent progression of disease at an early stage.[19–21] In fact, studies about severe reflux in rodents confirmed that inhibition of COX-2 with selective inhibitors resulted in a reduced rate of intestinal metaplasia and cancer development.[22,23]

Large prospective trials with the inclusion of cervical 24-h pH monitoring are needed to validate these preliminary findings.

Conclusion

In summary our findings suggest that alterations in COX-2 mRNA expression occur independently of endoscopic or histologic signs of GERD in the acid-exposed squamous epithelium of the distal esophagus. However, this early COX-2 increase in GERD is further upregulated in Barrett's metaplasia and BC development for yet unknown reasons.

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Chemotherapy-Induced Normalization of FDG Uptake by Colorectal Liver Metastases Does Not Usually Indicate Complete Pathologic Response

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Abstract Dramatic responses are being observed in colorectal cancer liver metastases treated with newer chemotherapeutic regimens. These have been associated with normalization of [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake (complete metabolic response) on follow-up Positron Emission Tomography with [^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) scans in some patients. It is unclear how often complete metabolic response is indicative of complete tumor destruction. We analyzed a subset of patients who had neoadjuvant chemotherapy for hepatic metastases from colorectal adenocarcinoma. Inclusion criteria were: (1) FDG-avid hepatic lesions before initiation of chemotherapy; (2) complete metabolic response of the same lesions after chemotherapy; and (3) histopathologic examination of hepatic lesions. Complete pathologic response was defined as no histologically identifiable viable tumor. Fourteen patients fit the inclusion criteria. All had synchronous, hepatic-only colorectal metastases. On microscopic examination, complete pathologic response to the neoadjuvant regimen was found in only 5 of 34 lesions (15%) and in only 3 of the 14 patients (21%). Seven lesions had complete metabolic response and disappeared on computed tomography (CT); of these, six still contained viable tumor. We conclude that complete metabolic response on FDG-PET after neoadjuvant chemotherapy is an unreliable indicator of complete pathologic response. Therefore, currently, curative resection of liver metastases in these patients should not be deferred on the basis of FDG-PET findings.

Keywords Colorectal cancer · Hepatic metastasis · FDG-PET · Response to therapy · Chemotherapy

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Introduction

Surgical resection is the most effective treatment for liver-only metastasis from colorectal cancer.[1–5] However, most patients with this problem have unresectable disease. Downsizing tumors in patients with unresectable tumors to render them resectable has been increasingly successful because of improved systemic therapies.[7,8] These include regimens combining 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI),[6–8] and the angiogenesis inhibitors bevacizumab (the anti-vascular endothelial growth factor monoclonal antibody) and cetuximab (the anti-epidermal growth factor receptor monoclonal antibody).[9–11] Patients with resectable disease may also be treated by these agents before referral to a liver surgeon.

Positron emission tomography with [^{18}F]fluoro-2-deoxy-D-glucose (FDG-PET) is the most sensitive imaging test for colorectal metastases.[12–15] It is usually combined with an anatomic imaging study such as computed tomography (CT) or magnetic resonance imaging (MRI) to complete surgical staging. In some cases, dramatic responses to neoadjuvant

chemotherapy have been associated with partial or complete normalization of FDG uptake (partial or complete metabolic response) on follow-up FDG-PET. How often complete metabolic response is due to complete tumor destruction by chemotherapy as opposed to another cause such as impairment of glucose uptake by residual viable tumor is unclear, but of critical importance in guiding further therapy. The purpose of this study was to determine how frequently complete metabolic response of hepatic metastases after neoadjuvant chemotherapy is associated with complete pathologic response.

Materials and Methods

Study Design

Patients undergoing neoadjuvant chemotherapy for colorectal hepatic metastases were identified from a prospectively maintained, IRB-approved database for the period June 2002 to June 2006. Patients were included in this study if they met the following three criteria: (1) whole-body FDG-PET demonstrating FDG-avid hepatic lesions before initiation of neoadjuvant therapy; (2) whole-body FDG-PET demonstrating complete metabolic response of the same hepatic lesions after completion of neoadjuvant therapy; and (3) histopathologic sampling of hepatic lesions by biopsy or resection to document extent of response to treatment.

Patient, radiographic, and histologic characteristics were reviewed for each patient. Patient characteristics included age, gender, carcinoembryonic antigen (CEA) levels, stage of the primary colorectal neoplasm, whether the hepatic metastases were synchronous or metachronous, and type of neoadjuvant chemotherapy given.

FDG-PET Procedure and Interpretation

Most FDG-PET studies were performed at the Mallinckrodt Institute of Radiology, Washington University in Saint Louis School of Medicine. When they were not performed at our institution, they were reviewed by our nuclear radiologists. If the images were not recent or not deemed of adequate quality, the FDG-PET scan was repeated.

All FDG-PET studies at our institution during the study interval were performed with a hybrid PET/CT scanner (Biograph LSO 2, Siemens Medical Solutions, Malvern, PA). The CT component of the PET/CT studies was performed without administration of intravenous contrast agents, although from late 2005, oral contrast (MD-Gastroview) was administered. Five FDG-PET studies (for four patients in total) were performed with oral CT contrast. CT images (5-mm slices) typically were obtained from the base of the skull through the proximal thighs at 130 kVp and 110 mA. Emission PET images were obtained over the same anatomical extent beginning 45–75 min after administration of 15–20 mCi FDG, with imaging times of 2–4 min per bed position depending on patient weight. PET images were scatter-corrected and reconstructed using ordered subset expectation maximization (OSEM) with the use of a post-reconstruction Gaussian filter at 5 mm full width at half maximum (FWHM).

Interpretation of all studies was performed in routine clinical fashion by an experienced nuclear radiologist. Subjective visual assessment was used in the interpretation of FDG-PET images. Complete metabolic response of hepatic metastases was defined as the normalization of FDG uptake at sites of lesions identified at baseline, such that the posttreatment uptake was equivalent to or less than that of normal hepatic parenchyma. For purposes of this study, this determination was based on review of the clinical reports of the pre- and posttreatment PET studies. The extent of tumor response by conventional imaging (contrast-enhanced CT or MRI) was based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[16] All imaging results were correlated with subsequent final histologic diagnosis.

Operative Therapy

Complete metabolic response was not considered to be a contraindication to surgical exploration. Hepatic resection was performed in patients still found to have operable disease after laparotomy and intraoperative ultrasonography. In one patient whose disease remained inoperable after chemotherapy, percutaneous biopsy of PET-negative lesions was performed to document histological response. The terminology for liver anatomy and resections used in this article is the Brisbane 2000 terminology of the International Hepato–Pancreato–Biliary Association.[17]

Results

Patient Demographics

From June 2002 through to June 2006, 14 patients with hepatic metastases from primary colorectal adenocarcinoma fit the inclusion criteria for the study. The patient population consisted of ten men and four women (Table 1). Mean age was 59 years, with a range of 32 to 84 years. The primary tumor was located in the colon in ten patients (71%) and in the rectum in four patients (29%). Complete information on stage and grade of the primary tumor was available in all patients except one, who underwent neoadjuvant chemoradiotherapy before resection of the primary (rectal) tumor. Of the remaining 13 patients, 12 had T3

Table 1 Patient and Tumor Characteristics

Characteristic (N=14)	Number of patients (%)
Mean age (years)	59
Age range	32–84
Gender	
Male	10 (71%)
Female	4 (29%)
Primary tumor location	
Colon	10 (71%)
Rectum	4 (29%)
Primary tumor grade	
Well-moderately differentiated	9 (64%)
Poorly differentiated	5 (36%)
Primary tumor stage*	
T2	1 (8%)
T3	12 (92%)
Primary tumor nodal status*	
N0	4 (29%)
N1	6 (43%)
N2	3 (28%)
Type of metastases	
Synchronous	14 (100%)
Number of metastases	
Single	4 (29%)
Multiple	10 (71%)
Distribution of metastases at presentation	
Unilateral	10 (71%)
Bilateral	4 (29%)
Extent of resection**	
<3 contiguous segments	8 (62%)
≥3 contiguous segments	5 (38%)
Response to treatment	
Complete response	3 (21%)
Incomplete response	11 (79%)

*Pretreatment staging not available for one patient
**One patient received only percutaneous biopsy of hepatic lesion (positive for metastatic adenocarcinoma).

tumors, with 1 patient having a T2 tumor. Four primary colonic tumors were node-negative, six had N1 disease, and three had N2 disease. Synchronous hepatic lesions were defined as those discovered before or within 1 year of the resection of the primary tumor. Metachronous lesions were defined as those diagnosed greater than 1 year after the resection of the primary tumor. All of the patients in the study had synchronous hepatic metastases.

Neoadjuvant Chemotherapy

Before treatment with neoadjuvant chemotherapy for their hepatic metastases, all patients underwent FDG-PET demonstrating FDG-avid hepatic lesions. These lesions were also detectable by CT or MRI, except for two lesions that were visible only by FDG-PET in a patient who had another lesion visible on both FDG-PET and CT scans. After completion of chemotherapy, all 14 patients had repeat FDG-PET demonstrating complete metabolic response of the same hepatic lesions (see Fig. 1). Seven of the lesions that became PET negative were also not visible on conventional axial imaging (CT or MRI).

The average time interval between pre-chemotherapy and post-chemotherapy imaging was 4.1 months (range, 1.6–9.9 months). During this period, patients in this study underwent a variety of chemotherapy regimens (see Table 2). Eleven of the 14 patients (79%) in the study were treated with chemotherapy that included an angiogenesis inhibitor (bevacizumab and/or cetuximab). Of the nine patients whose regimens included bevacizumab, the median number of doses was six (range 2–19). Of the three patients not receiving an angiogenesis inhibitor, two were treated with FOLFOX (5FU + oxaliplatin + leucovorin) alone for four and seven cycles each and the other with irinotecan alone (five cycles).

Response to Therapy

After neoadjuvant chemotherapy and reimaging, 13 of 14 patients were deemed eligible for, and subsequently underwent, hepatic resection with curative intent. One patient was inoperable because of biopsy-proven viable tumor in multiple sites in the liver despite a negative posttreatment FDG-PET study. Three of 14 patients (21%) had complete pathologic response to neoadjuvant therapy, i.e., no viable tumor was found on histological review of the resected specimen. The chemotherapy regimen for all these patients included bevacizumab: two of these patients were

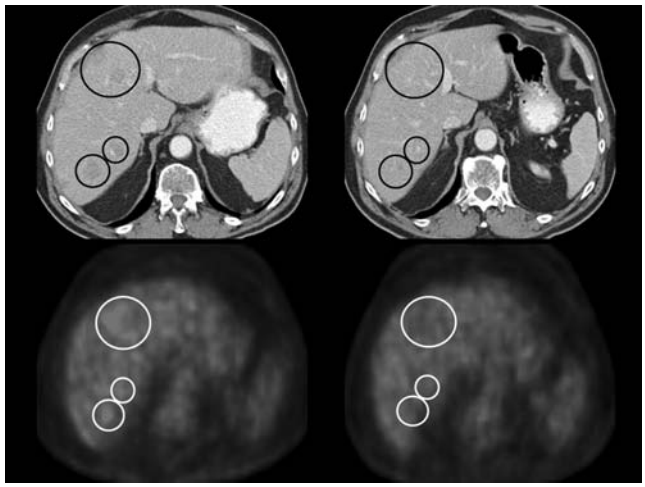

Figure 1 CT (*above*) and FDG-PET (*below*) images of a patient with colorectal hepatic metastases (*circled*). Before chemotherapy (*left*), the lesions demonstrated intense FDG uptake before chemotherapy. After chemotherapy (*right*), one lesion had disappeared on CT (complete RECIST response, *top*) with the other two also dramatically shrinking in size (partial RECIST response), with all three lesions demonstrating complete resolution of FDG uptake.

Table 2 Details of Chemotherapy Regimens of Patients with Total Loss of FDG Avidity in their Liver Metastases from Colorectal Cancer

Patient number	Interval between PET scans (months)	Neoadjuvant chemotherapy (during interval between PET scans)	Number of cycles	Number of bevacizumab doses	Number of cetuximab doses	Complete pathological response?
1	2.3	Irinotecan	5	0	0	No
2	4.6	FOLFOX	4	0	0	No
3	4.8	FOLFOX	7	0	0	No
4	4.5	FOLFOX + Cetuximab	6	0	13	No
5	3.9	FOLFOX + Cetuximab	5	0	9	No
6	4.0	Capecitabine + Oxaliplatin + Bevacizumab	4	4	0	No
7	1.6	FOLFOX + Bevacizumab	3	3	0	No
8	3.3	FOLFOX + Bevacizumab	6	6	0	No
9	1.8	FOLFOX + Bevacizumab	10	10	0	No
10	4.5	FOLFOX + Bevacizumab	8	8	0	No
11	4.8	FOLFOX + Bevacizumab	9	8	0	No
12	1.6	FOLFOX + Bevacizumab	3	2	0	Yes
13	5.7	FOLFOX + Bevacizumab	9	2	0	Yes
14	9.9	FOLFIRI + Bevacizumab	19	19	0	Yes
Median	4.3		6			
Range	1.6–9.9		3–19			
Average	4.1		7			

Complete pathological response defined as no viable tumor detectable on pathological review of the resected surgical specimen.
FOLFOX 5FU + leucovorin + oxaliplatin, *FOLFIRI* 5FU + leucovorin + irinotecan, *bevacizumab (Avastin)* anti-vascular endothelial growth factor (VEGF) receptor monoclonal antibody, *cetuximab (Erbitux)* anti-endothelial growth factor (EGF) receptor monoclonal antibody.

treated with FOLFOX plus bevacizumab, whereas the other was treated with FOLFIRI (irinotecan + 5FU + leucovorin) plus bevacizumab. However, the number of cycles of neoadjuvant chemotherapy was widely disparate, ranging from 3 to 19.

In all, 34 lesions in the 14 patients demonstrated complete metabolic response on FDG-PET after neoadjuvant chemotherapy *and* underwent pathologic sampling (see Table 3). Twenty-nine of the lesions (85%) still had residual viable tumor (see Fig. 2), with only five (15%) showing complete tumor destruction. Therefore, the predictive value of normalization of FDG uptake by chemotherapy as an indication of a complete pathologic response is quite poor at 0.15 (95% confidence interval 0.09–0.21). Of the five lesions with no residual viable tumor, two occurred in patients who had other hepatic lesions, which did contain residual viable tumor. Consequently, only 3 of the 14 patients, each having only a single hepatic metastasis, had no pathologically demonstrable viable tumor at the time of resection.

Using RECIST guidelines, 20 of 32 lesions (63%) demonstrated a response. There was a complete response in 7 lesions, and a partial response in 13 lesions. Two lesions showed disease progression, and ten lesions were stable. Sixteen of the 34 lesions (47%) were either not visualized by CT or MRI after treatment, or if detected, were smaller than 1 cm in diameter. An interesting subgroup consisted of the seven lesions that, in addition to demonstrating complete metabolic response on FDG-PET, were also not visible on CT or MRI after neoadjuvant chemotherapy (complete response by RECIST). Only one of these seven lesions had no viable tumor on histologic examination.

Discussion

It is currently unclear whether hepatic metastases that exhibit a complete metabolic response on FDG-PET after neoadjuvant chemotherapy are also likely to have a complete pathologic response, and consequently, whether such lesions require further treatment, such as surgical resection or radiofrequency ablation. The key result of our study is that, despite the absence of detectable metabolic activity above background on FDG-PET, viable tumor could still be found in 29 of 34 lesions (85%) and in 11 of 14 patients (79%). In an interesting subgroup of seven lesions, in which neoadjuvant chemotherapy resulted both in complete metabolic response and complete response by RECIST criteria, viable tumor was still detected histologically in six lesions.

There is a growing body of literature investigating the role of FDG-PET as a measure of response to adjuvant therapy.[18–21] Numerous studies in a variety of malignancies (as reviewed by Weber[21]) have demonstrated a survival advantage for patients whose tumors become less FDG-avid after chemotherapy and/or radiation therapy, compared

Table 3 Correlation of Lesions Demonstrating Complete Response by FDG-PET with Response by CT Criteria and Pathologic Response

Patient number	Lesions visualized on FDG-PET	Size of lesion on CT (cm)		Percent change in size by CT (%)	Response by CT (RECIST)	Pathology: viable tumor present?
		Pretreatment	Posttreatment			
1	1	1.7	1.0	−41	PR	Yes
2	2	0.6	NV	−100	CR	Yes
	3	NV	NV	–	–	Yes
	4	NV	NV	–	–	Yes
3	5	1.9	1.4	−26	SD	Yes
	6	1.0	1.3	+30	PD	Yes
	7	1.3	1.3	0	SD	Yes
4	8	3.7	2.5	−32	PR	Yes
	9	2.2	0.7	−68	PR	Yes
	10	1.1	NV	−100	CR	Yes
	11	1.1	0.5	−54	PR	Yes
5	12	3.1	1.4	−55	PR	Yes
	13	1.5	1.1	−27	SD	Yes
6	14	5.0	2.6	−48	PR	Yes
7	15	4.0	3.1	−23	SD	Yes
	16	1.3	1.8	−39	PR	Yes
	17	0.5	0.5	0	SD	No
8	18	1.8	0.8	−56	PR	Yes
	19	1.0	0.7	−30	PR	Yes
	20	1.8	0.5	−72	PR	Yes
	21	1.9	NV	−100	CR	Yes
	22	1.3	NV	−100	CR	Yes
	23	1.3	NV	−100	CR	No
9	24	2.6	0.8	−69	PR	Yes
	25	2.6	NV	−100	CR	Yes
	26	2.4	NV	−100	CR	Yes
10	27	2.0	1.6	−20	SD	Yes
	28	2.0	1.2	−40	PR	Yes
	29	2.0	1.6	−20	SD	Yes
11	30	1.5	1.2	−20	SD	Yes
	31	1.2	1.2	0	SD	Yes
12	32	1.0	1.7	+70	PD	No
13	33	4.7	2.8	−40	PR	No
14	34	7.7	5.5	−29	SD	No

All lesions were positive for FDG uptake before chemotherapy and had no FDG uptake after chemotherapy. All lesions required pathological sampling for inclusion in the analysis.
NV Not visualized, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

to those whose tumors do not. Similarly, a decrease in FDG uptake, usually quantified using standardized uptake values (SUV), has been shown to correlate with a degree of tumor response to neoadjuvant therapy for esophageal[22,23] and rectal[24] cancer. However, even in patients classified as responders, there was generally still residual FDG uptake and residual viable tumor cells. In contrast, as our study was aimed at determining whether patients whose tumors had complete metabolic response on treatment still required treatment for residual tumor, the appropriate endpoint was complete pathologic response.

The failure of FDG-PET to detect residual viable tumor after chemotherapy may be due to reduction of lesion size, decreased FDG uptake by tumor cells and/or heterogeneity in tumor destruction. It is well established that detection of metastatic lesions from colorectal carcinoma by FDG-PET is directly related to size of lesions, with low sensitivity for lesions less than 1 cm in diameter.[25] After chemotherapy, 16 of 34 lesions (47%) in this study were either undetected by CT or MRI, or if detected, were smaller than 1 cm. Thus, reduction in size may be an important reason why lesions were not seen by FDG-PET after treatment, but still contained viable tumor. A second reason may relate to the effect of chemotherapy on tumor cell FDG uptake. Chemotherapeutic agents may reduce FDG uptake by altering tumor glucose metabolism. Akhurst et al.[26] found that the FDG uptake of hepatic lesions was significantly lower after neoadjuvant chemotherapy compared to lesions

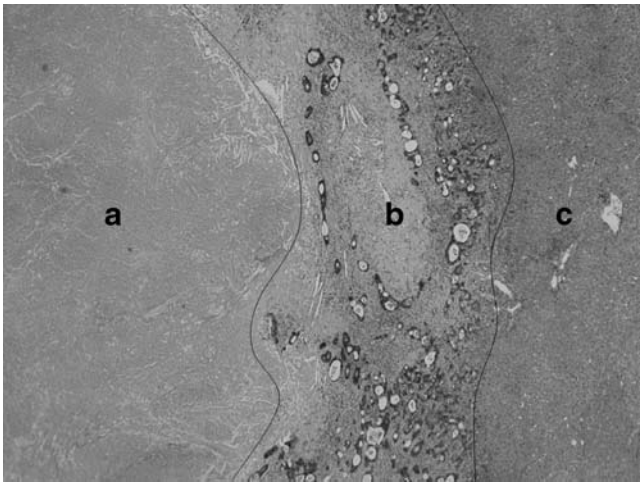

Figure 2 Hematoxylin and eosin (H&E)-stained histological section from a hepatic metastasis from colorectal cancer, demonstrating viable tumor present only at the marginal interface (*b*) between tumor (*a*) and normal liver parenchyma (*c*) (original magnification ×4).

of patients who did not receive neoadjuvant chemotherapy. This difference correlated with a decrease in the activity of the glycolytic enzyme hexokinase of tumor cells. Finally, after chemotherapy, tumors may display heterogeneous FDG uptake—for instance, the center may become necrotic and the periphery may remain FDG avid. Given that this metabolically active rim is often thin, underestimation of FDG uptake may occur in tumors up to 4 cm in diameter if a necrotic center is present.[21] Effectively, the tumor has been reduced to a size below current FDG-PET sensitivity. As an additional factor, the relatively high FDG uptake in normal hepatic parenchyma makes it more difficult to detect those lesions with a partial metabolic response resulting in uptake only slightly greater than that of the liver.

The relationship between FDG uptake and pathologic response has not been well studied in patients with hepatic metastases from colorectal cancer. We were only able to find two other studies that have examined this question in similar patient populations. Goshen et al.[27] used PET/CT to evaluate response to neoadjuvant irinotecan plus bevacizumab in a small study of seven patients. Of the 20 hepatic lesions identified, 13 had complete metabolic response post-chemotherapy. Only 10 of these 13 lesions subsequently underwent pathologic sampling, and five of these contained no identifiable viable tumor at the time of resection. Despite this, all seven patients in the study still had some residual tumor elsewhere in the liver. Takahashi et al.[28] performed a study in which FDG-PET was performed only after chemotherapy. They found that 20 (of a total of 27) hepatic lesions in seven patients were negative on FDG-PET at that time. Of these 20 lesions, 15 (75%) demonstrated no viable tumor. Critically, however, as none of the patients had baseline FDG-PET before commencement of neoadjuvant chemotherapy, it is unclear how many of these lesions were FDG-avid before chemotherapy. It should be noted that studies in other malignancies have emphasized that reliable prediction of response by FDG-PET is dependent upon demonstrating change in metabolic activity from the baseline scan in the subsequent follow-up scan.[21] The relationship between disappearance of colorectal cancer liver metastases on CT scan and disappearance of cancer pathologically was examined by Benoist et al.[29] who found that complete disappearance of colorectal liver metastases on CT scan after neoadjuvant chemotherapy also correlates poorly with complete pathologic response. As noted previously, in six of seven lesions which disappeared on CT scan *and* had a complete metabolic response on FDG-PET in our study, viable tumor was still detected histologically.

The present study is the largest and most complete analysis of patients and lesions treated with neoadjuvant chemotherapy, evaluated at baseline and posttreatment by FDG-PET, then assessed pathologically. Nonetheless, there are a number of limitations of this study. The study is still relatively small. Neoadjuvant chemotherapy was not standardized, either with respect to type or duration of treatment. These limitations restrict our ability to identify factors that might indicate that a complete pathologic response has occurred in a patient whose lesions have converted from detectable to undetectable on FDG-PET. Likewise, based on our data, one cannot determine whether use of the newer biologic agents bevacizumab and cetuximab is associated with a greater likelihood of complete metabolic response, and/or an increased likelihood of complete pathologic response if complete metabolic response does indeed occur.

Despite the limitations of our study, the results have clear implications for the surgical management of patients with metastatic colorectal cancer in the liver. Complete metabolic response on FDG-PET with current chemotherapy regimens is infrequently associated with complete pathologic response. Based on a small subset of seven lesions, this seems to be true even if the lesions also respond completely on CT or MRI. Therefore, at the present time, such findings should not dissuade medical and surgical oncologists from proceeding to potentially curative resection. Whenever feasible, the area containing the originally identified lesion should be resected whether or not the lesion is still detectable by CT or MRI. Our results are also supportive of the strategy to resect initially unresectable tumors when they are downsized to the point where they are resectable. The alternate strategy of continuing chemotherapy to the maximum response is more likely to result in circumstances in which it is difficult to identify the site of residual tumors and may, in addition, result in hepatotoxicity that limits the extent of resection as we and others have shown.[30,31] In the event that a specific lesion cannot be resected, then locoregional ablative therapy may be the most appropriate treatment.

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Authors' Disclosures of Potential Conflicts of Interest None

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Laparoscopic and Open Distal Pancreatic Resection for Benign Pancreatic Disease

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Abstract The aim of the study is to provide comparisons of the perioperative outcomes between open and laparoscopic distal pancreatic resection (DPR) for benign pancreatic disease. From 2002 and 2005, there were 28 patients (16 open, 12 laparoscopic) with a mean age of 52 who had presumptive diagnoses of benign pancreatic lesions. Pathology was neuroendocrine tumor (nine and five), mucinous cystic neoplasm (three and three), symptomatic pancreatic pseudocyst (two and two), and others (two and two). The mean operative time was 278 vs 212 min (p=0.05), the estimated blood lost was 609 vs 193 ml (p=0.01), and the success rate of preoperative intent for splenic preservation was 17 vs 62% (p=0.08) in the open and laparoscopic groups, respectively. Two patients (16%) were converted to an open procedure. There was no perioperative mortality. The mean hospital stay and total perioperative morbidity were 10.6 vs 6.2 days (p=0.001) and nine vs two events (p=0.03) in the open and laparoscopic groups, respectively. Ten of 12 patients (83%) with laparoscopic DPR had adequate oral intake within 72 h post operatively in contrast to 2 of 16 (12.5%) patients in the open DPR group (p= 0.0001). Laparoscopic DPR is technically feasible, safe, and associated with less perioperative morbidity and a shorter hospital stay than open DPR. In centers with the appropriate expertise, laparoscopic DPR should be considered the procedure of choice for putative benign lesions of the pancreatic body and tail.

Keywords Laparoscopic · Pancreatic resection · Pancreatic tumor · Outcomes

Introduction

Since the introduction of minimally invasive surgery, laparoscopy has been used extensively for tissue diagnosis and the staging of intra-abdominal malignancies.[1–3] Recently, there has been a growing interest in the therapeutic role of laparoscopy for both hollow and solid organ diseases. The advantages of laparoscopic surgery over their open counterpart have now been repeatedly demonstrated in the published literature.[4,5] These advantages include procedure-related safety and effectiveness and the reduction of postoperative morbidity. The laparoscopic approach has been incorporated in the field of solid-organ resection. The outcome of laparoscopic splenectomy, adrenalectomy, and nephrectomy have been similarly positive and encouraging.[6–9] Despite the current growing interest in laparoscopic pancreatic resection, the role of laparoscopic distal pancreatic resection (DPR) is unclear due to the paucity of published literature. The aim of this study was to provide one of the first comparisons of the perioperative outcome of open DPR to laparoscopic DPR for benign pancreatic disease.

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Materials and Methods

After Institutional Review Board approval, we conducted a retrospective study of all patients who underwent laparoscopic and open DPR from June 2002 to June 2005 performed at Oregon Health and Science University, Port-

land, Oregon. All clinical, operative and pathological data were abstracted from patient's medical records and tabulated. Other laparoscopic pancreatic procedures and surgery for pancreatic malignancy were excluded from this study.

Surgical Technique

Laparoscopic DPR is performed with a four-trocar technique. The location of the trocar placement depends on the body habitus of the patient. We have obtained maximum flexibility by utilizing three 12-mm trocars and one 5-mm trocar. A 12-mm camera trocar is placed lateral to the umbilicus; a second 12-mm trocar is placed about 10 to 12 cm lateral to the camera port. This will be the surgeon's working right hand. This trocar can also accommodate the flexible laparoscopic ultrasound probe and the articulated endo GIA staple. A third 12-mm working trocar is placed in the left upper quadrant, approximately 10 cm above the camera port. This port can be converted into a hand port if needed during the operation. A 5-mm assistant trocar is placed on the left anterior axillary line that allows the assistant to assist in suction and retraction. An additional port can be added for retracting the left lobe of the liver and stomach. After a thorough abdominal inspection and a survey is performed, the conduct of our laparoscopic DPR consists of a series of defined steps that includes: (a) lesser sac exposure, (b) splenic flexure and mesocolon mobilization from the spleen and the body of the pancreas, (c) intraoperative laparoscopic ultrasound, (d) pancreatic mobilization, (e) pancreatic transaction with or without individual splenic artery and vein isolation and ligation, and (f) pancreatic stump management. The lesser sac is entered by mobilizing the greater omentum from the greater curvature of the stomach within the right epiploic arch. Complete splenic mobilization from the diaphragmatic attachment is intentionally not performed. This attachment will serve as a lateral retraction to prevent the movement of the spleen, especially as the operating table will be tilted at several angles at each specific step of the operation to enhance laparoscopic view. After intraoperative ultrasound examination, pancreatic mobilization begins with inferior pancreatic dissection and extends laterally. The dissection is then continued superior to the border of the pancreas to create a circumferential dissection around at the tail of the pancreas. The use of a hand port will make this step easier and safer to perform. Once the circumferential dissection is achieved, the next step is to move the dissection plane medially. If the pancreas is thin, pancreatic parenchymal transection (including splenic vein and artery) can be done in one or two staplings. If the pancreas is thick, the splenic artery, vein, and pancreatic parenchyma are taken separately. The main pancreatic duct is routinely identified and oversewn with 3-O prolene in the figure-eight fashion. If the pancreatic duct cannot be identified, a row of 3-O prolene figure-of-eight sutures are placed at the end of the pancreas. The sutured pancreatic stumps are then covered with fibrin glue or "tissuseal" using a laparoscopic delivery system

Statistic Analysis

The Fisher's exact and *t* tests were used to compare binary outcome variables. Any *p* value less than 0.05 was considered statistically significant.

Results

From 2002 to 2005, there were 28 patients that underwent DPR at the Oregon Health and Science University in Portland, Oregon. There were 16 men and 12 women with the mean age being 52.5 years (age range, 23 to 81). Sixteen patients underwent open and 12 patients underwent laparoscopic DPR. Their preoperative comorbidities are shown in Table 1. Two patients in the open group and one patient in the laparoscopic group had previous exploratory laparotomy in another institution. In the open group, one patient had truncal vagotomy and gastrojejunostomy, and the other patient had laparotomy with cholecystectomy. In the laparoscopic group, the patient had a laparotomy with appendectomy. All patients underwent preoperative computer tomography scan and endoscopic ultrasound. A presumptive diagnoses of benign pancreatic lesions were made based on preoperative clinical, endoscopic, and

Table 1 General Demographic of Patients that Underwent Open and Laparoscopic Distal Pancreatic Resection for Benign Disease

	Open DPR (n=16)	Laparoscopic DPR (n=12)	P value
Age (years)	51.5	53.4	0.56
Gender (male)	12 (75%)	4 (33%)	0.03
BMI kg^2/m	27.5	26.4	0.86
Diabetes mellitus	2 (13%)	2 (17%)	0.76
Hypertension	3 (19%)	5 (42%)	0.18
COPD	2 (13%)	0	0.20
Cardiac disease	1 (5%)	0	0.57
Previous laparotomy	2 (13%)	1 (8%)	0.44
History of pancreatitis	5 (31%)	6 (50%)	0.34
ASA Class			
1	2 (13%)	1 (8%)	0.45
2	10 (62%)	10 (84%)	
3	4 (25%)	1 (8%)	

COPD Chronic obstructive pulmonary disease, *ASA* American Society of Anesthesia

radiolographic features. For the laparoscopic DPR group, laparoscopic intraoperative ultrasound was an integral part of the laparoscopic procedure.

Intraoperative Characteristics

Open DPR Group

There were 12 men and 4 women with the mean age of 51.5 years old (age range, 26–75) and a mean BMI of 27.5 kg^2/m (age range, 18–45). The mean operative time was 278 min (range, 180–420) with an estimated blood loss of 609 ml (range, 150–2,000). The operative time and the estimated blood loss for the two patients who had previous laparotomy were 360 and 240 min and 900 and 500 ml, respectively. Fifteen patients also had splenectomy.

The success rate of preoperative intent for splenic preservation was 17% (one out of six patients).

The pathology was nine neuroendocrine tumors (six functioning and three nonfunctioning), a mucinous cystadenoma in three, symptomatic pancreatic pseudocyst in two, intraductal papillary mucinous neoplasm in one, and sinistral portal hypertension from chronic pancreatitis in one. Table 2 demonstrates the tumor characteristics and Table 3 demonstrates the intraoperative characteristics of this group of patients with open DPR.

Laparoscopic DPR Group

There were four men and eight women with the mean age of 53.4 years old (age range, 23–81) and a mean BMI of 26.4 (age range, 21–36). The mean operative time was 212 min (range, 60–360, $p=0.05$), with an estimated blood loss of 193 ml (range, 25–800, $p=0.012$). The operative time and the estimated blood loss for the patient who had previous laparotomy were 240 min and 800 ml, respectively. The success rate of preoperative intent for splenic preservation was 62% (five out of eight patients), $p=0.08$. The final pathology demonstrated neuroendocrine tumors in five patients (nonfunctioning in three and functioning in two), a mucinous cystadenoma in three, symptomatic pancreatic pseudocyst in two, and pancreatic ductal dysplasia and sinistral portal hypertension in one each. Two patients (16%) required conversion to an open procedure secondary to intraoperative hemorrhage. In these two patients, all of the mobilization required for DPR was accomplished laparoscopically. In one patient with a nonfunctional neuroendocrine tumor, the conduct of the laparoscopic operation was challenging due to numerous adhesions secondary to alcohol-induced chronic pancreatitis. Intraoperative bleeding occurred at the time of pancreatic parenchymal transaction with secondary injury to the splenic vessel. The total operating time for this patient was 300 min, with an estimated blood loss of 500 ml. The second patient, with a mucinous cystadenoma, had a straightforward intraoperative conduct until a stapler malfunction at the time of pancreatic parenchymal transaction. This resulted in bleeding which required conversion to an open procedure. For this patient, the total operating time was 180 min with an estimated blood loss of 200 ml. Both of the patients with conversion to open surgery had a splenectomy. Of note, a hand port was used in eight (67%) patients in the laparoscopic DPR. The comparison of tumor characteristics and intraoperative characteristics between open and laparoscopic DPRs are shown in Tables 2 and 3.

Table 2 Tumor Characteristics of Patients that Underwent Open and Laparoscopic Distal Pancreatic Resection for Benign Disease

	Open DPR ($n=16$)	Laparoscopic DPR ($n=12$)	*P* value
Tumor size (cm, mean)	3.4	3.4	0.09
Type of lesions			0.72
Neuroendocrine tumor	9 (56%)	9 (42%)	
Functioning	6	3	
Nonfunctioning	3	2	
Mucinous cystadenoma	3 (34%)	3 (25%)	
Pancreatic pseudocysts	2 (6%)	2 (17%)	
Chronic pancreatitis	1 (2%)	1 (8%)	
Others	1 (2%)	1 (8%)	

Table 3 Operative Characteristics Between Open and Laparoscopic Distal Pancreatic Resection Group

	Open DPR ($n=16$)	Laparoscopic DPR ($n=12$)	*P* value
Operative times (min, mean)	278	212	0.05
Estimated blood lost (ml, mean)	609	193	0.01
Success of preoperative intent for splenic preservation	1/6 (17%)	5/8 (62%)	0.08
Hand port use	N/A	8 (67%)	N/A
Conversion to open	N/A	2 (16%)	N/A
Hospital stays (days, mean)	10.6	6.2	0.01

Hospital Stays and Perioperative Outcome

Open DPR Group

There was no perioperative mortality or reoperation in either group. There were a total of nine perioperative morbidity events in the open DPR group. Seven patients (44%) experienced more than one perioperative morbidity.

There were three wound infections and two pulmonary embolisms, and one patient had atrial fibrillation. An intra-abdominal abscess and delayed gastric perforation occurred in one patient each. These were treated with percutaneous drainage. We attributed the intra-abdominal abscess to a pancreatic leak. The mean hospital stay was 10.6 days (range, 7 to 19 days).

Laparoscopic DPR Group

There were two perioperative morbidity events in the laparoscopic DPR group, with one urinary tract infection and one low-output pancreatic leak. The pancreatic leak occurred in the patient who had laparoscopic DPR and splenectomy for sinistral portal hypertension. His surgical drain was noted to have increased output and a fluid amylase level of 1,000 u/l on postoperative day 3. He continued to make good progress clinically, his drain's output was less than 30 ml/day, and was removed prior to discharge to home on day 5. Ten out of the 12 patients in the laparoscopic DPR group (85%) achieved adequate oral intake within 72 h postoperatively. In contrast, only 2 out of 16 patients (12.5%) in the open DPR group achieved adequate oral intake within 72 h postoperatively (p= 0.0001). The two patients in the laparoscopic DPR group who had their oral intake delayed were the two patients who had their operation converted to an open DPR.

The mean hospital stay, including the two patients that were converted to an open procedure, was 6.2 days (range, 3 to 16 days, p=0.008). If these two patients were excluded, the mean hospital stay was 4.5 days (as demonstrated in Table 4).

Discussion

Advanced laparoscopic procedures for both hollow and solid organs are now being performed at an increasing rate in many surgical centers. In experienced hands and selected patients, advanced laparoscopic surgery may be performed safely and efficaciously with several advantages over their open counterparts.[6,8]

Table 4 Perioperative Characteristics Between Open and Laparoscopic Distal Pancreatic Resection Groups

	Open DPR	Laparoscopic DPR	*P* value
Total perioperative morbidity events[a]	9	2	0.03
Wound infection	3	0	0.17
Pulmonary embolism	2	0	0.32
Atrial fibrillation	1	0	0.57
Pancreatic leaks	1	1	0.83
Intra-abdominal abscess	1	0	0.38
Gastric perforation	1	0	0.38
Urinary tract infection	0	1	0.57

[a] Seven patients experienced >1 postoperative morbidity.

The laparoscopic approach in pancreatic surgery has been traditionally confined to its diagnostic and staging role. Progression to therapeutic laparoscopy in pancreatic surgery has evolved at a slower rate for a number of reasons. First, pancreatic resection was traditionally known for its association with significant perioperative morbidity and mortality. This was, in part, due to higher surgical complexity and the potential for postoperative pancreatic leaks. Second, pancreatic disease is relatively uncommon in contrast to other gastrointestinal (GI) pathology. In many centers that perform high volume pancreatic surgery primarily for pancreatic cancer, advanced laparoscopic surgery has not been routinely practiced. Therefore, an appropriately powered prospective study would be difficult to perform. However, with the refinement in both laparoscopic technical skill and instrumentation, the interest in therapeutic laparoscopic pancreatic surgery has been steadily growing.[10,11]

The two largest reports on therapeutic laparoscopy for the pancreas are from Park and Heniford[12] and Mabrut et al.[13] These two papers detail the full spectrum of laparoscopic pancreatic surgery. These are seminal reports with good outcomes; however, no comparison to open pancreatic surgery was available. Prior to these reports, series were small and descriptive in nature.[14–17] The aim of this study was to provide one of the first comparisons of the perioperative outcome of open DPR to laparoscopic DPR for benign pancreatic disease.

Both our report and others have consistently demonstrated that laparoscopic DPR is feasible and safe.[10,11,18,19] Our series of laparoscopic DPR has 12 patients. In the Mabrut et al. series, there were a total of 127 patients involving 25 European centers with the annual median of three cases. Intention to treat for laparoscopic DPR was greater than 85%. Our series demonstrated a success rate of 83% (10 out of 12 patients). Two patients in the laparoscopic group were converted to open procedure due to intraoperative bleeding at the stage of pancreatic parenchyma transection with the endostapler. Similarly, the success rate of preoperative intent for splenic preservation was 62% in our laparoscopic DPR group.

This retrospective study was designed to compare open and laparoscopic DPR for benign pancreatic disease to demonstrate equality. Without a randomized, prospective study this will remain a difficult challenge. However, the direct comparison of intraoperative characteristics did demonstrate the superiority of laparoscopic DPR. Operating time was shorter, and the estimated blood lost was less in the laparoscopic group as compared to

the open DPR group. In addition, the laparoscopic DPR group had a lower perioperative morbidity, and this group of patients were able to achieve adequate oral intake earlier than a similar group of patients undergoing open DPR.

Perioperative outcomes and the length of hospital stay were used to compare the advantages of open versus laparoscopic DPR. As noted by several tertiary referral centers, our series also reports zero mortality rates in either group of patients with DPR.[12,13,16] This is a reflection of a high volume pancreatic surgery practice and the advances in modern perioperative management. Perioperative morbidity, however, remains significant.[20] It is difficult to compare the perioperative morbidity rate in one series to the others. For example, Lillemoe et al. reported the largest current series of open DPRs. The overall perioperative morbidity was 31%. The most frequent perioperative complication was new onset diabetes (8%) and reoperation (6%). In our series, neither complication was encountered. Of note, our laparoscopic group did not experience wound infection or cardiopulmonary complications. Further, most of the laparoscopic DPR patients (85%) were able to start oral intake earlier and achieved an adequate volume by 72 h postoperatively. We believe that the laparoscopic DPR patients were likely to have less incisional pain due to their smaller laparoscopic incisions. This allowed them to ambulate earlier and minimize the risk of deep vein thrombosis and pulmonary embolic events. Laparoscopic DPR patients may also use less narcotic pain medication which, together with less bowel manipulation intraoperatively and early ambulation postoperatively, accounts for an earlier return of bowel function and oral intake. The combination of these factors may have allowed them to be discharged home earlier when compared to open DPR. We acknowledge, however, that in the absence of a prospective randomized study, our clinical observations in this retrospective study are at best speculative. One of the strengths of our current series is that one group served as the control to the other group, therefore making comparison more objective. The other objective assessment of procedure-related outcome is the length of hospital stay, which in our study demonstrated advantages in the laparoscopic group.

Many methods have been described and used in the attempt to decrease the incidence of pancreatic fistula following pancreatic resection. No one method has been proven better than the others.[21–24] We routinely used an articulated endostapler for pancreatic parenchyma transaction and nonabsorbable suture to close the pancreatic duct. More recently, we have used fibrin glue as an adjunct to minimize the incidence of pancreatic leaks. The incidence of pancreatic leaks and fistula is 1 out of 12 (8%) and 1 out of 16 (6%) in the laparoscopic and open groups, respectively. In the face of pancreatic resection without reconstruction, this incidence is comparable to other series. In the Mabrut series, the rate of pancreatic fistula was 13% in patients with laparoscopic DPR and 18% in patients with laparoscopic DPR and spleen preservation. Pancreatic fistula is likely to be faced by the pancreatic surgeon, regardless of the approach and the method utilized to close the pancreatic stump.

As in any retrospective study, there are limitations to our current study. Surgery performed at the beginning of the study period was more likely to be open case. As our experience in laparoscopic pancreatic surgery became more refined, more cases were being performed laparoscopically. Patients who had previous multiple abdominal operations may have been previously elected to be approached open. Operative time may have been longer due to this selection bias. However, in our current practice, there is no absolute contraindication to the laparoscopic approach except malignancy.

The role of laparoscopic pancreatic resection for pancreatic malignancy is controversial due to lack of data on the operative conduct and oncologic integrity. We do not currently perform laparoscopic resection if the presumed preoperative diagnosis is cancer. Mabrut has demonstrated that with the currently available preoperative imaging studies, only 4% of their patients with presumed benign pancreatic disease were found to have malignancy at final histology. Presumptive diagnoses of benign pancreatic lesions were made based on preoperative clinical, endoscopic, and radiologic features. Diagnostic intraoperative ultrasounds are used as an integral part of our laparoscopic and open pancreatic surgery practice. If intraoperative biopsy suggests a high likelihood of malignancy, an open procedure will be conducted.

In summary, to our knowledge, our current series is one of the first comparisons of the perioperative outcome of open DPR to laparoscopic DPR for benign pancreatic disease. Our results demonstrate that laparoscopic DPR can be performed safely. However, a prospective randomized study is needed to validate the safety profile and the long-term outcomes of this minimally invasive approach before it can be widely accepted.

Conclusion

Laparoscopic DPR is technically feasible, safe, and associated with earlier oral intake and a shorter hospital stay than open DPR. Splenic preservation remains a technical challenge, regardless of approach. In centers with the appropriate expertise, laparoscopic DPR should be considered as the procedure of choice for putative benign lesions of the pancreatic body and tail.

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Esophageal Manometry and Clinical Outcome After Laparoscopic Nissen Fundoplication

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Abstract
Introduction The outcome after laparoscopic Nissen fundoplication can be assessed by either clinical symptoms or objective tests. Outcomes from objective tests are often held in higher regard than clinical data when determining the merits, or otherwise, of various antireflux surgery procedures. In this study, we sought to determine whether there is a relationship between postoperative symptoms and parameters measured by esophageal manometry to determine whether early postoperative esophageal manometry is a useful investigation for the routine assessment of post fundoplication outcome.
Methods One hundred and forty-three patients who had undergone a laparoscopic Nissen fundoplication, clinical follow-up at 3 months and 5 years after surgery, and esophageal manometry at 3 months after fundoplication as part of routine follow-up in 1 of 5 clinical trials were studied. Nineteen of these patients also underwent manometry 5 years after fundoplication. Postoperative symptoms were prospectively determined by applying a standardized questionnaire, which assessed dysphagia, heartburn, bloat symptoms, and overall satisfaction using analog scales. Patients were classified into different groups according to the analog scores for clinical symptoms. Correlations between clinical and postoperative manometry outcomes were sought.
Results No significant associations were found between parameters measured by esophageal manometry (lower esophageal sphincter resting and residual relaxation pressures, peristaltic amplitude and normal peristaltic propagation) and clinical parameters (dysphagia, heartburn, bloating, and overall satisfaction) for all time points—3 months postoperative manometry vs symptoms at 3 months and 5 years, 5 years postoperative manometry vs symptoms at 5 years, except for a weak (r=−0.17, p=0.042) correlation between the percentage of successfully propagated swallows at 3 months and dysphagia for solids at 5 years.
Conclusion Postoperative esophageal manometry parameters at 3 months and 5 years after surgery were not associated with any clinically important differences in the postoperative symptoms of heartburn, dysphagia, bloat or with overall satisfaction with the surgical outcome. The routine use of esophageal manometry to assess the outcome after Nissen fundoplication does not predict clinical outcome.

Keywords Esophageal manometry · Clinical outcome · Laparoscopic Nissen fundoplication

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Introduction

Laparoscopic Nissen fundoplication is the most commonly applied surgical procedure for the treatment of gastroesophageal reflux disease.[1] Its indications are well-established, and follow-up studies now report a good clinical outcome for approximately 90% of patients at 5 years after surgery.[2,3] Outcome after antireflux surgery can be assessed in several ways. Arguably, the most relevant outcome for patients undergoing surgery is their overall satisfaction with the outcome, as this indicates whether they believe they made the correct decision to undergo surgery. Other clinical outcomes include specific symptoms of reflux, e.g., heart-

burn and regurgitation or side effects such as post fundoplication dysphagia or gas bloat. Most studies report the latter, more specific clinical outcomes, as these are often of greatest interest to surgeons and other medical practitioners.

Outcome can also be assessed by objective tests. Relevant investigations after antireflux surgery include gastroscopy, barium meal examination, 24-h ambulatory pH monitoring, and esophageal manometry. It has been suggested that these tests provide objective, reproducible outcomes, which are less likely to be influenced by bias from either the patient or the surgeon than might occur with the assessment of clinical symptoms. Hence, a reasonable proposition is that data from objective tests of outcome is superior to clinical data, which is obtained from interviewing patients who have undergone surgery. However, it is important that any objective evaluation of surgical outcome is still relevant to individual patients, and that it is a good predictor of clinical success.

Previous studies have shown that when esophageal manometry is performed before surgery, in particular laparoscopic Nissen fundoplication, it does not reliably predict which patients will have a good outcome after surgery.[4,5] Furthermore, it is uncertain whether the outcomes, which are measured by esophageal manometry after fundoplication are clinically relevant, and the relationship between postoperative manometry and postoperative symptoms has not been well studied.

Hence, the aims of this study were to determine whether there is a relationship between postoperative symptoms, clinical success, and parameters, which can be measured by postoperative esophageal manometry, and to determine whether any postoperative manometric parameters can be identified which will predict a greater likelihood of success or otherwise at short-term and longer-term clinical follow-up.

Patients and Methods

Patient Selection

Patients who had undergone a laparoscopic Nissen fundoplication, esophageal manometry 3 months after surgery, and standardized clinical follow-up 3 months and 5 years after surgery were included in this study. These patients were all included in one of five previously reported randomized controlled trials, which have investigated the aspects of laparoscopic antireflux surgery technique.[6–10] Between August 1994 and October 1999, 425 patients were enrolled into 1 of these trials. Of these patients, 310 underwent a laparoscopic Nissen fundoplication, 70 with division of the short gastric blood vessels, and 240 without. They all underwent clinical follow-up using an identical standardized clinical questionnaire, and where possible, esophageal manometry was performed 3 months after surgery as part of the follow-up protocol. Of these patients, 297 had reached 5 years follow-up at the time of the current study.

From these patients, a cohort was identified who met the following criteria for inclusion in the current study: (1) underwent a laparoscopic Nissen fundoplication, (2) underwent standardized clinical follow-up at 3 months after surgery, (3) at 5 years after surgery, and (4) underwent esophageal manometry at 3 months after fundoplication as part of routine follow-up within one of the trials, i.e., not for the investigation of clinical symptoms. Patients who had incomplete clinical data at either 3 months or 5 years after surgery (12 patients lost to clinical follow-up, 9 deceased, 3 incomplete clinical data at 5 years) and patients who had not undergone initial manometry at 3 months (130 patients) were excluded. Data from esophageal manometry studies, which were performed outside the clinical trial protocol, i.e., for clinical reasons, were not analyzed in this study.

One hundred and forty-three patients met the inclusion criteria. Seventy-nine (55%) were men and 64 (45%) were women, and their median age was 49 years (range 21–74). Nineteen of the patients also underwent esophageal manometry 5 years after fundoplication as part of follow-up within another study—this data was also included in a secondary analysis.

Operative Technique

Our technique for laparoscopic Nissen Fundoplication has been described previously.[11] In brief, a loose 1.5 to 2 cm 360° wrap was constructed. Hiatal repair was routine, and for most patients this was performed using posterior hiatal sutures. A subgroup underwent anterior hiatal repair. Short gastric blood vessels were not routinely divided.[6] The 52 patients who underwent division of these vessels all underwent this step as part of the first randomized trial protocol.

Esophageal Manometry

All patients were fasted for 6 h before manometry, and antireflux medication was discontinued 2 (H2 blockers and prokinetics) or 5 (proton pump inhibitors) days earlier, if necessary for concurrent pH monitoring. Esophageal manometry was carried out with an eight-lumen water-perfused catheter incorporating a sleeve sensor (Dentsleeve, Adelaide, Australia) with transducer pressure signals recorded on a polygraph chart recorder (Model 7D; Grass Instrument, Massachusetts, USA). The high-pressure region was located by the station pull-through technique and the center of the sleeve was positioned at the high-pressure region. The high-pressure region basal pressure was measured over a 5-min period. Ten wet swallows (5 ml each) were assessed for the extent of propagation and

amplitude of primary peristalsis. The parameters assessed in this study were "lower esophageal sphincter" resting pressure, "lower esophageal sphincter" residual relaxation pressure, distal esophageal peristaltic amplitudes, and the percentage of wet swallows which propagated the full length of the esophagus.

Postoperative Clinical Assessment

Postoperative symptoms were assessed prospectively by applying a standardized questionnaire 3 months and 5 years after surgery. Dysphagia and heartburn were assessed using visual analog scales from 0 to 10 (0=no dysphagia, 10= total dysphagia; 0=no heartburn 10=total heartburn). The presence or absence of symptoms suggesting gas bloat was determined by asking patients whether they experienced discomfort because of upper abdominal distension or a sensation of bloating of the upper abdomen (yes vs no). Overall satisfaction with the surgical outcome was determined using a 0 to10 visual analog scale (10=completely satisfied, 0=totally unsatisfied).

Patients were classified into different groups according to the analog scores of clinical symptoms. Dysphagia was classified as significant dysphagia (analog score 5–10) vs mild or no dysphagia (analog score 0–4). Heartburn was classified as troublesome heartburn (analog score 5–10) vs mild or no heartburn (analog score 0–4), and satisfaction was classified as satisfied (analog score 7–10) vs not satisfied (analog score 0–6).

Patients were also classified into different groups according to the outcome measured by esophageal manometry 3 months after surgery. Patients were divided into groups according to the pressure measured in the distal esophageal high-pressure zone: resting pressure of 25 mmHg or more vs 25 mmHg or less, and residual relaxation pressure of 10 mmHg or more vs 10 mmHg or less. Patients were also divided into two groups according to the peristaltic contraction amplitude measured in distal esophagus: 40 mmHg or more vs 40 mmHg or less. These parameters were compared to the dysphagia score. Patients were also divided into two groups according to the distal esophageal high-pressure zone: resting pressure of 10 mmHg or more vs 10 mmHg or less, and this data was compared to the heartburn score and other reflux-related outcomes. The cutoff points for each of these analyses were determined according to values used previously in our department.

Data Analysis

Unless otherwise stated, all figures are expressed as the mean and 95% confidence intervals. Changes in manometric outcomes before vs after surgery were assessed using the Wilcoxon matched pairs test. Differences in postoperative manometric outcomes for different groups of patients were assessed using the Mann–Whitney U test. Spearman's correlation coefficient was used to determine correlations between analog scores of clinical symptoms and postoperative manometry outcomes.

Results

Esophageal Motility Before vs After Surgery

Mean lower esophageal sphincter resting pressure increased from 8.2 (6.8–9.5) mmHg before laparoscopic Nissen fundoplication to 24.2 (22.1–26.3) mmHg at 3 months after surgery ($p<0.001$). There was also a significant increase in lower esophageal sphincter residual relaxation pressure from 1.4 (0.8–2.0) mmHg to 11.4 (10.1–12.6) mmHg ($p<0.001$). In the 19 patients who underwent a further manometry study 5 years after surgery, the lower esophageal sphincter resting pressure was 19.4 (14.5–24.3) mmHg at 5 years compared to 21.9 (18.8–25.1) mmHg at 3 months ($p=0.35$), and the lower esophageal sphincter residual relaxation pressure was 7.4 (4.7–10.0) mmHg compared to 8.9 (6.2–11.6) mmHg ($p=0.25$) at 3 months.

Postoperative Manometry vs Symptoms 3 Months After Nissen Fundoplication

Three months after surgery, there was no significant difference in the lower esophageal sphincter resting pressure, lower esophageal sphincter residual relaxation pressure or esophageal body motility between patients with vs without significant dysphagia, significant heartburn or bloating symptoms, and for patients who were satisfied vs unsatisfied (Table 1). There was also no significant correlation between any of the manometric outcomes and symptoms scores 3 months after surgery (Table 2).

Postoperative Manometry Outcomes at 6 Months vs Postoperative Symptoms at 5 Years

There was no significant difference in the lower esophageal sphincter resting pressure, lower esophageal sphincter residual relaxation pressure or esophageal body motility measured 3 months after fundoplication and the symptom scores 5 years after fundoplication (Table 3). There was a weak ($r=-0.17$, $p=0.042$) correlation between the percentage of swallows, which were successfully propagated at manometric assessment at 3 months, and the analog dysphagia score for solids at 5 years clinical follow-up. There were no other significant correlations between other manometric outcomes at 3 months and the symptom scores 5 years after surgery (Table 4).

Table 1 Manometric Outcomes for Patients with vs Without Symptoms at 3 Months After Fundoplication

	Dysphagia score for solids		p^a	Heartburn score		p^a	Bloat symptoms		p^a	Satisfaction score		p^a
	0–4	5–10		0–4	5–10		Absent	Present		7–10	0–6	
No. of patients	102	41		134	9		72	71		123	20	
LES resting pressure (mmHg)	24.4 (22.1–26.8)	22.2 (18.8–25.5)	0.36	23.9 (21.9–25.8)	22.7 (11.6–33.7)	0.67	28.8 (21.1–26.6)	23.7 (21.0–26.5)	0.93	23.6 (21.6–25.6)	24.7 (18.1–31.3)	0.86
LES residual relaxation pressure (mmHg)	11.0 (9.5–12.5)	11.5 (9.2–13.8)	0.53	11.3 (10.0–12.6)	9.3 (5.4–13.3)	0.64	10.5 (8.9–12.0)	11.8 (9.8–13.8)	0.50	10.8 (9.5–12.0)	13.4 (8.8–17.9)	0.23
Peristaltic contraction amplitude in distal esophagus	75.3 (67.5–83.2)	80.4 (69.3–91.6)	0.38	75.2 (68.9–81.4)	100.9 (58.7–143.1)	0.12	77.5 (68.6–86.4)	76.1 (66.7–85.4)	0.72	75.7 (69.0–82.4)	83.6 (63.4–103.7)	0.51
% successful esophageal peristalsis	83.8 (78.7–88.9)	80.0 (70.6–89.3)	0.59	82.7 (78.1–87.2)	83.3 (58.1–108.5)	0.84	83.5 (77.3–89.7)	81.9 (75.3–88.5)	0.62	83.0 (78.3–87.7)	81.0 (67.1–94.9)	0.62

Values are mean (95% confidence intervals).
LES: lower esophageal sphincter.
[a] Mann–Whitney *U* test.

Table 2 Correlations Between Manometry Outcomes and Analog Symptom Score Scores 3 Months After Laparoscopic Nissen Fundoplication

Comparison	*r* value	*p* value
LES resting pressure vs heartburn	−0.03	0.74
LES resting pressure vs dysphagia for solids	−0.07	0.37
LES resting pressure vs satisfaction	0.01	0.87
LES residual relaxation pressure vs heartburn	−0.12	0.17
LES residual relaxation pressure vs dysphagia for solids	0.16	0.06
LES residual relaxation pressure vs satisfaction	−0.07	0.42
Peristaltic contraction amplitude in distal esophagus vs heartburn	0.12	0.17
Peristaltic contraction amplitude in distal esophagus vs dysphagia for solids	0.09	0.28
Peristaltic contraction amplitude in distal esophagus vs satisfaction	0.03	0.72
% successful esophageal peristalsis vs heartburn	−0.07	0.40
% successful esophageal peristalsis vs dysphagia for solids	−0.07	0.41
% successful esophageal peristalsis vs satisfaction	0.06	0.49

LES: lower esophageal sphincter.

Postoperative Manometry Outcomes at 5 Years vs Postoperative Symptoms at 5 Years

There was no significant difference in the manometry parameters measured 5 years after fundoplication and the symptom scores at 5 years (Table 5). There were also no significant correlations between manometric outcomes and the symptom scores at 5 years.

3 Months Postoperative Manometry Outcomes by Various Categories vs 3 Months and 5 Years Dysphagia Scores for Solids

When the data set was reclassified according to high vs low lower esophageal resting and residual relaxation pressures, and peristaltic amplitudes, no significant differences was seen for the solid food dysphagia scores for the various groups at 3 months and 5 years follow-up (Table 6).

3 Months Postoperative Manometry Outcomes by Various Categories vs 3 Months and 5 Years Heartburn Scores

All but 4 (2.8%) patients had a resting lower esophageal sphincter pressure of more than 10 mmHg at esophageal manometry 3 months after surgery. The other four all had a pressure of 10 mmHg. At 3 months follow-up, all four patients were free of reflux symptoms (heartburn score=0). At 5 years follow-up, two had no reflux (heartburn score=0), one had occasional mild reflux symptoms, which did not require any treatment, and one had mild reflux symptoms, which were

Table 3 Manometric Outcomes for Patients 6 Months After Surgery vs Symptoms 5 Years After Fundoplication

	Dysphagia score for solids		p^a	Heartburn score		p^a	Bloat symptoms		p^a	Satisfaction score		p^a
	0–4	5–10		0–4	5–10		Absent	Present		7–10	0–6	
No. of patients	101	42		119	24		38	105		109	34	
LES resting pressure (mmHg)	23.6 (21.3–25.8)	24.4 (20.4–28.3)	0.52	23.5 (21.4–25.5)	25.4 (19.6–31.2)	0.59	25.3 (20.5–30.2)	23.2 (21.2–25.2)	0.71	23.5 (21.5–25.6)	24.6 (19.4–29.8)	0.76
LES residual relaxation pressure (mmHg)	10.9 (9.4–12.4)	11.8 (9.5–14.1)	0.33	11.1 (9.7–12.5)	11.2 (8.4–13.9)	0.67	11.5 (8.6–14.4)	11.0 (9.6–12.4)	0.93	12.3 (9.2–15.4)	10.8 (9.4–12.1)	0.44
Peristaltic contraction amplitude in distal esophagus	73.4 (66.1–80.8)	84.9 (72.1–97.7)	0.10	74.6 (67.5–81.8)	87.5 (73.5–101.5)	0.05	73.2 (62.9–83.5)	73.1 (70.2–86.0)	0.80	76.7 (69.2–84.2)	77.2 (64.6–89.8)	0.75
% successful esophageal peristalsis	83.4 (78.1–88.8)	81.0 (72.4–89.5)	0.38	80.9 (75.7–86.1)	91.7 (84.6–98.8)	0.10	86.0 (77.6–94.4)	81.5 (76.2–86.9)	0.31	82.7 (77.6–87.8)	82.7 (72.9–92.4)	0.97

Values are mean (95% confidence intervals).
LES: lower esophageal sphincter.
[a] Mann–Whitney *U* test.

Table 4 Correlations between Manometry Outcomes 6 Months After Fundoplication and Analog Symptom Score Scores 5 Years After Laparoscopic Nissen Fundoplication

Comparison	*r* value	*p* value
LES resting pressure vs heartburn	−0.05	0.59
LES resting pressure vs dysphagia for solids	0.03	0.76
LES resting pressure vs satisfaction	0.04	0.60
LES residual relaxation pressure vs heartburn	−0.06	0.49
LES residual relaxation pressure vs dysphagia for solids	0.13	0.13
LES residual relaxation pressure vs satisfaction	−0.02	0.77
Peristaltic contraction amplitude in distal esophagus vs heartburn	0.11	0.21
Peristaltic contraction amplitude in distal esophagus vs dysphagia for solids	0.09	0.28
Peristaltic contraction amplitude in distal esophagus vs satisfaction	0.02	0.78
% successful esophageal peristalsis vs heartburn	0.05	0.56
% successful esophageal peristalsis vs dysphagia for solids	−0.17	0.042
% successful esophageal peristalsis vs satisfaction	0.05	0.56

LES: lower esophageal sphincter.

controlled using a H2 receptor antagonist. All four of these patients were highly satisfied with the overall outcome at 5 years (satisfaction score $= 10 \times 2, 8 \times 2$).

Discussion

Laparoscopic techniques for the treatment of gastroesophageal reflux are now well-established, and the majority of patients who undergo a laparoscopic fundoplication report a good clinical outcome.[2,3] Unfortunately, some patients are unsatisfied after surgery, usually because they develop either recurrent reflux or troublesome side effects. The commonest procedure performed is the Nissen fundoplication. This is followed by a low incidence of recurrent reflux, although this is traded off against a higher risk of side effects, such as dysphagia and gas bloat, compared to partial fundoplication procedures.[7]

Further clinical research is required to define the optimal surgical technique. Such research must measure outcome. The outcomes, which can be measured, include clinical symptoms, quality of life, and the results of objective tests. The latter include gastroscopy, barium contrast x-rays, pH monitoring, and esophageal manometry. The choice of some outcome measures is obvious. For example, barium meal x-ray is the best method for determining whether or not a hiatus hernia is present, and pH monitoring provides important data about acid reflux.

Esophageal manometry provides functional information. In particular, it assesses esophageal body peristalsis and lower esophageal sphincter function. Relevant to the

Table 5 Manometric Outcomes for Patients With vs Without Symptoms 5 Years After Fundoplication

	Dysphagia score for solids			Heartburn score			Bloat symptoms			Satisfaction score		
	0–4	5–10	p^a	0–4	5–10	p^a	Absent	Present	p^a	7–10	0–6	p^a
No. of patients	16	3		18	1		7	12		17	2	
LES resting pressure (mmHg)	20.3 (14.5–26.2)	21.7		19.5 (14.6–24.4)	33		21.3 (10.3–32.2)	19.6 (13.5–25.6)	0.80	19.8 (14.6–25.0)	23.5	
LES residual relaxation pressure (mmHg)	8.1 (5.2–11.0)	8.0		7.2 (4.6–9.8)	17		6.6 (0.2–13.0)	8.3 (5.3–11.4)	0.42	7.4 (4.6–10.1)	10.5	
Peristaltic contraction amplitude in distal esophagus	64.4 (49.8–79.0)	93.3		66.8 (53.5–80.2)	107		66.1 (46.0–86.3)	70.6 (50.6–90.6)	0.84	69.2 (56.0–82.4)	66.5	
% successful esophageal peristalsis	80 (69.0–91.0)	100		82.2 (72.1–92.4)	100		81.4 (57.9–105.0)	84.2 (72.8–95.5)	0.97	84.1 (74.2–94.0)	75	

Values are mean (95% confidence intervals).
LES: lower esophageal sphincter.
[a] Mann–Whitney *U* test.

outcome assessment after fundoplication is the lower esophageal sphincter resting and residual relaxation pressures, and it is claimed that these pressures are relevant to the assessment of post fundoplication dysphagia.[12] In particular, Anvari and Allen reported that patients in whom esophageal manometry studies after surgery showed incomplete relaxation of the lower esophageal sphincter were more likely to experience dysphagia after fundoplication.[12] Furthermore, in a small series of patients studied previously using video manometry, we also found a weak correlation between dysphagia for solid food and lower esophageal sphincter residual relaxation pressure (r=0.37, p=0.04).[13]

Previous studies have also shown that laparoscopic Nissen fundoplication is followed by an increase in lower esophageal sphincter resting and residual relaxation pressures,[14,15] and the results of our current study are consistent with these findings. Other studies, including randomized trials, have shown that the increase in lower esophageal sphincter resting pressure is less after various anterior partial fundoplication procedures, and this is associated with a lower incidence of dysphagia.[9,16,17] This evidence supports a role for esophageal manometry in the assessment of physiological and anatomical changes at the gastroesophageal junction after fundoplication.

Various studies have examined esophageal manometry parameters before and after fundoplication and have compared this to some short-term clinical outcomes.[4,12,18] Some of these studies have suggested that the magnitude of the resting lower esophageal sphincter pressure is associated with the risk of postoperative dysphagia. However, these studies have reported conflicting results with some supporting a role for postoperative esophageal manometry[4,12] and others not.[18]

In our current study, we have investigated the role of esophageal manometry in the assessment of patients after Nissen fundoplication and compared this to both short-term and longer-term clinical follow-up. In doing this, we have not evaluated the role of preoperative esophageal manometry. Rather, we investigated the value of early postoperative esophageal manometry in the assessment of outcome, its ability to identify patients who are at risk of a poorer

Table 6 3 Months Postoperative Manometry Outcomes by Categories vs 3 Months and 5 Years Dysphagia Scores for Solids

	LES resting pressure (mmHg)		p	LES residual relaxation pressure (mmHg)		p	Peristaltic contraction amplitude in distal esophagus		p
	≤25	>25		≤10	>10		≤40	>40	
No. of patients	91	52		77	66		24	119	
3 months dysphagia score for solids	2.9(2.2–3.5)	2.3(1.5–3.0)	0.29	2.3(1.6–2.9)	3.1(2.3–3.8)	0.08	1.9(0.7–3.0)	2.8(2.3–3.3)	0.11
5 years dysphagia score for solids	2.6(2.0–3.1)	3.1(2.3–4.0)	0.34	2.7(2.0–3.3)	2.9(2.2–3.5)	0.37	2.6(1.6–3.7)	2.8(2.3–3.3)	1.00

Values are mean (95% confidence intervals).
LES: lower esophageal sphincter.
[a] Mann–Whitney *U* test.

clinical outcome, and we have extended this analysis to determine the ability of early postoperative esophageal manometry to predict long-term clinical outcome. Our data analysis showed no clinically significant relationship between data from manometry studies and clinical outcomes at either short-term or long-term follow-up. In particular, there was no relationship between lower esophageal sphincter pressures and dysphagia after surgery. These results suggest that routine postoperative esophageal manometry is a poor predictor of symptomatic outcome and it should not be used to determine the quality of the laparoscopic antireflux surgery performed.

To ensure that the manometry data was not biased by disproportionately selecting patients who had undergone manometry for the assessment of specific clinical problems, we only included patients who underwent manometry as part of a clinical trial, i.e., for nonclinical reasons. This included patients who did not have a clinical problem and some patients who were symptomatic. However, the evaluation of esophageal manometry studies undertaken primarily for research does mean that most patients had a good clinical outcome, and hence, only a minority had a poor outcome. This was most obvious when considering the small number of patients who had a lower esophageal sphincter pressure of 10 mmHg or less. Hence, the small number of patients with a poor outcome could reduce the apparent sensitivity of manometry and its ability to identify patients with a poor outcome. Nevertheless, the aim of our study was to determine manometry's usefulness as a tool for the routine assessment of post fundoplication patients within the context of research trials, and in this, its role appears to be limited.

Although all patients underwent clinical follow-up 5 years after surgery, only 19 underwent manometry at this time point. Hence, the data analysis for the 5-year post fundoplication manometry studies needs to be interpreted with much more caution as there is a risk of a type II error with analysis of this aspect of the data set. Nevertheless, the manometric outcomes at 5 years were consistent with those measured at 3 months.

What then is the role of esophageal manometry in patients undergoing surgery for reflux? Our study has not evaluated its role in preoperative assessment, and we continue to use it routinely in the work-up of patients for fundoplication. In particular, it is used to identify patients with achalasia, whose treatment is different, and to identify patients with significant esophageal dysmotility, for whom we would usually recommend a partial fundoplication. Despite this, there are studies which report that esophageal motility does not influence the outcome in patients who undergo a laparoscopic Nissen fundoplication.[5,20] Esophageal manometry also has a role in the investigation of some patients who have a poor outcome after antireflux surgery. For instance, it can demonstrate secondary achalasia in patients with esophageal obstruction, and if an absence of sphincter tone is demonstrated in patients with reflux symptoms, this might lead to additional tests such pH monitoring. It may also still be a useful research tool, as it provides information, which may inform the physiological assessment of antireflux procedures within clinical research protocols.

Our current study also has not addressed whether more sophisticated studies might prove helpful, particularly in the area of dysphagia. For instance, such measures as lower esophageal ramp pressures and assessment of lower esophageal sphincter bolus transit may have a role to play.[13] It seems, however, that esophageal manometry has a limited role in the routine evaluation of patients who have undergone a laparoscopic fundoplication, as it is difficult to find postoperative parameters which are associated with short-term or long-term clinical success after laparoscopic Nissen fundoplication. Other measures of outcome, including clinical symptoms, are almost certainly more relevant to the assessment of outcome of this type of surgery.

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Esophagectomy for End Stage Achalasia

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Abstract Esophageal myotomy is the standard primary therapy for achalasia. However, reports on long-term results of myotomy have suggested a deterioration of outcome over time with many patients presenting with end stage disease several years after esophagomyotomy. Eight patients who had previously undergone esophagomyotomy for achalasia presented with recurrent or worsening symptoms, and after preoperative evaluation, were treated by esophagectomy via laparotomy and right thoracotomy. The mean age at the time of myotomy was 52 years (range 18 to 62 years), and the mean time until esophagectomy was 12.5 years (range 2 to 18 years) after the initial myotomy. The median time until esophagectomy was performed after myotomy was 14 years. All patients in this series gained weight (mean, 23 pounds; range, 9 to 42 lbs) following esophagectomy, and none of the patients complained of dysphagia at follow-up or developed stricture. There were no major complications (including anastomotic leak) or deaths in this series. Five of the patients have been followed a mean of six years and remain well. Esophagectomy is a safe and appropriate treatment option in the setting of recurrent and end stage achalasia.

Keywords Achalasia · Esophagomyotomy · Esophagectomy

Achalasia is a primary motility disorder of the esophagus characterized by loss of peristalsis in the esophageal body and failure of relaxation of the lower esophageal sphincter.[1] The disease affects 0.5 to 1 per 100,000 population in the United States.[1] Treatment modalities are palliative as there is no cure for achalasia. Several treatment options have been utilized, including medical, endoscopic and surgical therapies, with varying degrees of success.[2,3] The esophageal myotomy, first described by Heller[4] in 1913, has been shown to be the superior first line therapy for achalasia in the early stages and is the most frequently performed surgical procedure for the disorder.[5]

Advancements in minimally invasive techniques have made the laparoscopic esophageal myotomy the preferred treatment for achalasia.[6] The increasing performance of laparoscopic antireflux procedures has made the anatomy more familiar to many general and gastrointestinal surgeons allowing for more frequent performance of laparoscopic esophageal myotomy.[7] Additionally, some thoracic surgeons are proponents of the thoracoscopic technique.[8]

The early results of esophageal myotomy performed by either technique have been favorable.[5,8,9] However, the failure rate for laparoscopic myotomy has been cited to be 10 to 20% requiring additional procedures to control persistent or recurrent symptoms.[10] Furthermore, some reports on the long-term results of esophageal myotomy have suggested a deterioration of outcome over time.[11–14] Therefore, with an increasing number of laparoscopic and thoracoscopic esophageal myotomies being performed, general and thoracic surgeons should be prepared to encounter more frequent myotomy failures and understand the appropriate evaluation and management of these patients.

The appropriate treatment for patients who present with recurrent dysphagia following esophageal myotomy is a topic of debate. Repeat myotomy may be an option for some. However, many patients who develop recurrent dysphagia present with weight loss and a dilated, "burned out" esophagus and are not amenable to preservation of the esophagus. Resection is generally recommended for these patients. This paper outlines the evaluation we use for patients who present with recurrent dysphagia, our indications for resection, and the outcomes following esophageal resection for patients with end stage disease treated at our institution.

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Patient Material

Eight patients with recurrent dysphagia were included in this series, and all were originally treated by one surgeon (J.D.R.) via transthoracic Heller myotomy several years before the resection. The original myotomy began several centimeters above the gastroesophageal junction with the longitudinal muscle being divided until the stomach was reached. The circular fibers were carefully divided, but the myotomy was not carried distally onto the stomach. An antireflux operation was not performed in any of the patients. All patients did well initially, although the youngest patient in the series developed recurrent symptoms after 18 months. Two patients subsequently underwent repeat operation: one patient at 20 months after the initial procedure via a laparoscopic approach and one patient at 5 years postmyotomy through a repeat thoracotomy. Neither patient benefited from reoperation.

Patients presenting to our institution with recurrent or worsening symptoms following esophageal myotomy undergo a full evaluation including contrast esophagography, flexible endoscopy, and esophageal manometry. The findings on contrast esophagography of patients in this series generally included a dilated esophagus often with a sigmoid configuration. The size of the diseased esophagi ranged from 4 to 16 cm. The youngest patient in the series had minimal dilation to 4 cm; the remainder had a markedly dilated esophagus. Five were sigmoid shaped and two were flask shaped.

Flexible esophagoscopy was performed in all patients to exclude stricture or cancer and to ensure that a recurrent muscular tightening had not occurred. All patients had retained food particles, and no mechanical causes of obstruction were noted. Biopsies were performed, and only one case of squamous metaplasia was noted.

Repeat manometry was done in five patients and generally demonstrated aperistalsis of the esophageal body.

Patients were not considered candidates for esophagectomy unless they had longstanding disease refractory to any other form of management. All patients had undergone attempts at dilation which were unsuccessful, and two patients had a second unsuccessful myotomy. Patients considered for resection had esophageal dilation with sigmoid or flask shaped esophagus.

All patients were treated by an esophagectomy utilizing an open approach via laparotomy and right thoracotomy. The esophagus was removed at a level above the azygos vein, and the anastomosis was performed in the chest using the mobilized stomach as the conduit.

Results

The average age at the time of myotomy was 52 years (range 18 to 62 years) of age, and the esophagectomy was required an average of 12.5 years after the initial myotomy (range 2 to 18 years). The median time to esophagectomy after myotomy was 14 years. Four patients were over 70 years of age at the time of their esophageal resection.

There were no anastomotic leaks, episodes of aspiration, or other major complications in this series, and all patients were discharged directly to their home postoperatively. None of the patients have complained of dysphagia at follow-up or developed stricture. There have been no complications associated with reflux esophagitis; however, routine endoscopy has not been performed for the surveillance of Barrett's esophagus. Only one patient has noted mild eructation.

There were no deaths associated with the operation either in the hospital or in the posthospitalization period. Three of the patients died of unrelated causes at 4, 6, and 7 years postesophagectomy. The remaining patients have been followed a mean of 6 years and remain well. Many of these patients had sustained considerable weight loss prior to their resection, but all had gained weight at 1 year postresection (Table 1). The mean weight gain at 1 year was 23 lbs (range 9 to 42 lbs).

An unexpected finding was the presence of occult carcinoma in two patients. One patient had an invasive squamous cell carcinoma in the midesophagus that was not appreciated at endoscopy, likely due to the presence of

Table 1 Clinical Features of Patients Requiring Esophagectomy

Age at Myotomy	Years to Esophagectomy (Postmyotomy)	Preoperative Weight (lbs) (Preoperative esophagectomy)	Postoperative Weight (lbs) at 1 year (Postesophagectomy)
18	2	133	171
49	14	118	160
53	18	149	163
56	16	114	138
56	11	133	145
58	6	161	170
61	15	112	140
62	18	130	148

retained food particles. Another patient had areas of diffuse carcinoma in situ located in plaque-like patches throughout the squamous-lined mucosa of the esophagus. In neither patient were these findings thought to be related to the dysphagia. Both patients remained cancer-free with long-term surveillance.

Discussion

Modalities for the treatment of achalasia have included medication, endoscopic dilation, and surgical therapies.[1–4] Studies comparing medical and endoscopic therapies to surgical management have demonstrated superior results with surgery.[5,13,14] Today, the most frequently performed first line treatment for achalasia is modification of the lower esophageal sphincter by myotomy first described by Heller[4] in 1913.

One criticism of the early data on esophageal myotomy is that many studies lack long-term follow-up. In fact, it has been cited that there is a paucity of data in the literature with regard to long-term outcomes of patients following myotomy regardless of the operative technique.[8] The data from this series emphasize the importance of continued follow-up as the average time for patients to present with end stage disease was 12.5 years. Additionally, the finding of esophageal cancer in two of the eight patients in this series echoes the significance of long-term surveillance. Furthermore, a study by Torbey et al.[15] demonstrated that 33% of patients who failed surgical myotomy did not seek treatment despite recurrence of symptoms underscoring the necessity for continuing follow-up.

This paper presents eight patients returning with end stage achalasia several years following esophageal myotomy (two of whom failed repeated myotomy) and confirms that myotomy may fail over time. Other reports on the long-term outcome of myotomy suggest that there is a deterioration of the early favorable results over time. Gaissert[11] reported one of the largest cohorts of patients who underwent esophageal myotomy for achalasia with follow-up of more than 10 years; 93% of the patients had good or excellent results at "short term" follow-up of 6 months, but only 63% reported good or excellent long-term results. The mean follow-up in this cohort of 52 patients was over 11 years.

Similarly, Malthaner reported 95% excellent results at 1 year, 77% good to excellent results at 5 years, but only two thirds remained improved at 20 years. No patients reported excellent results at 20 years.[13] Bloomston noted similar deterioration over time in a series of 112 patients.[14] Surgeons undertaking operative treatment of these patients should advise patients of this possibility of recurrent dysphagia and counsel them to seek attention even if they are not in an active surveillance or follow-up program.

We believe that patients presenting with recurrent dysphagia following myotomy should undergo a full workup including contrast esophagography, endoscopy, and manometry. This evaluation will aid in determining the etiology for the recurrence. Recurrent symptoms following myotomy have been attributed to the following: inadequate myotomy, healing of the myotomy, development of reflux esophagitis, obstruction due to fundoplication, incorrect original diagnosis, carcinoma, and development of paraesophageal hiatal hernia.[16]

The appropriate management of patients with recurrent dysphagia after initial myotomy is a therapeutic challenge. Some authors have advocated repeat esophagomyotomy for patients who present with persistent or recurrent dysphagia.[6,10] These reports described patients with symptoms that developed within the early follow-up period, and the etiology for recurrence in the majority of cases was inadequate initial myotomy or myotomy fibrosis. These situations are generally indications for an attempt at repeat myotomy. However, 20% of patients failed a second myotomy requiring further operative therapy.[10]

There are few reports in the literature dealing with the long-term results of reoperative achalasia surgery.[17,18,20] Ellis et al.[17] reported that only two thirds of patients undergoing repeat esophagomyotomy were improved long term. Similarly, our series included two patients who had a second myotomy (one laparoscopic, one transthoracic), both of which failed. Both patients were markedly improved by resection. Notably, all of the patients in the Ellis report who underwent esophagectomy, as well as all of the patients in our series, were improved following resection.

Indications for resection in our series included megaesophagus or sigmoid esophagus, esophageal aperistalsis, and multiple failed myotomies. The finding of cancer of the esophagus during the workup of recurrent dysphagia would obviously be an indication for resection as well as peptic stricture from reflux. Other, larger reports have found the most frequent indications for esophagectomy in the setting of achalasia to be tortuous megaesophagus (64%), failure of prior myotomies (63%), and associated reflux stricture (7%), and favorable outcomes were observed following resection.[19]

Other authors have also favored resection for patients with recurrent or end stage disease. Miller et al.[20] felt the that decision for esophagectomy should be individualized with attempted repeat myotomy for patients with minimal evidence of prior myotomy and without marked esophageal dilation. However, resection was recommended for patients with more than one failed myotomy or a markedly dilated esophagus characteristic of end-stage disease. Good to excellent results were reported in 91% of their patients.[20] Devaney et al.[19] noted that 95% of patients could eat

normal food without postprandial regurgitation at an average of 38 months following esophagectomy, and Orringer[16] reported that all but one of 25 patients could eat foods of normal consistency without postprandial regurgitation an average of 30 months follow-up after resection. Devaney et al. commented that in 93 patients who underwent esophagectomy for recurrent dysphagia, the only factor correlating significantly with a poor functional outcome was a history of multiple esophageal operations. These reports would support our hypothesis that esophagectomy is an appropriate alternative to repeat esophagomyotomy in the setting of recurrent dysphagia and end stage achalasia. We believe this is especially true if the patient has a sigmoid esophagus.

Major perioperative complications or deaths were not observed in our series, which admittedly is not representative actual risks of morbidity and mortality associated with esophagectomy performed in the US today. Perhaps the observed death and complication rate of zero in our series is related to the relatively small number of patients (n=8). The largest series of patients undergoing esophagectomy for achalasia in the literature included 93 patients and cited a perioperative mortality of 2%. Major complications associated with esophagectomy in that report included anastomotic leak (10%), recurrent laryngeal nerve injury (5%), delayed mediastinal bleeding (2%), and chylothorax (2%).[19]

Some long-term effects of esophagectomy have also been discussed in the literature. These would include nocturnal regurgitation, dumping symptoms such as postprandial diarrhea and cramping, and anastomotic stricture. The dumping symptoms are usually well controlled with diphenoxylate.[16] Anastomotic dilation can be performed on an outpatient basis and has been effective therapy for anastomotic stricture. The largest series reported 50% of patients undergoing at least one postoperative esophageal dilation when an aggressive approach to any degree of cervical dysphagia was employed.[19] None of the patients in our series experienced any of these symptoms or required dilation. Once again, our observations may be related to small sample size.

The results of our series correlates with the other authors in finding esophagectomy to be an appropriate option for treatment in the setting of recurrent and end stage achalasia. All patients in this series had good or excellent long-term functional results following resection. All patients in this series experienced weight gain following esophagectomy. There were no perioperative complications suggesting that the procedure is a safe alternative, even in patients of advanced age. In retrospect, they likely should have been offered resectional therapy sooner. Additionally, two patients in this series were found to have carcinoma at the time of esophagectomy for end stage disease indicating a need for long-term follow-up of all patients with achalasia who have not undergone esophagectomy.

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Long-Term Results (6–10 Years) of Laparoscopic Fundoplication

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Abstract Most papers report excellent results of laparoscopic fundoplication but with relatively short follow-up. Only few studies have a follow-up longer than 5 years. We prospectively collected data of 399 consecutive patients with gastroesophageal reflux disease (GERD) or large paraesophageal/mixed hiatal hernia who underwent laparoscopic fundoplication between January 1992 and June 2005. Preoperative workup included symptoms questionnaire, videoesophagogram, upper endoscopy, manometry, and pH-metry. Postoperative clinical/functional studies were performed at 1, 6, 12 months, and thereafter every other year. Patients were divided into four groups: GERD with nonerosive esophagitis, erosive esophagitis, Barrett's esophagus, and large paraesophageal/mixed hiatal hernia. Surgical failures were considered as follows: (1) recurrence of GERD symptoms or abnormal 24-h pH monitoring; (2) recurrence of endoscopic esophagitis; (3) recurrence of hiatal hernia/slipped fundoplication on endoscopy/barium swallow; (4) postoperative onset of dysphagia; (5) postoperative onset of gas bloating. One hundred and forty-five patients (87 M:58 F) were operated between January 1992 and June 1999: 80 nonerosive esophagitis, 29 erosive esophagitis, 17 Barrett's esophagus, and 19 large paraesophageal/mixed hiatal hernias. At a median follow-up of 97 months, the success rate was 74% for surgery only and 86% for primary surgery and 'complementary' treatments (21 patients: 13 redo surgery and eight endoscopic dilations). Dysphagia and recurrence of reflux were the most frequent causes of failure for nonerosive esophagitis patients; recurrence of hernia was prevalent among patients with large paraesophageal/mixed hiatal hernia. Gas bloating (causing failure) was reported by nonerosive esophagitis patients only. At last follow-up, 115 patients were off 'proton-pump inhibitors'; 30 were still on medications (eight for causes unrelated to GERD). Conclusion confirms that laparoscopic fundoplication provides effective, long-term treatment of gastroesophageal reflux disease. Hernia recurrence and dysphagia are its weak points.

Keywords Gastroesophageal reflux disease · Laparoscopic fundoplication · Paraesophageal hernia

Introduction

Laparoscopic antireflux surgery has become an increasingly popular form of therapy for gastroesophageal reflux disease (GERD) since its introduction in 1991;[1] it has been reported that 29,000 and 34,800 of such operations have been performed in the United States in 1998 and 1999, respectively, and although, no official data are available, the same trend has been observed in most European and Western countries. The reasons for the widespread success of laparoscopic antireflux surgery lie in a comparable control of GERD symptoms obtained with a lower postoperative pain and discomfort for the patients, a reduced hospital stay, and a similar morbidity when compared to open surgery. A large body of medical literature supports these findings[2–6] at least in the short-/mid-term period (1–5 years): few reports deal with the long-term results of laparoscopic antireflux surgery;[7,8] however, there is a lack of information on the crucial issue of the durability of the early positive results obtained by laparoscopic antireflux surgery.

The aim of this study was to report the long-term outcome of a cohort of patients who underwent laparoscopic antireflux surgery at a single unit and were followed up for a minimum of 6 years.

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Materials and Methods

Patient Population

Data were collected prospectively on all patients who underwent laparoscopic fundoplication for GERD or paraesophageal (type II) or mixed (type III) hiatal hernia with/without GERD at our Department between June 1992 and June 2005. Patients were divided into four groups based on the severity of their disease: GERD with nonerosive esophagitis (Group A), erosive esophagitis (Group B), Barrett's esophagus (Group C), and large paraesophageal or mixed hiatal hernia (one third of the stomach or more herniated in the chest; Group D).

Preoperative Work-Up

GERD symptoms GERD symptoms were recorded using a standard questionnaire. Severity and frequency of heartburn, acid regurgitation, chest pain, and dysphagia were scored, and final scores were calculated by adding the severity of each symptom (0=none, 2=mild, 4=moderate, 6=severe) to its frequency (0=never, 1=occasionally, 2=once a month, 3=every week, 4=twice a week, 5=daily).

Esophageal manometry Esophageal manometry was performed using a pneumohydraulic perfusion system. The lower esophageal sphincter (LES) pressure was calculated by averaging the pressures recorded by four side holes positioned at the same level, 90° apart, withdrawing the catheter twice using a motorized pull-through technique at a constant speed of 1 mm/s from the stomach to the esophageal body passing through the high-pressure zone (the LES pressure was the average of eight pressure recordings). The LES pressure was calculated as the midexpiratory pressure at the respiratory inversion point. Abdominal and overall LES lengths were calculated as the average distance from the point where the pressure trace rises steadily by at least 2–3 mmHg with respect to the intragastric baseline pressure, the respiratory inversion point (abdominal part), and the point where the pressure trace falls below the esophageal baseline pressure (overall length). Amplitude, duration, and coordination of esophageal contractions generated by swallowing 10 ml of water were also recorded along the esophageal body.[9] Esophageal body peristalsis was defined as being defective whenever the amplitude of the distal esophageal contractions was <30 mmHg, or there were more than 30% of simultaneous or ineffective (interrupted, dropped) esophageal contractions.

Twenty-four-hour pH monitoring Twenty-four-hour pH monitoring of the distal esophagus was used to evaluate abnormal GERD by positioning a glass electrode 5 cm above the upper border of the LES, according to the standard procedure used in our laboratory and described elsewhere.[10] The glass probe was connected to a portable solid state monitor (Digitrapper, Medtronics), and the acid reflux parameters assessed were: total percentage of the time when the pH was <4, percentage of the time when the pH was <4 while upright, percentage of the time when the pH was <4 while supine, number of episodes with a pH<4, number of episodes with a pH<4 lasting more than 5 min, and duration of the longest episode with a pH<4.

Endoscopy Endoscopy was performed under light sedation with midazolam. Any redness and velvety texture in the esophagus was assumed to indicate nonnative esophageal mucosa, but it was classified as Barrett's epithelium (BE) only after histological confirmation (hematoxylin and eosin [H&E]) of the presence of intestinal metaplasia (IM). BE was distinguished as short- (<3 cm) and long segment (≥3 cm). Any esophagitis, ulcers, or strictures was recorded; esophagitis was classified according to Savary.[11]

Barium swallow Barium swallow was obtained preoperatively in all patients to evaluate objectively, to measure, and classify the presence and the type of hiatal hernia (type I, sliding hernia; type II, paraesophageal hernia; type III, mixed hernia).

Histology and definitions of outcome in patients with BE Biopsy samples were fixed in 10% buffered formalin, embedded in paraffin, and stained with H&E. BE was defined as the presence of fully developed goblet cells (i.e., IM). IM was semiquantitatively scored pre- and postoperatively as the percentage of intestinalized glands detected in each set of biopsy samples (0=no IM; 1=intestinalized glands covering 1–30% of the biopsy samples; 2=IM covering 30–70% of the biopsy samples; 3=IM exceeding 70% of the biopsy samples).

The following conventional nomenclature was used to describe the clinicopathological outcome of BE: (a) "regression" when no intestinalized glandular mucosa was documented in any of the postsurgical biopsy samples. This meant both gastric-type mucosa without IM and native-type esophageal squamous epithelium; (b) "partial regression" meant a decreasing prevalence of intestinalized glands in the whole set of biopsy samples obtained at follow-up endoscopy; (c) "persistence (with no changes)" when the extension of IM detected at follow-up endoscopy remained the same as before surgery; (d) "progression" when the prevalence of intestinalized glands detected at follow-up endoscopy was higher than in the pre surgical biopsy set. According to the Padova international classification, noninvasive neoplasia (NiN; i.e., dysplasia) was classified as low and high grade.[12]

Surgical Technique

Principles of surgical technique included reduction of the hernia (when present), primary closure of the crura with one or two stitches calibrated over a 40 French bougie and 360-degree fundoplication sutured with three nonabsorbable stitches, and including the esophageal wall in the two distal sutures. Since 1995, the section of two to four short gastric vessels to mobilize the gastric fundus and obtain a floppy, and well-shaped fundoplication was routinely added to the procedure.

A partial fundoplication was performed only in patients with severe abnormality of esophageal peristalsis.

Starting from 1996, a U-shaped double mesh (Goretex® and propylene) was used to reinforce the suture of the pillars, in case of a large hiatal defect (as usually observed in paraesophageal hernias).

Postoperative Evaluations

Patients were seen at the outpatient clinic at 1, 6, 12, and 24 months after surgery and thereafter every other year: at each control, patient's symptoms were evaluated using the symptom questionnaire. Patients were also asked if they were taking antisecretive drugs (PPI). A barium swallow was obtained at 1 month and 2 years; physiologic studies (esophageal manometry and 24-h pH monitoring) were repeated at 6 months. Upper gastrointestinal endoscopy was obtained at 1 and 3 years. Thereafter, barium swallows, physiologic studies, and endoscopy were repeated whenever the patients complained of GERD symptoms recurrence or in case of new symptom onset. Patients with Barrett's esophagus entered in a standard follow-up protocol with endoscopy and biopsy every 2 years.

Definition of Surgical Failures

Failures were defined in case of:

1. Recurrence of GERD symptoms (score >10) either typical or atypical
2. Abnormal 24-h pH monitoring (De Meester score > 14.74) even in asymptomatic patients
3. Recurrence (or not healing) of endoscopic esophagitis
4. Recurrence of hiatal hernia or upward migration of the fundoplication in the chest (even in asymptomatic patients demonstrated by endoscopy or barium swallow)
5. Postoperative onset of dysphagia
6. Postoperative onset of gastrointestinal symptoms related to the fundoplication (like gas bloating)

Statistical Analysis

Data are expressed as medians and interquartile ranges. Proportions were compared using the chi-square or Fisher's exact test. Continuous variables were compared using the Mann–Whitney*U* test. Recurrence-free estimates were calculated by the Kaplan–Meier method, and comparisons were drawn using the log-rank test. A p value below 0.05 was considered significant.

Results

Demographics and Preoperative Assessment

One hundred and forty-five patients [87 men, 58 women, median age 48 years, interquartile range (IQR): 25–70] were operated between January 1992 and June 1999. These patients formed the study population. There were 80 patients with nonerosive esophagitis, 29 with erosive esophagitis, 17 with Barrett's esophagus, and 19 with paraesophageal or mixed hiatal hernia.

Floppy Nissen fundoplication was performed in 87.6% (127/145) of patients, a posterior partial fundoplication (270°) according to Toupet in 12.4% (18/145).

In 136/145 (93.7%) patients, the operation was completed laparoscopically with a conversion rate of 6.3%. Mortality as a result of the operation was nil. The intraoperative complication rate was 0.7% (one gastric lesion). Postoperative complications occurred in 15/145 (10.3%) patients (Table 1).

Six patients died during follow-up, three within 6 years (at 7, 38, 44, 82, 104, and 125 months) for unrelated causes; one patient was lost to follow-up after a 24-month follow-up.

The median preoperative symptom score was 14 (IQR: 2–24), and the symptoms' duration was 36 months (IQR: 6-169). The median duration of the operation was 175 min (IQR: 111–244). The median hospital stay was 4 days (IQR: 3–9). The median follow-up was 97 (IQR: 71–143) months.

Surgical Failures

Failure occurred in 37 (25%) patients. Hernia recurrence or slipping of the fundoplication was cause of failure in 16

Table 1 Intraoperative and Postoperative Complications

	N (%)
Intraoperative	
Gastric perforation	1 (0.7)
Postoperative	15(10.3)
Pneumonia	5 (3.4)
Pneumothorax	3 (2.1)
Pneumopericardium	1 (0.7)
Hematoma	1 (0.7)
Atrial fibrillation	1 (0.7)
Ileus	1 (0.7)
Renal colic	1 (0.7)
Subcutaneous emphysema	2 (1.4)

patients (11%). Five patients were asymptomatic, 11 were symptomatic; five were treated with medical therapy, six underwent reoperation with redo fundoplication and mesh reinforcement of the hiatus. The reoperation was effective in three of them; of the remaining three patients, two complained of dysphagia and were treated with pneumatic dilation first and then with medical therapy, one complained of reflux symptoms and was put on PPI.

Dysphagia was the cause of failure in nine (6.2%) patients. Three were sent straight to redo surgery, six had pneumatic dilation of the cardia, which was effective in five, one patient eventually underwent redo surgery.

Recurrence of reflux was the cause of failure in eight (5.5%) patients: six were treated with medical therapy, three had redo surgery, which was effective in two, one was put on PPI therapy because of symptoms persistence.

Gas bloating or other GI symptoms were the cause of failure in four (2.7%) patients. They received pneumatic dilation of the pylorus, which was effective in three of them; one patient for persistence of symptoms had redo surgery, followed by pneumatic dilation, and a third operation elsewhere; she is still symptomatic on medical therapy.

Results in the Four Groups of Patients

We further analyzed the long-term results in the four groups of patients of the study population. Causes of surgical failures are reported in details in Table 2. Both dysphagia and recurrence of reflux as causes of failures were prevalent in Group A patients (GERD with nonerosive esophagitis), although the difference with the other groups (overall and separately) was not statistically significant. On the other side, slipped fundoplication as cause of failure was prevalent in Group D patients (large paraesophageal or mixed hiatal hernia), accounting for 2/3 of the cases ($p=0.0012$ when compared to the other patients); slipped fundoplication was also the most common cause of failure in group B (erosive esophagitis) and C (Barrett's esophagus) patients without statistically significance when compared to group A. Atypical and bloating symptoms were reported by Group A patients only ($p<0.0001$ vs the other three groups).

The likelihood of remaining symptom-free after laparoscopic fundoplication at 10 years follow-up is shown in Fig. 1 for surgical treatment alone and for surgical treatment and complementary treatments, respectively. The likelihood of remaining symptom-free after laparoscopic fundoplication at 10-year follow-up is shown in Fig. 2 for the four groups of patients.

On univariate analysis (Table 3), only a higher symptom score predicted the surgical failure.

Patients with Barrett's Esophagus

Of the 17 patients with Barrett's esophagus [11 M and six F, median age 45.4 years (IQR: 38–53)], nine had a long segment [median length 6 cm (IQR: 5–6.5)], and eight had short segment of IM [median length 1.5 cm (IQR: 1–2)]. Table 4 summarizes changes in the extension of IM after fundoplication.

Patients with Large Paraesophageal and Mixed Hernia

There were four males and 15 females, with a median age of 65 years at surgery (IQR: 60.5–67.5). Five (26%) patients were asymptomatic at diagnosis, the majority of the patients reported dysphagia or regurgitation; two patients presented with anemia. All patients had a preoperative barium swallow study: 11% ($n=2$) had the whole stomach, 42% ($n=8$) had >1/2 of the stomach, and the other 47% ($n=9$) had 1/3 to 1/2 of the stomach migrated into the chest. All patients had esophageal manometry: two (10%) patients had a defective esophageal body function. Twenty-four-hour esophageal pH monitoring was performed in all but one patient: the median composite score was 9 (IQR: 3.5–19.1). Overall, acid exposure in the distal esophagus was abnormal in six (33%) patients. Fourteen of the 19 patients (74%) had their hiatal defect repaired with simple sutures; the remainder (26%) had a double mesh hiatoplasty.

Table 2 Causes of Failures in the Four Groups of Patients

	Esophagitis grade 0–I ($n=80$)	Esophagitis grade ≥2 ($n=29$)	Barrett's esophagus ($n=17$)	Large paraesophageal or mixed hernia ($n=19$)	Total ($n=145$)
Dysphagia	6 (7.6)	3 (10.3)	0	0	9 (6.2)
Slipped fundoplication	3 (3.7)	3 (10.3)	3 (17.6)	7 (36.8)*	16 (11)
Recurrence of reflux	5 (6.2)	2 (7)	1 (5.9)	0	8 (5.5)
Atypical or bloating symptoms	4 (5)*	0	0	0	4 (2.7)
Total	18 (22.5)	8 (27.6)	4 (23.5)	7 (36.8)	37 (25.5)

Data are expressed as *N* (%).
*$p<0.05$

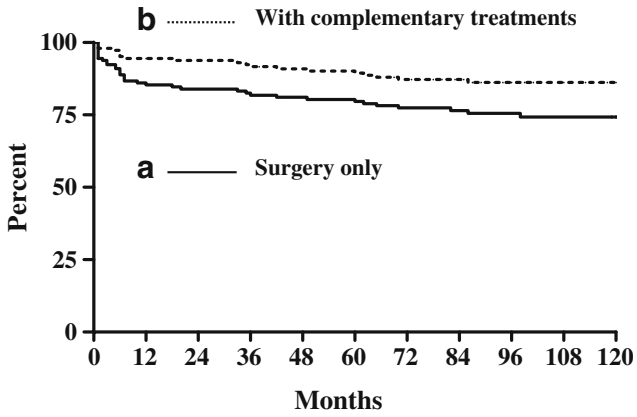

Figure 1 Probability of remaining symptom-free after laparoscopic fundoplication: surgical treatment alone (*continuous line*, a), surgical treatment, and complementary treatments (*dotted line*, b).

Medical Therapy

At a median follow-up of 97 (IQR: 71–143) months, 115 patients were off antisecretory medications. The percentage of patients on PPI or H2 blockers dropped from 84% before to 21% after surgery. Of the 30 patients still on medications after surgery, 29 were on PPI and one on H2 blockers. Twenty-six were symptomatic (complaining of heartburn and/or regurgitation), and four were asymptomatic. In three of the latter, there was radiologic or endoscopic evidence of slipping of the fundoplication. Among the 30 patients on medications, 17 had undergone recent endoscopic control, revealing grade A–B esophagitis in four, Barrett's esophagus in four, gastritis in four, and slipped fundoplication in six.

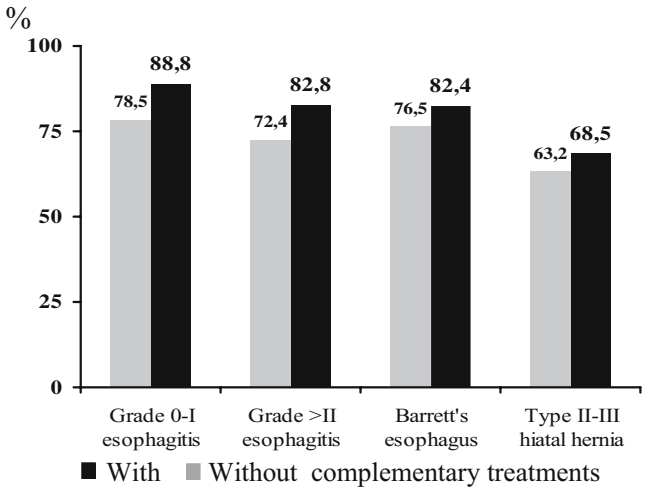

Figure 2 Probability of remaining symptom-free after laparoscopic fundoplication in the four groups of patients.

Discussion

The application of minimally invasive techniques to the surgical treatment of GERD and their widespread diffusion have contributed to the steadily rising number of antireflux procedures performed in the last decade. The initial concerns for safety and feasibility of laparoscopic procedure has been followed by the awareness of both patients and general practitioners of the benefits of minimally invasive surgery—in terms of reduced postoperative pain and hospital stay. This has brought to a constantly lowering threshold for surgical intervention in patients with GERD, which are now operated on at an earlier stage of the disease process. However, in parallel to the enthusiasm for this acceptable alternative to life-long treatment of GERD, concerns have been raised on the long-term durability of the results of antireflux surgery.

Most of the published studies on laparoscopic fundoplication have a follow-up of less than 5 years, refer to a small number of patients, and/or do not include objective and functional evaluation for the majority of the patients. Lafullarde et al.[7] reported a success rate of laparoscopic surgery for GERD of 90% with a follow-up between 5 and 8 years achieved in 99% rate of the 178 patients studied. Unfortunately, the follow-up was based on a clinical evaluation only and did not include objective/functional studies. Recently, a multicenter French study has been published with 84% of 1,340 patients followed for a mean of 7.1 years after surgery; however, once again, the supplied follow-up information was only clinical.[13] We reported our experience with 145 patients: of these, 141 (97%) were followed for at least 6 years (median 8.1 years), and radiologic, endoscopic, and functional (manometry/pH-metry) assessment was obtained in over 70% of the patients at least once during follow-up. Further, most of the patients who became symptomatic during follow-up underwent a thorough evaluation and repeated all the above-mentioned studies to better understand and treat the cause of surgical failure, whenever it occurred. This has allowed us to report a realistic analysis of long-term results of laparoscopic fundoplication in a single referral center.

At a median follow-up of 97 months, we have achieved an 86% success rate with surgery and 'complementary' (endoscopic in several cases) treatments; it was 74% when considering surgery alone. The main causes of surgical failures, similar to what experienced by other centers, were hernia recurrence or slipping of the fundoplication and dysphagia.

Hernia recurrence occurred mainly in patients with large type II or III hernias. After 1997, a routine a mesh reinforcement of the hiatus to the simple-suture hiatoplasty was added using a double-faced (goretex and propylene) U-shaped mesh. Six of the seven failures for hernia recurrence

Table 3 Univariate Analysis: Predictive Factors of Surgical Failures

	Success (n=108)	Failure (n=37)	p value
M/F	68/40	19/18	n.s.
Age (years)	48 (25–70)	50 (26–68)	n.s.
BMI	25.6 (20.2–32.4)	25.4 (21.5–34.5)	n.s.
Symptom duration (months)	36 (6–142)	36 (7–180)	n.s.
Symptom's score	12 (2–23)	16 (5–24)	0.02
LES resting pressure (mmHg)	8 (3–16)	7 (3–16)	n.s.
LES total length (mm)	31 (17–51)	30 (17–46)	n.s.
LES abdominal length (mm)	20 (10–35)	17 (9–35)	n.s.

Data are expressed as median (interquartile range).
BMI Body mass index; *LES* lower esophageal sphincter

in the group of patients with large hernias occurred in cases performed before 1997, in which the mesh had not been used. A significant reduction of hernia recurrence has been experienced (from 11 to 3%), since then.

Dysphagia was commonly observed in the early postoperative period (6–8 weeks), mostly because of edema or temporary hypomotility and usually resolved spontaneously, as already reported by others.[14] For the management of persistent dysphagia, we preferred an endoscopic approach with pneumatic dilation in case of mild-moderate symptom, which usually solved the problem, leaving the surgical revision in case of failed multiple attempts of dilation or in case of severe debilitating symptoms.

It has been suggested that the incidence of postoperative dysphagia could be lowered by the routine division of the short gastric vessels to obtain a floppy well-shaped fundoplication around the esophagus: in a prospective, nonrandomized study Hunter[15] reported a higher rate of dysphagia (54 vs 17%, $p<0.005$) in patients having their short gastric vessels (SGV) left intact. Although three prospective randomized studies comparing laparoscopic Nissen fundoplication with and without division of the short gastric vessels failed to demonstrate any significant difference in persistent dysphagia,[16–18] our experience is very similar to that reported by Hunter:[15] after the routine use of SGV division, a significant drop of persistent dysphagia (>8 weeks) was observed (from 12 to 3%). However, as in case of mesh use, the improved outcome could be explained by other factors, such as an improved mastering of laparoscopic fundoplication.

The vast majority of our patients received a total (360°) fundoplication (floppy Nissen): partial fundoplication being left to the few patients with severely deteriorated esophageal motility. The selective or routine use of partial fundoplication has been suggested to lower the incidence of post-Nissen dysphagia: three prospective randomized studies have compared Nissen fundoplication vs Toupet (partial posterior) or Dor (anterior) fundoplication. These three studies either did not show any clear advantage of one procedure over the other (Laws et al.[19]) or reported a lower rate of dysphagia for the Toupet or Dor fundoplication but had a very short term follow-up (4 months Zornig et al.[20]; 6 months Jamieson et al.[21]). The absence of a conclusive study, which would require a randomization of large number of patient to detect small differences among the procedures, make the issue of which fundoplication or which technique offers the best outcome for patients undergoing surgery for GERD still a matter of debate.

All our patients received preoperatively physiologic studies (24-h pH monitoring and manometry) to objectively proof and quantify GERD and detect any motor abnormalities. Other authors argue that a selective use of preoper-

Table 4 Changes in the Extension of Intestinal Metaplasia After Fundoplication

	Short-segment IM (n=8)	Long-segment IM (n=9)	p value
Reversion of IM	4 (50)	0	0.03[a]
Partial regression of IM	0	4 (45)	
Persistence of IM with no change	4 (50)	5 (55)	

Data are expressed as N (%).
IM Intestinal metaplasia
[a] Reversion of IM vs partial regression of IM or persistence of IM with no change. 'Reversion' of IM was considered as no intestinalized glandular mucosa in any of the postsurgical biopsy samples; 'partial regression' of IM was defined as decreasing prevalence of intestinalized glands in postop biopsies; 'persistence' of IM was considered when the extension of IM detected at follow-up biopsies remained the same as before surgery.

ative manometry and pH-metry might be cost effective, suggesting their use only in case of abnormal findings on upper GI endoscopy or fluoroscopy or atypical symptoms.[22] Careful selection of patients is the paramount for successful surgery: abnormal pH studies have been associated with greater satisfaction rates after antireflux surgery, whereas normal preoperative pH test is not uncommon in patients reporting higher postoperative heartburn and dysphagia scores.[23] In our opinion, an objective evidence of reflux must be clearly documented before taking a patient to the OR for a procedure with still a chance of one death per 2,000 procedures, which might not be the cure for the patients if reflux is not the cause of his or her symptoms.

Recently, there has been a growing interest for the role of laparoscopic fundoplication in preventing progression of Barrett's esophagus toward the now well-recognized metaplasia–dysplasia–adenocarcinoma sequence. To date, there is no evidence that antireflux surgery should be performed with the expectation of preventing esophageal adenocarcinoma. However, several studies[24,25]—one recent from our group as well[26]—show that a regression of IM and even of low-grade dysplasia, especially in case of short segments of Barrett, can be obtained in patients with an effective antireflux procedure. Given that esophageal adenocarcinoma has been reported even after Nissen fundoplication, patients with Barrett's esophagus, who have a fundoplication, should undergo surveillance endoscopy during follow-up in a similar manner as in those who do not have surgery.[27]

It was not the aim of this study to investigate the details of PPI use after surgery. However, of the 30 patients (21% of the study population) being still on medications after surgery, only 17 had performed an endoscopy before starting PPI or H2 blockers with their family practitioner. The high use of PPI after surgery has already been reported,[28] and other studies have shown that the sole presence of symptoms—although suggestive of reflux—is a poor indicator of recurrent reflux disease.[29] A reliable evaluation can be obtained only with endoscopy, barium swallow, and pH-metry. An advice for an appropriate use of medications after surgery should always be given to both patients and family practitioners.

Similar to other studies and to have enough patients for meaningful comparisons between subgroups of patients with different degrees of the disease, we included patients from the learning curve. This means that the long-term results obtained from patients operated on beyond the learning curve can be expected to be even better.

In conclusion, this study confirms what has been already reported in midterm follow-up studies that laparoscopic fundoplication can be definitely considered an effective long-term procedure and should be regarded as the valuable alternative to life-long medications for GERD.

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Lymph Node Involvement in Gastric Cancer for Different Tumor Sites and T Stage

Italian Research Group for Gastric Cancer (IRGGC) Experience

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Abstract
Background The aim of lymphadenectomy is to clear all the metastatic nodes achieving a complete removal of the tumor; nevertheless, its role in gastric cancer has been very much debated.
Materials and methods The frequency of node metastasis in each lymphatic station according to the International Gastric Cancer Association, was studied in 545 patients who underwent D2 or D3 lymphadenectomy from June 1988 to December 2002.
Results Upper third early cancers have shown an involvement of N2 celiac nodes in 25%. In advanced cancers, there was a high frequency of metastasis in the right gastroepiploic (from 10% in T2 to 50% in T4) and in the paraaortic nodes (26% in T2, 32% in T3, 38 % in T4). N3 left paracardial nodes involvement was observed in an important share of middle third tumors (17% in T3, 36% in T4). Splenic hilum nodes metastasis were common in T3 and T4 cancers located in the upper (39%) and middle (17%) stomach. N2 nodal involvement was frequent in lower third advanced cancers. Metastasis in M left paracardial and short gastric nodes were observed in a small percentage of cases.
Conclusion Given the nodal diffusion in our gastric cancer patients, extended lymphadenectomy is still a rationale to obtain radical resection.

Keywords Gastric cancer · Lymphadenectomy · Lymph nodes metastasis

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Introduction

Anatomy [10, 25, 27, 33] and physiology [9, 28, 32, 36] studies conducted on the gastric lymphatic drainage identified different pathways depending on the stomach's regions. Upper third lymphatic vessels run along left gastric artery, posterior gastric artery, and splenic artery, whereas the lower third has lymphatic vessels accompanying common hepatic artery and superior mesenteric artery. Middle third stomach has a mixed drainage in both ways. All these vessels are eventually connected to the paraaortic lymphatic network.

Such a drainage has been confirmed by means of studies on cancers with single nodal metastasis [15], and an Italian multicentric study [4] analyzed lymph node stations involvement for cardia adenocarcinoma. Nonetheless, there is no published study for gastric cancer investigating nodal metastasis incidence at different lymph node stations, considering the diverse tumor sites and T classes. Maruyama

and colleagues reported in 1989 their large experience in 1931 patients; however, in that study the relationship between incidence of nodal metastases and tumor's location or depth of invasion were considered separately [17].

The role of lymphadenectomy in gastric cancer surgery has been very much debated during the last three decades.

Extended lymphadenectomy (D2) has been formerly adopted by Japanese surgeons and more recently by many western colleagues as well, owing to encouraging results of several nonrandomized trials [18, 19, 21, 22, 24, 29–31]. Ensuing randomized trials, comparing extended lymphadenectomy (D2) to limited lymphadenectomy (D1), did not show, apparently, any prognostic advantage for D2, which had a higher morbidity and mortality [2, 3, 5, 6]. Incidentally, in some randomized and nonrandomized trials, admittedly, a more aggressive lymphadenectomy might have been useful, from a prognostic point of view, for advanced cases [2, 11, 23, 29].

Although there is still no standard approach, it is obvious that an adequate lymphadenectomy, removing all the possible metastatic nodes, remains a milestone in gastric cancer surgery.

The aim of the present study is to evaluate the incidence of nodal metastases in all the different lymph node stations changing tumor sites and T stages, as a basis for opting for optimal lymphadenectomy.

Materials and Methods

From June 1988 to December 2002, 774 patients with a histologically proven gastric adenocarcinoma underwent gastric resection in the first Department of General Surgery of the University of Verona and at the Department of Surgical Oncology of the University of Siena. After excluding 98 patients who underwent palliative (R1/R2) resections and 131 patients who underwent D1 or incomplete D2 lymphadenectomy due to age, very early stage of disease or associate disease, 545 patients (Verona, n=338 and Siena, n=207) who underwent extended or superextended lymphadenectomy (≥D2) were recruited for the study. In all these patients, at least a complete D2 lymphadenectomy was performed.

Eighteen patients affected by gastric stump cancer and 18 patients affected by linitis plastica were excluded from the study.

Clinical and pathological data regarding the 509 included patients are shown in Table 1.

Table 1 Main Clinicopathologic Characteristics of the 509 Patients Who Underwent Extended or Superextended (≥D2) Lymphadenectomy According to Tumor Location

	Upper Third (n=102) (%)	Middle Third (n=160) (%)	Lower Third (n=247) (%)	Total (N=509) (%)	P Value
Lymphadenectomy					
D2	45 (44)	87 (54)	152 (62)	284 (57)	P=0.011
D3	57 (56)	73 (46)	95 (38)	225 (44)	
Mean age (range)	65 (30–90)	64 (30–89)	64 (23–92)	64 (23–92)	P=N.S.
Gender (M:F)	82:20 (4.1:1)	105:55 (1.9:1)	144:103 (1.4:1)	331:178 (1.9:1)	P<0.001
Lauren histotype					
Intestinal	70 (69)	95 (59)	133 (54)	298 (58)	P=0.054
Diffuse	28 (27)	49 (31)	95 (38)	172 (34)	
Mixed	4 (4)	16 (10)	19 (8)	39 (8)	
Depth of invasion					
pT1	6 (6)	34 (21)	66 (27)	106 (21)	P<0.001
pT2	34 (33)	47 (29)	84 (34)	165 (32)	
pT3	49 (48)	61 (38)	89 (36)	199 (39)	
pT4	13 (13)	18 (11)	8 (3)	39 (8)	
Nodal status (TNM)					
pN0	20 (20)	56 (35)	102 (41)	178 (35)	P=0.003
pN1	34 (33)	49 (31)	59 (24)	142 (28)	
pN2	23 (22)	24 (15)	49 (20)	96 (19)	
pN3	25 (25)	31 (19)	37 (15)	93 (18)	
M1a (when D>2)	17 (30)	9 (12)	9 (9)	35 (16)	
Nodal status (JGCA, 1998)					
N0	20 (20)	56 (35)	102 (41)	178 (35)	P<0.001
N1	24 (23)	38 (24)	57 (23)	119 (23)	
N2	34 (33)	35 (22)	65 (26)	134 (26)	
N3-M	24 (23)	31 (19)	23 (9)	78 (15)	

TNM=tumor-node-metastasis; JGCA=Japanese Gastric Cancer Association

Table 2 Lymph Node Groups Using the Japanese Gastric Cancer Association Classification

Lymph Node Groups (Compartments)	Tumor Location[a]		
	U No.	M No.	L No.
N1	1	1	3
	2	2	4d
	3	3	5
	4sa	4	6
	4sb	5	
		6	
N2	4d	7	1
	7	8a	7
	8a	9	8a
	9	10	9
	10	11	11p
	11	12a	12a
			14v
N3	5	8p	4sb
	6	12b	8p
	8p	12p	12b
	12	14v	12p
	16a2	16a2	13
	16b1	16b1	16a2
			16b1
M	13	13	2
	14	14a	4sa
	15	15	10
	16a1	16a1	11d
	16b2	16b2	14a
			15
			16a1
			16b2

[a] U=upper third; M=middle third; L=lower third

Stomach was divided up in three portions (the upper, middle, and lower third) and the tumor site was identified considering the precise center of the neoplasm.

Lymphadenectomy was defined according to the second English edition of the Japanese Classification of Gastric Carcinoma, published in 1998 (Table 2) [12].

Involvement of nodal stations was catalogued as reported by the Japanese Gastric Cancer Association (JGCA), which identifies three groups of stations (N1, N2, N3) with regard to tumor location.

The overall number of dissected lymph nodes and the number of metastatic ones were recorded for every single patient and for every station of the single case.

For middle and distal cancers, left paracardial lymph node station (no. 2) was dissected in patient who underwent total gastrectomy, 108 (65%) and 53 (21%), respectively, and in some other cases with grossly involved nodes at this site, four (3%) and 17 (7%), respectively.

Up to 1998, in accordance with JGCA, superior mesenteric (station no. 14) and middle colic (no. 15) lymph nodes dissection was considered discretionary. Although it has been performed more frequently in the succeeding years, we were able to statistically analyze the nodal involvement of these stations at different T stages only for lower third gastric cancer cases.

Histological class was assigned in accordance with the Lauren classification, and the 1997 UICC pTNM staging was chosen as the pathological classification system.

Person's χ^2 test and t test were used for the association between clinicopathologic variables and site of the tumor.

Results

The overall number of dissected lymph nodes for the 509 selected cases was 20,389, with a mean number per patient of 40.1. A histologically proven nodal metastasis ($N+$) was found in 331 patients (65%), with an overall number of 3,846 lymph nodes and a mean number per case of 11.6 metastatic lymph nodes (range: 1–54).

Table 3 Incidence of Lymph Node Metastasis Using the 1997 Union Internationale Contre le Cancer (UICC) Classification

		N0 (%)	N1 (%)	N2 (%)	N3 (%)	*P* Value
Upper third	T1	3/6 (50)	3/6 (50)	0/6	0/6	$P=0.005$
	T2	8/34 (23)	16/34 (47)	4/34 (12)	6/34 (18)	
	T3–T4	9/62 (15)	15/62 (24)	21/62 (34)	17/62 (27)	
	Total	20/102 (20)	34/102 (33)	25/102 (25)	23/102 (22)	
Middle third	T1	30/34 (88)	4/34 (12)	0/34	0/34	$P<0.001$
	T2	18/47 (38)	19/47 (40)	2/47 (4)	8/47 (17)	
	T3–T4	8/79 (10)	26/79 (33)	29/79 (37)	16/79 (20)	
	Total	56/160 (35)	49/160 (31)	31/160 (19)	24/160 (15)	
Lower third	T1	52/66 (79)	10/66 (15)	1/66 (2)	3/66 (4)	$P<0.001$
	T2	36/84 (43)	26/84 (31)	8/84 (9)	14/84 (17)	
	T3–T4	14/97 (14)	23/97 (24)	28/97 (29)	32/97 (33)	
	Total	102/247 (41)	59/247 (24)	37/247 (15)	49/247 (20)	

N=lymph node metastasis

Table 4 Extent of Lymph Node Metastasis Using the 1998 Japanese Gastric Cancer Association Classification

		N0 (%)	N1 (%)	N2 (%)	N3-M (%)	*P* Value
Upper third	T1	3/6 (50)	2/6 (33)	0/6	1/6 (17)	*P*=0.082
	T2	8/34 (23)	11/34 (32)	7/34 (21)	8/34 (24)	
	T3–T4	9/62 (15)	11/62 (18)	17/62 (27)	25/62 (40)	
	Total	20/102 (20)	24/102 (23)	24/102 (23)	34/102 (33)	
Middle third	T1	30/34 (88)	1/34 (3)	0/34	3/34 (9)	*P*<0.001
	T2	18/47 (38)	17/47 (36)	4/47 (9)	8/47 (17)	
	T3–T4	8/79 (10)	20/79 (25)	27/79 (34)	24/79 (30)	
	Total	56/160 (35)	38/160 (24)	31/160 (19)	35/160 (22)	
Lower third	T1	52/66 (79)	9/66 (6)	1/66 (2)	4/66 (6)	*P*<0.001
	T2	36/84 (43)	19/84 (23)	6/84 (7)	23/84 (27)	
	T3–T4	14/97 (14)	29/97 (30)	16/97 (16)	38/97 (39)	
	Total	102/247 (41)	57/247 (23)	23/247 (9)	65/247 (26)	

N=lymph node metastasis.

Tables 3 and 4 show how the *N* parameter varies with regard to tumor site and T class according to the UICC and the JGCA classifications, respectively. On the whole, upper third gastric cancers show the highest percentage of metastatic lymph nodes (80%), whereas the lowest was registered for distal third cases (59%).

Considering the 225 patients submitted to superextended lymphadenectomy (>D2), 1,065 lymph nodes were dissected from the paraaortic station (no. 16), with a mean number per patient of 4.7. Thirty-five patients (16%) had a nodal metastasis in this station, with an overall number of 107 positive nodes.

Nodal metastasis distribution for upper, middle, and lower third gastric adenocarcinoma, from station nos. 1 to 11, is shown in Tables from 5, 6, and 7. Table 8 reports in detail the data about station nos. 12 and 13.

- Upper third adenocarcinoma

Early gastric cancers, all with submucosal involvement (T1sm), demonstrated a nodal invasion in up to 50% of cases, especially lesser curvature (17%) and celiac axis (25%).

Advanced gastric cancers, increasing the T parameter, showed a progressively augmented nodal involvement, although lesser curvature remains the most invaded station: from 59% in T2 tumors to 92% in T4. N3 perigastric stations, suprapyloric (no. 5) and infrapyloric (no. 6), were drawn in by the tumor only in advanced neoplasms.

In one patient (1%) with a T2 tumor we recorded a N2 station involvement, celiac axis (no. 9), without invasion of any of the six perigastric stations nor the left gastric artery (no. 7).

Among the 57 patients who underwent a >D2 lymphadenectomy, the overall N3/M paraaortic (no. 16) nodal metastases incidence was 30%: 26% for T2 tumors, 32% for T3, and 38% for T4. Solely considering station no. 16 for every case, nine patients (16%) had its nodal involvement (three cases with a T2 tumor, four with a T3, and two with T4) without a simultaneous invasion of the N3 hepatic–duodenal ligament (no. 12) and M retropancreatic (no. 13) lymph node stations.

Four more advanced cases (7%), three T2 and one T4, had a paraaortic nodal diffusion with only a simultaneous involvement of either the right paracardial station (no. 1) or the lesser curvature station (no. 3).

- Middle third adenocarcinoma

We registered 21 T1m cases of middle third stomach, none of them had positive lymph nodes.

Considering all the other T classes, lesser curvature nodes (no. 3) were the most interested ones with the following percentages: 23% in T1sm cases, 36% in T2, and 91% in T3/4.

Table 5 Incidence of Lymph Node Metastasis in 102 Patients with Upper Third Gastric Adenocarcinoma According to the Depth of Tumor Invasion

Depth of Invasion	Lymphatic Station									
	No. 1 %	No. 2 %	No. 3 %	No. 4 %	No. 5 %	No. 6 %	No. 7 %	No. 8 %	No. 9 %	No. 11 %
T1sm 6 c.	0	0	17	0	0	0	0	0	25	0
T2 34 c.	52	38	59	13	0	6	31	10	18	4
T3 49 c.	54	44	68	28	0	13	48	23	39	26
T4 13 c	75	29	91	60	25	50	50	30	50	43
Total	51	38	65	25	2	13	39	18	33	19

Table 6 Incidence of Lymph Node Metastasis in 160 Patients with Middle Third Gastric Adenocarcinoma According to the Depth of Tumor Invasion

Depth of Invasion	Lymphatic Station									
	No. 1 %	No. 2 %	No. 3 %	No. 4 %	No. 5 %	No. 6 %	No. 7 %	No. 8 %	No. 9 %	No. 11 %
T1m 21 c.	0	0	0	0	0	0	0	0	0	0
T1sm 13 c.	9	0	23	8	0	0	8	8	0	9
T2 47 c.	23	3	36	28	6	15	13	7	10	5
T3 61 c.	52	17	93	61	15	51	43	28	33	16
T4 18 c.	54	36	82	56	20	40	50	25	50	27
Total	33	11	51	38	9	28	26	15	21	11

Right paracardial station (no. 1) resulted metastatic in 9% of T1sm cancers, whereas left paracardial station (no. 2) was involved only in advanced cases and particularly in T3 (17%) and T4 (36%).

Three advanced cases (2%), one T2 and two T3, presented N3 compartment nodal metastases, at left gastric artery (no. 7), splenic artery (no. 11) and celiac axis (no. 9), without a simultaneous involvement of perigastric nodes.

Seventy-three patients with a middle third gastric cancer underwent a D3 nodal dissection, 12% of them presented N3 compartment/M paraaortic metastases, in particular, those having cancer with a serosal infiltration (19% in T3 cases, 30% in T4). One (1%) T4 case had a paraaortic nodal metastasis associated to perigastric nodal metastases only, thus skipping all the interposed compartments.

In five more patients (4%), one T2 case, three T3, and one T4, the paraaortic station (no. 16) was metastatic, being N3 stations no. 12 and no. 13 negative.

- Lower third adenocarcinoma

As shown in Table 7 in this region of the stomach, even T1m cancers presented nodal metastases, involving infrapyloric station (no. 6) in 7% of cases, lesser curvature (no. 3) in 6% and left gastric artery (no. 7) in 3% of them.

This trend was confirmed in T1sm cases, with the following percentages for the same stations: 22% for no. 6, 15% for no. 3, and 3% for no. 7.

Left paracardial station (no. 2), which is an M class for tumors of this region, was hardly ever involved, only 2% of cases even considering advanced cases.

In three cases (1% of lower third tumors), one T2 and two T3 we recorded N2/N3 compartments lymph nodes metastases, at stations nos. 7, 8, and 9, without N1 nodal involvement.

Interesting enough is the behavior of stations no. 14 (superior mesenteric artery) and no. 15 (middle colic artery). T1 lower third gastric cancers did not infiltrate any of these stations. Station no. 14 was positive in 20% of T2 cases and 25% of T3/4 cases. Station no. 15 was never infiltrated in T2 cases as well, whereas it was drawn in 33% of T3/4 cases.

Ninety-five patients of this group were submitted to a D3 nodal dissection, N3/M paraaortic nodal metastases were present in 9% of cases, namely 7% for T1 cancers, 8% for T2, 10% and 25% for T3 and T4, respectively.

We believe that nodal stations no. 4 (gastro-epiploic vessels), no. 10 (splenic hilum), and no. 16 (paraaortic) deserve a further mention. Tables 9 and 10 show lymph node involvement in these stations singularly. Forty-eight patients presented a single nodal metastasis. These were in the perigastric compartment only for middle and lower third cancers, whereas upper third tumors presented single nodal metastases in N2 stations as well, such as no. 9 and no. 10.

Table 7 Incidence of Lymph Node Metastasis in 247 Patients with Lower-third Gastric Adenocarcinoma According to the Depth of Tumor Invasion

Depth of Invasion	Lymphatic Station									
	No. 1 %	No. 2 %	No. 3 %	No. 4 %	No. 5 %	No. 6 %	No. 7 %	No. 8 %	No. 9 %	No. 11 %
T1m 33 c.	5	0	6	0	0	7	3	0	0	0
T1sm 33 c.	8	0	15	0	0	22	3	7	0	0
T2 84 c.	17	0	34	30	11	43	22	23	10	6
T3 89 c.	18	2	69	47	27	68	35	37	20	11
T4 8 c.	40	0	87	50	20	50	28	50	67	0
Total	15	1	42	29	15	44	22	24	12	6

Table 8 Incidence of Node Metastasis According to the Site and Depth of Invasion at Hepatoduodenal Ligament (number 12) and in the Retropancreatic Station (number 13)

	No. 12 Hepatoduodenal Ligment Nodes %	No. 13 Retropancreatic Nodes %
Upper third		
pT1	0	0
pT2	0	0
pT3–T4	12	20
Total	7	12
Middle third		
pT1	0	0
pT2	0	0
pT3–T4	11	8
Total	5	5
Lower third		
pT1	2	0
pT2	4	9
pT3–T4	7	23
Total	5	15

Discussion

The present study demonstrated the existence of preferential lymphatic drainage routes for the different gastric regions, thus allowing to draw considerations regarding current surgical debates, particularly on the appropriate treatment of early gastric cancer (EGC).

We found out that upper third EGCs, which were all T1sm in our series, never involved distal perigastric stations (no. 4d, no. 5, no. 6), whereas N2 nodal metastases were not uncommon. Therefore, as others [7] advocate, an extended lymphadenectomy, even sparing the distal portion of the stomach, is appropriate for these tumors. Some Japanese Centers already adopt a proximal gastrectomy with D2 lymphadenectomy for such tumors [13, 14].

Table 9 Incidence of Lymph Node Metastasis according to the Site and Depth of Invasion along the Greater Curvature

	No. 4d Right Gastroepiploic Artery %	No. 4sb Left Gastroepiploic Artery %	No. 4sa Short Gastric Vessels %
Upper third			
pT1	0	0	0
pT2	10	0	5
pT3–T4	29	28	19
Total	21	15	13
Middle third			
pT1	3	0	0
pT2	23	5	4
pT3–T4	54	37	21
Total	34	19	12
Lower third			
pT1	0	0	0
pT2	30	3	0
pT3–T4	46	8	2
Total	28	4	1

Table 10 Incidence of Lymph Node Metastasis According to the Site and Depth of Invasion at Splenic Hilum (number 10) and in the Paraaortic Station (number 16)

	No. 10 Splenic Hilum Nodes %	No. 16 Paraaortic Nodes %
Upper third		
pT1	0	0
pT2	0	26
pT3–T4	39	39
Total	26	30
Middle third		
pT1	0	0
pT2	4	0
pT3–T4	17	23
Total	10	12
Lower third		
pT1	0	7
pT2	0	8
pT3–T4	2	11
Total	1	9

Results of paraaortic nodes are limited to 225 patients who underwent D3 dissection.

T1m cancers of middle third stomach never infiltrated lymph nodes in our series, whereas T1sm involved proximal perigastric nodes (no. 1), distal perigastric (no. 4d) and N2 stations as well (nos. 7, 8, 11). Given these data, a limited lymphadenectomy is warranted only for T1m tumors of middle stomach. Some authors recently proposed a limited gastric resection with partial perigastric lymphadenectomy and an irregular sampling of N2 stations such as nos. 7, 8, and 11 for ECG of this region. This conservative approach, by the way, although justified for T1m cancers not suitable to endoscopic mucosal resection (EMR), was equally applied to differentiated T1sm less than 5 cm wide [20]. Another trial [8] compared limited gastrectomy with D0-1 lymphadenectomy to subtotal gastrectomy with D2 lymphadenectomy, favoring a conservative approach. The authors, though, used the first technique for T1m protruding types (Type I and IIa) and depressed types (IIc) less than 2 cm, which are potentially curable with EMR solely [1], and adopted the more aggressive approach for T1m tumors of any other type.

EGCs of lower stomach were associated, in our experience, to perigastric nodal metastases and, albeit in small percentages, to N2 stations involvement like nos. 1, 7, and 8. Because of their behavior, these EGCs do not fit the features for a limited lymphadenectomy. T1m tumors of lower stomach, in fact, can infiltrate N2 stations, namely,

nos. 1 and 7, in our series, with percentages of 5% and 3%, respectively.

Since early cancers of any region of the stomach are supposed to give nodal metastases quite rarely and more frequently to perigastric stations, a limited lymphadenectomy (D1) is generally considered sufficient. Our results, instead, show that regularly adopting a D1 nodal resection might lead to incomplete resection in those who have an EGC with N2 stations involved, whereas EGCs could be cured if submitted to a radical intervention.

Selecting those EGCs, which need a D2 nodal resection, is still a tough task. In literature, different parameters have been considered, such as the endoscopic morphology according to the Japanese Endoscopic Society [12], diameter, depth of invasion, histological type and grade. Although many morphologic and pathologic features were identified as predictive of a nodal involvement, is quite difficult to verify them before and during surgery with an adequate accuracy [34, 35]. Sentinel lymph node technique is a matter of debate nowadays to resolve this problem.

Concerning the treatment of advanced gastric cancers (AGC), T2 tumors of our series, independent of their location in the stomach, were quite consistently associated to N2 stations nodal infiltration. Such a behavior, although less frequent than in T3/4 tumors, does not allow a conservative surgical conduct in terms of nodal resection.

Previous studies from our group have shown a potential benefit of extended lymphadenectomy expecially in T2 tumors [16]. In case of gastric cancer involving the serosa, extended lymphadenectomy could probably reduce non-peritoneal relapses; however, it does not seem to reduce the incidence of peritoneal recurrence [26].

Upper third advanced gastric cancers showed a preferential infiltration of lesser-curvature station (65%), right paracardial (51%) and left paracardial (38%) stations. N2 stations have a significant involvement as well and, interestingly enough, the paraaortic location (no. 16) is frequently infiltrated (30% overall), even skipping N2 stations and N3/M stations like no. 12 and no. 13. This clearly justifies a superextended lymphadenectomy (D3).

T3/4 cancers of upper third stomach frequently spread to N3 nodal sites like hepatic-duodenal ligament, no. 12, (12%) and splenic hilum, no. 10 (39%). It seems sensible, hence, to dissect these stations for a radical treatment.

AGCs of middle third stomach did not show a paraaortic nodal infiltration as important as for upper third cancers. T3 and T4 tumors of this region, though, have a station no. 16 involvement of 19% and 30%, respectively. Thus, a radical surgical treatment of these cancers cannot rule out a D3 dissection again.

Lower third stomach AGCs, frequently spreading to N2 stations, require an extended lymphadenectomy. It is noteworthy, by the way, that their behavior with regard to station no. 4 allows, in safety, a subtotal gastrectomy even for T3/T4 tumors (metastases to no. 4sa station are only 2%), whereas upper and middle third advanced cancers, given the high incidence of metastases to stations nos. 4sb, 4d, and 6, require a total gastrectomy. Given the high incidence of nodal metastases in station nos. 14 and no. 15 for T3/T4 cases, lower third gastric tumors definitely require a dissection of them. Station no. 14 dissection is warranted in T2 cancers as well, because of a 20% metastasis incidence.

Infiltration of station no. 16, albeit less frequent than for proximal and middle third cancers, is not irrelevant for lower third tumors, thus justifying a D3 dissection for them as well.

Conclusion

In conclusion, we can state that lymphadenectomy is still a mainstay of gastric surgery. Although extended nodal dissection has been criticized during the past years in terms of prognostic benefit versus morbidity and mortality rate, in our opinion, given the nodal diffusion incidence we recorded in our gastric cancers patients, there is still a rationale in adopting this approach to obtain a radical surgery.

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Regeneration After Two-Stage Hepatectomy vs Repeat Resection for Colorectal Metastasis Recurrence

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Abstract
Background Two-stage hepatectomy aims to minimize liver failure risk by performing a second resection after regeneration, assuming that remnant liver hypertrophy after the second resection is similar to that seen in repeat hepatectomy, yet the impact of a two-stage strategy on liver volume and function remains to be demonstrated.
Patients and Methods Twenty patients undergoing two-stage hepatectomy for multiple colorectal cancer metastases and 21 patients with more than two sections of liver parenchyma totally removed by repeat liver resections for recurrence were enrolled. Liver volumes after final hepatectomy and postoperative liver function were compared.
Results Median total liver volumes before initial hepatectomy and after final hepatectomy of multiple resections were 942 and 863 ml in patients with repeat hepatectomy, whereas volumes at corresponding time points were 957 and 777 ml in patients with two-stage hepatectomy. The ratio of total liver volume after both hepatectomies to preoperative volume in the two-stage group (81.7%) was lower than that in the repeat resection group (92.0%, $P=0.027$). Greater aspartate aminotransferase and prothrombin time and lower platelet count 1 month postoperatively and lower albumin at 6 months were evident after two-stage hepatectomy compared with repeat hepatectomy.
Conclusions Two-stage hepatectomy is characterized by diminished hepatic regenerative capacity and postoperative liver function.

Keywords Liver metastases · Colorectal cancer · Two-stage hepatectomy · Repeat hepatectomy

Abbreviations

Alb	albumin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDDP	Cisplatin
CT	Computed tomography
5-FU	5-fluorouracil
FA	l-folinic acid
Hx	Hepatectomy
Moderate	Moderately differentiated adenocarcinoma
PLT	platelet count
PS	Prediction score
PT-INR	Prothrombin time international normalized ratio
PVE	Portal vein embolization
TB	Total bilirubin
Well	Well-differentiated adenocarcinoma

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Introduction

Hepatic resection is the only form of treatment that currently offers a chance of long-term survival in patients

with colorectal liver metastases, with an approximate 5-year survival rate of 40%.[1–4] However, despite modern hepatic surgical techniques, curative resection is not always possible in patients with multiple liver metastases because a dangerously extensive hepatectomy would be necessary. Extensive hepatectomy involves considerable reduction of hepatic mass that can lead to clinical manifestations of decompensation including hepatic insufficiency. As an unfortunate result, only 20 to 30% of patients with metastatic colorectal cancer are candidates for liver resection,[5] with resection frequently precluded by multisegment involvement. Planned two-stage hepatectomy with or without portal vein embolization (PVE) has been studied as an effective way to completely remove diffuse bilobar liver metastases from colorectal cancer,[6–8] broadening indications for curative resection in these patients. The rationale for two-stage hepatectomy is to minimize risk of liver failure by completing the resection after regeneration has occurred. Performing the second resection 1 to 2 months after the first could allow cumulative regeneration of the liver of over 80% after the two procedures.[9] These procedures were accomplished successfully in 70 to 81% of patients[6,8] otherwise destined to a very poor outcome, achieving 3-year survival rates of 35 to 54.4%. However, risk of perioperative morbidity in connection with the second-stage procedure was significant, 45 to 56%, and perioperative mortality ranged up to 15%.

On the other hand, repeat liver resection for recurrence of colorectal metastasis to the liver has been performed increasingly in the context of recent advances in hepatic resection and growing evidence of survival benefit.[10–14] Although repeat liver resections are technically more demanding and difficult, studies of repeat liver resection have demonstrated ranges of death and complication rates similar to those reported for primary hepatic resections.

Both two-stage hepatectomy and repeat hepatectomy depend upon observations that liver resection is followed by remnant liver hypertrophy. While hepatocytes possess remarkable ability to regenerate, the impact of two-stage procedures on liver volume hypertrophy is even less well understood, and postoperative liver function in patients undergoing two-stage hepatectomy has not been well defined until now. Furthermore, neither liver volume hypertrophy nor postoperative liver function has been directly and unambiguously compared between patients undergoing two-stage hepatectomy and those with repeat hepatectomy, although techniques and underlying concepts are similar. We retrospectively investigated differences between two-stage hepatectomy for multiple bilobar liver metastases from colorectal cancer and repeat hepatectomy for liver recurrence of these lesions, with special attention to liver volume hypertrophy and postoperative liver function.

Patients and Methods

Patients

From 1992 to 2004, a total of 232 patients diagnosed with liver metastasis from colorectal cancer underwent liver resection with curative intent at the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine. Of these 232 patients, one patient (0.4%) died within 60 days of surgery as a result of postoperative bleeding, sepsis, and multiple organ failure. Of the remaining 231 patients, three other patients were excluded because of incomplete resection of liver metastasis. In the 228 patients with R0 liver resection, 22 were treated with two-stage hepatectomy with (n=16) or without (n=6) portal vein embolization (PVE). Two of these two-stage hepatectomy patients later underwent repeat resection for liver recurrence, as the interval for observing remnant liver regeneration was too short. All told, data from 20 patients treated for cure with two-stage hepatectomy were included in the analysis.

During the follow-up period after hepatectomy, liver recurrence ultimately developed in 98 patients. Among these patients, 36 underwent repeat liver resection for recurrent disease. A second liver recurrence followed in 17 patients, ten of whom were treated with a third resection. Of these ten patients, five developed a third recurrence, with two of them undergoing a fourth resection. One patient ultimately underwent a fifth resection. Among the 36 patients who underwent repeat liver resection, total extent of liver parenchyma removed by the multiple repeat resections was more than two sections in 22. Of the 22 patients, one underwent repeat liver resection immediately after initial hepatectomy to treat a tumor retrospectively recognized on computed tomography (CT) performed before initial hepatectomy. Only data from the other 21 patients were subjected to analysis.

Preoperative staging included a physical examination, measurement of serum carcinoembryonic antigen and carbohydrate antigen 19-9, colonoscopy, barium enema, abdominal imaging with ultrasonography and CT, and chest imaging by routine chest radiographs or CT. After 2002, positron emission tomography (SET-2400, Shimadzu, Kyoto, Japan) was used for preoperative staging.

Hepatectomy Procedures

Hepatectomy was not necessarily performed according to anatomic principles of resection: The guiding principle was assurance of tumor-free margins. To determine whether or not a hepatectomy procedure was acceptably safe for the patient, we used a prediction score (PS) system introduced by Yamanaka et al.[15] When a one-stage combined resection

was precluded by insufficient estimated postoperative liver volume, PVE or two-stage hepatectomy was performed. The PS was calculated using the formula $PS = -84.6 + 0.933\,a + 1.11\,b + 0.999\,c$ where a was the anticipated resection fraction (%) calculated from CT volumetry; *b*, indocyanine green retention rate at 15 min (%); and *c*, the age (years) of the patient. A PS less than 50 indicated that a given hepatectomy would be acceptable. Patients with a PS of 50 or more underwent either two-stage hepatectomy or prehepatectomy PVE.

Intraoperative ultrasonography was used to identify any occult tumors not detected preoperatively and to confirm relationships between tumors and vasculobiliary structures. Parenchymal dissection was performed using ultrasonic dissectors. The Brisbane 2000 terminology of the International Hepato-Pancreato-Biliary Association was used to designate operative procedures.[16]

Principles underlying selection criteria for resection of recurrent hepatic metastases were the same as those for initial hepatectomy. As quality and quantity of remaining hepatic parenchyma were highly important considerations, patients were excluded from repeat hepatic resection when the PS exceeded 50 based on volumetric, indocyanine green, and age considerations.[15]

CT Volumetry

Preoperatively, conventional enhanced CT, helical CT, or CT with arterioportography was performed to define hepatic metastases. As follow-up evaluation after hepatectomy, enhanced CT first was performed 1 or 2 months after hepatectomy and repeated every 3 months as a rule. CT was performed with Asteion scanners (Toshiba Medical, Tokyo, Japan). Serial transverse scans at 5- to 10-mm intervals from the dome of the liver to the most inferior part of the organ were obtained with enhancement of contrast. Each slice of the liver was traced with a cursor, and total liver volume and corresponding area was calculated by computer. Liver neoplasm volume was subtracted from the total liver volume to assess functional liver volume. This was calculated within 1 month before initial hepatectomy and, as a rule, 2 to 6 months later after final liver resection.

Perioperative Factors for Calculation

Perioperative biochemical liver function tests performed after second-stage resection of two-stage hepatectomy and also after final liver resection of multiple repeat hepatectomies included serum albumin (Alb), total bilirubin (TB), platelet count (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time as the international normalized ratio (PT-INR). Data were compared before and, 1 month and 6 months, after hepatectomy. Data at 6 months after hepatectomy for four patients in the two-stage group were excluded from analysis because the disease recurred in the liver earlier than 6 months after the final procedure.

Neoadjuvant and Adjuvant Chemotherapy

Some patients with multiple liver metastases in a bilobar distribution first received neoadjuvant hepatic arterial chemotherapy with a combination of 5-fluorouracil (5-FU), l-folinic acid (FA), and cisplatin (CDDP). After resection for liver metastases or liver recurrence, adjuvant chemotherapy was carried out via hepatic artery infusion or intravenously, usually with 5-FU and FA with or without addition of CDDP or irinotecan. In the two-stage group, neoadjuvant chemotherapy (before initial or second hepatectomy) was carried out in 13 patients, whereas adjuvant chemotherapy (after the second liver resection) was administered to 14 patients. In the repeat hepatectomy group, neoadjuvant chemotherapy was carried out in two patients, and adjuvant chemotherapy was given in 19 of the 21 patients after initial hepatectomy or repeat liver resection.

Data Analysis

Statistical comparisons of baseline data were performed by the Mann–Whitney *U* test or Fisher's exact test. A difference was considered significant when *P* had a value below 0.05.

Results

Impact of a Staged Surgical Procedure vs Repeat Resections on Volumetric Measurements

When characteristics were compared between patients who had two-stage hepatectomy (n=20) and those who had repeat hepatectomy (n=21), the number of metastases was greater in patients with two-stage hepatectomy (P=0.02), and two-stage hepatectomy patients were more likely to undergo PVE before hepatectomy (P<0.001). However, the two groups were comparable in terms of other prehepatectomy variables and treatment-related variables. In patients with repeat hepatectomy, 12 had two liver resections, seven had three resections, and one patient each had four or five resections. The total number of hepatectomies in the repeat hepatectomy group averaged 2.6 (median, 2; range, 2 to 5). The median interval from initial to final hepatectomy for the two-stage hepatectomy group was less than for the repeat hepatectomy patients (P<0.001). No difference was evident between groups for interval between final hepatectomy and liver volume estimation by CT (P=0.29, Table 1).

Table 1 Demographic and Clinical Characteristics in Patient Groups Defined by Surgical Management

Variables		Two-stage hepatectomy (n=20)	Repeat hepatectomy (n=21)	P, two-stage vs repeat
Age (years)		61±10 (range, 38–76; median, 60)	61±10 (range, 32–80; median, 63)	
Gender	Male	13	10	
	Female	7	11	
Primary tumor site	Colon	12	15	
	Rectum	8	6	
Dukes stage	A/B	6	6	
	C	14	15	
Histology	Well	5	4	
	Moderate/ others	15	17	
Liver metastases timing	Synchronous	17	–	
	Metachronous	3	–	
Number		11±7 (range, 2–27; median, 9)	6±5 (range, 2–21; median, 5)	0.02
Maximum size (mm)		68±45 (range, 20–185; median, 49)	44±17 (range, 15–80; median, 45)	
Serum CEA (ng/ml)		826±2,338 (range, 1–10,536; median, 84)	85±146 (range, 1–559; median, 21)	
Extrahepatic disease	Present	8	5	
	Absent	12	16	
Treatment-related				
PVE as adjunct to hepatectomy	Performed	15	3	<0.001
	Not performed	5	18	
Local ablation as adjunct to hepatectomy	Performed	7	3	
	Not performed	13	18	
Tumor-free margin (mm)	≤5	16	18	
	>5	4	3	
Neoadjuvant chemotherapy	Performed	13	2	<0.001
	Not performed	7	19	
Adjuvant chemotherapy	Performed	14	19	
	Not performed	6	2	
Interval between initial and final hepatectomy (days)		91±64 (range, 19–238; median, 81)	952±697 (range, 191–2,322; median, 707)	<0.001
Interval between final hepatectomy and CT estimation (days)		170±72 (range, 25–323; median, 170)	153±32 (range, 77–190; median, 153)	

Well Well-differentiated adenocarcinoma, *Moderate* moderately differentiated adenocarcinoma, *CEA* carcinoembryonic antigen, *PVE* portal vein embolization, *CT* computed tomography

Liver portions totally removed by multiple hepatectomy procedures, total liver volumes before hepatectomy, and final liver volumes are summarized in Table 2. In the group with two-stage hepatectomy, mean total liver volumes before the initial hepatectomy and after the second hepatectomy were 957.4 ml (median, 976.9; range, 720.6 to 1,153.5) and 776.9 ml (median, 766.9; range, 423.5 to 1,113.9; P<0.001 vs before the initial hepatectomy). In the repeat hepatectomy group, the mean total liver volumes before the first hepatectomy and after the final hepatectomy of the multiple resections were 941.5 ml (median, 930.9; range, 624.9 to 1,295.4) and 863.2 ml (median, 814.1; range, 581.5 to 1,379.1; P=0.155 vs before the first hepatectomy). The ratio of total liver volume after to before hepatectomy procedures was expressed as percentage of postoperative liver volume to preoperative size: (volume of total liver volume after the final hepatectomy/total liver volume before the initial hepatectomy)×100%. This ratio was 81.7±15.2% (mean±SD) in the two-stage hepatectomy group and 92.0±11.7% in the repeat hepatectomy group (P=0.027, Fig. 1).

Thirteen patients in the two-stage group and two patients in the repeat hepatectomy group had substantial chemotherapy before hepatectomy (P<0.01). In the two-stage group, the postoperative-to-preoperative liver volume ratios were 82.1±17.3% in patients with neoadjuvant chemotherapy (n=13) and 81.1±11.6% in patients without neoadjuvant chemotherapy (n=7, P=0.72). In the repeat hepatectomy group, they were 79.5±10.0% in patients with neoadjuvant chemotherapy (n=2) and 93.4±

Table 2 Resected Portion of Liver and Total Liver Volume Before and After Hepatectomy

Variables	Two-stage hepatectomy (n=20)	Repeat hepatectomy (n=21)	P value
Resected portion of liver			
Trisections + monosegment + partial	0	2	0.178
Trisections + partial	5	3	
Trisections	4	0	
Bisections + monosegment + partial	2	4	
Bisections + partial	8	11	
Bisections	1	1	
Volume before Hx (ml)	957±132	942±187	0.658
(Median, range)	(977, 721–1,154)	(931, 625–1,295)	
Volume after the final Hx (ml)	777±152	863±197	
(Median, range)	(767, 424 –1,114)	(814, 582–1,379)	0.230

Data are mean±standard deviation
Hx Hepatectomy, *Partial* partially resected segments

11.3% in patients without neoadjuvant chemotherapy (n=19, P=0.09).

Postoperative Liver Function

Results of liver function tests were compared between groups. No significant differences were evident between groups in ALT or TB over time. However, 1 month postoperatively, both AST and PT-INR in the two-stage group (mean±SD, 36.4±16.8 IU and 1.20±0.12) were greater than in the repeat hepatectomy group (23.9±7.1 IU and 1.11±0.14; P=0.017 and P=0.033, respectively). At the same time point, PLT count in the two-stage group (17.4±5.6×10^4/ml) was lower than in the repeat hepatectomy group (21.8±4.4×10^4/ml, P=0.011). Furthermore, at 6 months postoperatively, serum Alb was 3.8±0.3 g/dl in the two-stage group vs 4.1±0.3 g/dl in the repeat hepatectomy group (P=0.041, Fig. 2).

Discussion

No consistent data have been reported concerning the amount of time needed for complete restoration after hepatectomy; estimates have ranged from 2 to 3 month[17–20] to 4 to 6 months.[21–23] This discrepancy may be due to methodologic

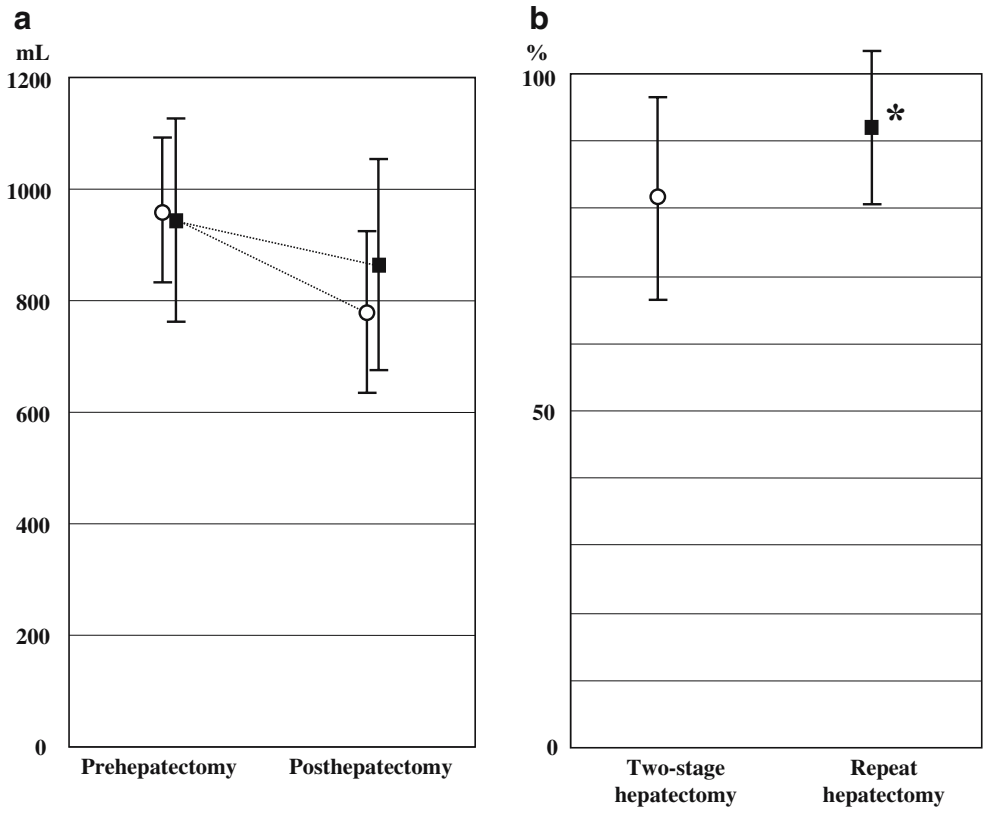

Figure 1 Total liver volume before and after procedures (**a**) and ratio of total liver volume after hepatectomies to that before any procedure (**b**). Each value is the mean±SD. Two-stage hepatectomy (*open circle*), n=20; repeat hepatectomy (*filled square*), n=21; *P<0.05 vs two-stage hepatectomy.

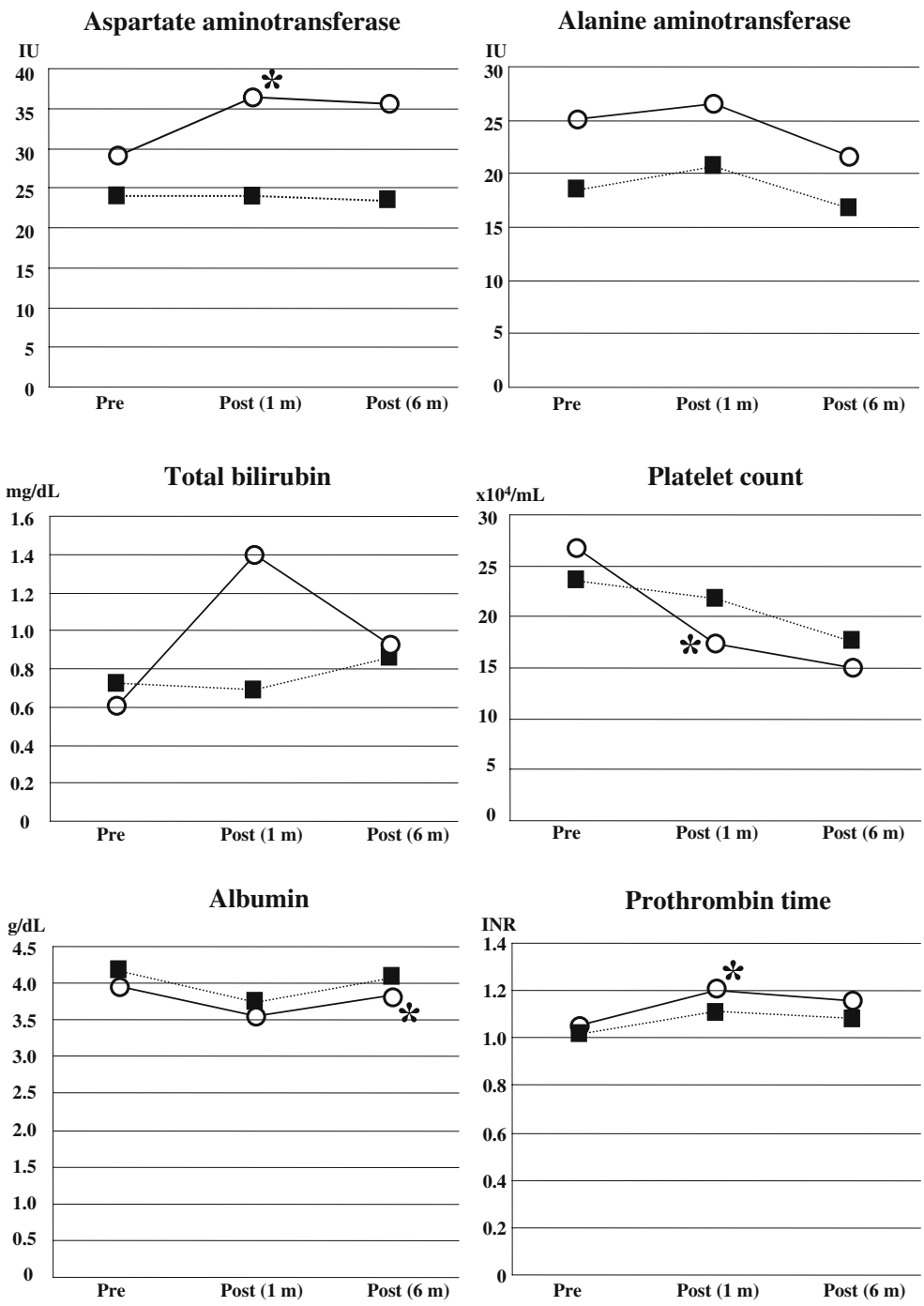

Figure 2 Results of postoperative liver function tests performed sequentially in all patients undergoing hepatectomy. Each value is the group mean. Two-stage hepatectomy (*open circle*), $n=20$; repeat hepatectomy (*filled square*), $n=21$; *$P<0.05$ vs repeat hepatectomy. *Pre* Preoperative, *Post* postoperative.

differences in observation, varying extent of resection, or presence or absence of coexisting liver disease. Human liver regeneration after hepatectomy is influenced by several factors including extent of liver resection,[24–29] liver function,[24,27–32] age,[30] and hepatotrophic factors in portal blood.[33,34] In patients whose extent of hepatectomy was intermediate (30 to 50%), normal livers quickly regained or exceeded preoperative initial volumes in 1 month, followed by a gradual return to preoperative size when preoperative volume had been exceeded. In contrast, injured livers regenerated less rapidly than normal liver, with volumes 2 to 3 months after hepatectomy representing only 80% of those preoperatively. After a large resection in normal liver (resection of more than 50% of preoperative volume), approximately 90% of initial volume was regained within 2 to 3 months, whereas injured livers were restored only to 70 to 80% of initial volume in 3 to 5 months.[24] Likewise, liver regeneration reached a plateau at approximately 75% about 6 months to 1 year after major hepatectomy for biliary cancer.[35] No patient in the present study had chronic

hepatitis, cirrhosis, or obstructive jaundice before hepatectomy. To obtain comparable extent of liver resection between groups, patients with more than two sections of the liver removed by multiple repeat resections for liver recurrence were enrolled so that liver parenchymal status and resection volume, which strongly influence liver regeneration, were comparable between groups. Nonetheless, patterns of liver regeneration differed between groups and total liver volumes after completion of both procedures were greater after repeat hepatectomy (90% or more of functional preoperative volume) than two-stage hepatectomy (about 80%). Differences in clinical factors were observed between groups in proportion of patients with chemotherapy before hepatectomy, total number of metastatic nodules, presence or absence of tumor burden in the remnant liver during regeneration the first hepatectomy, and intervals between initial to final hepatectomy. With respect to the influence of chemotherapy before hepatectomy on liver regeneration, no difference in postoperative-to-preoperative liver volume ratios was observed between patients with neoadjuvant chemotherapy and those without. Influences of tumor presence within the liver upon liver regeneration after hepatectomy are unclear. Dluzniewska et al.[36] reported the proliferation rate of liver cells, and portal vein hepatocyte growth factor concentrations were higher in patients with malignant than benign liver tumors. Although this result appears to be at odds with our present findings, some relationship between liver regeneration and tumor burden would seem likely. Thus, we presumed that tumor burden in a remnant liver during regeneration before final hepatectomy or sequential hepatectomy within a relatively short period restricted the regenerative capacity of the liver after final hepatectomy so that liver restoration was slowed and less volume recovery was possible with the two-stage strategy.

The two-stage hepatectomy patients in this study group were more likely to have perioperative PVE than repeat hepatectomy patients. Nagino et al.[35] reported that preoperative PVE significantly induces regeneration of the future liver remnant before hepatectomy. Liver regeneration therefore would likely be reduced after hepatectomy following PVE. However, the same authors concluded that PVE was not a significant determinant of the ultimate regenerated liver volume.

Seven patients in the two-stage group and three patients in the repeat hepatectomy group had local ablation therapy as an adjunct to hepatectomy. However, no differences in postoperative liver function or in postoperative-to-preoperative liver volume ratios (87.1±11.0 vs 87.0±15.4) were observed between patients with and without ablation therapy (data not illustrated).

Major hepatectomy is associated with hypoproteinemia, cholestasis, and coagulopathy until the remnant liver has regenerated. In patients with hepatectomy whose extent of resection was intermediate (30 to 50%), liver function has been reported to recover concomitantly with liver volume. In contrast, in patients with extensive hepatectomy (>50%), functional parameters generally lagged behind liver volume in recovery—particularly in patients with injured livers.[24] Serum albumin concentrations were reported to decline during the first postoperative month after major hepatectomy whether or not parenchymal liver disease was present. Later, after 4 to 5 months following surgery, albumin steadily normalized in patients with normal liver parenchyma. However, albumin concentrations in patients with cirrhosis had failed to reach preoperative values at 5 months.[24] Greater extent of resection and more severe coexisting liver disease predicted lagging functional recovery, particularly concerning protein synthetic capacity. Likewise, Ezaki et al.[37] reported that platelet counts in patients with chronic hepatitis were significantly decreased at 3 months postoperatively and later tended to remain low. In the present study, AST and PT-INR were higher at postoperative month 1, PLT counts were lower at postoperative month 1, and Alb was lower at postoperative month 6 in the two-stage group than in the repeat hepatectomy group. These results suggest that functional recovery after two-stage hepatectomy appeared less prompt than after repeat hepatectomy. Furthermore, restoration of liver function after two-stage hepatectomy resembled that after hepatectomy in the presence of parenchymal injury.

We concluded that liver volume hypertrophy and liver function recovery after two-stage hepatectomy differed from those seen after repeat hepatectomy for liver recurrence. Regeneration and function of the liver after two-stage hepatectomy were similar to those observed in hepatectomy patients with liver injury. Sequential major hepatectomy within a relatively short period or tumor burden in a remnant liver during liver regeneration after initial hepatectomy compromised regenerative capacity and postoperative liver function in two-stage hepatectomy. Indications for a two-stage procedure as well as the interval between first and second hepatectomy should be considered carefully to minimize risk of liver failure after the procedure.

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Costs and Utilization of Intraoperative Cholangiography

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Abstract
Background Routine intraoperative cholangiography (IOC) has been advocated as a viable strategy to reduce common bile duct injury (CDI) during cholecystectomy. This is predicated, in part, on the low cost of IOC, making it a cost-effective preventive strategy. Using billed hospital charges as a proxy for costs, we sought to estimate costs associated with the performance of IOC.
Methods The 2001 National Inpatient Survey (NIS) database was assessed for IOC utilization and associated charges. Average charges for hospital admission where the primary procedure was laparoscopic cholecystectomy were compared for those associated with and without the performance of IOC.
Results Eighteen percent of cholecystectomies were performed in facilities that never perform IOC. Routine IOC (defined as >75% of cholecystectomies performed in any one hospital having a concomitant IOC) was performed in only 11% of hospitals. In the remaining 71% of hospitals, selective IOC was performed. IOCs were associated with US $706–739 in additional hospital charges when performed in conjunction with laparoscopic cholecystectomy. We project a cost of US $371,356 to prevent a single bile duct injury by using routine cholangiography.
Conclusion We conclude that only a minority of hospitals performs cholecystectomies with routine IOC. Because of the significant amount of hospital charges attributable to IOC, routine IOC is not cost-effective as a preventative measure against bile duct injury during cholecystectomy.

Keywords Intraoperative cholangiography · Choledocholithiasis · National inpatient survey · Comorbidity · Cost effectiveness analysis

Abbreviations
CDE common duct exploration
IOC intraoperative cholangiography
CDI common bile duct injury
LOS length of stay

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Introduction

Whether routine intraoperative cholangiography (IOC) is necessary or not during the performance of cholecystectomy remains unknown. Many factors contribute to the decision to perform IOC. There is little disagreement that IOC is indicated when there are suspected common bile duct (CBD) stones or if the biliary anatomy is unclear during the operation. Consensus is lacking regarding the need to routinely perform IOC with every cholecystectomy.

IOC cost effectiveness factors into the decision to perform routine IOC. IOC introduces some extra cost when performing cholecystectomy; however, the extent of that cost is unclear. Several studies have presented IOC cost data and cite figures ranging from US $77 to 738 per IOC. In cost effectiveness analysis, the costs of a procedure are multiplied by the number of times the procedure is performed and compared to the expense associated with

caring for the complications that would be avoided had the procedure been performed. Given the rarity of CBD injury, very large numbers of IOCs would be required to avoid a single CBD injury. One conservative estimate is that 526 IOCs would be required to prevent a single CBD injury[1]. With this large multiplication, substantial errors in cost-benefit calculations will result if the IOC cost data is inaccurate. For this reason, it is important to establish as accurately as possible the true cost of IOC.

Determining IOC cost is not a simple matter. First and foremost is separating the actual costs from hospital charges. Most studies of IOC costs have actually examined hospital charges. Although charges are proportionate to costs, they generally exceed actual costs by some unknown degree. Because of contracting issues, true cost data is considered proprietary and rarely shared. However, when performing cost effectiveness analysis, use of hospital charges will result in fair comparisons as long as hospital charges are used for all the treatments assessed.

The true cost of IOC has many components. There are obvious expenses such as the cost of the IOC catheter, dyes, and other supplies necessary for performing IOC. Although most series report that an IOC can be performed in 15 min; operating rooms cost over $1,000 per hour to run such that every minute of OR utilization adds greatly to operative costs. The procedure requires fluoroscopy so that there are costs associated with the technician operating the fluoroscope, as well as costs associated with the machine use. Less obvious are fluoroscopy costs attributable to the equipment's depreciation, maintenance, and replacement expenses. Additional expenses are accrued resulting from a radiologist's review of the IOC images. Rarely captured in any analysis is the time lost or additional professional fees for the surgeons performing the cholecystectomy and cholangiogram.

Most IOC cost studies determined IOC charges as they appeared on hospital bills. Several of them assessed only the most obvious expenses such as charges attributable to the IOC supplies used. Having not accounted for the OR time, equipment use, radiologist billing, etc., these studies may underestimate the true cost of IOC. When hospital rates are established they generally account for the totality of costs. Projections for equipment replacement, depreciation, facility costs, etc. are prorated into the overall charge structure. Thus, estimation of procedure costs should be made from charges derived from the overall hospital bill to account for these indirect expenses. Comparison of hospital charges for similar patients matched for the presence or absence of the procedure of interest will result in the best cost estimates. This has been done for IOC, but only for a single institution experience. Because rate structures may vary considerably between hospitals, hospital charge data used for establishing policy must be obtained from multi-institution analyses. To date, this has not been done.

We sought to determine the best estimate for IOC expenses, using hospital charges as a proxy for cost. To do so, we analyzed the 2001 National Inpatient Survey. The NIS acquires annual clinical and hospital charge information from 20% of all hospitalizations in the USA. The sample is population adjusted from US Census information such that national-level estimates of hospital utilization, disease, and procedure incidence can be made. This extensive database lends itself to providing the best estimate of hospital charges attributable to IOC. Given that it is population representative, IOC charge data derived from the NIS will be applicable to the nation as a whole, facilitating cost–benefit estimates that will apply not only to academic but community-based surgical practices.

Methods

A subset of the 2001 NIS[2] was created for all those with any diagnosis of gallbladder disease. These included any patients with a diagnostic code of 574.XX (cholelithiasis), 575.X (other disorders of gallbladder), or 576.X (other disorders of biliary tract). Only those patients having a primary diagnostic code of cholelithiasis (574.XX) or other diseases of the gallbladder (575.XX) were included in the analysis.

Patients undergoing laparoscopic cholecystectomy were identified if they had a procedure code of 51.23. Those having open cholecystectomies were identified with procedure code 51.22 but not being simultaneously encoded with 51.23. Conversion from laparoscopic to open cholecystectomy was assumed if procedure codes 51.22 and 51.23 were present for the same patient or if a diagnostic code of v64.4 (laparoscopic procedure converted to open) was present. Disease burden was estimated by calculation of Charlson comorbidity scores[3] using the Romano modification[4].

Patients with cholelithiasis were identified if they had a diagnostic code of 575.20 (calculus of gallbladder without mention of cholecystitis). If any of the diagnostic codes were 574.0 (calculus of gallbladder with acute cholecystitis), 574.1X (calculus of gallbladder with other cholecystitis), or 575.00 to 575.12 (acute or chronic cholecystitis without mention of calculus), the patient was assumed to have cholecystitis.

Teaching status for a hospital was provided in the NIS database. The hospital size is classified as small, medium, or large, based on a complex assessment of the hospitals' bed capacity and resources in its immediate region such that this categorization is relative to hospital capacities in its immediate vicinity. The size is established such that one third of the hospitals in any region are categorized as small, medium, or large. Thus, small hospitals have anywhere from 1–200, medium 25–550, and large >45 beds[2].

Table 1 Characteristics of Patients Undergoing Cholecystectomy With and Without Intraoperative Cholangiography

	Cholangiogram		
	Yes	No	*p* value
Age	54±20	51±19	<0.0001
% Female	72	73	0.045
LOS (+/− SD)	2.6±1.5	2.5±1.5	<0.0001
Only cholelithiasis	3	4	<0.0001
Calculus of gallbladder with acute cholecystitis	31	35	<0.0001
Calculus of gallbladder with other cholecystitis	57	58	0.0311
Calculus of bile duct with acute cholecystitis	1.2	0.7	<0.0001
Calculus of bile duct with other cholecystitis	1.9	0.9	<0.0001
Calculus of bile duct without mention of cholecystitis	0.4	0.2	0.0003
Acute cholecystitis (only)	8	10	<0.0001
Charlson score (%)			
0	79.0	79.1	NS
1	17.0	16.9	NS
2	3.2	3.2	NS
3	0.5	0.6	NS
4	0.2	0.2	NS
5	0.0	0.1	NS

Continuous data are presented as the mean±SD. Statistical significance for mean differences were determined by Student's *t* testing and for proportions by chi-square analysis. Their proportions of patients with Charlson comorbidities scores that range from 0 (none) to 5 (extensive comorbid disease) are presented with the statistical significance for the difference between IOC groups determined by chi-square analysis.

Population estimates for the number of procedures performed were estimated from the discharge-weighting statistic provided by NIS2001. This weighting factor accounts for the multi-stage stratified design of the NIS, allowing for the information contained in the NIS database to be used for estimating the incidence of hospitalizations, procedures, and diseases in the USA. This weighting factor is not valid for hospital charges information and, therefore, was not used for calculating charges.

Charges attributable to IOC were estimated from the corrected total charges provided by the NIS and only for admissions with length of stay (LOS)≤2 times the median LOS. This was performed to minimize the effect of outliers on IOC cost data.

Costs were recalculated to minimize the effect of associated illnesses, concurrent procedures, or charge variability between hospitals. This was accomplished by grouping the hospitals together based on the NIS hospital identifier code. Once grouped, admissions with the same set of diagnostic and procedure codes were compared with the only difference being the presence or absence of IOC. Hospitals were included in this analysis only if they had at least one match for a set of diagnoses and procedures differing only by the presence or absence of IOC. The mean values for the matched sets were calculated and the mean for charges for admissions with IOC was subtracted from the mean for those without IOC.

We reviewed the studies reporting IOC costs that are commonly cited[5], as well as those we found from literature searches. These studies were systematically evaluated for the type of institution and methodology used for reporting costs.

Statistical analysis and database extractions were performed using the SAS V.9 package (Statistical Analysis Software, Cary, NC). Proportions were compared by chi-square analysis and means by Student's *t* test. Statistical significance was established if the *p* values were <0.05.

Table 2 Differential Charges Attributable to Intraoperative Cholangiography

	Cholangiogram	*n*	Mean Charges	IOC Cost	% Increase
Laparoscopic cholecystectomy	No	154,862	11,899		
	Yes	73,550	12,638	739	6

The percent increase refers to the percent increase in charges relative to charges from hospitalizations where cholecystectomy is performed without intraoperative cholangiography.

Table 3 Effect of Hospital Size and Teaching Status on IOC Utilization and Cost

	Bed Size						Teaching Hospital			
	Small		Medium		Large		Not Teaching		Teaching	
	Charges	*n*	Charges	*n*	Charges	*n*	Charges	*n*	Charges	*n*
With IOC	13,347	7,667	14,593	18,866	14,644	47,017	12,729	51,829	12,336	21,721
No IOC	13,800	16,639	13,745	44,608	13,520	93,615	12,017	97,667	11,688	57,195
IOC cost	-453		848		1124		712		648	
% Cases with IOC		32		30		33		35		28

Results

In 2001, there were 730,048 admissions for gallbladder disease. Of these, 337,729 (75%) underwent laparoscopic cholecystectomy and 112,874 (25%) had open operations.

The median LOS for those undergoing laparoscopic cholecystectomy was 3 days with the mean±SD being 4.0± 5.0. To avoid the effect outliers might have on hospital charges, only those patients with LOS less than two times the median were considered for further analysis. For laparoscopic cholecystectomy, this was six or fewer days. Table 1 presents the clinical features of those undergoing cholecystectomy. Data were stratified by the presence or absence of IOC. Although many of these characteristics demonstrated statistical significance, mean values and proportions were very similar because of the extremely large numbers of patients in each group. Despite the statistical significance, patients were reasonably similar in each group with the exception of more patients having diagnoses of choledocholithiasis and being slightly older in the IOC groups. Although patients were slightly older in the IOC group, the Charlson comorbidity scores were the same between the groups, suggesting that patients having an IOC did not have a greater disease burden than those not undergoing IOC.

When considering the entire cohort of patients, the excess charges attributable to IOC when performed in conjunction with laparoscopic cholecystectomy were US $739 or a 6% increase in hospitalization costs (Table 2). Further refinement of this analysis was achieved by examining the charges from single hospitals with admissions grouped by having the same diagnostic and procedure codes differing only by the presence or absence of IOC. By comparing charges with and without IOC from the same hospital, we minimized the effect of differing rate structures at various hospitals. We also minimized the potential confounding effects of comorbid disease or collateral operations on patient's hospital course and consequent billed charges by assessing a patient cohort that only included the same primary diagnosis (cholecystitis or cholelithiasis) and primary procedure (laparoscopic cholecystectomy). We were able to complete these matches for 894 facilities. This analysis yielded laparoscopic cholecystectomy IOC costs of US $706 per case, similar to the US $739 estimated from the much larger cohort where these exclusions were not made.

An appreciable number of hospitals, 18%, did not report IOCs being performed for any cholecystectomies. There was a trend for these to be smaller, non-teaching hospitals. Fifty-eight percent of cholecystectomies performed in the USA have an IOC rate ranging between 1–50%. A relatively small number of hospitals, 11%, performed IOCs on 75% or more of all cholecystectomies.

Table 4 IOC Costs Previously Reported in the Literature

Reference	Type of Institution	Number of Patients	Study Period	Cost Analysis	IOC Cost
Traverso [7]	Community	55	8/1990–5/1994	Selective	NS[a]
Philips [11]	Community	840	1/1991–7/1992	Total Bill	US $500–725
Berci [14]	Community	2,400	NS[b]	Selective	US $315
Fletcher [6]	Academic	40	NS[b]	Selective	NS[a]
Ladosci [10]	Community	734	1/1991–12/1993	Selective	US $738
Soper [12]	Academic	164	4/1991–2/1992	Total Bill	US $700
Flowers [8]	Academic	364	9/1989–1/1991	Selective	US $299
Podnos [9]	Academic	NS[c]	1/1996–12/2000	Total Bill	US $675

Two of the studies had been cited as providing IOC cost data but no specific reference could be found.
[a] IOC costs not explicitly stated
[b] Study period not explicitly stated
[c] Number of patients assessed not explicitly stated

Thus, routine cholangiography is infrequently practiced in the USA.

We also assessed the data as a function of hospital size and teaching status (Table 3). Small hospitals did not have increased costs attributable the performance of IOC. With progressively increased size, IOC costs increased. Teaching status did not impact IOC costs. Notably, fewer cholecystectomies were performed with IOC in teaching relative to non-teaching facilities.

Discussion

Although there was some variability between facilities based on size and volume of IOCs performed, IOCs done in conjunction with laparoscopic cholecystectomy cost approximately US $700. Arguments supporting the performance of routine cholangiography rely on minimal costs associated with this procedure because common bile duct injury (CDI) is so rare. The most recent population-based studies from the Medicare database have shown that CDI occurs in 1 of every 172 cholecystectomies when cholangiography is not performed. When IOC is done in conjunction with cholecystectomy there is 1 CDI for every 256 cholecystectomies performed. From these data, one can conclude that 526 routine cholangiograms must be performed to prevent a single CBD injury[1,5]. Under these circumstances, if IOC costs US $706, the costs attributable to preventing a CBD injury would be $371,356. Reduced CBD injury has not been definitely linked to routine cholangiography, making it difficult to justify, especially in light of the fact that CBD injury is rare. Additionally, the surgical community remains unconvinced of the need for routine IOC; as indicated by our finding, only 11% of facilities perform routine IOC.

The impact of variation in published IOC cost estimates on the apparent cost-effectiveness of routine IOC use to avoid CDI has been examined[5]. With estimated IOC costs ranging from US $77 to 738, costs attributable to routine IOC were $57,846 to 554,417 per CDI avoided. This tenfold difference in cost-effectiveness estimation illustrates the sensitivity of cost–benefit analysis to the estimated IOC cost. If IOC is inexpensive, the conclusion would be that routine IOC is a cost-effective prevention strategy contrasted to a lack of effectiveness if IOC costs are high.

The same study cited costs US $13,612 to 300,000 per patient, attributable to the treatment of complications or deaths caused by CDI. Based on Washington State data, it was estimated that 714 IOCs are required to prevent one CDI and estimated IOC costs at US $122 per study. The authors concluded that IOC is cost effective in preventing CDI because $87,100 was expended to prevent one CDI. Our population-based data from a national rather than a regional sample concluded that IOC was much more costly than US $122 per case. We estimated that IOCs cost US $706 per case such that US $504,084 must be expended to avoid a complication that costs approximately US $300,000 to treat. These figures argue against routine IOC as a cost-effective strategy for CDI risk reduction.

We reviewed the previously published analyses of IOC cost. Among them, two studies previously cited[5] as reporting costs had not explicitly done so[6,7]. These were eliminated from further consideration. Of the remaining studies, there was a wide range of costs attributed to IOC ranging from US $299 to 738 (Table 4). Both academic and community hospitals reported IOC costs in the same range. Although costs at academic medical centers are often thought to be higher than their community counterparts, this was not observed in our analysis. IOC cost data has also been reported in studies from as early as 1989 to 2000[8,9]. There was no consistent trend of increased costs

with time as one would expect to occur because of inflation. This most likely occurred because cost data was extrapolated from hospital charges that tend to remain relatively constant with time and do not change at the same pace as medical inflation. We found that the US $706 IOC cost we estimated from population-based data is very similar to the approximately US $700 reported in four prior published series[9–12]. This confluence of findings at the US $700 range suggests that this is the most accurate estimate of the cost of IOC and should be the value used for cost–benefit analysis.

Arguments in favor of routine IOC include reduced CBD injury when it is used. CBD injury is a rare event so that demonstrating reduced injury rates requires analysis of very large series. Studies examining administrative databases have shown that routine cholangiography is associated with reduced CBD injury rates[13]. Although these studies had power by virtue in the very large numbers of operations evaluated, administrative databases have limited patient information. This constrains the analysis because the overall outcomes of patients with these injuries is not known. Administrative databases are also limited by the accuracy of discharge coding that can be highly variable from one hospital to another.

The simple occurrence of a CBD injury is undesirable but may have little clinical significance. Although injury in proximity to the hepatic confluence may be difficult to repair, some lower CD injuries recognized at the time of operation can be easily repaired with little patient morbidity. Alternatively, these injuries can substantially impact patients if they are unrecognized, resulting in postoperative sepsis and requiring complex major reconstructive operations. Thus, the range of adverse outcomes attributable to CDI is great. When determining the merits of routine IOC, the entire range of outcomes must be considered. Because some injuries are of little consequence, only CBD injuries that result in significant complications should be considered in the arguments in favor of routine IOC. To date, this has not been the case, and proponents of routine IOC have cited total, overall CBD injury rates, and their reduction by virtue of routine IOC in support of this practice.

In conclusion, we have found that routine IOC is not widely practiced by the surgical community. Seventy-one percent of laparoscopic cholecystectomies are done with a selective IOC approach. Analysis of a very large database of nationally representative data revealed that IOC costs, on average, US $706 per case. This estimate appears reliable, as it is similar to those arrived at in four other studies reporting from single institution analysis.

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Vascular Resection and Reconstruction for Pancreatic Malignancy: A Single Center Survival Study

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Abstract

Introduction Pancreatic cancer is one of the leading causes of cancer-related death in the USA. Recently, several centers have introduced portal and superior mesenteric vein resection and reconstruction during extended pancreatectomy, rendering the previously inoperable cases resectable.

Aim The aim of this study is to confirm whether patients with locally advanced pancreatic cancer and mesenteric vascular invasion can be cured with extended pancreatectomy with vascular reconstruction (VR) and to compare their survival to patients treated with pancreatectomy without VR and those treated without resection (palliation).

Methods Survival of 22 patients who underwent pancreatectomy with VR was compared with two control groups: 54 patients who underwent pancreatectomy without the need for VR and 28 patients whose pre-operative imaging suggested resectability but whose laparotomy indicated inoperability.

Results A slight survival benefit was noted in patients who did not require VR (33.5%) compared to those who did require VR [20%, $p=0.18$], although not reaching statistical significance. Despite a low 15% three-year survival in patients treated palliatively, this was not statistically different compared to survival after resection with VR ($P=0.23$). The presence of nodal metastasis was associated with worse survival ($p=0.006$), and the use of adjuvant therapy was associated with better survival ($p=0.001$).

Conclusion Pancreatic cancers that require VR to completely resect the tumor have a similar survival to those not requiring VR. Long-term survival was achievable in approximately 1 out 5 patients requiring VR, although we were not able to demonstrate statistically improved survival compared to palliative care.

Keywords Pancreatic cancer · Vascular reconstruction · Post operative survival

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Background

Pancreatic cancer is one of the leading causes of cancer-related deaths in the USA, second only to colorectal cancer as a cause of gastrointestinal-related death.[1] More than 37,000 new cases are expected to be diagnosed in 2007 with mortality in excess of 33,300.[1] The overall 5-year survival rate has remained <5% for the last three decades despite all the recent advances in diagnosis and staging. Treatment of pancreatic cancer includes multiple modalities but surgical resection is the only potentially curative treatment. Unfortunately, because of the late presentation of the disease, only 15 to 20% of patients are considered for pancreatectomy. Although surgery offers the only potential chance for long-term survival, the prognosis in most patients is poor even in those with resectable disease, where the 5-year survival remains less than 20%.[2–4]

Approximately 40% of patients with pancreatic cancer present with locally advanced nonmetastatic disease. Tumor adherence or invasion into adjacent structures, particularly the celiac and superior mesenteric vasculature (T4 or stage III disease) makes complete resection very difficult or impossible. Portal or superior mesenteric vein involvement with the tumor has previously been staged as T4,[5] and therefore, is considered a contraindication to surgery in most cases. However, for the last several decades, pancreatic surgeons have been able to resect and reconstruct either or both of those veins resulting in a reclassification by the American Joint Commission on Cancer (AJCC) of tumors invading the mesenteric veins at T3.[6] In a large single center series published by Tseng et al. at M.D. Anderson Cancer Center,[7] a total of 141 patients underwent pancreaticoduodenectomy (PD) with vascular reconstruction (VR). The authors concluded that patients undergoing VR had survival similar to those who underwent standard PD (median of 2 years) and superior to historical patients with locally advanced disease who were treated non-operatively.

The aim of this study is to confirm whether patients with locally advanced pancreatic cancer and mesenteric vascular invasion have similar survival with extended pancreatectomy with VR and to compare their survival to patients treated with pancreatectomy without VR. Further, we compared survival for resected groups to unresectable patients. We hypothesized that a proportion of patients requiring VR are curable by surgery but with a prognosis worse than patients without mesenteric vascular invasion.

Methods

Patient Selection

This minimal-risk study was approved by Mayo Clinic Institutional Review Board. In a retrospective review, data were reviewed on 104 patients with pancreatic adenocarcinoma, who underwent an exploratory laparotomy with the intent of pancreatic resection for adenocarcinoma between February 1998 and February 2005 at Mayo Clinic in Jacksonville, FL. Vein resection was performed if it permitted complete resection of tumor.

Patients underwent standard or pylorus-preserving pancreaticoduodenectomy (PD), distal pancreatectomy or total pancreatectomy, depending on the primary pathology and location. Twenty-two patients underwent VR of either portal vein, superior mesenteric vein (SMV) or both (VR group) because of gross tumor involvement. It should be noted that the surgeons involved usually attempt to dissect the tumor from the vein initially, and only proceed with VR if it appeared there was direct venous invasion.

To maintain a homogenous group of patients, only VRs involving tangential or segmental resection with subsequent venous patching, interposition grafting, or primary anastomosis were included. The remaining patients were categorized into two control groups to separately determine the survival benefit of pancreatic resection and vascular reconstruction. The first control group "palliative care" (P group) included 28 patients with pancreatic cancer whose pre-operative imaging suggested resectability but whose laparotomy identified metastatic disease or arterial vascular encasement that precluded vascular reconstruction. The patients were typically treated with biliary-enteric bypass, followed by palliative therapy. The second control group included 54 patients with pancreatic cancer who underwent an exploratory laparotomy with pancreatectomy *without* the need for PV or SMV reconstruction (R group). Data on patients' demographics, treatment, histopathology, and follow-up were recorded. Patients who underwent chemoradiation were confirmed to have completed the treatment courses recommended.

Surgical Eligibility

Preoperative evaluations included history and physical examination, routine laboratory testing, chest radiography, electrocardiography, contrast-enhanced computed tomography (CT), and/or magnetic resonance imaging (MRI/MRCP). The majority of patients underwent pre-surgical endoscopic ultrasound (EUS) to assess resectability and to obtain tissue to confirm the diagnosis. All patients in this series had invasive ductal adenocarcinoma, all of which were confirmed by final surgical pathology. Patients with the following additional criteria were excluded:

1. Tumor extension to the superior mesenteric artery (SMA) or celiac axis, as defined by the absence of a fat plane between the tumor and these arteries by CT, MRI or EUS.

Table 1 Summarizes the Demographics, Tumor Staging (TNM status), and Type Surgical Resection in All 76 Patients Who Underwent Pancreatectomy, and 28 Patients Who Underwent Exploratory Laparatomy

	R Group (n=54)	VR Group (n=22)	P Group (n=28)	P Value
Median age (range)	71 (39–89)	70 (48–82)	73 (47–87)	0.3[a]
ECOG	1 (0–2)	1 (0–2)	1 (0–2)	0.9[a]
Male	57% (31)	50% (11)	61% (17)	0.8[b]
Advanced T Stage (T 3–4)	48% (26)	91% (20)	100% (28)	<0.001[b]
Nodal Metastasis	48% (26)	59% (13)	21% (6)	0.014[b]
Distant Metastasis	4% (2)	5% (1)	61% (17)	<0.001[b]
Type of surgery				
Pancreaticoduodenectomy	70% (38)	86% (19)	N/A	
Total pancreatectomy	11% (6)	9% (2)		
Distal pancreatectomy	19% (10)	5% (1)		
Adjuvant (or palliative) therapy	52% (28)	59% (13)	85% (24)	
Chemoradiotherapy	44% (24)	55% (12)	82% (23)	
Chemotherapy alone	6% (3)	4% (1)	0% (0)	
Radiotherapy alone	2% (1)	0% (0)	0% (0)	

[a] Kruskal–Wallis test
[b] Fisher's exact test

2. The presence of extra pancreatic metastatic disease identified by presurgical imaging studies.
3. Severe medical comorbidities including oxygen-dependant obstructive pulmonary disease, unstable coronary artery disease, and other uncontrolled malignancies.

The extent of venous involvement by the primary tumor was not a contraindication for operation as long as there was no CT evidence of tumor extension to the celiac axis or SMA, and there was a suitable SMV below and PV above the site of venous involvement. In this study, the patient who underwent previous attempts of pancreatectomy and those with other indications for pancreatectomy including islet cell or neuroendocrine tumors were excluded.

Surgical Technique

The technique of venous reconstruction generally depended on the length of the venous involvement by the tumor. No heparin was administered. Involvement of the lateral portal or superior mesenteric vein was managed by proximal and distal control, excision of the involved vein, and primary closure. In cases where hemodynamically significant narrowing of the vein would result from primary closure, a vein patch closure was utilized. Cases with >180° of vein involvement usually required segmental resection and primary end-to-end anastomosis. If the segmental resection resulted in tension, or the resected portion was too long for primary anastomosis, a vein graft including composite graft reconstructed with gonadal and inferior mesenteric veins was utilized. The last option was to utilize a synthetic graft (FEP ringed Goretex vascular graft, 14-mm diameter, catalogue number R14030030). All resections and reconstructions were carried out with at least ×2.5 magnification. Cross-clamp time of the SMV and PV was kept to a minimum to avoid edema of the bowel.

Pathologic Analysis

All surgical pathology specimens were evaluated by the department of pathology of the Mayo Clinic Jacksonville. Data was reported using as standard the College of American Pathologist (http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html)/AJCC template for pancreatic cancer,[8] which includes a description of the size the specimen, histologic grade, regional lymph nodes, pancreatic, bile duct, and gastric, or duodenal margins, radial margins, venous lymphatic invasion, and perineural invasion. A post-surgical staging was provided by the pathologist (TNM system) and verified on all patients. The TNM classification of the 2002, sixth edition of the AJCC[6] was used in all cases. In cases before 2002, the gross and microscopic descriptions of vascular involvement were reviewed in each case and restaged using the current 2002 criteria. The status of vein invasion by gross and microscopic criteria was recorded in all patients in the VR group.

Statistical Analysis

All data analyses were performed using Statistical Package for the Social Sciences (SPSS) version 13.0 software (SPSS, Inc., Chicago, IL). Continuous variables were summarized using medians and ranges, whereas categorical variables were summarized using proportions. Because the data were small and not normally distributed, comparisons

of patient characteristics were performed using nonparametric tests. Fisher's exact test was used to compare categorical variables, whereas Kruskal–Wallis and Wilcoxon rank–sum tests were used for continuous variables in the univariate analysis.

Survival and follow-up were calculated from the time of exploratory laparoscopy to date of death or last available follow-up. All deaths from any cause were included in the survival analysis and subsequent multivariate analysis. Overall survival was demonstrated using the method of Kaplan and Meier. Log-rank test was used to evaluate differences between survival curves. All differences and associations were considered significant at two-sided $P<0.05$.

Univariate and multivariate analyses determining the effects of potential prognostic factors on survival were done using log-rank test and Cox proportional hazards analysis. To assess the differences among three groups, two pair-wise comparisons were performed. The first comparison was performed between the patients who underwent pancreatic resection with vascular reconstruction and those who underwent pancreatic resection without VR. Covariates included VR, advanced T stage, nodal metastasis, Eastern Cooperative Oncology Group (ECOG) status,[9] pancreatic resection margin involvement, and adjuvant therapy. The second comparison was between the patients who underwent resection with VR and those without pancreatic resection. Covariates included pancreatic resection, nodal metastasis, distant metastasis, ECOG status, and adjuvant therapy.

Results

During the study period, records from 104 patients who underwent pancreatectomy for adenocarcinoma were evaluated. The baseline characteristics of the study and two control groups were comparable, as demonstrated in Table 1 that also summarizes tumor staging (TNM status), type of surgical resection, and adjuvant therapy status. It should be noted that the T staging in the P group was based on pre- and intra-operative assessment but could be inaccurate as no resection was carried out. Using the same argument, the N stage in this group was based on pre-operative imaging, and based on that, we estimated lymph node involvement in at least 21% of the cases.

Twenty-two patients underwent pancreatectomy with VR including 19 patients with pancreaticoduodenectomy (Whipple procedure), 2 with total pancreatectomy, and 1 with distal pancreatectomy. This last patient was found to have adherence at the junction of the splenic vein and the portal vein. The splenic vein was transected, encroaching into the wall of the portal vein, which was then repaired directly (Table 2 summarizes the type of VR in this group).

Table 2 Type of VR in All Cases

Type of Surgery (*N*)	PV Reconstruction	SMV Reconstruction	PV/SMV Reconstruction
Total pancreatectomy (2)	2	0	0
Whipple (19)	14	4	1
Distal pancreatectomy (1)	1	0	0

Surgical pathology confirmed the type of tumor that included adenocarcinoma (ductal origin), adenosquamous carcinoma, mucinous adenocarcinoma, and intraductal papillary mucinous neoplasms with invasive carcinoma. The final surgical pathology in all three groups is summarized in Table 3.

PV or SMV tumor invasion was confirmed in 14 out of 22 cases of VR (64%) by gross or microscopic pathologic examination. The depth of invasion ranged from adventitial to transmural invasion. No invasion was noted in 5 out of 22 cases (23%), and no data could be obtained about vessel invasion in 3 out of 22 cases (14%).

None of the 76 patients who underwent resection died within 30 days of surgery, whereas two patients from the palliative group expired during the same period of time. A total of 11 surgeons were involved in pancreas resections within the study timeframe. Out of those, only five performed the VR, with one surgeon performing 45% of the overall VR. Intraoperative blood flow was assessed clinically at the completion of reconstruction, and color-flow Doppler ultrasound was performed during the post-op period to assess patency of the reconstructed veins. No patient was found to have superior mesenteric or portal venous thrombosis after reconstruction.

Table 3 Final Surgical Pathology in All Three Groups

Post Surgical Pathology	R Group (n=54)	VR Group (n=22)	P Group (n=28)
Adenocarcinoma (ductal origin)	42	17	27
Acinar cell variant	4	1	0
Adenosquamous carcinoma	1	1	0
Mucinous adenocarcinoma	4	2	1
IPMN with invasive carcinoma	3	1	0

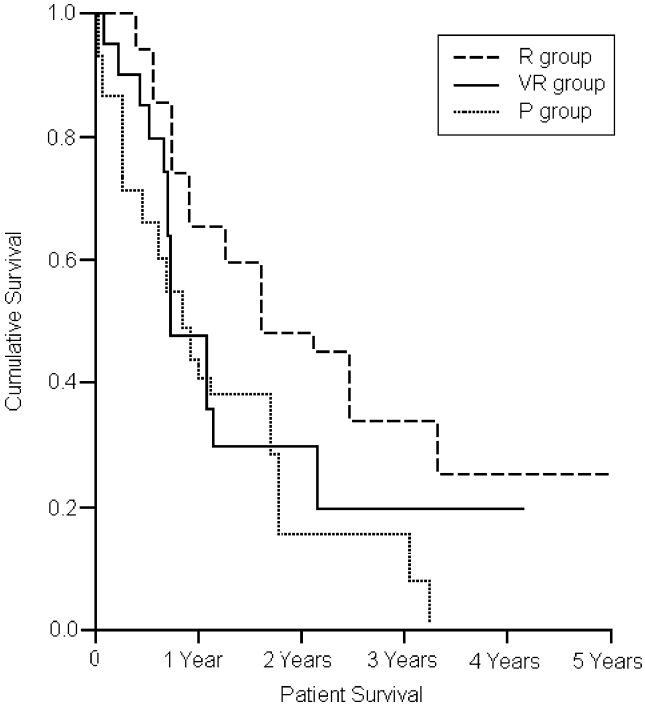

Figure 1 Kaplan–Meier survival curve for the three study groups.

Survival Analysis

The median follow-up time for the R, VR, and P groups was 339, 264, and 130 days, respectively. The estimated 5-year survival after pancreatectomy in this series of patients is 25%, and for patients requiring major venous resection is 20%. There is no statistical difference in survival between the two groups. Figure 1 demonstrates long-term survival in all three groups. Although not reaching statistical significance, there was a slight survival benefit noted in the R group of patients (33.5%) compared to the VR group (20%, p=0.18). Despite a low 15% 3-year-survival in the P group, this was not statistically different compared to survival after resection with VR (P=0.23), although the study may be underpowered to detect small, but clinically significant differences (Table 4).

To further explore other factors associated with survival and control for confounding variables, we performed univariate and multivariate analysis in two pairwise comparisons. First, we compared patients who underwent pancreatic resections (R and VR group). The presence of nodal metastasis was significant and negatively associated with survival. Multivariate analysis using Cox proportional hazard analysis confirmed that nodal metastases remained independently and significantly associated with mortality after controlling for T stage and adjuvant therapy (Table 5).

The second comparison was performed between all patients who went pancreatectomy (groups R and VR combined) and P group of patients to examine the effect of pancreatectomy. Similar analyses were used, and the results are demonstrated in Table 6 (multivariate analysis). Only adjuvant therapy was found to be significantly and positively associated with survival in the univariate analysis. In the multivariate analysis, the presence of nodal metastasis was associated with worse survival and the use of adjuvant therapy was associated with better survival (Table 7).

Discussion

Pancreatic adenocarcinoma is one of the most aggressive gastrointestinal malignancies with limited long-term survival even in cases undergoing surgical resection with curative intent. Thus, treating clinicians remain reluctant to refer patients for such a surgery that has significant morbidity and mortality.

The first report of SMV resection and reconstruction came from the University of Minnesota by Moore and his colleagues in 1951.[10] Subsequent studies established the long-term patency of autologous vein grafts compared to the synthetic prosthesis where occlusion is not uncom-

Table 4 The Estimated Survival with Corresponding 95% Confidence Intervals

Estimated Patient Survival (95% Confidence Interval)	R Group	VR Group	P Group
Number at risk	54	22	28
1 year	64.7% (50.2%–79.2%) 24	41.9% (19.4%–64.4%) 7	38.4% (16.4%–60.4%) 7
2 years	49.6% (33.5%–65.7%) 12	30.0% (8.6%–51.4%) 3	15.4% (0%–34.0%) 2
3 years	33.5% (14.9%–52.1%) 4	20.0% (0%–41.4%) 1	15.4% (0%–34.0%) 2
4 years	25.1% (5.1%–45.1%) 2	20.0% (0%–41.4%) 1	
5 years	25.1% (5.1%–45.1%) 2		

Table 5 Multivariate Analysis Using Cox Regression Analysis Comparing R and VR Groups

Factors	*P* Value	Hazard Ratio (95% Confidence Interval)
PV or SMV reconstruction	0.18	1.80 (0.76–4.22)
Advanced T stage	0.82	1.10 (0.47–2.61)
Nodal metastasis	<0.001	4.27 (1.90–9.52)
ECOG status	0.48	1.30 (0.63–2.69)
Positive margin	0.27	1.68 (0.67–4.25)
Adjuvant therapy	0.30	0.68 (0.32–1.41)

mon.[11] Although Japanese surgeons used this method to improve survival by widening the margins of pancreatectomy to involve surrounding structures,[12] it was not until the 1973 when the concept of "en bloc" pancreatectomy was further defined by Fortner.[13] These authors speculated that resecting a wider margin of healthy tissue and the involved vessels would translate into survival benefit.

VR was initially performed in an effort to maximize soft tissue and lymphatic excision. However, from subsequent work done by Yeo et al., it became evident that widening the surgical margins to include more lymph tissue had little effects on survival.[14] One large series demonstrated that with proper patient selection and surgeon experience, VR can be performed safely with complication rate similar to standard pancreatic resections.[7] The low complication rate reported with vascular reconstruction and the improving operative morbidity and mortality after PD makes it reasonable to consider vascular resection to achieve an R0 resection. Despite that, VR at the time of pancreatic resection remains a controversial approach because of the complexity of the surgical procedure itself and the lack of evidence of survival benefit. Our study suggests that approximately one in three patients with mesenteric vascular invasion can achieve long-term survival with surgery including VR. Although the long-term survival after surgery with VR was numerically better than palliative care group, the small number of patients did not allow demonstration of statistically improved survival.

Table 6 Multivariate Analysis Using Cox Regression Analysis Comparing Patients Who Underwent Pancreatectomy (Groups R and VR Combined) and P Group

Factors	*P* Value	Hazard Ratio (95% Confidence Interval)
Resection	0.23	0.55 (0.20–1.47)
Nodal metastasis	0.006	3.66 (1.46–9.19)
Distant metastasis	0.07	2.72 (0.94–7.92)
ECOG status	0.11	1.83 (0.87–3.85)
Adjuvant therapy	0.001	0.17 (0.06–0.51)

There remains no consensus on the specific indications for vascular resection of the SMV or its confluence with PV. In half of the cases in our study, the decision to proceed with VR was made before the laparotomy, based on evidence for PV or SMV invasion by endoscopic ultrasound (EUS), computed tomography (CT scan), or magnetic resonance imaging (MRI). In a previous series by Tseng et al.,[7] this decision was primarily made at the time of surgery where tumor adherence to these venous structures prevented the surgeon from mobilizing the SMPV confluence from the pancreatic head and uncinate process, as is necessary for standard PD.

The need for VR may be due to adherence to vasculature without actual invasion. In this series, pathology of the excised pancreas confirmed vascular invasion in 64% of cases, compared to 61% of cases in the series by Tseng et al.[7] Peritumoral inflammation with adherence to surrounding vasculature may necessitate VR even in the absence of pathologically confirmed invasion. This makes pre-operative staging and decision-making more challenging since all current imaging methods (EUS, CT, MRI) have limited ability to distinguish vascular abutment, adherence, and invasion.[15] A recent emerging technique involves the use of intravascular ultrasound intraoperatively to assist the differentiation of true vascular invasion versus adherence only. It further suggests that surgeons should be prepared to perform VR regardless of whether the pre-operative staging indicated vascular invasion. In some cases, involvement of the lateral superior mesenteric or portal vein was evident only after the pancreas was transected. At that point, vein resection must be performed to achieve an R0 resection.

The major limitation of this study is the retrospective nature that could result in variations in pre-operative selection criteria and mixed patient populations. We have made specific efforts to minimize these limitations.

The success of pancreatectomy with VR requires careful selection of patients. Only recently has there been an effort to establish criteria for resectable, borderline resectable, and unresectable pancreatic cancer. In our series, we applied strict preoperative criteria for local tumor resectability in line with NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines for Criteria Defining Resectability Status.[8] These

Table 7 Univariate Analysis of Survival

Type of Comparison	Log–Rank Analysis (*P* Value)
VR group	0.07
R group (comparison 1)	
P group (comparison 2)	0.49
VR group	
R group	0.003
P group (comparison 3)	

include patients with evidence of arterial involvement, aortic or inferior vena cava invasion or encasement, involvement of the SMV below the transverse mesocolon, involvement of long segments of vein, or occlusion of the SMV or PV. Regional lymph node involvement and direct extension of the primary tumor to adjacent organs were not considered contra-indications to resection. Such criteria are necessary to avoid the inclusion of patients with grossly incomplete resections. Survival duration in this group may be affected more by the failure to remove all gross tumor than by other potential prognostic variables. Varadhachary et al.[16] have emphasized that survival of patients who do not have an R0 resection is no different from patients with locally advanced unresectable disease. The only exception in our study was the inclusion of one patient with VR, whereby surgical pathology revealed SMA invasion (in addition to known SMV invasion), which was not detected on pre-operative radiographic assessment.

Our study included only patients with pathologically confirmed malignant tumors of the pancreas that minimized differences among the three patient groups (one study and two control groups). In addition, all resections performed in this study were primary, excluding patients who had previous exploration or unsuccessful attempts of pancreatic resections that might increase the likelihood of peritoneal seeding[17] or influence the tumor's subsequent behavior. The fact that most of the resections were performed by two experienced surgeons helps reduce the technical differences in performing the reconstruction between the different surgeons and likely contributed to the absence of operative mortality in this particular group. In addition, we have adequately controlled for co-morbidities by including the ECOG performance status in the analysis of all the groups.

In the analysis of patients who underwent pancreatectomy, we found no statistically significant survival difference between the VR and the two other control groups, after controlling for potentially confounding variables. Although there may be a small survival difference among patients with locally advanced metastatic disease compared to metastatic disease within the P group, we elected to combine these subgroups due the small number of patients and to facilitate the analysis. Despite the fact that long-term survival after surgery with VR was numerically better than palliative care, the small number of patients did not allow demonstration of statistically improved survival.

In summary, we were able to achieve a 3-year survival of 20% in patients requiring VR, although we were not able to demonstrate statistically improved survival compared to the palliative care group. Future studies may be needed to further identify a subgroup of patients who may benefit from this surgical approach. Until then, we suggest that this type of procedure be performed by skilled pancreatic surgeons in high-volume centers.

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Pancreatic Redo Procedures: To do or Not To Do—This is the Question

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Abstract
Background Pancreatic redo procedures belong to the most difficult abdominal operations because of altered anatomy, significant adhesions, and the potential of recurrent disease. We report on our experience with 15 redo procedures among a series of 350 consecutive pancreatic operations.
Patient and Methods From January 1, 2004 to May 31, 2006 a total of 350 patients underwent pancreatic surgery in our department. There were 15 patients identified who had pancreatic redo surgery for benign (14) or malignant (1) disease. Perioperative parameters and outcome of 15 patients undergoing redo surgery after pancreatic resections were evaluated.
Results Operative procedures included revision and redo of the pancreaticojejunostomy after resection of the pancreatic margin (6), completion pancreatectomy (3), conversion from duodenum-preserving pancreatic head resection to pylorus-preserving pancreaticoduodenectomy (3), classic pancreaticoduodenectomy after nonresective pancreatic surgery (1), redo of left-sided pancreatectomy (1), and classic pancreaticoduodenectomy after left-sided pancreatectomy (1). Histology revealed chronic pancreatitis in 14 and a mucinous adenocarcinoma of the pancreas in 1 patient. Median operative time was 335 min (235–615 min) and median intraoperative blood loss was 600 ml (300–2,800 ml). Median postoperative ICU stay was 20 h (4–113 h) and median postoperative hospital stay was 15 days (7–30 days). There was no perioperative mortality and morbidity was 33%.
Conclusion Pancreatic redo surgery can be performed with low morbidity and mortality. Redo surgery has a defined spectrum of indications, but to achieve good results surgery may be performed at high-volume centers.

Keywords Surgery · Chronic pancreatitis · Pancreatic carcinoma · Complication · Outcome

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Introduction

Pancreatic surgery belongs to the most demanding operative procedures in abdominal surgery. Remarkable progress has been achieved during the last three decades and pancreatic surgery can nowadays be performed safely with low morbidity and mortality.[1] However, excellent results seem only to be reported from institutions with significant expertise. There is growing evidence in the literature that outcome is inversely related to hospital volume, i.e., higher-volume hospitals show a significantly reduced mortality compared to low-volume hospitals,[2] a fact that is paralleled with other major oncologic resections such as esophagectomy, gastrectomy, or rectal resections.[3–5] In addition, long-

term survival is significantly superior when performed in high-volume centers with more than 25 cases per year.[6] Furthermore, up to 67% of patients deemed to have unresectable disease on previous exploratory laparotomy can be operated on with curative intent in specialized centers.[7] It is increasingly realized that the surgeon is a critical and important prognostic factor.[8] Therefore, centralization of this type of surgery seems to be reasonable to optimize treatment success.

Whether these facts also apply for benign diseases of the pancreas remains to be determined, but it seems likely to be true. The standard of treatment of chronic pancreatitis has significantly changed during the last decade in conjunction with the advent of a better understanding of the pathophysiology of chronic pancreatitis. Because pain as the principle symptom is mainly related to perineural eosinophilic infiltration and ductal hypertension,[9] a pancreatic head resection is only rarely performed. Instead, duodenum-preserving pancreatic head resection (DPPHR) according to Beger et al.[10] or with the "Bern modification" or a procedure according to Frey and Smith[11] are increasingly applied with equally effective outcome.[12] However, the correct indication for surgery and application of the correct procedure for the individual patient seem to be of paramount importance to prevent an unsuccessful outcome.

Whereas primary pancreatic surgery requires significant expertise, pancreatic redo surgery may be even more demanding. The anatomy is significantly altered, especially after pancreaticoduodenectomy (PD). Adhesions may be substantial and in the case of complicated postoperative period after the index operation, access to the pancreatic remnant can be a fortuitous trial. Usually, the Roux-en-Y limb has to be resected and another limb must be mobilized for reconstruction. In addition, in the presence of a stenosis of the hepaticojejunostomy a redo of the bilioenteric anastomosis has to be performed near the bifurcation when percutaneous balloon dilatation or stenting has failed, which can be extremely difficult. However, any redo procedure may be abandoned if unresectable recurrent disease is detected during the operation.

There is a plethora of reports in the literature on reoperative surgery for pancreatic adenocarcinoma.[7,13–15] However, these studies relate only to the scenario when a patient with a pancreatic carcinoma is explored and deemed unresectable or has undergone palliative surgery, such as bilioenteric or gastroenteric bypass, and is reexplored. In contrast, up to now there is a significant lack of literature on redo surgery after pancreatic resection[16] and indications, perioperative results, and long-term outcome remain to be defined. Thus, we aimed at reviewing our experiences with pancreatic redo procedures after having launched a new pancreatic program in our hospital starting last January 1, 2004 with more than 350 patients operated on as of May 31, 2006.

Patients and Methods

Between January 2004 and May 2006, 350 patients underwent surgery for pancreatic disease. Among this patient population we identified 15 (4.4%) patients in our prospective database who underwent either a PD, a left-sided distal pancreatectomy, a DPPHR, or a pancreatico-cystojejunostomy as primary operation for either benign or malignant disease. Pancreatic redo procedures were defined as procedures after a partial resection of the pancreas or a drainage procedure. Patients who had undergone an exploratory laparotomy or a palliative procedure such as gastroenterostomy or bilioenteric bypass for suspected inoperability were not included in this analysis.

All pathologic specimen were reviewed by a single pathologist (A. T.) to confirm the diagnosis of either pancreatic adenocarcinoma or chronic pancreatitis. The primary original histology was reviewed when available. Perioperative imaging included a computed tomography (CT) scanning and endoscopic ultrasound in all instances. Magnetic resonance imaging, magnetic resonance cholangiography, or endoscopic retrograde cholangiopancreatography were performed when indicated.

Procedure-related parameters like operative time, intraoperative blood loss, ICU stay, and postoperative hospital stay were collected. Red blood cell transfusions were divided by time in the perioperative and postoperative period. The perioperative period included the procedure itself and the first 8 h after the operation; the postoperative period is the remaining time until discharge. The overall incidence of postoperative complications was evaluated. A pancreatic fistula was defined as a drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content greater than three times the serum amylase activity. This definition is in accordance with the International Study Group for Pancreatic Fistula (ISGPF).[17] Wound infection was defined as any wound requiring reopening for the drainage of pus together with a positive wound culture. Mortality was defined as any death during postoperative hospitalization or within 30 days of surgery. Follow-up information was obtained through direct contact with the patient during pancreas clinic visits and review of hospital charts and operative notes. Pain control was estimated semiquantitatively by three categories. "Improvement" of pain control was defined as discontinuation of former continuous pain medication during the follow-up period. "Impairment" of pain control was defined as escalation of pain medication in terms of dosage, frequency of application, and step-up in substance classes (e.g., from NSAID to opioids). The category "no change" was attributed to patients who experienced neither improvement nor impairment. Follow-up data were complete for every patient (100%). All continuous data are presented as mean±SE of the mean.

Results

During the study period, 350 patients underwent pancreatic surgery for either malignant or benign disease. Of these 15 (4.4%) had undergone previous pancreatic surgery with partial resection of the pancreas or a drainage procedure. There were nine men and six women with a mean age of 50 years (range 11–75 years). Only 1 patient had undergone surgery in our institution, whereas the remaining 14 patients had surgery elsewhere.

The indication for the primary operation was chronic pancreatitis (10 patients), adenocarcinoma of the pancreas

Table 1 Patient Characteristics: Diagnosis, Original Histology, and Previous and Current Operation

Patient	Sex	Age	Diagnosis	Original histology	Previous operation (time ago)	Operation
1	F	51	CP with occlusion of PJ	pT3, pN0, M0 adenocarcinoma	CPDE (3 years, 4 months)	RE-PJ with new GE
2	F	45	Recurrent pancreatitis after pancreaticogastrostomy	Mucinous pancreatic cystadenoma	PD with pancreaticogastrostomy (10 years, 0 months)	RE-PJ
3	M	64	CP of pancreatic tail	Adenocarcinoma of the distal common bile duct	CPDE (11 years, 1 months)	RE-PJ with new HJ and GE, resection of segment IV for benign liver tumor
4	M	59	Recurrent CP with stenotic PJ	Pancreatic head metastasis of renal cell carcinoma	CPDE (2 years, 11 months)	RE-PJ with new GE
5	M	59	Recurrent cholangitis and pancreatitis with occlusion of HJ because of lost stent	Adenocarcinoma of the papilla, confined to the mucosa	PPPDE (2 years, 9 months)	RE-PJ with new HJ
6	F	65	CP of pancreatic remnant	CP	PPPDE (7 years, 6 months)	RE-PJ with new HJ and GE
7	M	50	CP	CP	Left-sided pancreatic resection, splenectomy (3 years, 2 months)	Completion pancreatectomy, CCE, transversum resection
8	M	51	CP	CP	Left-sided pancreatic resection, splenectomy (8 years, 2 months)	Completion pancreatectomy, CCE, extended right hemicolectomy, partial portal vein resection
9	F	48	CP	CP	PPPDE (6 years, 11 months)	Completion pancreatectomy, B-II resection
10	M	40	CP	CP	DPPHR (8 months)	PPPDE
11	M	43	CP	CP	DPPHR (3 years, 0 months)	PPPDE
12	M	46	CP	CP	DPPHR, bilioenteric anastomosis (2 years, 5 months)	PPPDE
13	W	75	Mucinous cystadenocarcinoma, pT3, pN0 (0/3), pM1	CP	PJ (2 years, 6 months)	CPDE, segmental resection of portal vein
14	W	11	CP	Cystic hamartoma of pancreas	Left-sided pancreatic resection, B-II resection, PJ (4 years, 3 months)	Redo left sided pancreatic resection, CCE
15	M	40	CP	CP	Left-sided pancreatic resection, splenectomy, PJ (1 year, 2 months)	CPDE leaving small pancreatic remnant

CP = Chronic pancreatitis, DPPHR = duodenum-preserving pancreatic head resection, PPPDE = pylorus-preserving pancreaticoduodenectomy, CPDE = classic pancreaticoduodenectomy, GE = gastroenterostomy, HJ = hepaticojejunostomy, PD = pancreaticoduodenectomy, PJ = pancreaticojejunostomy, RE-PJ = revision and redo of the Pancreaticojejunostomy after resection of the pancreatic margin, CCE = cholecystectomy, B-II = Billroth II

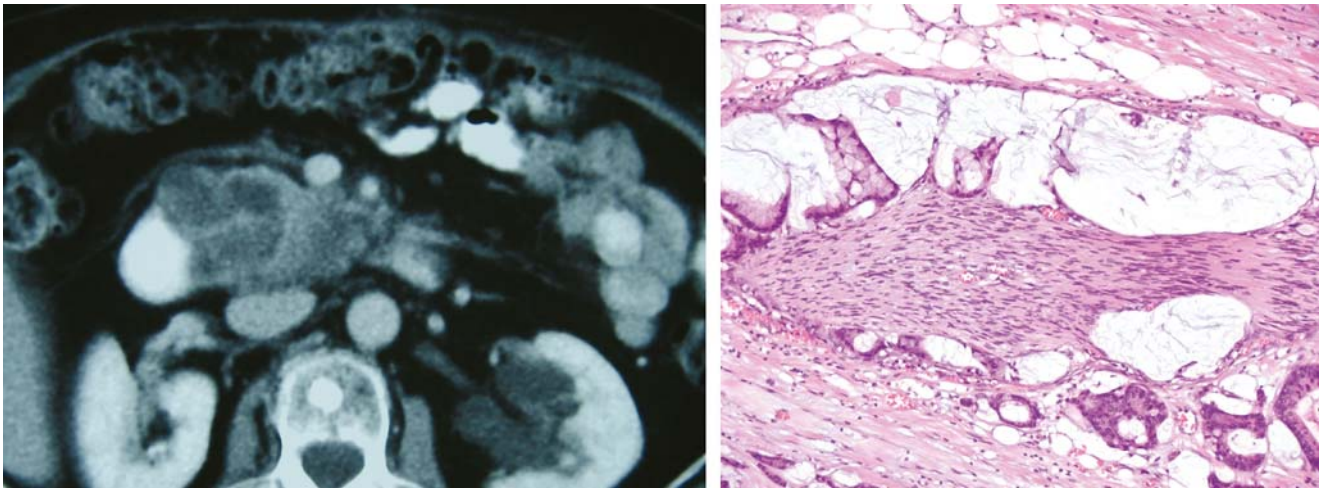

Figure 1 Preoperative CT scan of patient 13 showing a cystic tumor of the pancreatic head 2 years after pancreaticojejunostomy for calcifying pancreatitis. After duodenohemipancreatectomy, pathological examination revealed a mucinous cystadenocarcinoma of the head [pT3, pN0 (0/3), pM1]. Hematoxylin and eosin staining showing cystadenocarcinoma cells within the perineurium with mucous production (original magnification ×40).

(1), adenocarcinoma of the distal common bile duct (1), mucinous pancreatic cystadenoma (1), adenocarcinoma of the papilla confined to the mucosa (1), and a metastasis of a renal cell carcinoma (1) (Table 1). The indication for redo was chronic pancreatitis in the pancreatic remnant in 14 (94%) cases. One patient (patient 13) presented with a cystic mass, which proved to be a mucinous cystadenocarcinoma in the final histology (Fig. 1). Among the 14 patients with chronic pancreatitis, 7 had a stenosis or occlusion of the pancreaticojejunostomy (Fig. 2), leading to inflammatory changes and calcification in the remaining organ (Fig. 3). One patient had recurrent pancreatitis after a pancreaticogastrostomy (patient 2). In one patient a synchronous obstruction of the bile duct after a pylorus-preserving pancreaticoduodenectomy was caused by a stent in the hepatic duct proximal to the bilioenteric anastomosis, which was not retrieved at the time of the original resection 2 years before. This "missed stent" caused obstruction of the bilioenteric anastomosis with recurrent cholangitis. In this patient, the pancreaticojejunostomy was also occluded (patient 5).

The mean time interval between original operation and redo procedure was 4 years and 8 months (±10 months, SEM) (Table 1). The most frequent operative procedure was revision and redo of the pancreaticojejunostomy after resection of the pancreatic margin. In five of these six cases the procedure was completed by redo of the gastroenterostomy or hepaticojejunostomy. Other procedures included completion pancreatectomy (3) after left-sided resection or pylorus-preserving pancreaticoduodenectomy (3), conver-

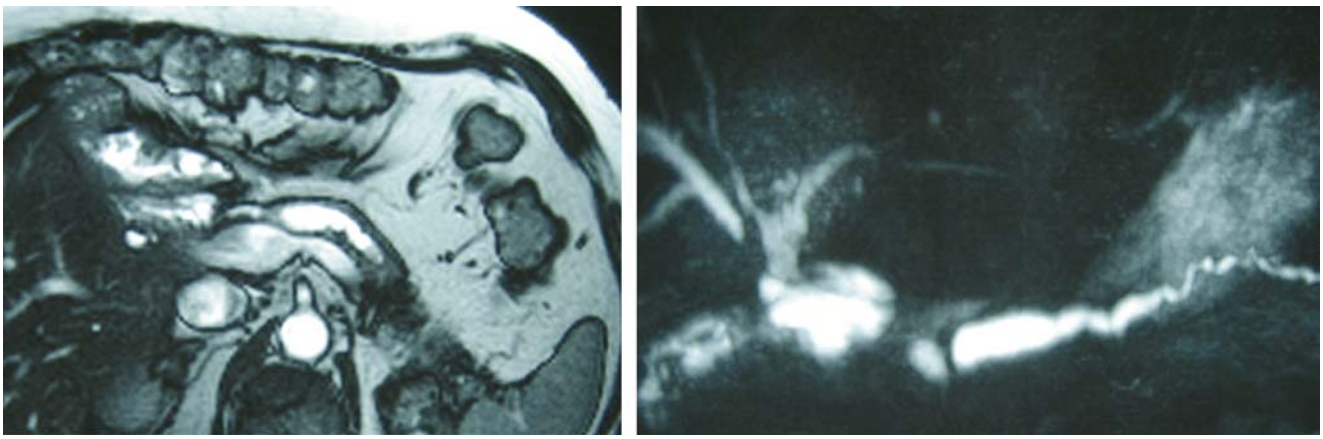

Figure 2 Magnetic resonance tomography and magnetic resonance cholangiopancreatography of patient 4 indicating a stenosis of the pancreatic duct in the proximal body of the pancreas and pronounced dilation distally after duodenohemipancreatectomy for a pancreatic metastasis of a malignant melanoma.

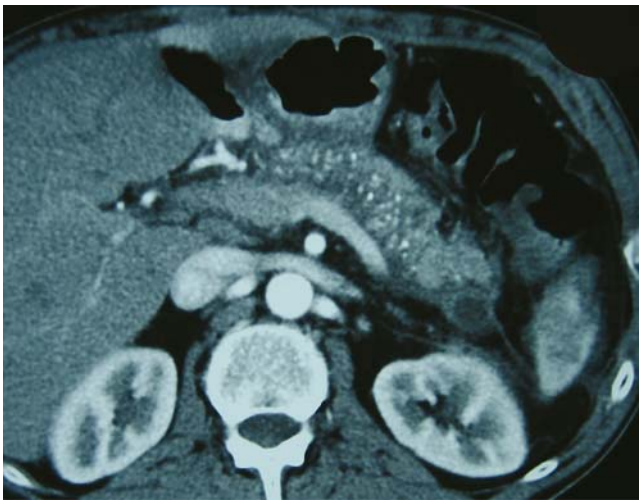

Figure 3 CT scan of patient 11 with a history of DPPHR 2 years ago. Pronounced calcifications throughout the whole remaining organ and pseudocysts in the tail of the pancreas.

sion from DPPHR to pylorus-preserving pancreaticoduodenectomy (3), classic pancreaticoduodenectomy after a pancreaticojejunostomy (1), redo of left-sided pancreatectomy (1), and classic pancreaticoduodenectomy after left-sided pancreatectomy leaving a small pancreatic remnant (1). Table 1 outlines the details of each patient.

Additional operative procedures were performed in four patients. In one patient a liver tumor was detected preoperatively in segment IV, which was resected. Histological examination revealed benign hepatic tissue. One patient had a synchronous transverse colon resection, one patient required a segmental portal vein resection in combination with an extended left hemicolectomy, and one patient with a mucinous cystadenocarcinoma required a segmental portal vein resection for tumor clearance.

The median operative time was 335 min (range 235–615 min), and the median estimated blood loss was 600 ml (range 300–2800 ml) (Fig. 4). Red blood cell transfusions were necessary in 3 (20%) patients in the perioperative period and in 5 (33%) patients in the postoperative period (Table 2).

There was no perioperative death and the overall morbidity rate was 33% (Table 3). The mean postoperative hospital stay was 15 days (Fig. 4). Follow-up was available for all (100%) patients with a median follow-up of 10 months (4 months–26 months). Among the patients receiving a revision and redo of the pancreaticojejunostomy after resection of the pancreatic margin, only one developed diabetes, which was treated with antidiabetic medication (patient 2). Four other patients in this group did not develop diabetes (patients 1, 3, 4, and 5) (Table 4). None of the three patients who underwent a pylorus-preserving pancreaticoduodenectomy after a DPPHR developed a diabetes mellitus. Pain control was improved in 11 patients (73%) after pancreatic redo surgery as illustrated in Fig. 5, i.e., for these patients no continuous pain medication was necessary. One patient (7%) experienced impairment of pain requiring continuous transdermal opioids, whereas he had required only NSAID on demand preoperatively (patient 10; Table 4). In three (20%) patients pancreatic redo surgery resulted in no change of pain control (Table 4, Fig. 5). Further follow-up details (diabetes and readmission) are summarized in Table 4.

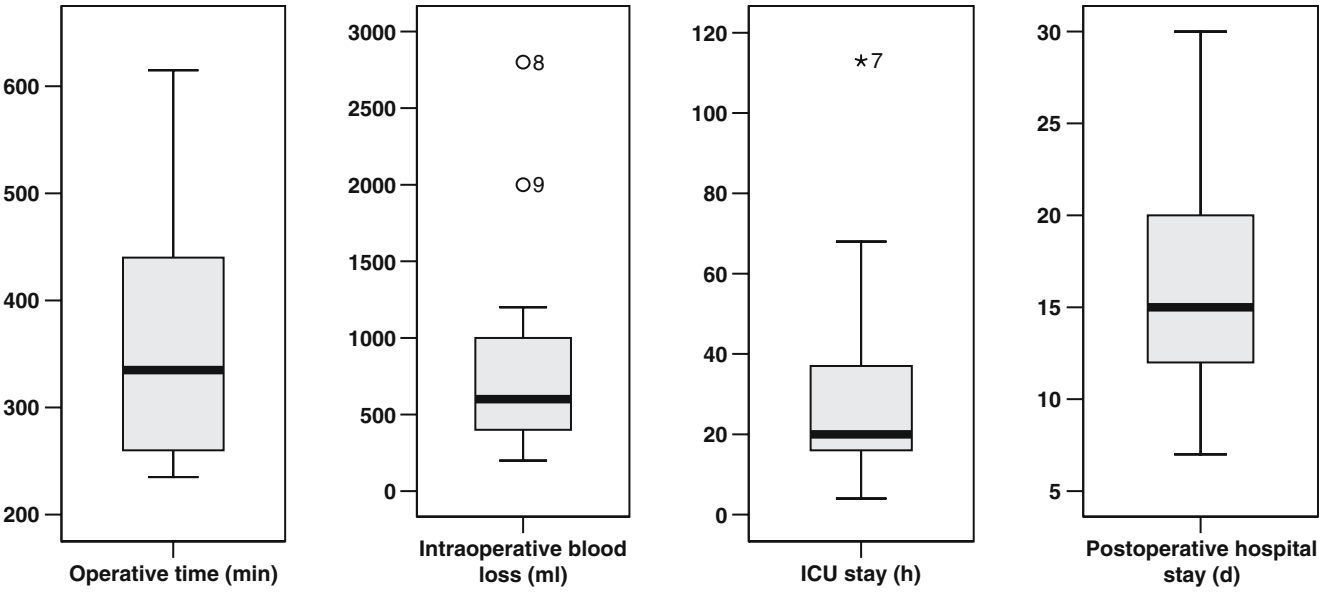

Figure 4 Procedure-related parameters of patients receiving pancreatic redo surgery (n=15). Box and whisker plot for operative time, intraoperative blood loss, ICU stay, and postoperative hospital stay. The gray box indicates the lower and upper quartiles; the black bar indicates the median. Whiskers represent 5th and 95th percentile.

Table 2 Perioperative and Postoperative Red Blood Cell Transfusions

RBC transfusion	Frequency	Mean	Min–max	SD	SEM
Perioperative RBC transfusion	20% (3/15)	0.67	0–5	1.99	0.38
Postoperative RBC transfusion	33% (5/15)	0.67	0–2	0.97	0.25

RBC = Red blood cell, perioperative = beginning of operation and first 8 h after operation, postoperative = remaining time until discharge

Discussion

In the literature, reports on reoperative surgery for pancreatic disease usually cover patients who were explored but not resected because of suspected unresectable disease. Under these circumstances 60 to 67% of patients can undergo a curative resection in experienced centers and long-term survival is reported to vary between 7 and 24 months.[7,13] In contrast, reports on reoperative surgery in patients who underwent duodenohemipancreatectomy or left-sided pancreatic resections for malignant disease are scarce. This may be, in part, the result of the low long-term survival rate of patients suffering from pancreatic carcinoma. Recurrent or metastatic disease is the leading cause for rehospitalization and palliative therapy remains the only option for the majority of patients. In addition, recurrent disease at the bilioenteric anastomosis in malignant disease is rare. In a recently published study, House et al.[18] reported a stricture rate of the bilioenteric anastomosis of 2.6% after pancreaticoduodenectomy for either benign or malignant disease. Recurrent malignant disease was detected in only 3 of 32 patients (9%) and initial treatment in all cases was percutaneous balloon dilatation with only two patients finally requiring redo hepaticojejunostomy. In our experience, symptomatic obstructions of the pancreaticojejunostomy or the hepaticojejunostomy because of recurrent or metastatic disease are usually not surgically curable.

Recurrent pain is the principal symptom of patients with recurrent chronic pancreatitis after pancreatic resections and occurs with a frequency of 25 to 40%[19] and long-term pain relief ranges from 44 to 89%, depending on the type of surgery perfomed.[16] Major reasons for long-term failure in these patients include insufficient primary operation, recurrent or persistent inflammatory disease in the remaining pancreatic tissue, stricture of the anastomoses, duodenal obstruction, and unrecognized or newly developed pancreatic carcinoma.[16] Treatment is primarily aimed at symptomatic relief, which can be accomplished with effective analgesia. However, when a mechanical obstruction can be identified and conservative treatment is unsuccessful, redo surgery is an important option.

Table 3 Postoperative Complications and Morbidity

Complication	*N* (%)
Prolonged postoperative ileus	2 (13)
Urinary tract infection	1 (7)
Cholangitis	1 (7)
Wound dehiscence requiring relaparotomy	1 (7)

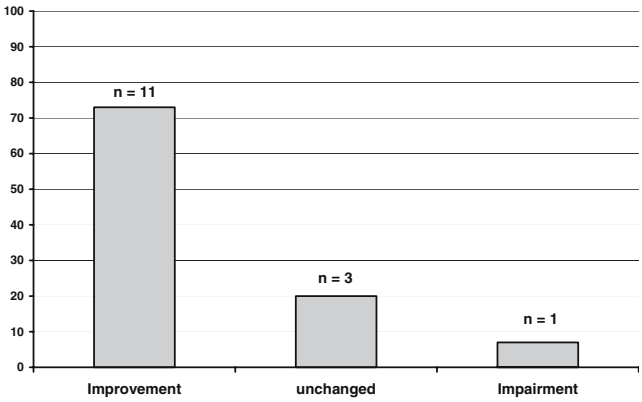

Figure 5 Estimation of postoperative pain control by categories "improvement," "impairment," and "no change" after a mean follow-up of 12 months (±1.7 months). Follow-up data were complete for every patient (100%).

Among our patient population recurrent chronic pancreatitis with significant pain was the leading cause for reoperation in 14 of 15 patients (93%). However, a stenosis of the bilioenteric anastomosis was also present in 1 (7%) case (patient 5). This patient underwent a PPPDE in another hospital. He presented with recurrent cholangitis and pancreatitis. During operation a lost stent with complete obstruction of the anastomosis was detected when the bilioenteric anastomosis was taken down.

In our series we had five patients who underwent pancreatic resection for malignant (patients 1, 3, 4, and 5) or premalignant (patient 2) disease. In none of these patients was recurrent malignant disease detected. One of these patients was detected intraoperatively to harbor a 5-mm liver tumor in segment IV, which was resected (patient 3). Histology proofed the tumor to be liver tissue with unspecific chronic inflammatory changes. The leading problem in all five patients was recurrent pancreatitis because of a stenotic pancreaticojejunostomy, which had to be taken down. Unfortunately, details on the technique used for the anastomosis during the primary operation are not available. Because we did not observe this problem in our patients who underwent pancreatic head resection for pancreatic or periampullary cancer (n=120), we believe that technical details of the pancreaticojejunostomy are of utmost importance to prevent this complication.

Of the patients with former pancreatitis (n=10), one patient displayed a mucinous cystadenocarcinoma of the head after a pancreaticojejunostomy 2 years ago (Fig. 5).

Table 4 Follow-up Data: Endocrine Function, Pain Control, and Further Details

Patient	Endocrine function		Pain control		Further F/U details	F/U (months)
	Preoperative	Postoperative	Preoperative	Postoperative		
1	No diabetes	No diabetes	Postprandial pain requiring continuous NSAID medication	Improvement: no continuous pain medication	Recurrent episode of cholangitis with hospitalization and i.v. antibiotic treatment	26
2	No diabetes	Development of NIDDM, medical therapy with metformin	Recurrent episodes of pain requiring NSAID and oral opioid intake	Improvement: no pain medication	One readmission (5 days) for a mild episode of pancreatitis	20
3	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID medication	Improvement: no pain medication		16
4	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID medication	Improvement: no pain medication	No recurrence of renal carcinoma	10
5	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID and opioid medication	Improvement: no pain medication		4
6	IDDM	IDDM	Postprandial pain and recurrent episodes of pancreatitis requiring NSAID medication	Improvement: no pain medication		9
7	IDDM	IDDM	Severe pain requiring high doses of opioids, resulting in opioid dependence	Unchanged: Still poor pain control, dose reduction of opioids but intrathecal spinal pump	Reoperation for abdominal hernia	24
8	IDDM	IDDM	Severe pain requiring continuous transdermal opioid medication	Still requiring continuous transdermal opioid medication	Readmissions (2×) for severe diarrhea	16
9	IDDM	IDDM	Severe pain requiring continuous transdermal opioid medication	Improvement: no pain medication		7
10	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID and opioid medication	Impairment: continuous transdermal and oral opioid medications		9
11	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID medication	No pain medication		4
12	No diabetes	No diabetes	Recurrent episodes of pain requiring NSAID and oral opioid intake	Improvement: no pain medication		5
13	NIDDM (dietary)	NIDDM (dietary)	Increasing episodes of pain requiring NSAID medication	Improvement: no pain medication	Current cyclophosphamide with gemcitabine	12
14	No diabetes	No diabetes	Constant pain requiring acetaminophen	Unchanged: Still requiring acetaminophen for pain control		8
15	No diabetes	No diabetes	Recurrent episodes of pancreatitis with pain requiring NSAID medication	Improvement: no pain medication		5

F/U = Follow-up, IDDM = insulin dependent diabetes mellitus, NIDDM = non-insulin dependent diabetes mellitus, NSAID = non-steroidal antiinflammatory drug

This underlines that close follow-up of patients with chronic pancreatitis is of high importance because of their increased risk to develop cancer.[20]

Despite the fact that final histology revealed the presence of chronic pancreatitis, extensive resections including segmental portal vein resection, resection of transverse colon, and hemicolectomy were required. This underlines that technical difficulties may be substantial in these patients and the full armamentarium of reconstructive surgery should be available when operating on these patients. Although segmental portal vein resection for tumor clearance has no proven effect on survival, it may be necessary for technical reasons or because of potential intraoperative complications such as accidental tearing of the vein.

In patients with chronic pancreatitis the problem leading to the primary operation may recur in the pancreatic remnant and may result in recurrent pancreatits.[12] However, if the principle problem is not adequately treated by the first operation recurrence is likely to occur. This scenario may arise when chronic pancreatitis is mainly located in the tail but the underlying cause of a stenotic pancreatic duct is located within the pancreatic head. This was particularly true in patient 15. The patient underwent limited left-sided pancreatic resection and pseudocystojejunostomy because of chronic pancreatitis. Because of recurrent pancreatitis he developed a new pseudocyst with subsequent upper gastrointestinal bleeding and a rupture of the cyst into the duodenum. He finally underwent a duodenohemipancreatectomy with a pancreaticojejunostomy to a small part of the tail to prevent diabetes mellitus. The patient remained asymptomatic during follow-up and required no antidiabetic medication or insulin.

We believe that every effort should be undertaken to preserve functional pancreatic tissue to prevent the patient from the potential negative consequences of an apancreatic state. This is increasingly important because of the relatively young age and the longer survival of these patients. However, pancreatic-preserving surgery may not be possible in all instances. In three of our patients with chronic pancreatitis a total pancreatectomy had to be performed. All of these patients suffered from recurrent pain in the pancreatic remnant. In two cases the problem was located in the pancreatic head after left-sided resection, whereas the third patient had significant chronic pancreatitis in the tail after DPPHR. Isolation of pancreatic β-cells and subsequent implantation into the portal vein may be a future option to prevent insulin-dependent diabetes mellitus when total pancreatectomy is required.

The long operative time is one indicator for the complexity of this kind of surgery. We believe that this kind of surgery is very demanding and should only be performed by surgeons who have a profound experience with pancreatic surgery. Ninety-three percent of patients in the study population underwent their primary operation at another hospital and were referred to our center. Only one patient (patient 10) underwent surgery for the first time in our institution. He underwent DPPHR for chronic pancreatitis. However, because of continued pain and recurrent pancreatitis, he was operated again 8 months later and a duodenohemipancreatectomy was performed. Unfortunately, this patient is still not asymptomatic and total pancreatectomy remains the only option.

Conclusion

Pancreatic redo procedures are demanding operations and represent the only therapeutic option for recurrent chronic pancreatitis because of a stenosis at the pancreaticojejunostomy after pancreatic resectional procedures. Surgery can be performed with a low morbidity and mortality in institutions with high expertise.

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Liver Metastasis Resection: A Simple Technique That Makes It Easier

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Abstract Liver resection is the only therapeutic option that achieves long-term survival for patients with hepatic metastases. We propose a technique that causes traction and countertraction on the resection area, thus easily exposing the structures to be ligated. Because the parenchyma protrudes like a cork from a bottle, we named this procedure the "corkscrew technique". The objective of this work was to describe an original surgical technique to resect liver metastases. We delimit the resection area at 2 cm from the tumor. We place separated stitches, in a radiate way. The needle diameter must allow passing far from the deepest margin of the tumor. The stitches must be tractioned all together to separate the tumor from the normal parenchyma. Between the years 1983 and 2006, we perform 1,270 liver resections. We used the corkscrew technique-like procedure in only 612 patients, whereas in 129 patients, we associated it to an anatomic resection. Mortality was 1%. Morbidity was 16% with a reoperation rate of 3%. The corkscrew technique is simple and safe, spares surgical time, avoids blood loss, ensures free tumor margins, and is easy to perform.

Keywords Liver resection technique · Wedge resection · Oncological margins

Introduction

Surgical resection is the only therapeutic option that guarantees long-term survival and even cure in patients with liver metastases of colorectal, neuroendrocrine, or non-colorectal non-neuroendocrine origin.[1] Liver resection of small lesions (1 to 4 cm) located in the liver surface is a procedure that, due to its low complexity, has a low morbidity and mortality.[2,3] However, the oncological long-term prognosis can be jeopardized because of the small or positive resection margin. De Matteo et al.[4] state "Two factors contribute to inadequate tumor clearance following nonanatomic wedge resection. First, traction on the specimen during division of the liver parenchyma tends to produce a fracture at the interface of the fragile soft liver tissue and the hard colorectal metastasis. Second, because of limited exposure and the lack of vascular control, hemorrhage commonly occurs at the base of the wedge resection. Bleeding may obscure the plane of the intended parenchymal transection and consequently compromise the final margin."

To successfully perform metastasis resection and achieve satisfactory short and long-term results, some requirements should be met:

- Margin greater than 1 cm
- Preservation of the maximal amount of normal liver parenchyma
- Appropriate hemostasis
- Meticulous bile branches ligation in the cut surface

For these requirements to be met, it is necessary to clearly identify the vascular and bile duct branches in the cutting surface.

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The surgical technique we propose aims to produce traction and countertraction in the area to be resected to expose the vascular and biliary elements in the section line. Besides, as the hemostasis is almost perfect due to the total identification and control of the vascular elements, it helps to detect the biliary elements, thus avoiding postoperative biliary fistula.

This procedure is most useful not only for the treatment of liver metastasis but also for small liver tumors, in multiple isolated superficial liver resections, or in combination with a contralateral major liver resection. Furthermore, when a general surgeon is performing a colorectal resection and finds a metastatic lesion in the anterior surface of the liver, the use of this technique allows facilitating the resection and improving long-term results.

Primary liver tumors, cystic tumors, and/or hemangiomas constitute a formal contraindication for the use of this technique. During the performance of this technique, we cut the Glisson's capsule allowing the parenchyma to protrude like a cork. Therefore, we decided to name this technique the "corkscrew technique".

In summary, the objective of this paper is to describe an original surgical technique of liver resection that saves operative time, avoids blood loss, ensures free surgical margins, and is simple to perform.

Technique

Once the lesion has been identified, either by intraoperative ultrasonography or by palpation, the Glisson's capsule is marked with electrocautery 2 cm away from the tumor margin (Fig. 1). This marked area is anchored with stitches that are placed all around it. When the lesion is smaller than the needle diameter, the suture passes under the lesion (Fig. 2). When the lesion is bigger, the needle enters the hepatic parenchyma 3 cm away from the lesion and leaves the parenchyma at 2 cm from the margin so as to prevent the needle from entering the tumor (Fig. 3).

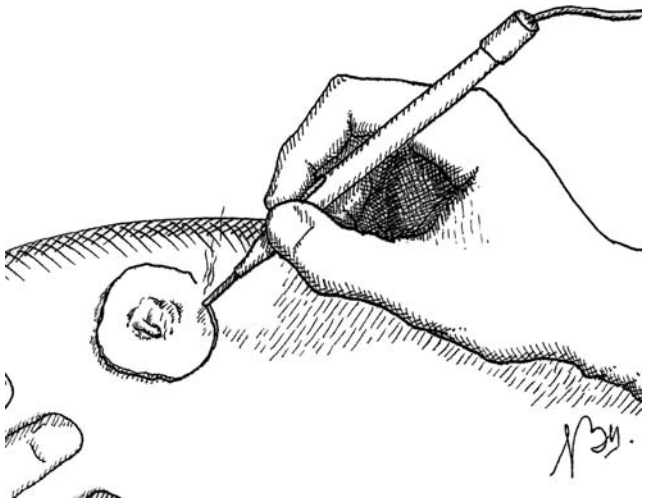

Figure 1 Marking the lesion is the first step to perform the resection.

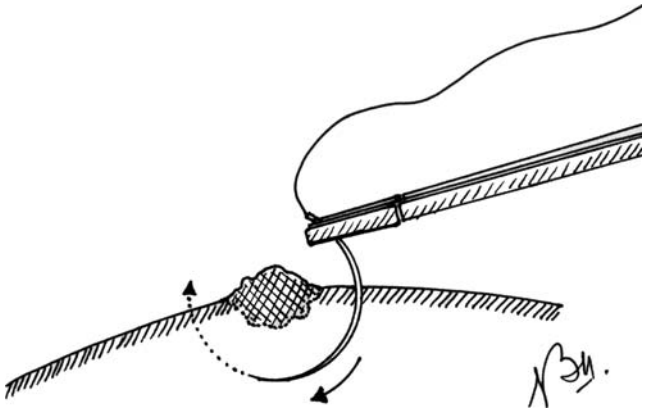

Figure 2 When the lesion is small, stitches are passed under it.

When the last stitch is made, all the sutures are held together (Fig. 4) to hold the area to be resected. The traction and countertraction exercised when holding the ties facilitate the identification of the vascular and biliary structures (Fig. 5).

The parenchymal transection can be carried out with the instrument the surgeon is used to (Kellyclasia, ultrasonic dissector, electrocautery, water jet, etc.) (Fig. 6). We usually use the ultrasonic dissector. This transection has to be performed a few millimeters away from the anchorage line to obtain a margin of at least 1.5 cm. With the use of this technique, it is very easy to identify the structures in the

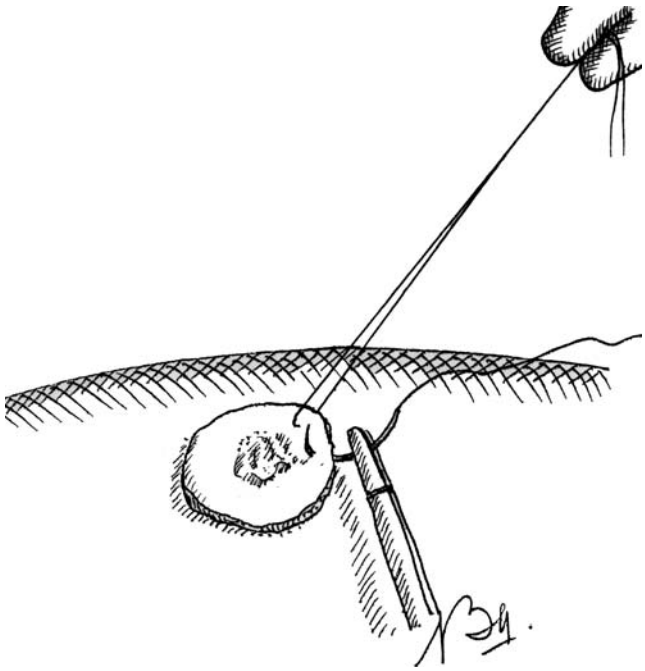

Figure 3 When the lesion is bigger, stitches are passed outside the lesion because it is a risk to pass stitches under it.

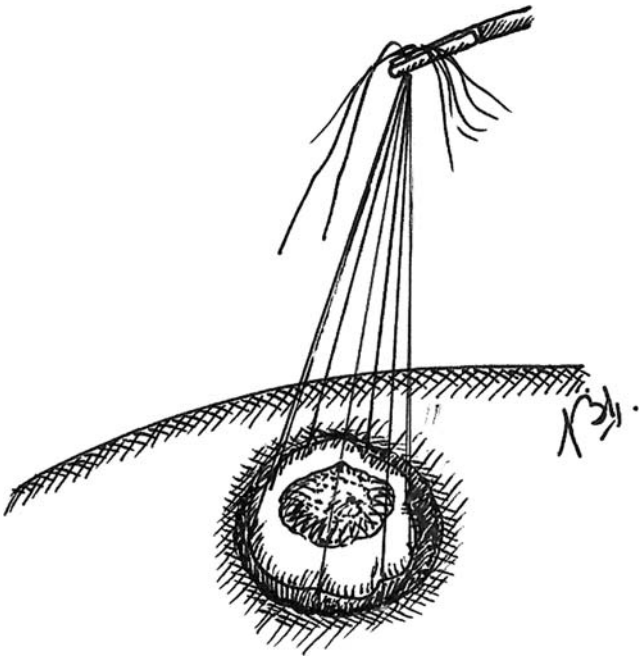

Figure 4 Once the stitches are passed, they are pulled together in an even fashion to avoid fracture of the parenchyma.

cutting line, so we use clips and ties of absorbable material to control them.

The control of the distance between the margin and the lesion is made by the use of ultrasonography and the introduction of a polypropylene mesh in the section line.

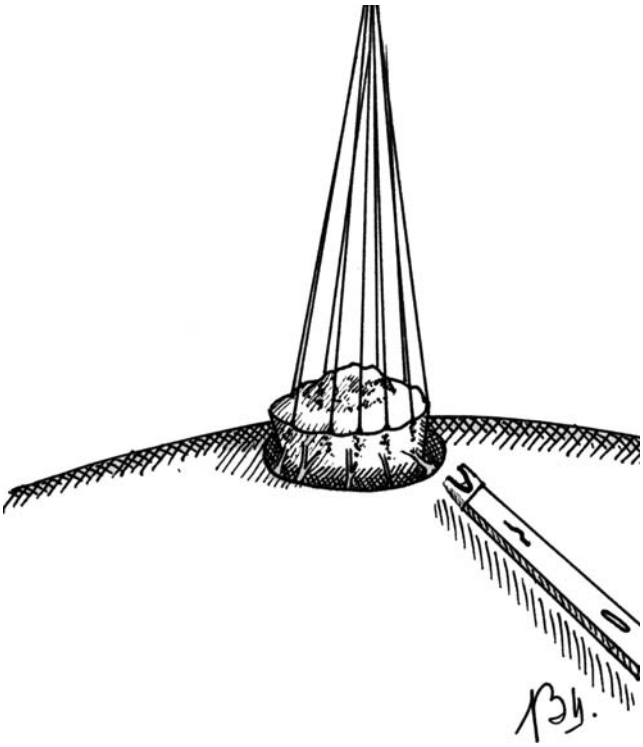

Figure 5 Identification of vascular and biliary elements allows a satisfactory control of hemostasis and bilistasis.

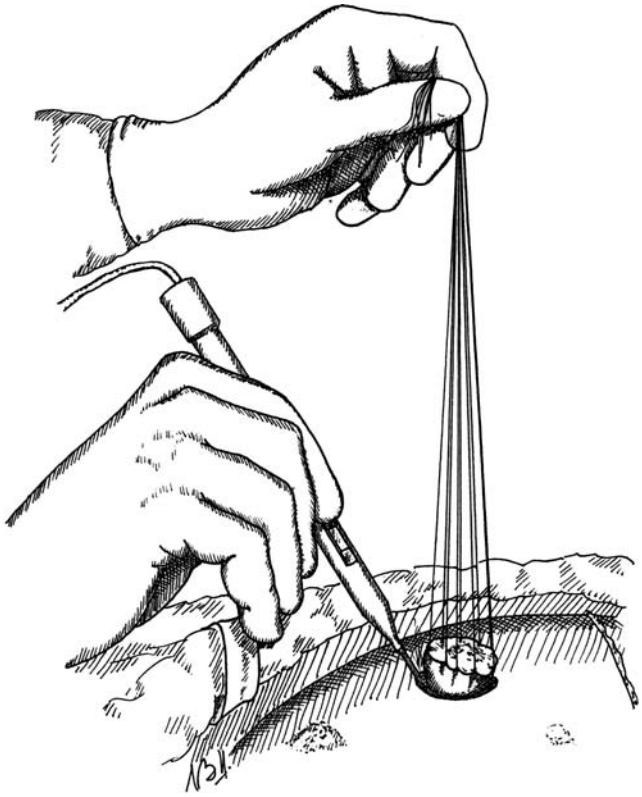

Figure 6 With the identification of vascular elements, the electrocautery is a safe and simple resource in the performance of the metastasectomy.

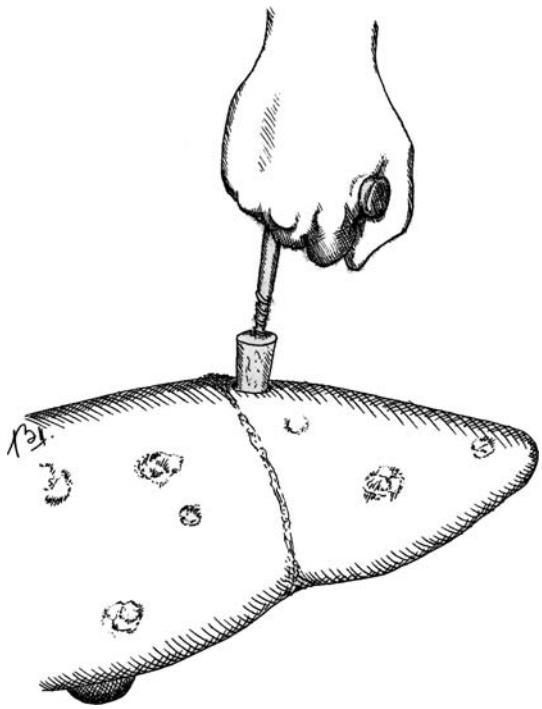

Figure 7 The technique allows multiple resections with good margin and preservation of liver parenchyma.

This maneuver produces an excellent contrast and allows a clear identification of the distance between the metastasis and the cutting line.

Once the section depth reaches 2 cm under the tumor, the section becomes horizontal, which is helped by the traction of the ties. As this traction makes the parenchyma protrude like a cork, we decided to call this procedure "corkscrew technique" (Fig. 7).

Discussion

Neoplastic cell migration from the splanchnic area enters the liver through the portal branches and sometimes nests in a terminal branch. The metastasis growth does not always occur in the middle of a segment; it can grow anywhere and it can develop in the segment margins. Dissection through non-anatomic planes has allowed resection of lesions that were previously considered irresectable.[5] If we consider the surgical procedure, in accordance with many reports, it confirms, that for liver metastasis, the type of resection does not significantly affect patient survival.[6,7]

According to Zorzi et al.,[8] who compared hepatic wedge resection and anatomic resection for colorectal liver metastases, "the type of resection(s) selected should be based on the anatomy of the lesion(s) and the goal of preserving an adequate volume of functional liver parenchyma." So, nonanatomic wedge resection should remain an integral component of the surgical treatment of colorectal metastases.

Yasui and Shimizu,[9] who reviewed the English literature in colorectal liver metastasis with case series of more than 50 curative hepatectomies, did not find any difference in morbidity, mortality, recurrence, and survival rates between anatomic and atypical resections. Malafose et al.[10] state that selection of the technique to be used depends on the number and location of liver metastases. The anatomic or non-anatomic resections do not influence the overall survival. Kokudo et al.[3] state that, to minimize surgical stress and operative risk, nonanatomic limited liver resection should be a basic surgical procedure for the treatment of colorectal liver metastases.

During liver resection of small superficial liver metastases, the difficulty to pull the lesion, together with the bleeding in the cutting line, produces lack of exposure and vascular control, which develops in the compromise of the tumor margin. The corkscrew technique allows the lesion to be held as if it were in a basket and to be pulled upward, with an even traction, allowing the identification and control of the vascular and biliary elements. Therefore, it facilitates the exposure, which develops in an excellent oncological margin. This meticulous exposure of the vascular elements avoids, in many cases, the use of vascular clamping (Pringle maneuver). Any atypical resection can be performed under surgical oncological rules. On the other hand, Yamamoto et al.[11,12] have shown that the occurrence of satellite nodules around the main metastatic lesion is rare, and therefore, wedge resection is justified, even with a tumor-free margin of less than 0.5–1 cm, but with exposure of neither the tumor nor the cut surface. As we employ this technique in lesions smaller than 4 cm, the 1-cm oncological margin is thus assured. If this is not possible, a smaller oncologically acceptable margin can be left.[13]

When the metastases are located in the caudate lobe, the exposure is sometimes difficult. The traction that we employ with this technique makes the exposure of the accessory suprahepatic veins easier, and it also makes the control safer. The use of this technique in combination with contralateral major resections saves time and decreases blood loss.

Between 1983 and 2006, we performed 1,270 liver resections. The corkscrew technique was used as the sole procedure in 612 patients, whereas it was associated with an anatomic resection in 129 patients. Mortality was 1% and morbidity was 16%, with a reoperation rate of 3%. The overall 1–3- and 5-year survival rates for the entire cohort were 91, 46, and 33%, respectively. Therefore, the corkscrew technique allows carrying out nonanatomic liver resection of liver metastases in a simple, easy, and safe fashion, permitting the attainment of satisfactory short- and long-term results.

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Surgical Management of Gallbladder Carcinoma: A Review

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Abstract Gallbladder cancer is a relatively unusual, but often lethal malignancy. Surgical management has historically been palliative only; however, with the advancement of techniques in hepatobiliary surgery, varying extents of surgical intervention have been advocated for cure. This article reviews the current approach to the surgical management of gallbladder cancer and discusses the rationale for an aggressive approach to this disease.

Keywords Gallbladder carcinoma · Extended resection · Staging · Review

Gallbladder cancer (GBCA) is a rare, but often lethal malignancy. It is the fifth most common gastrointestinal malignancy and the most common biliary tract cancer, surpassing cholangiocarcinoma. Like all biliary and pancreatic malignancies, patients with GBCA usually have advanced disease at the time of diagnosis, except for a subset of patients who are diagnosed incidentally at the time of elective cholecystectomy. Even with advances in diagnosis and treatment of GBCA, long-term survival remains dismal. Chemotherapy and radiotherapy are ineffective as a primary treatment, and resection remains the only chance for cure. Only a minority of patients are candidates for resection at the time of diagnosis. Even after curative resection, most series quote a long-term survival of only 5–12%.[1–3] However, curative resection continues to be the only hope for survival, and recent data suggests that aggressive resections may improve long-term survival, even in patients with advanced stage disease.[4] The goal of this editorial is to review the surgical treatment and outcomes for patients with GBCA.

Nevin et al. published the initial staging system for GBCA in 1976.[5] This developed into the TMN staging system by the American Joint Committee on Cancer (AJCC). The AJCC TMN staging was based on extent of tumor penetration into the gallbladder wall, which correlates with prognosis. Most reported series of resections for GBCA before 2002 use the fifth edition of the AJCC classification (Table 1). The revised sixth edition of this system, published in 2002, has caused some controversy among the hepatobiliary surgery community (Table 1). The major changes in the 2002 version include moving T2N0M0 tumors from stage II to stage IB, changing T3N1M0 from stage III to stage IIB, and T4NxM0 tumors were moved from stage IVA to stage III. Criticisms include that the changes in stages were not based on data analysis and do not correlate with prognosis. Also, the changes do not conform with the standard staging with stage I/II disease being local and more treatable, with stage III and IV being large tumors, with nodal or metastatic spread.[6] Fong et al. analyzed over 10,000 cases of GBCA with more than 5-year follow-up and compared AJCC fifth edition, sixth edition, and a new schema that was a revision of the fifth edition, which further separates T3 (stage III) and T4 (stage IV) lesions by presence of lymph node spread. In their analysis, the sixth edition did not offer benefit over the fifth edition, and the proposed new system building on the fifth

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Table 1 AJCC Fifth and Sixth Edition Staging Systems and a Proposed New Edition by Fong et al. [6]

Stage	Fifth Edition	Sixth Edition	Proposed Edition
0	TisN0M0	TisN0M0	TisN0M0
IA	T1N0M0	T1N0M0	T1N0M0
IB		T2N0M0	
IIA	T2N0M0	T3N0M0	T2N0M0
IIB		T1-3N1M0	
IIIA	T3N0M0, T1-3N1M0	T4NxM0	T3N0M0
IIIB			T1-3N1M0
IVA	T4N0M0, T4N1M1	TxNxM1	T4N0M0
IVB			TxNxM1, TxN2Mx T4N1M0

TNM: *T* Indicates primary tumor, *Tx* primary tumor cannot be assessed, *T0*, no evidence of primary tumor, *Tis* carcinoma *in situ*; *T1* tumor invades lamina propria or muscle layer, *T1a* tumor invades lamina propria, *T1b* tumor invades muscle layer, *T2* tumor invades perimuscular connective tissue, no extension beyond serosa or into liver, *T3* tumor perforates the serosa (visceral peritoneum) or directly invades once adjacent organ, or both (extension ≤2 cm into liver), *T4* tumor extends more than 2 cm into liver, and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of liver), *N* regional lymph nodes, *Nx* regional lymph nodes cannot be assessed, *N0* no regional lymph node metastasis, *N1* metastasis in cystic duct, pericholedochal, and/or hilar lymph nodes (hepatoduodenal ligament), *N2* metastasis in the peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes, *Mx* distant metastasis cannot be assessed, *M0* no distant metastasis, *M1* distant metastasis

edition had improved discrimination of stage over the previous two editions. The sixth edition is currently in use. We will attempt to describe the pathology in this editorial as confusion may arise in using the sixth edition terminology when discussing literature reported using fifth edition terminology.

Only 15 to 47% of patients are candidates for resection at the time of diagnosis.[7–14] Patients with early-stage disease are generally asymptomatic; however, they may present in the setting of acute or chronic cholecystitis. The diagnosis in these patients is frequently made as an incidental finding at cholecystectomy. Patients with symptomatic disease that present with jaundice or clinical symptoms of malignancy such as weight loss, abdominal distension or symptoms of compression of adjacent organs, have advanced disease and are usually not candidates for resection.

Determining resectability preoperatively has improved as advances in preoperative imaging with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) have occurred. However, there remains a role for staging laparoscopy and intra-operative ultrasound in GBCA. The detection of peritoneal and small liver metastases remains difficult with standard imaging techniques, and an estimated two-thirds of patients with T3 lesions and over 80% of patients with T4 lesions have peritoneal spread.[15] In a study of 11 patients with potentially resectable GBCA, 7 of 11 (64%) were found at laparoscopy to have liver or peritoneal metastases that precluded resection.[16] Unfortunately, the preoperative stage of these patients was not included in the paper. It is reasonable to conclude that preoperative diagnostic laparoscopy and ultrasound may be beneficial before contemplating extended resection.

In contemplating surgical options for resection, an understanding of how gallbladder carcinoma spreads is required. The gallbladder lymphatics are drained by a lymphatic plexus that empties initially into first-level lymph nodes along the biliary tract, which include the cystic duct lymph node and lymph nodes along the common bile duct and common hepatic duct. The spread is then down into the pancreaticoduodenal lymph nodes and nodes around the common hepatic artery and celiac axis. Nodes involved farther along the body and tail of the pancreas are considered metastatic disease.[17] Lymph node involvement occurs in over 50% of patients with GBCA and correlates with the depth of invasion.[18] Blood from the gallbladder drains into segment 4B or 5 either from veins that drain directly into the liver or via venous collaterals that run along the duct. Approximately two-thirds of veins draining the gallbladder drain into the right lobe only, 28% to the left lobe only, and 28% drain to both lobes.[19] Venous drainage and direct extension explain the predisposition of GBCA to involve the liver bed. Perineural invasion also occurs in approximately 25% of patients and must be considered in contemplating the options for resection.

The surgical options for the treatment of GBCA have evolved over the last 10 years, as it has become clear that patients benefit from extended resections, which can be done with a low morbidity and mortality at major hepatobiliary surgery centers.[20] The procedures range from a simple cholecystectomy to a radical or extended cholecystectomy, which at a minimum, includes the gallbladder plus 2 cm of liver tissue from the gallbladder bed. The radical cholecystectomy has been further extended to include more substantial liver resections, from segmentectomies (4B/5) to right hepatectomies and trisectionectomy. Extended procedures should also include regional lymphadenectomy of the porta hepatis and periduodenal and pancreatic nodes. Many surgeons (including the authors) include a resection of the bile duct to completely clear the lymphatics in the porta hepatis (Fig. 1). Some surgeons now include periaortic lymph node dissection for staging purposes, whereas if the tumor is distal or involves the head of the pancreas, a pancreaticoduodenectomy is added to achieve R0 resection status (Fig. 2).

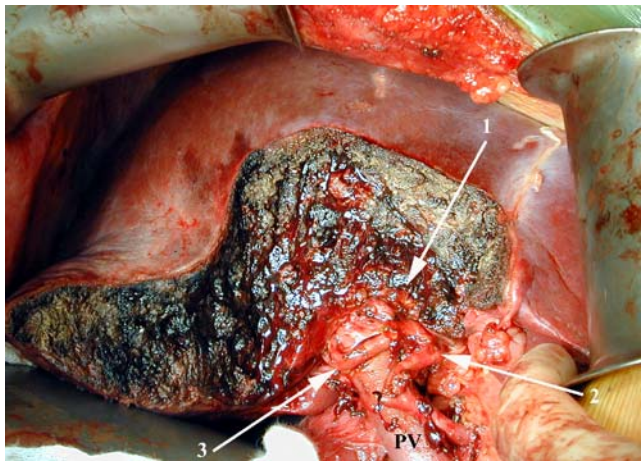

Figure 1 Segment 4B/5 resection along with bile duct resection and regional lymphadenectomy. *1* Hepatic duct, *2* left hepatic artery takeoff, *3* right hepatic artery at takeoff of anterior and posterior sectoral branches, *PV* portal vein.

Initially, it was recommended that all laparoscopic port sites should be excised after finding GBCA incidentally at laparoscopic cholecystectomy, as up to 17% of port sites can be involved after the incidental finding of GBCA at the time of a laparoscopic cholecystectomy.[21] Disease spread to laparoscopic port sites is now considered by most surgeons as stage IV disease that is unlikely to be cured. We continue to resect port sites mainly as a staging tool, as it is not uncommon to remove what appears to be an uninvolved port site scar only to find microscopic invasive adenocarcinoma.

For all stage patients, a complete or R0 resection (negative margins and nodal dissection one level past microscopically involved lymph nodes) clearly improves survival, as does the absence of lymph node spread. A recent study of 48 patients over 20 years had an overall 5-year survival of 13%; however, in those patients who underwent complete resection, 5-year survival was 31%.[22] Dixon et al. recently published the results of 38 patients with GBCA who underwent an R0 resection during two separate time periods. During the second time period, the resections were more aggressive, including liver and bile duct resections; 5-year survival improved from 7 to 35%.[4]

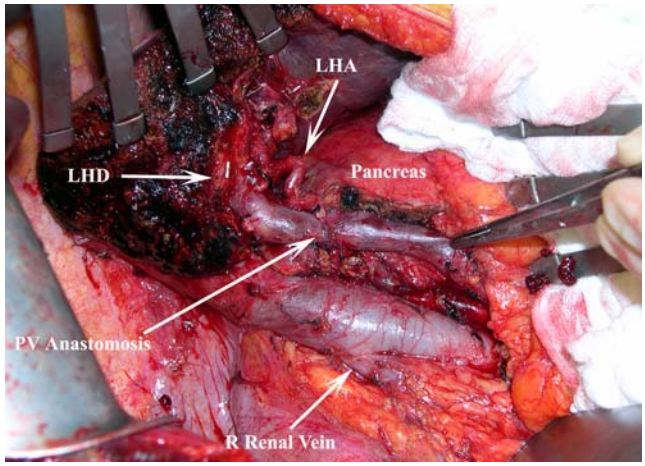

Figure 2 Right trisectionectomy with pancreaticoduodenectomy and portal vein resection. *LHA* Left hepatic artery, *LHD* left hepatic duct, *PV* portal vein, *R* renal vein = right renal vein.

Five-year survival for patients with T1 tumors is greater than 85% with simple cholecystectomy.[23–25] For patients with a T1 tumor (invading lamina propria and muscle layer), the value of radical resection depends on whether it is a T1a tumor (into the lamina propria but not muscle) or T1b tumor (into the muscle). In a retrospective study of 25 patients with T1a GBCA who underwent either simple cholecystectomy (13) or radical resection (12), there was no difference in recurrence or survival between the two groups.[25] Also, no positive lymph nodes were found in the 147 lymph nodes sampled from the 12 patients who underwent radical resection. There is general agreement that for T1a tumors (not into muscle) only simple cholecystectomy is required. For T1b (muscle invasion), there is evidence that a more aggressive surgical approach is required. T1b tumors are associated with lymph node metastases in 15% of cases, whereas only 2.5% of T1a tumors are reported to have lymph node involvement.[26] Several reports show T1b lesions treated with cholecystectomy alone have a recurrence rate of 30% which can be reduced to about 10% with extended operation.[26–28] While not unanimous, there is generally a consensus among hepatobiliary surgeons that T1b tumors require an extended procedure.

Patients with T2 (invading perimuscular connective tissue, not penetrating the serosa) tumors may be the only subset of patients with GBCA where there is little argument about the value of radical resection. Most cholecystectomies are completed through a subserosal plane, and therefore, further resection is necessary for clean margins.[29] Also, approximately one-third of patients with T2 tumors have lymph node metastasis at the time of resection.[7,10,13,22] In a series of 28 patients with T2 cancers, radical surgery resulted in overall 5-year survival of 59%, compared to 17% in patients who underwent less radical procedures. In patients with stage II disease (no lymph node or distant metastases), the 5-year survival was 75%.[30] Similarly, Fong found that patients with T2 tumors who underwent a simple cholecystectomy had a 5-year survival or 19%, whereas those who underwent radical resection had a 5-year survival of 61%.[10] Several other studies document improved survival with radical cholecystectomies for T2 tumors.[7,31,32]

The role of radical resection in T3 and T4 tumors remains debatable. Many series report no 5-year survival for patients with T3 and T4 lesions.[22] However, other

studies report an up to 15–63% (T3) and 7–25% (T4) 5-year survival in patients with T3 and T4 disease.[29] Increased survival is clearly associated with the extent of resection, and most centers reporting survival in these patients are doing extended radical resections. In T3 and T4 patients, a complete R0 resection is associated with increased survival. Behari et al. looked at 35 patients with T3 disease, of which 13 had a successful R0 resection, which had a 28% 5-year survival.[33] None of the T4 patients could undergo an R0 resection, and they had no 5-year survival. Bartlett et al. had a 67% 5-year survival in patients with T3 disease who were completely resected.[7] They also had two of three patients with T4N0 disease who survived 4 years after resection.

Importantly, many centers advocate an extended resection for these patients, even if the prognosis is poor because prolonged survival is possible, and many patients have extended lives before recurrence.[7,11] Kurokawa et al. had five long-term survivors (>4 years) with of 40 patients who were resected for advanced disease.[34] Zhang et al. found that patients with Nevin stage V GBCA (direct extension into liver) who underwent resection with a curative intent survived longer than patients who underwent resection with a palliative intent, and they survived longer than patients who just underwent a biopsy or drainage procedure.[35] They concluded that a "radical resection was still the unique way to a better prognosis."

Even if radical resections are warranted, there is still controversy as to what is an aggressive or radical resection, both in terms of the amount of liver to be resected and whether the bile duct requires resection.[36] Yoshikawa et al. demonstrated that a segment 4B/5 resection may be superior to a radical cholecystectomy (with a 2-cm margin of liver around the gallbladder bed).[37] In their series of 201 patients, they found segment 4B/5 resection was beneficial if the liver invasion was less than 20 mm. Right hepatic lobectomies are also controversial, as 34% of GBCAs invade the left ductal system.[29] The anatomic location of the tumor should dictate the hepatic resection. Tumors in the fundus can be treated with a segment 4B/5 resection, but those in the infundibulum, gallbladder neck, or invading the triangle of Calot may require a right trisectionectomy with bile duct resection and reconstruction to achieve negative margins.[4] In the absence of tumor involvement of the bile duct, there is no evidence that resecting the bile duct improves survival, and yet many surgeons (including the authors) perform a bile duct resection to improve the clearance of lymphatic and neural tissue along the vascular inflow to the liver. Distal bile duct involvement mandates pancreaticoduodenectomy (Fig. 2) if negative margins are to be achieved. Surprisingly, several series report long-term survivors after a trisectionectomy–pancreaticoduodenectomy for GBCA.[34,38]

Approximately 2% of GBCAs are diagnosed during laparoscopic or open cholecystectomy for benign disease.[29] In this case, a biopsy needs to be sent for frozen section to confirm the pathology, and the extent of disease must be assessed. If the surgeon is comfortable with the necessary radical resection, then it can be done at that time. Otherwise, the procedure can be aborted and the patient sent to a referral center for further treatment. Any patient with a positive cystic duct margin should have a common bile duct resection. Cancers diagnosed postoperatively can be treated according to their T stage as above. T1b, T2, and T3 tumors should undergo further exploration and resection, as 40–76% of cases have residual tumor after cholecystectomy.[7,10,29–32] Laparoscopic cholecystectomies should be converted to open procedures when cancer is diagnosed because of the risk of port site spread and residual disease.[39] Misra et al. found that six of eight patients who had a radical resection after initial laparoscopic cholecystectomy had disease in their lymph nodes, gallbladder bed, and port sites.[29]

Universally, lymph node spread at the time of surgery is a poor prognostic factor, with many series reporting no patients surviving in 5 years. However, Chijiawa et al. reported a 50% 5-year survival in patients with N1 (hepatoduodenal ligament) nodal involvement.[40] Regional lymphadenectomies should be performed in an attempt to achieve an R0 resection, which is associated with improved survival in all stages.[4,10,32,33,41] Nodal involvement outside the hepatoduodenal ligament is associated with no long-term survival in several studies.[7,9,40] Periaortic lymph node involvement is found in an estimated 20% of patients with locally advanced disease,[11] and para-aortic lymphadenectomy has not shown a definitive survival advantage in patients undergoing a radical cholecystectomy for advanced disease.[42] Local invasion of adjacent organs does not necessarily make a patient unresectable. Nakamura et al. reported a 15% 5-year survival for patients with stage IV disease that underwent aggressive resections, some including the colon and kidney,[43] although with a high morbidity.[26]

Although large randomized, prospective trials are lacking in this relatively rare disease, there is a possible survival benefit to adjuvant chemoradiotherapy. Adjuvant radiotherapy has been shown to have a survival benefit, especially in patients with microscopic positive margins or residual disease after resection.[44] Similarly, an improvement in a 5-year disease-free survival and a 5-year overall survival was seen with postoperative mitomycin and 5FU.[45] In 21 patients with GBCA resected with negative margins, 5-FU plus external beam radiation was associated with a 64% 5-year survival, whereas surgery alone had a 33% 5-year survival.[46] With success in the treatment of pancreatic cancer and cholangiocarcinoma, gemcitabine is now being investigated in GBCA.[47]

Surgical resection remains the only cure for patients with GBCA. Because of the possibility of long-term survival, aggressive resection should be pursued in all patients, except those with lymph node involvement outside the hepatoduodenal ligament and metastatic disease. Adjuvant chemoradiotherapy should be considered for patients with advanced disease in the setting of clinical trials.

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Clinical and Radiologic Resolution of IgG 4 Normal, Nonoperatively Diagnosed Lymphoplasmacytic Sclerosing Pancreatitis (LPSP) after Initiation of Steroid Therapy

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Case Report

A 49-year-old female was referred for surgical evaluation of a pancreatic mass. The patient gave a history of moderate to severe mid-epigastric pain radiating to the back that had been ongoing for approximately 1 year. She complained of occasional early satiety and had lost 10 lbs since the onset of symptoms. There was no history of jaundice, fever, chills, or night sweats. Upper and lower endoscopies were unremarkable. Five months before this evaluation, a laparoscopic cholecystectomy was performed without relief of symptoms. Past medical history was significant only for hypertension with no history of any autoimmune disorder. The patient did not smoke or consume alcohol.

On physical exam, the patient was afebrile with normal vital signs. There was no evidence of cachexia. The sclera were anicteric. No peripheral adenopathy was noted. The abdomen was soft with no palpable mass. Computed tomography (CT) of the abdomen demonstrated a diffuse, isohomogenous mass of the pancreas predominantly involving the pancreatic head with encasement of the mesenteric vessels and surrounding adenopathy (Fig. 1). Liver function tests were normal except for a mildly elevated alkaline phosphatase of 153 U/l (normal, 30–100). CA19-9 and CEA levels were normal.

Given the atypical presentation for pancreatic adenocarcinoma and the CT findings, a preliminary diagnosis of pancreatic lymphoma was entertained. Fine needle aspiration (FNA) of the pancreas was performed and returned consistent with chronic pancreatitis. Because of a continued concern of an underlying neoplasm, a core biopsy was obtained and pathologic analysis was consistent with lymphoplasmacytic sclerosing pancreatitis (LPSP) (Fig. 2). In retrospect, features consistent with LPSP were present on fine needle biopsy but were not recognized by the initial pathologist. Total IgG [1,140 mg/dl (normal, 600–1500)] and IgG4 [120 mg/dl (normal 8–140)] levels were unremarkable. The patient was started at 40 mg of prednisone daily. Because of significant side effects of weight gain and mental status changes, the dose was decreased after 2 weeks to 5 mg per day. Six months after initiation of steroid therapy, the patient was completely asymptomatic. A repeat CT scan demonstrated significant resolution of the pancreatic mass. The encasement of the mesenteric vessels noted on the initial survey had nearly completely resolved (Fig. 3). The patient remains on 5 mg of prednisone daily.

Discussion

Lymphoplasmacytic sclerosing pancreatitis is a benign pancreatic disease diagnosed histologically by a diffuse lymphoplasmacytic infiltration of the pancreas with associated periductal inflammation, interstitial fibrosis, and an obliterative phlebitis.[1] A relatively recently described

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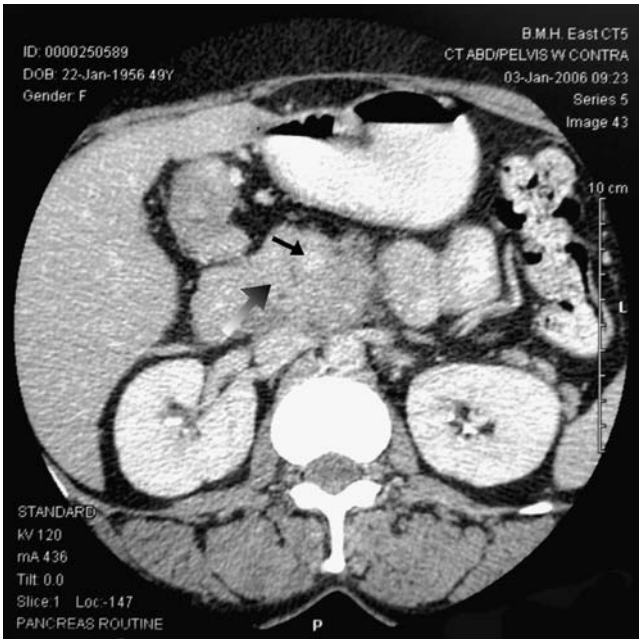

Figure 1 CT at presentation demonstrating diffuse homogenous enlargement of the pancreas (*large arrow*) with encasement superior mesentric vein (*small arrow*).

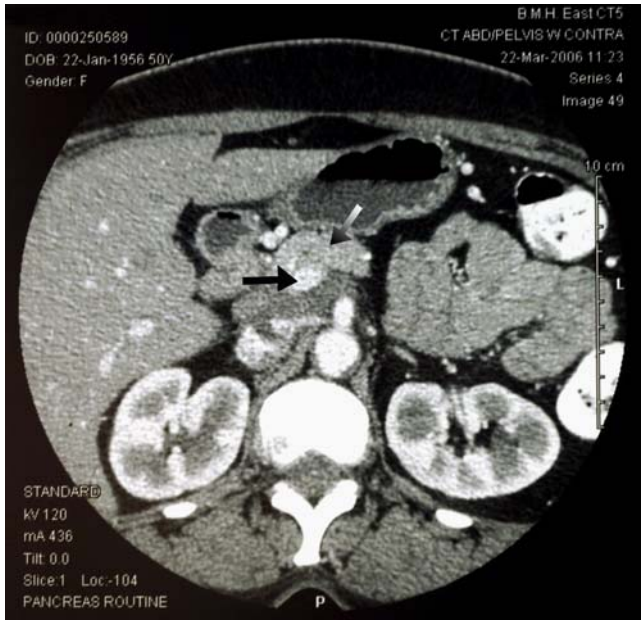

Figure 3 Posttreatment CT demonstrating resolution of pancreatic mass with a near normal pancreatic contour (*shaded arrow*) and resolution of superior mesentric vein encasement (*black arrow*).

entity, it remains diagnostically challenging and often clinically and radiologically mimics those with pancreatic adenocarcinoma.[2–4] LPSP continues to be a challenging diagnostic entity with respect to differentiation from pancreatic adenocarcinoma. However, several clinical, laboratory and radiologic findings might warrant inclusion of LPSP in the differential diagnosis for those presenting with a pancreatic mass. As noted in our patient, jaundice and hyperbilirubinemia, while common, are not universally found even in those with an enlarged pancreatic head.[5,6] Another concomitant autoimmune disorder may suggest LPSP, but this is found in no more than 25% of all patients with LPSP in large series.[2,3] Tumor markers including CA19-9 and CEA are not uncommonly normal as was noted in our case.[2,5] Finally, while CT scan of the pancreas may demonstrate a mass consistent with adenocarcinoma, more frequently, findings of diffuse, homogenous enlargement of the pancreas are noted.[1–3,5,7]

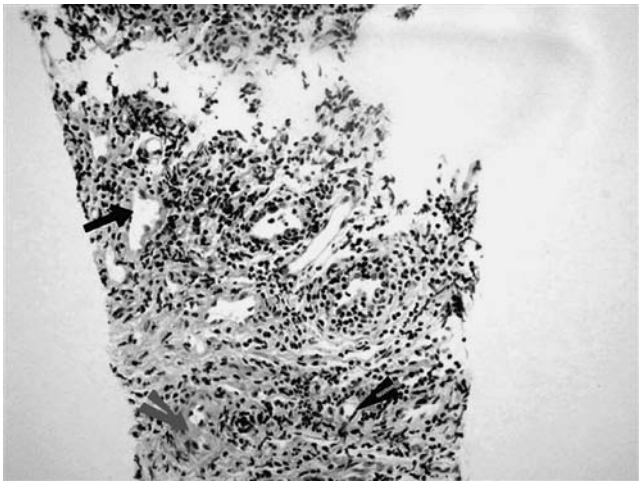

Figure 2 Core biopsy of pancreas demonstrating lymphoplasmacystic infiltrate with periductal inflammation (*black arrow*), sclerosis (*gray arrow*), and venulitis (*black and white arrow*).

If the diagnosis is entertained, most would agree that an assessment of immunoglobulin, and more specifically IgG4, levels is warranted. It is important to emphasize that these levels will not always be elevated in those with LPSP as noted here and by others.[1,7,8] While an elevated IgG4 level in the appropriate clinical setting is reported to be 95% specific for LPSP, many would prefer a tissue diagnosis (particularly if immunoglobulin levels are normal) before embarking on a treatment regimen.[9] In those with a normal IgG4 level, a biopsy to diagnose LPSP and exclude carcinoma would be important especially if nonoperative intervention is planned. Many authors have reported poor results in diagnosing LPSP with percutaneous biopsy of the pancreas and have therefore cautioned against a nonoperative approach in this disease entity when a definite exclusion of an underlying neoplasm cannot be made.[2,3] Indeed, there remains considerable controversy in the pathology literature with regard to the diagnostic criteria on a given sample size necessary to make the diagnosis of LPSP.[8,10] The lack of a definitive diagnosis of LPSP on tissue sampling may be related to the quantity of tissue obtained. LPSP has been diagnosed on FNA and core biopsies in some studies but has required open biopsy in

others. Furthermore, perhaps because of the low incidence and lack of awareness of the disease, LPSP may go unrecognized by the pathologist. Our case was diagnosed by core biopsy on the basis of a classic lymphoplasmacytic infiltrate with associated sclerosis, periductal inflammation and phlebitis. On further analysis, most of these features were demonstrated on FNA but were unrecognized by the initial pathologist. With a greater awareness of this disease process, we and others feel confident that a nonoperative diagnosis can frequently be made, sparing the patient a laparotomy.[10] Clearly, further data on the reliability of diagnosis based on minimum tissue samples will need to be forthcoming.

The treatment regimen for LPSP continues to remain controversial due, in no small part, to the difficulty in making the diagnosis as patient presentations are variable.[9] Hamano and colleagues treated 20 patients with a diagnosis of sclerosing pancreatitis and an elevated IgG4 level with steroids.[9] They did not state how the diagnosis of LPSP was made. All 20 patients improved with this therapy. In common with Hamano, we noted dramatic improvement in the CT appearance of the pancreas and in the resolution of symptoms in our patient with a normal IgG4 level. It is clear from the literature that one can expect an excellent response to steroid therapy in the appropriately diagnosed patient.[5–7,11,12] Without a proven histologic diagnosis of LPSP, most surgeons have been reluctant to embark on nonoperative therapy especially in those with normal immunoglobulin levels.[2–4,6] Results of surgical intervention have been quite good as well, albeit, with the generally accepted morbidity occurring after pancreatic resection. Interestingly, despite only partial pancreatic resection in the majority of the reported literature, the recidivism rate with respect to LPSP appears to be quite low even if postoperative steroid therapy is not instituted.[2–4]

Based on our limited experience and a review of the literature, several observations are suggested. A high index of suspicion for this lesion must be considered especially in those with a pancreatic mass and an atypical clinical, laboratory, or radiologic presentation for adenocarcinoma. Obtaining an IgG4 level would be most appropriate if the diagnosis is suspected. If elevated, some would argue for the initiation of steroid therapy without a tissue diagnosis, although we feel that further study with biopsy is necessary given the relatively low number of patients thus treated to date.[13] We believe that fine needle biopsy, and if equivocal, core biopsy are often reliable and prudent when considering the diagnosis of LPSP especially in those with normal immunoglobulin levels. If a histologic diagnosis can be made, data from our case and others would suggest that surgical resection for this entity may be avoided by treatment with very modest doses of systemic steroids. Future work will need to focus on the necessary duration of steroid therapy and the natural history of LPSP following both surgical and nonsurgical treatment.

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SSAT Patient Care Guidelines

Management of Colonic Polyps and Adenomas

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Introduction

Polyps of the colon are mucosal lesions, which project into the lumen of the bowel. According to autopsy studies, colonic polyps occur in more than 30% of people over the age of 60. Approximately 70–80% of resected polyps are adenomatous. Adenomatous lesions have a well-documented relationship to colorectal cancer. This adenoma–carcinoma progression represents a significant public health problem, as colorectal cancer is the second leading cause of cancer-specific mortality in the United States. Therefore, appropriate management of colonic polyps may reduce the risk of death from colorectal cancer.

Types of Polyps

There are four types of colonic polyps: adenomatous, hyperplastic, hamartomatous, and inflammatory. In addition to these histologic features, polyps are generally described as being either sessile (flat) or pedunculated (having a stalk). Inflammatory and small hyperplastic polyps do not have malignant potential and therefore do not require any further intervention and should not alter surveillance intervals. While most hamotomatous polyps do not have malignant potential, those associated with Peutz-Jeghers syndrome and juvenile polyposis do contain a risk for malignant transformation and therefore require more aggressive intervention and monitoring. Adenomatous polyps are considered precursors for invasive colon and rectal cancer. Histologically, these polyps are either villous, tubular, or tubulovillous. The risk of malignancy increases with both the size of the polyp and the degree of villous component.

Symptoms

Most colonic polyps are asymptomatic. Those that are symptomatic usually present with lower GI bleeding. This may range from occult bleeding, as detected by fecal testing for occult blood or the presence of iron deficiency anemia, to frank blood per rectum. Polyps are rarely the source of a significant lower GI bleeding. Some low rectal polyps may cause a mucus discharge from the rectum. Most polyps cannot be discovered by physical exam. However, some low-lying rectal polyps can be detected by digital rectal examination.

There are asymptomatic patients who are at high risk. These include patients with a family history of polyps or colon and rectal cancer, patients with ulcerative colitis or Crohn's disease, and patients with a polyposis syndrome [i.e., familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer (HNPCC)].

Methods of Diagnosis

There are several methods available to detect colonic polyps. These include fecal occult blood testing, sigmoidoscopy, colonoscopy, and the combination of barium enema and sigmoidoscopy. Fecal testing for occult blood testing is a simple, non-invasive test done by most primary care physicians. There are several studies suggesting that yearly fecal occult blood testing, especially if combined with sigmoidoscopy, may decrease the mortality of colorectal cancer. Proper follow up testing, usually colonoscopy, is mandatory for patients with positive results. Colonoscopy is now accepted as the most accurate method of detecting colonic polyps. Colonoscopy also allows simultaneous removal of most lesions.

However, colonoscopy is clearly the most invasive and the most expensive of our screening tools. Nevertheless, colonoscopy is rapidly becoming the most common method for colon polyp and cancer screening. Current recommendations for non-high-risk patients (i.e., no family history) is to begin surveillance at age 50 with routine colonoscopy. Since most clinically significant colon polyps are located

distal to the splenic flexure, flexible sigmoidoscopy may be a reasonable alternative to colonoscopy.

However, lesions in the right colon may go undetected and those patients found to have a polyp on flexible sigmoidoscopy will then need a full colonoscopy, subjecting these patients to both tests. The combination of double contrast barium enema and sigmoidoscopy is better tolerated by some patients and is less expensive and safer than routine diagnostic colonoscopy, but obligates many patients to a second procedure for therapeutic intervention. The incidence of significant bleeding and perforation is less than 1% for colonoscopy, as compared to only 0.01% for the barium enema. Virtual colonoscopy, while seemingly effective at detecting polyps, is still not considered ready for routine clinical use. Genetic testing of stool may also be able to non-invasively detect polyps and colon cancers, but still needs considerable development before it can be used in routine clinical practice.

Management of Colonic Polyps

Patients undergoing treatment of colonic polyps require mechanical bowel preparation before colonoscopy. Most polyps can be removed during colonoscopy using electrocautery techniques. Surgical removal is indicated only when an experienced endoscopist cannot completely remove the polyp safely. To minimize the risk of future malignancy, polyps should be completely removed or destroyed. While total excision of the polyp is desirable, small polyps (0.5 cm or less) can be treated by biopsy and fulguration. Most pedunculated polyps are amenable to snare polypectomy using electrocautery.

Sessile polyps larger than 2 cm usually contain villous features, have a higher malignant potential, and tend to recur following colonoscopic polypectomy. If complete or safe colonoscopic resection is not possible for technical reasons, the lesion should be biopsied and the patient referred for primary surgical therapy. In cases where the lesion can be removed via the colonoscope, follow-up endoscopy should be done in 3–6 months to confirm complete resection. Residual adenomatous tissue noted at follow-up colonoscopy should be removed and another confirmatory colonoscopy performed 3 months later. Surgical resection is recommended for residual abnormal tissue at the polypectomy site after two or three attempts at colonoscopic removal.

The resected polyp must be completely examined pathologically. Histologically, adenomatous polyps can show a benign adenoma (tubular, tubulovillous, or villous), carcinoma in situ, or invasive cancer. Colonoscopic removal is definitive therapy for benign adenomatous polyps or inpatients having polyps with carcinoma in situ. If pedunculated polyps contain invasive carcinoma, colonoscopic removal is adequate treatment in the uniform presence of favorable prognostic indicators such as complete excision, no lymphovascular invasion, clear margins, and well-differentiated histology. A follow-up examination within three months is mandatory to confirm the presence or absence of residual or recurrent disease. Any patient with lesions not meeting these criteria should undergo elective resection of the involved segment of the colon or rectum. Additional staging procedures such as computed tomographic scanning, endoscopic ultrasound, or endorectal magnetic resonance imaging may be helpful.

Post-polypectomy Surveillance

The entire colon must be examined during the polypectomy, so that any synchronous lesions can be detected and removed. Approximately 50% of patients will have a second adenomatous polyp at the time of initial colonoscopy, while metachronous polyps are found in 20–50% of patients within 5 years of the initial polypectomy. If follow-up colonoscopy verifies that no residual polyps exist, colonoscopy should be repeated within 3 years and thereafter every 5 years. Patients who undergo complete removal of a solitary tubular adenoma smaller than 1 cm should have a surveillance colonoscopy 5 years post polypectomy. However, even longer intervals have been suggested. In the future, new evidence may indicate the interval in these patients.

Complications of Colonoscopic Polypectomy

Colonoscopic polypectomy has an overall complication rate of 1–2%, with bleeding as the most common complication. Other complications include free perforation of the bowel, microperforation, transmural electrocautery burn, pneumatosis cystoides intestinalis, splenic capsular tear, and avulsion of a mesenteric blood vessel. Many of these complications can be treated as necessary, but peritonitis or unrelenting hemorrhage requires urgent laparotomy.

Surgical Treatment of Colonic Polyps

A colonic polyp that is deemed unresectable endoscopically requires a colonic resection. Localization is critical before surgical removal. Lesions can be endoscopically tattooed before surgery to assist in localization. Introperative colonoscopy may also be necessary if the lesion is not readily identifiable. The specimen should be opened at the time of surgery to confirm resection of the suspicious lesion. Because surgery is reserved only for those polyps

deemed endoscopically unresectable, these polyps must be considered high risk for containing an invasive malignancy. Therefore, surgery, whether laparoscopic or open, should follow the principles of colorectal cancer surgery.

Effective surgical treatment of rectal polyps requires full thickness excision for lesions of moderate size to an extensive mucosectomy for larger lesions. Such techniques may save patients the significant morbidity of having a proctectomy. For patients with endscopically unresectable polyps of the upper rectum, transanal endoscopic microsurgery (TEM) may be an option, but requires specialized expertise.

Qualifications for a Surgeon Treating Colonic Polyps

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

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Keywords

Patient, Guideline, Colorectal, Colonic, Polyps, Surveillance, Polypectomy, Colectomy, Neoplasia, Colonoscopy, Adenoma

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SSAT Patient Care Guidelines

Surgical Treatment of Cancer of the Colon or Rectum

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Introduction

Cancer of the colon and rectum (or colorectal cancer) is the third most common form of cancer and is the second leading cause of cancer mortality in the USA.

Although the majority of colorectal cancers have no identifiable underlying cause, they are thought to arise from a series of genetic events that result in precursor lesions such as polyps (http://www.ssat.com/cgi-bin/guidelines.cgi; see "Management of Colonic Polyps and Adenomas") leading to the formation of cancer. Nearly 20% of patients with colorectal cancer have a positive family history of at least one first or second degree relative with colorectal cancer. Five to ten percent have a known inherited predisposition to develop this disease, with familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) being the two major syndromes. Patients with FAP develop hundreds to thousands of colorectal adenomatous polyps during the second or third decade of life. If untreated, virtually all patients will develop colorectal carcinoma by the age of 45. Patients with HNPCC have a high lifetime risk of developing colorectal cancer and typically are characterized by an early onset of carcinoma (average age 45 years) and a tendency to develop cancers in the proximal colon and synchronous and metachronous cancers. Other conditions that predispose to colorectal cancer include ulcerative colitis, Crohn's colitis, schistosomal colitis, exposure to radiation, and nonfamilial colorectal adenomatous polyps.

Symptoms and Diagnosis

Screening measures used to detect early cancers or premalignant polyps in asymptomatic persons include digital rectal examination, fecal occult blood testing, endoscopy, and radiographic imaging. Colorectal cancer may be asymptomatic. When present, symptoms may include anemia, rectal bleeding, and change in bowel habits or tenesmus (painful incomplete fecal evacuation) depending on the location and extent of the tumor. Systemic manifestations such as weight loss and fatigue because of chronic anemia suggest advanced disease. Obstruction, perforation, and acute bleeding may occur as complications of colon cancer.

Physical examination may reveal a palpable abdominal or rectal mass. Abdominal distention suggests high-grade rectal or colonic obstruction and, rarely, the presence of malignant ascites.

The entire colon should be examined preoperatively by colonoscopy or barium enema if cancer of the colon or rectum is suspected, unless contraindicated by colonic obstruction or other circumstances. With colonoscopy, cancers can be seen and biopsied, and synchronous neoplastic polyps can be removed if not contained within the segment of resected bowel.

Metastases can be detected by chest X-ray and suggested based on elevation of carcinoembryonic antigen (CEA) level or liver function tests. CEA is not an accurate diagnostic test for colorectal cancer in a curable stage, but may be helpful in detecting recurrence after curative resection. Ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) scans of the abdomen may be used to search for hepatic metastases. CT or MRI scans of the pelvis or endorectal ultrasonography in patients with rectal cancer may assist in tumor staging and treatment planning.

Preoperative histological confirmation is not required if the primary lesion in the colon or rectum has the characteristics of a cancer not under consideration for preoperative chemoradiation treatment. For suspected liver metastasis, histological confirmation can usually be obtained at the time of surgery.

Operative Treatment

Surgical removal is the preferred treatment for colorectal cancer. Surgical treatment is indicated in nearly all patients with newly diagnosed cancer of the large intestine unless survival is unlikely or life expectancy is very short because of advanced cancer or other diseases. Even in the presence of metastases, palliative surgical resection of the primary tumor may be advisable to prevent further bleeding and impending obstruction.

Operative treatment for colorectal cancer consists of wide surgical resection of the involved bowel segment and regional lymphatic drainage. Primary anastomosis of a prepared bowel is possible in elective cases. Laparoscopic colectomy for colon neoplasia has been shown to be equivalent to open colectomy when performed by experienced surgeons.

Operative treatment of rectal cancer includes en bloc resection of the rectum as an intact unit with its lymphovascular drainage contained within the fascia propria of the mesorectum using sharp dissection techniques (total mesorectal excision). Preservation of the anal sphincters and avoidance of a permanent colostomy is preferred in rectal cancer if eradication of the cancer with adequate margins is also achieved. A temporary diverting colostomy may be necessary depending on intraoperative findings. Transanal local excision of rectal cancer may be appropriate and curative for selected patients with small, early stage, and accessible tumors that exhibit favorable histologic features. Palliative treatment for unresectable rectal cancers includes fulguration, laser photocoagulation, radiation therapy, and endostenting.

Radiation therapy and chemotherapy are used for advanced disease and in conjunction with surgical resection. Although radiation therapy has little role in management of colon cancer, it is an important treatment modality for rectal cancer. Bulky rectal cancers may be treated preoperatively to improve resectability. For stage II (invasion through the muscularis propria of the rectal wall) or stage III rectal cancer (metastases to regional lymph nodes), radiation therapy is a useful preoperative or postoperative adjunct and is also used in combination with chemotherapy.

Patients with colon cancer and lymph node metastases (Stage III) and selected patients without lymph node metastases (Stage II) should be considered for postoperative adjuvant chemotherapy.

Risks

Postoperative complications of resection for colorectal cancer generally involve infections related to the bacterial flora of the large bowel. The most common postoperative complication is wound infection (2–4% in elective cases), which is minimized by mechanical and antibiotic bowel preparation and prophylactic intravenous antibiotics. Other risks include bleeding, anastomotic leakage, pelvic abscess, damage to neighboring organs (such as the spleen or ureter), sexual and urinary dysfunction, and wound dehiscence.

Expected Outcomes

The length of hospitalization is generally determined by the return of normal bowel function and, in most cases, is usually within 1 week. The resumption of normalized physical activity is affected by the mode of surgery, either laparoscopic or open approach. Elderly or debilitated patients may have a longer recovery period.

Bowel movements after operation may either be normal or may be more loose and frequent, depending upon the portion and length of bowel removed. Although these changes are rarely severe, disordered bowel habits after anterior resection with a very low anastomosis can be quite troublesome. Most patients with colostomies adjust well with the help of support groups and family. Long-term dietary restrictions are generally not necessary.

The clinicopathologic stage of disease is the most important determinant of survival after surgical resection. Five-year survival rates vary from 90% for tumors confined to the mucosa and submucosa to less than 5% for those with distant metastases. About 70% of these patients can be cured by operation.

Follow-up after curative resection of colorectal cancer involves measurement of serum CEA levels every 3–6 months for the first 3 years, colonoscopy 1 year after surgery and then every 3 years. Based on clinical indications, radiographic imaging such as chest X-ray, ultrasound, CT, and/or MRI scan may also be indicated to evaluate for regional recurrence or metastatic disease. Whole-body FDG-PET scanning is a new modality that may be useful in selected circumstances for identifying metastatic disease. Patients with recurrent colon or rectal cancer who do not have evidence of distant disease may be candidates for surgical resection with or without adjuvant radiation therapy. Localized hepatic or pulmonary metastases detected during follow-up should be evaluated for possible resection. If one or a few lesions can be completely resected, survival is significantly prolonged.

Qualifications for Performing Operations on the Colon

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. At a minimum, surgeons who are certified or eligible for certification by the American Board of Surgery or the Royal College of Physicians and Surgeons of Canada or their equivalent should perform colonoscopy and/or colectomy. These surgeons have successfully com-

pleted at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the colon. When performing laparoscopic colon surgery, it is highly desirable that the surgeon has advanced laparoscopic skills. The level of training in advanced laparoscopic techniques necessary to conduct minimally invasive surgery of the colon is important to assess.

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Keywords

Colorectal cancer, Colorectal neoplasms, Colectomy, Colostomy, Familial, Proctocolectomy, Proctectomy, Laparoscopy, Guideline, Patient

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SSAT Patient Care Guidelines

Management of Ulcerative Colitis

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Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease that results in inflammation of the inner lining of the colon and rectum. While UC can occur at any age and affects both sexes equally, the peak age at onset of symptoms is about 20 years, with a second smaller peak at about 60 years. The disease has marked geographical and racial differences in incidence, with the highest prevalence in northern climates (e.g., North America, Europe). Ulcerative colitis is unusual in Asia and Africa. The incidences of UC in Minnesota or Japan are about 15 and 0.5 cases/year per 100,000 people, respectively.

The cause of UC is unknown. There is evidence that genetic factors may play a role in determining susceptibility to the disease, hence the tendency towards familial aggregation and differing incidences in different races. It is clear, however, that unknown environmental factors also interact with genetic factors to trigger the disease.

The immune system is the key mediator of the changes of UC. The mucosa of the colon and rectum of patients with UC contains active immune cells, which produce damage to the tissue. Similarly, the so-called extraintestinal symptoms associated with UC (e.g., arthritis, skin disorders, sclerosing cholangitis) are caused by complexes of immune cells that result in tissue damage.

Symptoms and Diagnosis

Ulcerative colitis usually begins with inflammation of the rectum, also known as "ulcerative proctitis." The disease process then tends to extend proximally into the colon (i.e., "colitis"). The hallmark clinical signs are bleeding and diarrhea. However, the severity of symptoms varies markedly, ranging from insidious changes in bowel habits with intermittent diarrhea to rapid onset of profuse bloody diarrhea, abdominal pain, and fever.

The diagnosis of UC can be made by flexible sigmoidoscopy because the rectum is virtually always inflamed. The characteristic appearance should be confirmed with biopsies and microscopic examination. Colonoscopy (or barium enema) frequently provides useful information, not only helping to assess the proximal extent of disease, but also to look for skip areas, polyps, or other features that would challenge or confirm the diagnosis. The differential diagnosis includes Crohn's disease, infectious colitis (e.g., Clostridium difficile, Campylobacter), and collagenous colitis. In all cases, stool cultures should also be obtained to rule out infectious causes of diarrhea.

Medical Treatment

The goal of the medical treatment of UC is to induce clinical remission while avoiding toxic medications. Medications such as 5-ASA products (e.g., Asacol®, Pentasa®, Dipentum®, Azulfidine®, etc.) are often used to maintain remission. Whereas the 5-ASA medications are safe, chronic corticosteroids and other immunosuppressive agents are not. Therefore, when clinical remissions are induced with corticosteroids and/or cyclosporine, additional medications should be considered to facilitate weaning of these drugs. 5-ASA compounds or immunosuppressants such as azathioprine and 6-MP are recommended. It is probably wise to attempt weaning off azathioprine or 6-MP after 1 to 2 years of remission.

The medical treatment should be tailored to the severity of symptoms and extent of disease. Patients with proctitis and proctosigmoiditis are best treated with topical treatment such as 5-ASA or corticosteroid enemas or suppositories. As the disease extends proximally to the left colon, oral or systemic treatment becomes necessary. The first line of treatment should be 5-ASA products. In patients with severe colitis or moderate colitis that is not responding to maximal doses of 5-ASA, corticosteroids are initiated. Most patients with severe colitis (more than six stools/day, blood in stool, fever, tachycardia, and anemia) require hospitalization with bowel rest, intravenous corticosteroids, and parenteral nutrition. Approximately 50% of patients admitted to the hospital for treatment of severe or fulminant disease will respond to bowel rest, antibiotics, and corticosteroids and will not require urgent operation. The addition of intravenous cyclosporine results in improvement in another 20–30% of

patients. Thus, about 50–80% of patients can be discharged home without urgent surgery. Despite this, the majority of patients requiring hospitalization for treatment of severe UC undergo colectomy within 1 year.

Indications for Surgery

It is difficult to predict which patients with UC will require surgery. Approximately 85% of patients with severe or fulminant disease will undergo colectomy within 1 year. However, this subgroup represents only 10–20% of patients.

The majority of patients with mild or moderate disease have an unpredictable course. The cumulative likelihood of requiring colectomy by 25 years is about 32%. The most common indications for elective colectomy are inability to wean off steroids over 6 to 9 months and/or a poor quality of life [e.g., fatigue, high stool frequency (>6 day), anemia]. The development of dysplasia or cancer is an absolute indication for colectomy.

Patients with ulcerative proctitis or proctosigmoiditis have a risk of developing colon cancer similar to that of the normal population. On the other hand, patients with UC proximal to the splenic flexure have an increased risk for the development of colon cancer and warrant surveillance. Subsets of patients have different degrees of risk. The well accepted colon cancer risk factors in patients with UC are extent of disease and duration of disease. The increased risk for cancer in patients with pancolitis begins 8 years after onset of disease, with an incidence of about 0.5–1.0%/year thereafter. The optimal strategies for surveillance, diagnosis, and treatment of cancer in patients with UC are controversial and were recently addressed by a consensus panel of experts in gastrointestinal disease. This panel posed several questions, some of which are summarized below:

1. Is there a risk of developing colon cancer in patients with ulcerative colitis? Yes. The patients at highest risk are those with pancolitis and duration of disease greater than 8 years. The subset of patients who also have primary sclerosing cholangitis or who have a family history of colon cancer have additional risk. Early age at onset of disease is likely an additive risk factor. In one study, 50% of patients with onset before the age of 15 years developed cancer by the age of 50 years.
2. Is dysplasia a reliable and valid histologic marker in the identification of patients at risk for developing colon cancer in the face of ulcerative colitis? Yes and no. Patients with low-grade dysplasia, high-grade dysplasia, and especially dysplasia associated with a visible lesion or a mass (DALM) have a cancer risk that mandates elective colectomy. The problem with using dysplasia as a diagnostic test is its poor negative predictive value. That is, at least 20% of colectomy specimens from patients with UC who have developed cancer have no detectable dysplasia.
3. Is colonoscopic surveillance of benefit in reducing cancer in patients with ulcerative colitis? There have been no prospective randomized trials that could answer this question. Retrospective studies indicate that mortality is reduced when patients are in surveillance programs. Colonoscopy should probably be performed every 1 to 2 years starting 8 years after onset of disease and then yearly 15 years after onset of disease. Multiple biopsies (>25) should be taken randomly and of any macroscopic lesions.
4. Is there a role for prophylactic colectomy in patients with ulcerative colitis? DALM or low-grade or high-grade dysplasia is usually an indication for elective colectomy. Some experts continue to recommend colectomy at 10 years after diagnosis of pancolitis. After 20 years, especially in patients with a family history of colon cancer and/or in patients with young age of onset, the case becomes strong for true “prophylactic” colectomy.

Surgical Treatment

There are four surgical options in patients with UC: (1) total proctocolectomy and ileostomy, (2) total proctocolectomy with continent ileostomy (Kock pouch), (3) total proctocolectomy with ileal pouch–anal anastomosis (IPAA), and (4) colectomy with ileorectal anastomosis. With the refinement of the IPAA procedure, it has become the operation of choice in virtually all patients. The Kock pouch is typically reserved for patients with previous total proctolectomies who are very unhappy with their ileostomies. Old age, advanced rectal cancer, and previous anal sphincter damage are relative contraindications for the IPAA procedure. The IPAA is not indicated in patients with Crohn’s disease.

The technical aspects of the IPAA continue to evolve. Although the use of protecting ileostomies at the time of IPAA was routine for years, many centers are now performing selective one-stage IPAA with excellent long-term results in patients who are well nourished and not taking corticosteroids. Similarly, the traditional procedure includes rectal mucosectomy followed by hand-sewn IPAA. Many surgeons now perform a “double-staple” technique without mucosectomy. In experienced hands, excellent results have been reported with either surgical technique.

Risks and Expected Outcomes

Mortality rates for patients undergoing elective operation for UC are less than 1%. Technical problems such as major

hemorrhage and abdominal infections are infrequent. Patient satisfaction is very high in patients with UC who undergo colectomy. When the IPAA procedure is performed at centers with significant experience, at least 85–90% of patients have long-term functioning pouches. Nearly all patients would recommend the surgery to others, regardless of their operation (i.e., proctocolectomy with ileostomy or with IPAA). Quality of life, as measured with tools such as the SF-36, is normal. Stool frequency in patients after IPAA averages about six per day. At least 85% of patients have perfect fecal continence. In general, sexual function is preserved. However, retrograde ejaculation, impotence, and dyspareunia are potential complications, which should be discussed with most patients. Recently, there have also been several restrospective reviews that suggest that women are less likely to get pregnant after an IPAA when compared with matched controls. Fortunately, assisted reproduction is a viable option. In some patients, particularly those with other life-threatening problems, discussing these issues might be a distraction rather than a help. The most common long-term problem after IPAA is acute and/or chronic inflammation of the ileal pouch, or pouchitis. Symptoms include increased stool frequency, urgency, soilage, bleeding, and malaise. With long-term follow up, about 50% of patients will report at least one episode of pouchitis. The cause of pouchitis is likely multifactorial; one factor may be bacterial overgrowth of the ileal pouch. While most patients respond quickly to a short course of antibiotics (e.g., metronidazole or ciprofloxacin), some patients develop a chronic syndrome. Newer treatments with probiotics have shown promise in treating pouchitis. Other therapies for pouchitis, such as topical anti-inflammatory agents, volatile fatty acids, or systemic corticosteroids, are not consistently efficacious. Other causes of bad outcome after IPAA are technical failures and Crohn's disease.

Other problems to be aware of after IPAA are small bowel obstruction, which occurs in about 28% of patients, and clinical dehydration, seen in about 14% of patients.

Qualifications for Performing Surgery for UC

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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 UC. Colonic surgery should preferably be performed by surgeons with special knowledge, training, and experience in the management of colonic disease. It is desirable that surgeons who perform IPAA (or Kock pouch) have specific training or significant experience with the procedure. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the colon.

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Keywords

Ulcerative colitis, Inflammatory bowel disease,
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SSAT Patient Care Guidelines

Surgical Treatment of Reflux Esophagitis

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Introduction

Gastroesophageal reflux disease (GERD) occurs when gastric or duodenal contents back up (reflux) into the esophagus. About 10% of adult Americans have daily symptoms of heartburn. Repeated episodes of reflux can damage the esophageal epithelium leading to esophagitis. A small proportion of patients progress to severe esophagitis.

In most cases, the underlying cause of reflux is a defective lower esophageal sphincter. The risk of GERD is higher in patients with a hiatal hernia. Inability of the esophagus to clear refluxed material may compound the problem in some patients. Symptoms of heartburn can usually be controlled with medical therapy directed at buffering or suppressing secretion of gastric acid.

A surgical procedure directed at creating a functional lower esophageal sphincter is also an effective treatment for patients whose reflux esophagitis is either dependent upon or uncontrolled by continuous medical therapy. Patients who have regurgitation and aspiration of gastric contents into the tracheobronchial tree are also candidates for surgical treatment.

Symptoms

GERD can usually be diagnosed by a careful history. GERD typically results in substernal burning discomfort or heartburn, which is often relieved by antacids. Some patients may also experience esophageal spasm with a squeezing chest pain that is often confused with angina. Refluxed material can be aspirated into the larynx, causing hoarseness, or into the tracheobronchial tree, causing wheezing and coughing. Dysphagia may occur as a complication of chronic reflux.

Diagnosis

The diagnosis of GERD and the determination of the extent of damage to the esophageal epithelium may require a series of investigations. The mainstay of diagnosis is flexible esophagoscopy, in which demonstration of mucosal erosion or ulceration is evidence of reflux damage. Endoscopy is also essential in the diagnosis of Barrett's metaplasia (replacement of the normal squamous epithelium of the lower esophagus by intestinal type columnar cells). Barrett's esophagus, a consequence of chronic reflux, is associated with an increased risk of adenocarcinoma of the esophagus. Barium esophagography is a useful diagnostic test to evaluate for hiatal hernia, strictures, and esophageal shortening.

Esophageal manometry is important prior to planning surgery to evaluate lower esophageal sphincter function and peristaltic activity in the body of the esophagus. Impaired motor activity in the body of the esophagus may influence the choice of surgical procedure.

Ambulatory 24- to 48-h pH monitoring can document reflux episodes by indicating a drop in esophageal pH to acid levels (less than 4.0). It is particularly useful in patients with atypical symptoms or in those with typical symptoms but normal endoscopic findings. It is best to perform pH testing off of all antisecretory medications. It is preferable to stop proton pump inhibitors 14 days prior and H2 antagonists 72 h prior to testing. A gastric-emptying scan should be performed in patients at risk for delayed gastric emptying (i.e., diabetes, scleroderma) or in patients with atypical symptoms.

Treatment

Patients with typical gastroesophageal reflux symptoms should initially be managed by lifestyle modifications. Foods

and beverages that can relax the lower esophageal sphincter should be avoided, including chocolate, peppermint, fatty foods, coffee, and alcoholic beverages. Also to be avoided are foods and beverages that can irritate an inflamed esophageal mucosa, such as citrus fruits and juices, tomato products, and pepper. Elevation of the head while sleeping, not lying down immediately after meals, and abstinence from smoking are also helpful.

Medical therapy, including antacids, H2 receptor-blocking drugs, and proton pump inhibitors, is directed at reducing the acid content of refluxed material. Acid inhibition is most effectively achieved with proton pump inhibitors. Promotility drugs (including metoclopramide and domperidone) are of little benefit in patients with severe reflux symptoms, unless they have delayed gastric emptying.

Although medical therapy is highly effective in controlling the signs and symptoms of gastroesophageal reflux, approximately 80% of patients will relapse within 3 months if therapy is discontinued, and up to 50% will require escalating doses of proton pump inhibitors.

Indications for Surgery

Surgery should be considered for patients who do not respond to medical therapy, have complications of gastroesophageal reflux (such as a stricture), are noncompliant with medical therapy, or are totally dependent upon medical treatment to prevent recurrence of their symptoms. Some patients choose surgery because of the expense and inconvenience of long-term medical therapy and concern about the possible consequences of long-term acid suppression. The indications for surgery in patients with Barrett's esophagus are addressed in another SSAT guideline (See Barrett's Esophagus). There are several innovative endoscopic techniques aimed at treating reflux disease. The long-term effectiveness of these procedures has not been established.

Fundoplication may be more cost effective than long-term medical therapy, and it has been clearly shown to improve the patient's quality of life. The most common surgical procedures include those described by Nissen, Hill, Belsey, Dor, and Toupet. These techniques are designed to create a functional lower esophageal sphincter and to repair a hiatal hernia if present. The most common antireflux procedure is the Nissen fundoplication or a modification of this technique, which involves mobilization and wrapping of the fundus of the stomach completely around the lower esophagus.

All surgical procedures incorporate some form of fundoplication, which is a wrap of the gastric fundus completely or partially around the distal esophagus. The Belsey procedure is performed through a thoracotomy, and the others are usually performed using either open abdominal or laparoscopic approaches.

Risks and Expected Outcomes

The most common risks associated with open or laparoscopic operations include bleeding or damage to structures such as the spleen, vagus nerves, esophagus, or stomach. These complications occur at a rate of less than 5%. Respiratory complications, such as atelectasis or pneumonia, are less frequent after laparoscopic surgery than after open upper-abdominal surgery.

Most patients will experience temporary difficulty in swallowing after surgery, especially with solid foods, but nearly all patients are able to swallow normally and eat an unrestricted diet by 6 weeks after surgery. A feeling of fullness (satiety) is another common but temporary occurrence. Gas-bloat syndrome, a sensation of bloating associated with inability to belch, may occur after fundoplication. Before surgery, in a subconscious effort to neutralize refluxed gastric acid with saliva, many patients with reflux esophagitis swallow frequently. Persistent aerophagia after surgery may cause bloating and increased flatus. The majority of patients require a hospital stay of 1–3 days after laparoscopic fundoplication or 3–5 days after an open operation. Hospitalization may be prolonged in the presence of other comorbid conditions or postoperative complications. Data suggest that long-term outcome is equivalent after open or laparoscopic procedures, with relief of reflux symptoms equivalent to that achieved with optimal medical therapy. Recurrent symptoms should be investigated for cause and appropriate medical or surgical treatment determined.

Qualifications for Performing Surgery for Gastroesophageal Reflux

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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 reflux esophagitis. Antireflux surgery should preferably be performed by surgeons with special knowledge, training, and experience in the management of gastroesophageal disease. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the esophagus and stomach. When performing laparoscopic fundoplication, it is highly desirable that the surgeon has advanced laparoscopic skills. The level of training in advanced laparoscopic

techniques necessary to conduct minimally invasive surgery is important to assess.

Suggested Readings

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Keywords

Patient, Guideline, Heartburn, Barrett's esophagus, Esophagitis, Nissen fundoplication, Gastroesophageal reflux, Reflux esophagitis, Deglutition disorders, Regurgitation

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SSAT Patient Care Guidelines

Esophageal Achalasia

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Introduction

Esophageal achalasia is a primary esophageal motility disorder of unknown etiology 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 experienced by virtually all patients. Regurgitation is the second most common symptom and is present in about 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 about 40% of patients and is usually experienced at the time of a meal. Heartburn is experienced by about 40% of patients. In untreated patients, this symptom is usually due to stasis and fermentation of food or esophageal distension.

Diagnosis

In addition to careful symptomatic evaluation, the following tests should be routinely performed: barium swallow usually shows narrowing at the level of the gastroesophageal junction ("bird beak") and various degrees of esophageal dilatation. Endoscopy is important to rule out the presence of a peptic stricture or cancer and gastroduodenal pathology. In patients older than 60 years of age, with recent onset of dysphagia and excessive weight loss, secondary or pseudoachalasia (obstruction because of a submucosal neoplasm in the distal esophagus) should be ruled out. Because a cancer of the gastroesophageal junction is the most common cause of pseudoachalasia, an endoscopic ultrasound or a computed tomography scan of the gastroesophageal junction can help to establish the diagnosis. Esophageal manometry is the key test for establishing the diagnosis. The classic manometric findings are as follows: (a) absence of esophageal peristalsis and (b) hypertensive or normotensive LES, which fails to relax completely in response to swallowing.

Treatment

Treatment is directed toward elimination of the outflow resistance at the level of the gastroesophageal junction. The following treatment modalities are available to achieve this goal:

Traditionally, pneumatic dilatation has been the first line of treatment for esophageal achalasia, while 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. When properly performed, a Heller myotomy can be expected to result in permanent relief of dysphagia in 85–100% of patients. Critical details of the operation include a generous myotomy of the lower esophagus, extending well 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. A recent prospective randomized study demonstrated that Heller myotomy plus a partial fundoplication is superior to Heller myotomy alone in regard to the incidence of postoperative reflux as measured by 24-h pH testing. Patients can usually eat the morning of the first postoperative day and can be discharged home after 1 or 2 days. In the only prospective randomized trial performed comparing balloon dilation with surgery, myotomy outperformed balloon dilation 95–65%.

Historically, the most popular treatment for achalasia has been by forceful pneumatic dilation. The success rate of this procedure is 55–70% with a single dilation but can be increased to nearly 90% with multiple dilations. However, the risk of perforation with each dilation is at least 3–5% and has been reported as high as 12% in some series. These patients may require open surgery to close the perforation and perform a myotomy. Furthermore, when stratified by age, balloon dilation is less than 50% effective in patients younger than 40 years old and is rarely effective in adolescents.

Intrasphincteric injection of botulinum toxin (Botox) injection is less effective than balloon dilation and requires retreatment to maintain an efficacy rate of 65%. Of greater concern is the fact that Botox injection leads to scar formation in the submucosal plane, which results in a more difficult myotomy and higher mucosal perforation rate (up to 30%) during dissection. Thus, Botox should be reserved for the treatment of patients who are poor candidates for surgery and poor candidates for balloon dilation (dilated sigmoid esophagus) or as a bridge to surgery. An additional utility for Botox is in aiding in the diagnosis of patients who have equivocal findings on initial evaluation. A good response to Botox is usually an indication that the patient will have long-term relief following surgical myotomy.

In selected patients, such as a hostile, multiply-operated abdomen or following a failed abdominal myotomy, the thoracic or thoracoscopic approach may be preferred. The thoracic approach is also appropriate in managing patients with proximal esophageal motility abnormalities.

Occasionally, the degree of esophageal aperistalsis is so advanced that myotomy alone will not relieve the dysphagia, and the patient is better served with esophagectomy. Esophagectomy should be considered in a patient who has had a previous myotomy with a resting LES pressure of less than 10 mmHg and a dilated sigmoid esophagus. The need for esophagectomy for achalasia is very 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 and adenocarcinoma.

Risks

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 5–10% of patients. The combination of intraoperative manometry and endoscopy can better guide the extent of the myotomy and can improve the adequacy of myotomy and are useful tools in decreasing the incidence of significant dysphagia after antireflux surgery. A complete work-up is necessary to evaluate the cause of the dysphagia in these patients, and 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 pH monitoring. In patients undergoing elective myotomy, the mortality rate is less than 1%.

Expected Outcomes

About 90% of patients have long-term relief of dysphagia after a myotomy with a low incidence of symptomatic acid reflux. There is often a poor correlation between symptoms of reflux and measurable reflux as demonstrated by pH study. All patients should be studied by postoperative pH study. Patients with demonstrated reflux by pH study or with reflux symptoms after surgery should be treated long term with proton pump inhibitors.

Qualifications for Performing Operations for Achalasia

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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. Achalasia surgery should preferably be performed by surgeons with special knowledge, training, and experience in the management of gastroesophageal swallowing disorders. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the esophagus and stomach. When performing laparoscopic or thoracoscopic operations, it is highly desirable that the surgeon has advanced videoscopic skills. The level of training in advanced videoscopic techniques necessary to conduct minimally invasive surgery is important to assess.

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Keywords

Achalasia, Esophageal motility disorders, Dysphagia, Pneumatic dilatation, Heller myotomy, Partial fundoplication, Botulinum toxin

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SSAT Patient Care Guidelines

Management of Barrett's Esophagus

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Introduction

Barrett's esophagus or intestinal metaplasia is defined as the replacement of the normal esophageal stratified squamous epithelium with any length of endoscopically visible columnar epithelium that on biopsy demonstrates acid-mucin containing goblet cells (i.e. intestinal metaplasia). It is estimated to develop in 10–20% of patients with chronic gastroesophageal reflux disease (GERD). Middle-aged white men are at highest risk. The clinical significance of Barrett's esophagus lies in its relationship with adenocarcinoma of the esophagus. The risk of developing esophageal cancer in patients with Barrett's esophagus is about 0.5–1% per year.

Symptoms and Diagnosis

Patients with Barrett's esophagus may experience the typical symptoms of GERD (i.e. heartburn, regurgitation, and dysphagia), atypical symptoms of GERD (i.e. asthma, cough, repeated pneumonia, and chest pain), or may be relatively asymptomatic. Because heartburn is so common in the general population, the symptoms may be ignored by patients or their physicians until serious complications develop. Barrett's esophagus can develop despite symptomatic control of GERD; therefore, all patients who require long-term medical therapy should be considered for endoscopic evaluation to detect the development of Barrett's metaplasia. Diagnosis of Barrett's metaplasia requires biopsy of the columnar mucosa. To exclude the presence of dysplasia in Barrett's, current recommendations include multiple biopsies taken in a systematic fashion throughout the entire length of columnar mucosa.

Treatment

The goals of treatment of Barrett's esophagus in the absence of dysplasia are essentially the same as for uncomplicated GERD: (1) control of symptoms and (2) prevention of gastroesophageal reflux (which may also reduce the risk of the development of, or progression to, dysplasia and adenocarcinoma). Therapeutic options include medical therapy with proton pump inhibitors, H-2 receptor antagonists, and/or prokinetic agents, or a surgical antireflux procedure. There are advantages and disadvantages of each. Medical therapy is directed at acid suppression. It is noninvasive and is effective at controlling reflux symptoms and maintaining the healing of esophagitis. However, many patients treated medically will continue to demonstrate reflux on pH testing, which may contribute to the development of dysplasia and adenocarcinoma.

Surgical antireflux therapy effectively controls the symptoms of reflux, prevents both acid and nonacid reflux, and has been shown to be superior to medical therapy in several prospective studies for the treatment of GERD. There is suggestive evidence that antireflux surgery may halt the progression of Barrett's esophagus to dysplasia and adenocarcinoma more effectively than medical therapy; this remains controversial. Fundoplication is the surgical procedure of choice for control of gastroesophageal reflux. Fundoplication can usually be accomplished using minimally invasive techniques, which require a short hospital stay and convalescence. Serious complications are rare.

Because the abnormal mucosa generally does not disappear with treatment, patients with documented Barrett's esophagus should have surveillance endoscopy and biopsy every 2 years, regardless how the underlying GERD is treated. Because inflammation can be confused with dysplasia, patients demonstrating low-grade dysplasia should be treated with intensive medical therapy with the goal of complete acid suppression, then rebiopsied at approximately 3 months. If low-grade dysplasia is confirmed, surveillance should be performed annually to rule out progression to high-grade dysplasia and/or cancer. If high-grade dysplasia is detected and confirmed, such patients should be referred to a center with expertise in esophageal resection because there is a high likelihood of occult cancers in these patients.

There are several innovative techniques designed to ablate or excise the abnormal mucosa. These include photodynamic therapy, treatment using other energy sources, or excisional techniques. There are studies that have documented reversal of Barrett's metaplasia to squamous epithelium, but no studies to date have documented that this results in a decreased risk of adenocarcinoma. In addition, squamous mucosa may regrow over incompletely eradicated columnar mucosa, rendering it endoscopically invisible without abolishing the risk of malignant transformation. These techniques should be considered experimental at this time as data are being accumulated regarding the efficacy and complications associated with each of them. At this time, these investigational nonoperative therapies should be reserved for patients with high-grade dysplasia who pose significant operative risks. Their role, in comparison to surgery, for the management of patients with high-grade dysplasia will be clarified by further study.

Risks and Expected Outcomes

The most common risks associated with open or laparoscopic antireflux operations include bleeding or damage to structures such as the spleen, vagus nerves, esophagus, or stomach. These complications occur at a rate of less than 5%. Respiratory complications, such as atelectasis or pneumonia, are less frequent after laparoscopic surgery than after open upper abdominal surgery.

Most patients will experience temporary difficulty in swallowing after surgery, especially with solid foods, but nearly all patients are able to swallow normally and eat an unrestricted diet by 6 weeks after surgery. A feeling of fullness (satiety) is another common but temporary occurrence. Gas-bloat syndrome, a sensation of bloating associated with inability to belch, may occur after fundoplication. Before surgery, in a subconscious effort to neutralize refluxed gastric acid with saliva, many patients with reflux esophagitis swallow frequently. Persistent aerophagia after surgery may cause bloating and increased flatus. The majority of patients require a hospital stay of 1–3 days after laparoscopic fundoplication, or 3–5 days after an open operation. Hospitalization may be prolonged in the presence of other comorbid conditions or postoperative complications. Data suggest that long-term outcome is equivalent after open or laparoscopic procedures, with relief of reflux symptoms equivalent to that achieved with optimal medical therapy. Recurrent symptoms should be investigated for cause, and appropriate medical or surgical treatment determined.

Surveillance of the Barrett's mucosa should continue after surgical therapy. Endoscopy every 2 to 3 years with four quadrant biopsies at 2-cm intervals in the Barrett's mucosa is needed.

Qualifications

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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 Barrett's esophagus or reflux esophagitis. Antireflux surgery should preferably be performed by surgeons with special knowledge, training, and experience in the management of GERD. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the esophagus and stomach. When performing laparoscopic fundoplication, it is highly desirable that the surgeon has advanced laparoscopic skills. The level of training in advanced laparoscopic techniques necessary to conduct minimally invasive surgery is important to assess.

Further Reading

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SSAT Patient Care Guidelines

Surgical Treatment Of Esophageal Cancer

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Introduction

Esophageal carcinoma is a relatively uncommon but highly lethal malignancy comprising 5% of gastrointestinal cancers in the USA. It is estimated that over 12,000 patients will develop carcinoma of the esophagus in the USA each year. In most Western countries, the prevalence of esophageal carcinoma is increasing at a rate of approximately 10% per year, which is faster than any other malignancy. The disease has also undergone a profound epidemiologic change, from predominantly squamous cell carcinoma seen in association with tobacco and alcohol abuse to that of adenocarcinoma in the setting of gastroesophageal reflux disease (GERD) and Barrett's metaplasia. This sequence from GERD to intestinal metaplasia to dysplasia to adenocarcinoma has now been recognized and is translating to a better understanding of and improved treatment for this disease. By contrast, the incidence of squamous cell carcinoma of the esophagus is stable or diminishing.

Symptoms and Diagnosis

Dysphagia is the most common presenting symptom and usually manifests as difficulty swallowing hard, solid foods (i.e., meats and bread) with ultimate progression to softer foods and liquids. Odynophagia, regurgitation, and weight loss are also commonly described in advanced cases. Local tumor extension invading into the tracheobronchial tree or recurrent laryngeal nerves can result in stridor, cough, choking, aspiration pneumonia, and hoarseness. Physical exam is usually normal but may reveal signs of generalized wasting as a consequence of poor nutrition or metastatic disease. Tumors are now being increasingly diagnosed in earlier stage patients without dysphagia who have been followed because of reflux or Barrett's esophagus in programs of surveillance endoscopy.

A systemic approach to the diagnosis and staging of esophageal cancer is mandatory. Once a histologic diagnosis of esophageal carcinoma has been confirmed by endoscopic biopsy, a detailed staging evaluation of the local, regional, and metastatic extent of the disease is performed. Computed tomography scans of the chest and abdomen are useful to search for metastatic disease. Endoscopic ultrasound should be performed to evaluate depth of tumor invasion in the esophageal wall and regional nodal involvement. Its accuracy in disease detection is approximately 80–85% for tumor depth and 70–75% for nodal status. Fluorodeoxyglucose-positron emission tomography scans may help to identify unsuspected metastatic disease. Accurate staging before treatment is important not only for survival analyses, but also for clinical decision-making.

Treatment

Treatment may be either curative or palliative, depending on the stage of the disease and the patient's condition. Curative treatment is most applicable to early lesions. If the lymph node spread is limited, even moderately advanced tumors may be cured by surgery. The earliest forms of cancer—high grade dysplasia and cancer contained within the mucosa—may be treated by an esophagectomy with a high expectation of cure. Therapies directed at ablating the mucosa endoscopically for early cancer are still experimental. For more advanced but still potentially curable cancers, 5-year survival rates as high as 41% have been reported. For patients with locally advanced (stage III) disease, long-term survival can be achieved in 25–35% of patients after esophagectomy. Esophagectomy can be performed by either transthoracic or transhiatal approaches. Morbidity and mortality rates are now less than 5% as a result of improvements in surgical technique and perioperative care when performed at high volume esophageal referral centers. The addition of chemotherapy or radiotherapy after operation

(adjuvant therapy) has not been shown to be beneficial. The preoperative administration of chemotherapy and radiation (neo-adjuvant therapy) is gaining in popularity and may possibly be superior to surgery alone in appropriately selected and staged patients with locally advanced cancer, but the evidence is not strong. The morbidity of the surgery does not appear to be increased by the use of preoperative therapy even in the elderly when performed in high volume centers.

In patients with advanced cancers, the disease is essentially incurable and the focus shifts toward palliation. If the tumor is resectable, the best palliation is generally obtained by surgery. In unresectable tumors or where distant metastases are present, the survival is much shorter and excisional surgery is rarely justified. Dysphagia or tracheoesophageal fistula can be fairly well palliated by a stent inserted endoscopically.

Risks and Expected Outcomes

Data suggest that esophagectomy is most safely performed in high volume units. The mortality rate of esophagectomy is 2–6% in such centers. However, serious complications are frequent and may occur in 20–40% of cases—the most common being pulmonary (10–50%), cardiac dysrhythmias (10%), and anastomotic leak (5–10%). When the anastomosis is made in the neck, a leak is rarely the cause of serious morbidity. However, dissection in the neck does carry the potential risk of temporary or even permanent recurrent laryngeal nerve injury. Average hospital stay after esophagectomy is 10–14 days.

Overall 5-year survival after resection is approximately 20–35%. For patients with early tumors limited to the mucosa, 5-year survival rates can exceed 80%. Patients free of lymph node metastases have 5-year survivals of 60%, whereas survival decreases to 10–20% in lymph node positive patients. Palliative resection provides relief of dysphagia in 90% of patients.

Qualifications of Personnel Providing Care or Surgery

The qualifications of a surgeon to perform any operative procedure should be based on education, training, experience, and outcomes. At a minimum, the surgical treatment of esophageal cancer should be performed by surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or the equivalent. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the esophagus and stomach. When performing laparoscopic esophageal surgery, it is highly desirable that the surgeon has advanced laparoscopic skills. The level of training in advanced laparoscopic techniques necessary to conduct minimally invasive surgery is important to assess.

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SSAT Patient Care Guidelines

Surgery for Obesity

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Introduction

Clinically severe obesity (CSO) is a prevalent health care problem throughout the world. In the USA, more than 6 million people currently suffer from this chronic disease. It has been estimated that obese individuals have a 5- to 12-fold increased risk of death as compared to age-matched controls.

The morbidity and mortality of CSO is related to associated medical comorbid conditions that include, but are not limited to, heart disease, type 2 diabetes mellitus, obstructive sleep apnea, hypertension, dyslipidemia, gastroesophageal reflux disease, urinary stress incontinence, osteoarthritis, lower extremity edema, gynecologic disorders, and certain cancers.

Nonsurgical treatments including diet, exercise, behavior modification, and medication have thus far proven to be ineffective. Surgical treatment of CSO has been well established as being safe and effective. Both short- and long-term improvements of comorbidities have been well documented. Recent studies suggest improved long-term survival in patients who have undergone bariatric surgical procedures.

Symptoms and Diagnosis

Patients with CSO typically have a long history of obesity and multiple failed attempts at weight loss. Patients may have multiple comorbidities depending on the duration and severity of their obesity. A positive family history of obesity is common and suggests that hereditary factors play a strong role in the development of obesity.

Criteria for consideration for surgical therapy include the following:

1. Body mass index of greater than 40 kg/m^2 or greater than 35 kg/m^2 with obesity-related medical comorbidities
2. A documented history of failed dietary attempts at weight control
3. A commitment to, and mechanisms available for, lifelong follow-up

Contraindications to surgical therapy include substance dependence, suicidal ideation, untreated eating disorders, and prohibitive medical conditions. Age <16 or >60, cirrhosis, inflammatory bowel disease, or a history of cancer within 5 years are all relative contraindications, and the decision to proceed with surgery should be made on an individual basis in these patients.

Treatment

The overall care of patients undergoing bariatric surgery requires programs that address both perioperative care and long-term management. Careful preoperative evaluation and patient preparation are critical to success. Patients should have a clear understanding of expected benefits, risks, and long-term consequences of surgical treatment. Surgeons must know how to diagnose and manage complications specific to bariatric surgery. Patients require lifelong follow-up with nutritional counseling and biochemical surveillance. Surgeons also must understand the requirements of severely obese patients in terms of facilities, supplies, equipment, and staff necessary to meet these needs and should ensure that specialized staff and/or a multidisciplinary referral system are included in treatment of these patients. This multidisciplinary approach includes medical management of comorbidities, dietary instruction, exercise training, specialized nursing care, and psychological assistance as needed on an individual basis.

Bariatric surgical procedures rely on two primary mechanisms to promote weight loss: gastric restriction and intestinal malabsorption. Purely restrictive operations include various gastric banding procedures and the vertical banded gastroplasty (VBG). In the adjustable gastric band, the amount of restriction can be adjusted, whereas in the VBG, it remains fixed. The Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) procedures also cause gastric restriction, but rely on varying amounts of intestinal malabsorption as an additional weight loss mechanism. An NIH conference in 1991 recognized VBG

and Roux-en-Y gastric bypass as acceptable procedures based on available outcome data.

Minimally invasive approaches have been used in bariatric surgery since 1993. Potential benefits of a laparoscopic approach include shorter recovery and earlier return to normal activity. The indications for laparoscopic treatment of obesity are the same as for open surgery. Laparascopic bariatric surgery may not be possible in certain patients including those with extreme obesity, previous abdominal surgery, intolerance of pneumoperitioneum, or unsuitable body habitus.

Virtually all bariatric operations can be performed with laparoscopic techniques. For safe and effective laparoscopic treatment of obesity, advanced laparoscopic skills are required. Therefore, appropriate training in advanced laparoscopic techniques is mandatory. These skills are most appropriately acquired through a residency or fellowship or in courses that teach the indications for surgically inducing weight loss, the various surgical approaches (both open and laparoscopic) and the advanced technical skills necessary to perform these operations. Before performing laparoscopic bariatric operations, surgeons must meet all local credentialing requirements for the performance of open bariatric procedures and advanced laparoscopic operations. Finally, these procedures require a well-trained operating team familiar with the equipment, instruments, and techniques of weight loss surgery.

Risks

The risk of death after bariatric surgical procedures is approximately 1%. Risk factors predicting increased mortality include age, weight, and male gender. Intraoperative complications include bleeding, inadvertent injury to the gastrointestinal tract, and stapling misadventures (e.g., stapling the nasogastric tube). These occur rarely, and morbidity can be minimized by prompt recognition and surgical correction. Early postoperative complications include pulmonary embolism (1–2%), anastomotic leaks (1–2%), wound infection or seroma, fascial dehiscence or evisceration (1%), gastrointestinal bleeding, small bowel obstruction, cardiorespiratory complications, and stomal stenosis. The development of symptomatic gallbladder disease is common in patients who have undergone bariatric surgical procedures, and prophylactic cholecystectomy may be considered for patients with preexisting cholelithiasis. Some bariatric surgeons may place patients on ursodiol 600 mg per day, as this has been shown to decrease the incidence of gallstone formation. Late complications include incisional hernia (10–20%), marginal ulceration (5–10%), small bowel obstruction, anemia, and nutritional deficiencies (iron, vitamin B_{12}).

The employment of laparoscopic techniques results in significant improvements in the rates of wound complications, such as wound infection and incisional hernia. Anastomotic leak rates are slightly higher (5%), but appear to be improving with experience. Overall mortality is comparable to that achieved with open surgery.

Expected Outcomes

It has been well established that the described procedures result in effective short- and long-term weight loss. Approximately 70% of patients who have undergone RYGB will lose 50–70% of their excess body weight. It is crucial that patients have a realistic understanding of the expected outcomes of these procedures. Numerous studies demonstrate objective improvement in medical comorbidities such as diabetes, congestive heart failure, musculoskeletal pain, sleep apnea, hypertension, and gynecological disorders. Finally, several recent reports suggest that bariatric surgical procedures (RYGB, VBG) may impart improved long-term survival in patients with CSO—particularly those who overcome the short-term morbidity and mortality of these procedures.

Although effective at inducing weight loss and improving medical comorbities, the VBG appears to result in inferior results when compared to the RYGB. A notable subset of patients will suffer from weight regain and/or obstructive symptoms (“large pouch syndrome”), and many of these patients will require further surgical procedures to revise the VBG to a RYGB. Revisionary procedures are associated with an approximately fivefold increased risk of anastomotic leak.

The malabsorptive procedures, such as the BPD, are effective in inducing weight loss, but may be associated with a higher incidence of metabolic complications. Additional data regarding their efficacy and safety will undoubtedly accumulate as experience with these procedures progresses.

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Keywords

Adjustable gastric banding, Bariatric surgery, Biliopancreatic diversion, Laparoscopy, Minimally invasive surgery, Obesity, Roux-en-y gastric bypass, Vertical banded gastroplasty

Board Approved (Insert Date Here)
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SSAT Patient Care Guidelines

Treatment of Gallstone and Gallbladder Disease

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Introduction

Gallstone disease represents a national health care problem, resulting in more than 750,000 cholecystectomies per year. The overwhelming majority of operations are for symptomatic gallstone disease, and 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 only 20% of patients with asymptomatic gallstones incidentally discovered will ultimately develop symptoms. Presenting symptoms of gallstone disease include biliary colic, cholecystitis (calculous and acalculous), gallstone pancreatitis, and choledocholithiasis (common duct stones). Typical biliary pain because of gallstones is a temporary (between 1/2 and 24 h) epigastric or right upper abdominal pain after meals. The pain may at times radiate to the right flank or back and frequently is associated with nausea. 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 is useful in detecting acute cholecystitis. Patients with biliary dyskinesia present with typical symptoms of biliary pain without radiographic evidence of cholelithiasis. Often they will have a decreased gallbladder ejection fraction (<30%) on cholecystokinin stimulated radionucleide scanning.

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 be seen the same day. The presence of gallstones without abdominal symptoms is not an indication for cholecystectomy unless the patient is immunosuppressed or there is a predisposition for malignancy, i.e., 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, and cholangitis require immediate surgical consultation. Patients with recurrent symptoms typical of biliary pain, but without gallstones on ultrasound, should be referred for surgical evaluation. Consideration for cholecystectomy in these patients might be supported by cholecystokinin stimulated biliary scitingraphy, endoscopic evaluation, and/or gastroenterology 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. Oral dissolution therapy has limited efficacy and is costly. Percutaneous cholecystostomy is a viable treatment option for critically ill patients presenting with acute cholecystitis. If the patient subsequently recovers, cholecystectomy should be considered when the inflammatory changes have resolved in the appropriate patient.

Risks

The risks are low in patients undergoing elective cholecystectomy and include 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% for laparoscopic cholecystectomy. The presence of anatomic variations and/or inflammation contribute to an increased risk of complications, as does the frequent coexistence of serious illnesses in the elderly. 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. The preoperative degree of coagulopathy, rather than the Child's class, should guide the surgeon's approach and expectations when laparoscopic cholecystectomy is performed in a cirrhotic patient.

The Role of Open Cholecystectomy

Open cholecystectomy may be the proper approach for a certain subset of patients. This may include cirrhosis, gallbladder mass, suspicion of malignancy, extensive upper abdominal surgery, and late third trimester of pregnancy. Otherwise, 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 or acute cholecystitis. The incidence of conversion to an open procedure is between 2 and 5%, depending on the patient population.

Expected Outcomes

The majority of good-risk patients undergoing elective laparoscopic cholecystectomy can usually be discharged the same or next day. High-risk patients and those undergoing emergency operations or open cholecystectomies typically require longer hospital stays. Hospitalization may be prolonged in patients requiring placement of abdominal drains, exploration of the bile duct, or those with complicated biliary tract disease. Laparoscopic surgery is now proving to be as safe as open surgery in pregnancy, especially in the second trimester.

Nearly 95% of all patients undergoing cholecystectomy experience relief of biliary pain. The remaining 5% have something other than gallstones as the cause of their pain. Cholecystectomy for biliary dyskinesia offers significant symptomatic relief over nonoperative therapy. 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 approximately 3% of cases. Surgical removal of common duct stones can be performed using 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 the acutely ill. Since most common duct stones arise from the gallbladder, cholecystectomy is also indicated.

Costs

Cholecystectomy is cost effective compared to alternative treatments, because it definitively treats the disease and reliably alleviates the symptoms.

Qualifications for Performing Surgery on the Gallbladder

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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 gallbladder disease. Gallbladder surgery should preferably be performed by surgeons with special knowledge, training, and experience in the management of gallbladder and biliary tract disorders. These surgeons have successfully completed at least 5 years of surgical training after medical school graduation and are qualified to perform operations on the gallbladder and biliary tract.

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Keywords

Gallstones, Choledocholithiasis, Cholecystitis, Cholelithiasis, Cholecystectomy, Gallbladder disease, Acute disease, Acalculous cholecystitis, Common bile duct stones, Guideline, Patient

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SSAT Patient Care Guidelines

Cystic Neoplasms of the Pancreas

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Introduction

Cystic neoplasms of the pancreas are uncommon but confusing diagnostic problems that are being encountered with greater frequency. They account for fewer than 10% of all pancreatic malignancies but up to 30% of pancreatic resections performed, and they encompass a spectrum of benign, premalignant (borderline), and malignant lesions. Although they are less common, it is important to distinguish cystic *neoplasms* from the far more prevalent entity of benign pseudocysts, which are usually associated with a clinical history and radiographic evidence of pancreatitis. Cystic neoplasms of the pancreas can be classified into four major categories.

Categories

Serous cystadenoma, the most common classification, is a distinctly benign lesion characterized by a glycogen-rich epithelial lining. However, because of large size, they are often symptomatic, causing pain, fullness, or early satiety. Some even cause biliary obstruction with jaundice and/or segmental pancreatitis. They are radiographically recognized by a microcystic "ground-glass" or "cluster-of-grapes" appearance. Alternatively, they may demonstrate a classic "central scar." These, if asymptomatic, can be safely observed since its malignant counterpart *serous cystadenocarcinoma* is an exceedingly rare occurrence. Symptomatic lesions are best treated with surgical resection.

Mucinous cystadenoma/adenocarcinoma harbor malignancy 50% of the time (30% invasive, 20% carcinoma in situ). They typically affect middle-aged women and are usually seated within the body or tail of the gland. They are characterized pathologically by mucin secretion from an ovarian-type stromal epithelial lining that generally is *not* in communication with the pancreatic ductal system. Radiographically, they appear as single or multiple septated macrocystic spaces. The presence of papillary growths or wall calcification portends overt malignancy. Once diagnosed, surgical resection is recommended given the high frequency of malignancy. Operation is usually curative.

Solid pseudopapillary tumor (*Franz tumor*, *Hamoudi tumor*) is a rare, but distinct, entity that is characterized by masses with both solid and cystic components. It is usually found in young (average age=40) females and children, often in the body/tail of the pancreas. These large tumors are local–regionally invasive, but rarely metastatic, and demonstrate a more indolent course than pancreatic adenocarcinoma for which it may be confused. When limited to the pancreas, surgical resection is highly curative.

Intraductal papillary mucinous neoplasm (*IPMN*/*IPMT*) is a newly recognized but poorly characterized neoplastic process involving the pancreatic duct epithelium in a fashion analogous to the "adenoma-to-carcinoma" sequence of colorectal cancer. Although morphologically variable, tumors can be classified into main-branch and side-branch variants with the latter, thought by some, as having a better prognosis. The hallmark is pancreatic ductal dysplasia to various degrees, although carcinoma in situ and overt invasive adenocarcinoma are present in around 50% of these tumors—more frequently in main-branch disease. It is classically, but infrequently, identified as a "fish-mouthed," mucin-secreting Ampulla of Vater on endoscopy in a patient with identified cystic ductal changes on imaging. Some IPMNs can be safely watched/monitored (side-branch, <2 cm), but most require resection of the diseased portion of the pancreas.The presence of biliary obstruction usually portends malignancy.

Symptoms

Cystic neoplasms present in a variety of ways. Many indeed are asymptomatic and are first discovered incidentally

during radiographic [computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US)] investigations of the chest, abdomen, and pelvis for other conditions. This form of recognition appears to be increasing in frequency. Unexplained abdominal or back pain is the most common complaint. This is often vague, nagging, and progressive in scope. Nonspecific fullness, bloating, and early satiety are frequent complaints. Some lesions present in a similar fashion to pancreatic adenocarcinoma with obstructive jaundice because of impingement of the bile duct. This finding is highly suggestive of underlying malignancy within the cyst. Similarly, pancreatitis (both acute and recurrent) can be the heralding sign. Often, this may manifest as left upper quadrant (LUQ) and/or back pain as a result of segmental pancreatitis from distal pancreatic duct obstruction.

Diagnosis

Management options hinge upon accurate diagnosis. Usually mucinous vs non-mucinous lesions can be determined preoperatively based on high quality imaging, endoscopy, and/or endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) biopsy. Obviously, it is imperative to rule out a pancreatic pseudocyst, and this largely can be correlated with a history, physical, and imaging exam indicative of pancreatitis. "Screening" radiographic techniques such as single phase CT or transabdominal US initially define that a cystic process is present in the pancreas. However, they are not powerful or specific enough to properly define the true nature of the cyst. Either triple-phase helical CT or MRI is ideal for delineating finer detail including internal septations, papillary growths, heterogeneity, mural calcification, and connections with the main pancreatic duct or its side branches. Often, these are complementary modalities. The use of positron-emission tomography (PET) scanning for defining malignancy in these cysts shows promise but is not widely accepted currently.

Cyst fluid evaluation is an important diagnostic adjunct and is easily performed via aspiration under EUS guidance. Contents can be sampled for cellularity, mucin, amylase, viscosity, and tumor markers such as CEA and CA 19.9. An aspirate CEA level over 200 is highly suggestive of a mucinous lesion but not necessarily malignancy.

Treatment

Surgical consultation is advised, as most cystic neoplasms will require operative intervention for either definitive diagnosis or treatment. The decision to perform a pancreatic resection should be based on the suspicion of malignancy compared with the relative risk to the individual patient. In some cases, such as asymptomatic patients with either serous cystadenoma or side-branch variant IPMN (<2 cm), no intervention is required. However, serial clinical and radiographic follow-up is recommended. Asymptomatic equivocal lesions for which no intervention is planned must also be followed with vigilance. Changes in character, growth of the lesion, or development of symptoms during watchful observation indicate reasons for operative intervention. In cases of mucinous lesions and most IPMNs, surgical resection is advised given their premalignant nature. In fact, many of these (up to 50%) will harbor carcinoma in situ or overt invasive malignancy at time of diagnosis. Solid pseudopapillary tumor is a true malignancy that warrants surgical resection when diagnosed.

If resection is indicated, a variety of procedures are employed, dictated largely by anatomic position of the lesion within the gland. Head and uncinate process-based tumors require pancreaticoduodenectomy (Whipple's resection). Body and tail lesions require distal pancreatectomy, with or without splenectomy. In selected cases, and only by highly trained specialists, this may be achieved in a minimally invasive laparoscopic fashion. For some premalignant lesions in the body, a central pancreatic resection may be feasible, or simple enucleation of the cyst may be possible. Total pancreatectomy may be necessary in those rare occasions when IPMN involves the whole gland.

Risks and Outcomes

Pancreatic resections remain significant interventions for any patient. Hospital stays range from 10 to 14 days in most instances. Morbidity rates range from 30 to 40%. The most significant postoperative complication is pancreatic fistula, occurring around 25% of the time in skilled hands (for both head and tail resections). The primary risk factors for development of a fistula are glandular characteristics such as a soft texture and/or a small pancreatic duct diameter. Today, this problem is usually managed conservatively and rarely requires reoperation. Operative risks may also arise from co-morbid conditions such as cardiac, pulmonary, or renal disease. The mortality rate in a good-risk patient undergoing elective operation is 2–5% for pancreaticduodenectomy and under 1% for distal pancreatectomy.

Other considerations include the potential development of postoperative diabetes and exocrine insufficiency. This is often the case after total pancreatectomy, where patients may develop brittle diabetes. Oral enzyme replacement pills are available to assist with digestive malabsorption. If splenectomy is performed, consensus has not generally been

reached for post-splenectomy immunization in adults. In children, polyvalent vaccination is given to immunize against the future development of infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Meningococci* species. Adults should receive, at the very least, the pneumococcal vaccine. Some authors recommend that the adult receive all three vaccinations as well; however, there is no evidence that the addition of the other two vaccinations provide any additional benefit. Vaccination should be given either 2 weeks before or after splenectomy, with the most recent evidence showing that 2 weeks after splenectomy is ideal.

Surgical resection is a definitive and complete procedure in most cases, and long-term follow-up is rarely required. The exception is with IPMN where radiographic surveillance of the remnant pancreas is justified. Currently, annual CT or MRI evaluation after resection is practiced; however, precise guidelines for this sort of surveillance are not clearly defined in that the natural history of this process is still poorly defined. In those cases of IPMN, mucinous, or solid pseudopapillary tumors that harbor invasive malignancy, appropriate adjuvant chemo and/or radiation therapy may be justified. In these cases, oncologic outcomes (i.e., long-term survival) mirror those for any other invasive pancreatic adenocarcinoma.

Qualifications for Performing Surgery on the Pancreas

The qualifications of a surgeon performing any operative procedure should be based on training (education), experience, and outcomes. 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 pancreatic resections. In addition to the standard residency training, qualifications should be based on advanced training, experience, and outcomes. More favorable outcomes have been demonstrated in the hands of surgical specialists who practice in centers where a high volume of these procedures are performed each year.

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Keywords

Pancreas, Cystic neoplasm, Pseudocyst, IPMN/IPMT, Serous cystadenoma, Mucinous cystadenoma, Solid pseudopapillary tumor, Whipple's resection, Distal pancreatectomy, Guideline, Patient

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SSAT Patient Care Guidelines

Surgical Repair of Groin Hernias

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Introduction

Groin hernias include inguinal and femoral hernias. Repair of groin hernias is one of the most commonly performed outpatient surgical procedures, and it is estimated that 750,000 inguinal hernia repairs are performed yearly in the USA. Inguinal hernias occur most commonly in men. While these hernias afflict persons of all ages, this guideline will address only the adult patient.

A groin hernia is not a "rupture"per se but rather a groin bulge or mass that develops due to weakened layers of the abdominal wall and protrusion of intra-abdominal contents through the defect. Numerous classification systems for groin hernias have been described, but none have gained universal acceptance. The traditional classification system includes direct, indirect, and femoral hernias. Direct inguinal hernias develop when the posterior portion of the inguinal canal attenuates, allowing the underlying contents of the abdominal cavity to protrude. An indirect inguinal hernia occurs along the spermatic cord or round ligament in the inguinal canal. A femoral hernia passes behind the inguinal canal and herniates alongside of the femoral vessels.

Symptoms and Diagnosis

Inguinal hernias may be asymptomatic (discovered incidentally during physical examination) or present as a bulge discovered by the patient. They may be associated with vague groin pain, commonly made worse by straining or physical activity. Patients may also present with complications of groin hernias such as incarceration (not reducible) or strangulation of bowel, which causes an obstruction in that segment. As most hernias should be repaired, the patient should be referred to a surgeon for evaluation and operative treatment. Ultrasound or other radiologic studies are not required because the diagnosis can usually be made by physical examination. This is best performed with the patient standing and straining against a held breath (Valsalva maneuver).

More difficult to diagnose is the occasional patient with groin pain, or inguinodynia, but no history of groin bulge and no physical findings. 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 still possible. Femoral hernias can present as pain in the upper thigh rather than a bulge and are particularly difficult to diagnose in the elderly or obese patient. Ultrasound or axial imaging may be useful in delineating the abnormality. Although these rarer hernias occur mostly in elderly women, the most common type of groin hernia seen in this patient population is still the indirect inguinal hernia.

Most 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 due to the risk of strangulated bowel or other viscera. 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 also mandate immediate referral to a surgeon.

Treatment

Most groin hernias can be electively repaired. Urgent repair is required for an acutely non-reducible hernia or for a chronically incarcerated hernia that suddenly becomes painful, as this indicates impending strangulation. While significant morbidity and mortality can be avoided by prompt diagnosis, this clinical emergency causes the death of more than 2,000 patients per year in North America.

Inguinal hernias should be repaired surgically. Hernia belts or trusses should be discouraged and should be limited

to patients who are not candidates for an elective operation. Chronic scarring from their use can lead to a more difficult repair and higher risks of complications. Femoral hernias should always be repaired because of the high incidence of associated bowel herniation. Elderly patients with minor co-morbid conditions will easily tolerate an outpatient elective hernia repair, which can be accomplished with intravenous sedation and local anesthesia. All attempts should be made to avoid emergent repairs of chronically incarcerated hernias, which occur primarily in the elderly. 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: (1) *open repair* (the traditional repair, utilizing the patient's own tissue); (2) *open tension-free repair* (in which mesh is used to bridge or cover the defect); and (3) *laparoscopic repair*, a tension-free repair also utilizing mesh. In general, the traditional, tissue-based repairs have been replaced by tension-free or mesh-based repairs. These include the Lichtenstein, Plug and Patch, laparoscopic, and "hybrid" techniques. No particular technique has been found to be superior, and all of them can be expected to result in excellent outcomes when performed by adequately trained surgeons with sufficient experience in their performance. Open techniques of hernia repair may be safely performed under local, regional, or general anesthesia with equivalent outcomes, whereas laparoscopic hernia repair requires general anesthesia.

Some selected hernias can be treated nonoperatively with careful observation. Suitable hernias for nonoperative management are direct hernias with a wide neck that easily reduce particularly in elderly asymptomatic patients or patients at a heightened risk for operative intervention.

Risks

The risk of infection or significant hematoma is approximately 1%. With contemporary tension free techniques, hernia recurrence occurs in 2–5% of patients and requires another repair. Chronic groin pain (inguinodynia) may be seen after groin hernia repair (approximately 5%) and is a difficult problem to treat and may require multimodality pain management or further surgery.

Expected Outcomes

Short-term outcome studies suggest that a quick return to normal activities can be achieved after both open and laparoscopic hernia repairs. 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. Heavy lifting and exercise are commonly discouraged for 4 to 6 weeks after inguinal hernia repair, although patients can typically resume any physical activity that is comfortable to them and progress at their own pace.

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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Keywords

Patient, Guideline, Groin hernia, Inguinal hernia, Femoral hernia, Open repair, Tension-free repair, Laparoscopic repair, Recurrence, Groin pain, Complications, Mesh, Incarcerated

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DISCLAIMER

SSAT Patient Care Committee Guidelines

These patient care guidelines were written for primary care physicians on a variety of digestive diseases to assist on when to refer the patient for surgical consultation. Their goal is to guide Primary Care physicians to the appropriate utilization of surgical procedures on the alimentary tract or related organs, and they are based on critical review of the literature and expert opinion. Both of the latter 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 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.

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SSAT Patient Care Guidelines

Surgical Repair of Incisional Hernias

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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 3–13% of primary abdominal incisions. Recurrence rates after incisional hernia repair are markedly higher, 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 (1) symptoms, (2) gradual enlargement over time, and (3) avoidance of 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 abdominal wall defect and is greatest at the fascial margins. It is usually dull in nature and typically does not radiate. Straining maneuvers may exacerbate symptoms 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 with tissue necrosis; urgent surgical referral is necessary.

The diagnosis can usually be 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 exam represents the "tip of the iceberg"; additional fascial defects not appreciated preoperatively are often identified at surgery. A palpable mass in a suspected incisional hernia should not be aspirated because this mass may contain bowel. A computed tomography scan may be a useful adjunct in confirming the diagnosis and determining the contents and extent of the hernia. This is particularly helpful in obese patients.

Treatment

There are many ways to surgically repair incisional hernias. Smaller incisional hernias (<3 cm) can be repaired with primary tissue approximation. Repair of larger defects generally requires the use of prosthetic materials, which allows for a tension free repair. Techniques for application of the mesh include onlay, preperitoneal, and intraperitoneal locations. There are advantages and disadvantages of the different prostheses utilized in various circumstances. Alternatively, tissue release techniques such as component separation, use of tissue flaps, and the application of tissue expansion techniques may obviate the need for a prosthetic repair. Laparoscopic techniques may be used for repair of incisional hernias in selected patients. Potential benefits of laparoscopy 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. Recurrence rates range from 25 to 50% following an initial primary repair. The risk of recurrence increases dramatically in patients who have had previous failed repairs, in patients with very large hernias, obese patients, and in cases where one or more margins of the hernia defect is bone or cartilage. The use of a mesh support during open surgical repair has been shown to decrease recurrence rates to 5–35%. The early experience with laparoscopic repairs employing mesh has been favorable with recurrence rates as low as 1–10%. However, it must be emphasized that these studies reflect very short-term (less than 3 years) follow-up periods. Furthermore, there is not yet any

strong evidence-based literature that directly compares laparoscopic to open approaches for this problem.

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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