Patterns of Failure and Survival for Nonoperative Treatment of Stage c0 Distal Rectal Cancer Following Neoadjuvant Chemoradiation Therapy

Angelita Habr-Gama, M.D., Ph.D., Rodrigo O. Perez, M.D., Igor Proscurshim, M.S., Fábio G. Campos, M.D., Ph.D., Wladimir Nadalin, M.D., Ph.D., Desiderio Kiss, M.D., Ph.D., Joaquim Gama-Rodrigues, M.D., Ph.D.

Neoadjuvant chemoradiation therapy (CRT) is the preferred treatment option for distal rectal cancer. Complete pathological response after CRT has led to the proposal of nonoperative approach as an alternative treatment for highly selected patients with complete clinical response. However, patterns of failure following this strategy remains undetermined. Three hundred sixty-one patients with distal rectal cancer were managed by neoadjuvant CRT including 5-FU, leucovorin, and 5040 cGy. Tumor response assessment was performed at 8 weeks following CRT. Patients with complete clinical response were not immediately operated on and were closely followed. One hundred twenty-two patients were considered to have complete clinical response after the first tumor response assessment. Of these, only 99 patients sustained complete clinical response for at least 12 months and were considered stage c0 (27.4%) and managed nonoperatively. Mean follow-up was 59.9 months. There were 13 (13.1%) recurrences: 5 (5%) endorectal, 7 (7.1%) systemic, and 1 (1%) combined recurrence. All 5 isolated endorectal recurrences were salvaged. Mean recurrence interval was 52 months for local failure and 29.5 months for systemic failure. There were five cancer-related deaths after systemic recurrences. Overall and disease-free 5-year survivals were 93% and 85%. Even though surgery remains the standard treatment for rectal cancer, nonoperative treatment after complete clinical response following neoadjuvant CRT may be safe and associated with good survival rates in a highly selected group of patients. Survival in these patients is significantly affected by systemic failure. Exclusive local failure occurs late after CRT completion and is frequently amenable to salvage therapy. (J GASTROINTEST SURG 2006;10:1319–1329)

KEY WORDS: Rectal cancer, neoadjuvant therapy, survival, recurrence

Management of distal rectal cancer remains a significant challenge for colorectal surgeons. Optimal treatment strategy remains controversial and highly dependent on accurate disease staging, tumor location, and distance from anal verge. Neoadjuvant chemoradiation has been considered the preferred treatment option for stages II and III distal rectal cancer.[1,2] Significantly high local recurrence rates following local excision for stage I rectal cancer, led colorectal surgeons to consider neoadjuvant chemoradiation also for T2 rectal cancer, especially in distal rectal cancer.[2–4]

The widespread use of neoadjuvant chemoradiation for distal rectal cancer is due to the observation of significantly lower local recurrence, decreased toxicity, similar postoperative complications, and

Presented at the Plenary Session at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, May 20–25, 2005.

From the Departments of Gastroenterology (A.H.-G., R.O.P., I.P., F.G.C., D.K., J.G.-R.) and Radiology (W.N.), University of São Paulo School of Medicine, and Hospital Alemão Oswaldo Cruz (HAOC), São Paulo, Brazil.

Reprint requests: Dr. Rodrigo Oliva Perez, Rua Manuel da Nóbrega, 1564, São Paulo, Sao Paulo 04001-005 Brazil. e-mail: rodrigo.operez@gmail.com

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.005

improved functional results when compared to postoperative chemoradiation therapy.[5,6] Furthermore, the neoadjuvant approach is associated with variable degrees of tumor downstaging and increased rates of sphincter saving procedures.[7–11]

Tumor downstaging may ultimately lead to complete tumor regression in a significant proportion of patients. The observation of absence of viable tumor cells in resected specimens following CRT and surgery raised the issue of the benefit of surgical resection over an initial nonoperative approach after complete pathological response (ypT0 N0 M0).[12–14]

Several arguments against nonoperative treatment for distal rectal cancer have been raised such as the risk of lymph node metastases even after the absence of persistent primary rectal cancer (ypT0) and the low accuracy of clinical determination of a complete response.[15,16] On the other hand, surgical resection may lead to significant immediate morbidity, mortality, and sexual and urinary dysfunction, besides the requirement for temporary or definitive stomas in a significant number of patients. In this setting, the role of surgery when not a single tumor cell is excised, has been questioned.[12]

The definitive role of an initially nonoperative treatment strategy has not yet been determined and no definitive conclusions can be drawn before long-term results concerning local and distant failure are available. We report the patterns of recurrence and survival of a large series of patients with distal rectal cancer following neoadjuvant chemoradiation therapy and complete clinical response managed by initial nonoperative treatment.

MATERIAL AND METHODS

Patients with distal rectal adenocarcinoma, located 0–7 cm from the anal verge during rigid proctoscopy, with nonmetastatic disease, and managed by neoadjuvant chemoradiation therapy at the Colorectal Surgery Division of the University of São Paulo School of Medicine and Hospital Alemão Oswaldo Cruz, São Paulo, Brazil, between 1991 and 2005 were retrospectively reviewed. Pretreatment staging included full clinical examination including digital rectal examination and rigid proctoscopy. Colonoscopy was performed before CRT for nonobstructive tumors and postoperatively for persistent obstructive tumors. Radiological staging was completed using endorectal ultrasound, spiral CT scans, chest radiographs, and serum CEA. Patients with metastatic disease were excluded from the study.

Radiation therapy consisted of 5040 cGy delivered by three fields during 6 weeks. Concomitant chemotherapy was given during the first and last 3 days of radiation with 5-FU and leucovorin as described elsewhere.[10]

Assessment of tumor regression was performed at 8 weeks following CRT completion. Patients were restaged using the same clinical, endoscopic, and radiological parameters used before treatment. Any suspicious area or ulcer was biopsied or excised and sent for pathological examination. Patients with clinically or endoscopic persistent ulcers, and/or radiological or histological evidence of tumor persistence were referred for immediate radical surgery. Patients with complete clinical tumor regression defined by absence of residual mass or ulcer, no signs of residual tumor seen in radiological studies were considered as complete clinical response and were not immediately operated on. Full excisional biopsy was performed whenever a small suspicious scar, fibrous tissue, or ulcer was detected. In this situation, patients with negative pathological findings for residual neoplasia were considered stage c0 and were also managed nonoperatively. These patients were fully informed that this condition could be temporary and tumor persistence could be detected any time during follow-up requiring immediate radical surgery. These patients were enrolled in a strict follow-up program including full clinical examination, rigid proctoscopy, biopsies of any suspicious area, and serum CEA levels. Visits were scheduled monthly, every 2 months, every 3 months, and every 6 months for the first, second, third, and fourth years, respectively. After this period, patients were followed with annual visits. CT scans and chest radiographs were performed every 6 months during the first year and yearly after this. Other radiological studies were performed according to each patient's requirements. Patients with complete tumor regression sustained for at least 12 months were considered stage c0 and were included in the study. Recurrence was defined as endorectal recurrence when there was clinical and histological evidence of tumor recurrence in the rectal lumen or confined to the rectal wall. Pelvic recurrence was defined as clinical and radiological evidence of recurrent disease in the pelvis outside the rectal wall. Systemic recurrence was considered in patients with evidence of metastatic disease to distant sites including liver, lungs, lymph nodes (inguinal, periaortic, retroperitoneal, axilar, or cervical), central nervous system, adrenal, bone, and others.

Radical treatment of recurrent disease was considered for patients with localized recurrent disease. Patients with systemic or unresectable disease were referred to clinical oncologists for palliative therapy.

Table 1. Characteristics of patients related with neoadjuvant chemoradiation therapy for distal rectal cancer

Characteristic (N = 361)	n (%)
Mean age (yr)	59.1 ± 13.9
Gender (n)	
Male	157 (43.5%)
Female	204 (56.5%)
Pretreatment characteristics	
Serum CEA (ng/dl)	8.8 ± 15.2
Tumor size (diameter) (cm)	3.8 ± 1.3
Distance from anal verge (cm)	3.9 ± 1.7
Stage* (n)	
I	28 (11.1%)
II	154 (61.1%)
III	70 (27.8%)
Response to treatment (n)	
Complete response	99 (27.4%)
Incomplete response	262 (72.6%)

*Pretreatment staging available for 252 patients.

RESULTS

Between 1991 and 2005, 361 patients with nonmetastatic distal rectal cancer were managed by neoadjuvant chemoradiation therapy and whose characteristics are summarized in Table 1. Following chemoradiation therapy, 122 (33.7%) patients were considered to have initial complete clinical response after at least 8 weeks from CRT completion. However, only 99 patients (27.4%) had a sustained complete tumor regression for at least 12 months and were considered stage c0 and included in our study. The remaining group of patients with incomplete tumor regression immediately after 8 weeks from CRT or those 23 patients with tumor regrowth detected before 12 months of follow-up were referred to immediate surgery and excluded from this study.

Stage c0

Of the 99 patients with sustained complete clinical response, 52 (52.5%) were female and 47 (47.5%) male, with mean age of 60.8 ± 14.1 years. Mean duration of symptoms was 7.1 ± 5.9 months and the most frequently observed symptom was rectal bleeding, occurring in 74 patients (74.7%). Mean initial tumor size estimation was 3.7 ± 1.3 cm and mean distance from anal verge was 3.9 ± 1.7 cm. Pretreatment staging was available in 78 patients (79%) and revealed 14 (18%) patients with cT2, 60 (76.9%) with cT3, and 4 (5.1%) with cT4. Regarding N status, 56 (71.8%) patients were considered cN0 and 22 (28.2%) were considered cN+. Overall, there were 10 patients with stage I, 46 with stage II, and 22 with stage III disease, according to clinical and radiological studies (Table 2).

Table 2. Overall characteristics of patients with nonoperative management of a complete clinical response after neoadjuvant therapy for distal rectal cancer

Characteristic (N = 99)	n (%)
Mean age (yr)	60.8 ± 14.1
Gender (n)	
Male	47 (47.5%)
Female	52 (52.5%)
Pretreatment characteristics	
Tumor size (diameter) (cm)	3.7 ± 1.3
Distance from anal verge (cm)	3.9 ± 1.7
cT*	
2	14 (18.0%)
3	60 (76.9%)
4	4 (5.1%)
cN*	
Negative	56 (71.8%)
Positive	22 (28.2%)
Stage*	
I	10 (12.8%)
II	46 (59.0%)
III	22 (28.2%)
Recurrence	13 (13.1%)
Endorectal	5 (5.0%)
Pelvic	0
Systemic	7 (7.1%)
Combined (systemic/local)	1 (1.0%)

*Pretreatment staging available for 78 patients.

Recurrences

Overall, there were 13 (13.1%) recurrences among patients with stage c0 disease. Of the 99 patients, 78 had pretreatment staging available, 69 (80%) without recurrence and 9 (69.7%) with recurrences. Table 3 summarizes patient and tumor characteristics according to presence of recurrence.

Five patients (5.0%) developed exclusively endorectal recurrences at 18, 43, 56, 64, and 79 months of follow-up. Three of these patients were managed by radical surgery at 18, 43, and 79 months of follow-up. Salvage operations included two abdominalperineal resections (APR) and one low anterior resection (AR) resulting in ypT3 N1 M0 in two (APR and AR) and ypT1 N0 M0 in one patient (APR). Two patients with endorectal recurrences at 56 and 64 months of follow-up refused radical surgery; one was managed managed by local excision, resulting in a ypT1 with free margins and one with brachytherapy alone. None of these patients developed further recurrent disease during follow-up.

Table 3. Clinical and pathological features of patients with and without recurrent disease following nonoperative management of a complete clinical response after neoadjuvant therapy for distal rectal cancer

	Nonrecurrent disease	Recurrent disease	*P*
n	86	13	
Mean age (yr)	60.4 ± 14.7	63.8 ± 9.4	0.41
Gender (n)			
Male	39 (45.3%)	8 (38.5%)	0.53
Female	47 (54.7%)	5 (61.5%)	
Pretreatment characteristics			
Tumor size (diameter) (cm)	3.8 ± 1.2	3.9 ± 2.3	0.78
Distance from anal verge (cm)	4.0 ± 1.7	2.8 ± 1.8	0.036
cT*			
2	12 (17.4%)	2 (22.2%)	0.76
3	54 (78.3%)	6 (66.7%)	
4	3 (4.3%)	1 (11.1%)	
cN*			
Negative	50 (72.5%)	6 (66.7%)	0.72
Positive	19 (27.5%)	3 (33.3%)	
Stage*			
I	8 (11.6%)	2 (22.2%)	0.72
II	42 (60.9%)	4 (44.5%)	
III	19 (27.5%)	3 (33.3%)	

*Pretreatment staging available for 69 (80%) patients without recurrence and in 9 (69.7%) patients with recurrence.

Two patients died of unrelated diseases at 24 and 60 months of follow-up. The remaining three patients are still alive and being followed at 72, 94, and 150 months. Mean endorectal recurrence interval was 52.0 ± 23.1 months.

There were no pelvic recurrences in patients with stage c0 disease.

One patient (1%) developed combined endorectal and systemic disease recurrence at 18 months of follow-up (bilateral lung metastases). This patient was managed by APR followed by systemic chemotherapy. However, she died of disease progression at 24 months of follow-up. This patient was considered to have systemic disease for analysis purposes.

Seven patients (7.1%) developed exclusively systemic recurrences at 9, 14, 16, 18, 24, 48, and 90 months of follow-up. There were two patients with unresectable lung recurrences, managed by chemotherapy alone. Both patients died of disease progression at 17 and 18 months of follow-up. Three patients developed distant lymph node metastatic disease (one with associated bone metastases) and two died of disease progression at 72 and 92 months of follow-up (the patient with associated bone metastases was lost at follow-up). One patient developed an unresectable liver recurrence and died at 22 months of follow-up. Finally, one patient developed a solitary liver recurrence, was managed by liver resection, and is currently alive at 152 months of follow-up. Mean systemic recurrence interval was 29.5 ± 26.9 months.

There were no significant differences between patients with recurrence and patients without recurrence in terms of age, gender distribution, tumor size estimation, depth of invasion, lymph node status, and disease stage. However, patients with recurrences had significantly more distal tumors (2.8 ± 1.8 versus 4.0 ± 1.7, $P = 0.036$) (Table 3).

To further characterize the patients with recurrences we compared these patients according to the location of the recurrence, endorectal, or systemic (Table 4). Pretreatment staging was available for three (60%) of the patients with endorectal and in six (75%) of the patients with systemic recurrence. There were

Table 4. Clinical and pathological features according to recurrent disease site of patients with recurrent disease following nonoperative management of a complete clinical response after neoadjuvant therapy for distal rectal cancer

	Endorectal recurrence	Systemic recurrence	*P*
n	5	8	
Mean age (yr)	64.2 ± 12.6	63.6 ± 7.8	0.92
Gender (n)			
Male	4 (80%)	4 (50%)	0.28
Female	1 (20%)	4 (50%)	
Pretreatment characteristics			
Tumor size (diameter) (cm)	4.6 ± 2.7	3.0 ± 1.6	0.33
Distance from anal verge (cm)	3.2 ± 1.1	2.5 ± 2.3	0.54
cT*			
2	0	2 (33.3%)	0.22
3	2 (66.7%)	4 (66.7%)	
4	1 (33.3%)	0	
cN*			
Negative	0	6 (100%)	0.03
Positive	3 (100%)	0	
Stage*			
I	0	2 (33.3%)	0.01
II	0	4 (66.7%)	
III	3 (100%)	0	
Mean recurrence interval (mo)	52.0 ± 23.1	29.5 ± 26.9	0.15

*Pretreatment staging available for 3 (60%) patients with endorectal and in 6 (75%) patients with systemic recurrence.

no significant differences between patients with recurrence and patients without recurrence in terms of age, gender distribution, tumor size estimation, distance from anal verge, depth of invasion, and interval between treatment and recurrence. However, there was a significant difference in pretreatment lymph node status and disease stage. Patients with endorectal recurrences had positive lymph node status (100% LN+ versus 0% LN+, $P = 0.03$) and a more advanced pretreatment stage (100% stage III versus 33.3% stage I and 66.7% stage II, $P = 0.01$) when compared to patients with systemic recurrences (Table 4).

Survival

Overall, mean follow-up was 59.7 ± 45.7 months. The 5-year overall and disease-free survival rates were 92.7% and 85.0%, respectively. The 10-year overall and disease-free survival rates were 90.0% and 75.4%, respectively (Figs. 1, *A*, *B*). Overall, 5-year survival was 100% for patients without recurrent disease and 58.3% for patients with recurrent disease, which was significantly different ($P < 0.0001$) (Fig. 2).

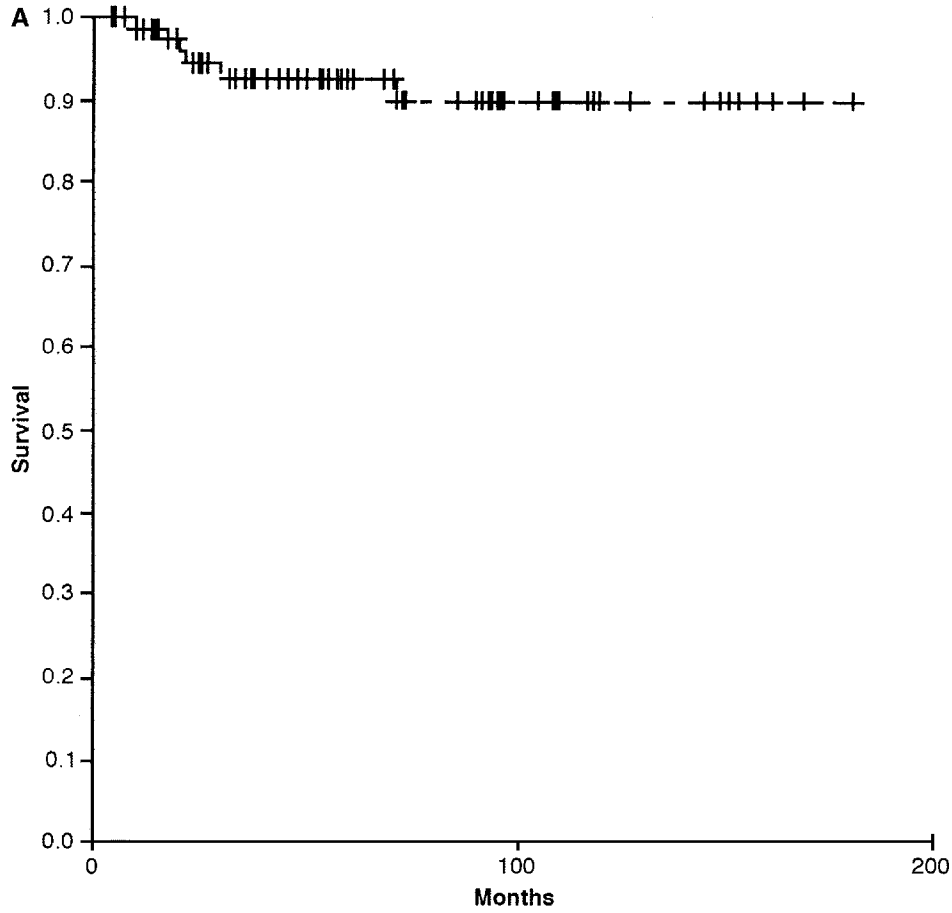
DISCUSSION

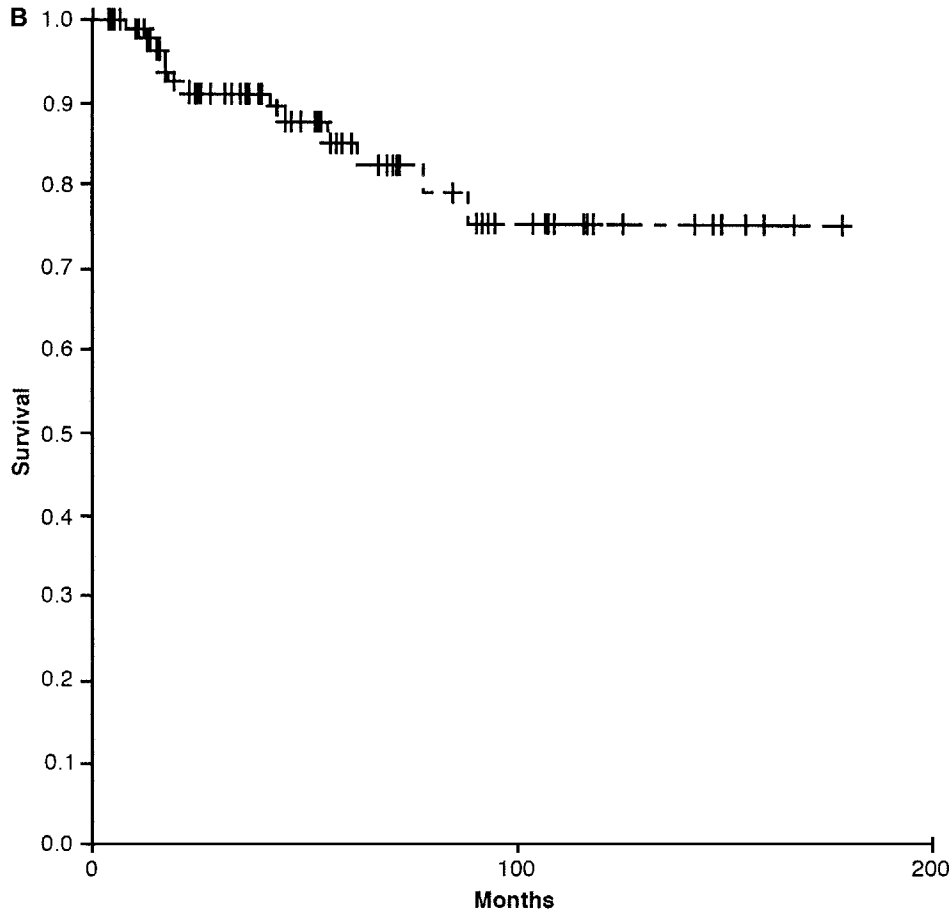
Management of distal rectal cancer remains a challenge for colorectal surgeons worldwide in terms of optimal treatment strategy. Even though total mesorectal excision has led to a significant decrease in local recurrence rates after radical surgery for distal rectal cancer, surgery alone seems to be sufficient for local disease control only in select patients.[17,18] Therefore, adjuvant and neoadjuvant therapy have been considered useful tools despite optimal surgical therapy.[19]

The significantly lower toxicity rates, improved local disease control associated with tumor downstaging, and increased rates of sphincter-saving operations led neoadjuvant chemoradiation therapy to be considered the preferred initial treatment strategy for distal rectal cancer.[5,6,8]

Tumor downstaging resulting in complete tumor regression in a significant proportion of patients raised the question of the value of radical surgery in these patients.[10] This observation led to the proposal of a nonoperative management of select patients with complete clinical response. The role of surgery in this setting was challenged when no significant differences in oncological outcomes were observed between patients with complete clinical response managed nonoperatively and patients with complete pathological response following radical surgery.[12] As such, if there is in fact no difference in oncologic outcome between these patients, their exposure to the immediate morbidity and mortality risks; to a significant risk of long-term urinary and sexual dysfunction, and fecal incontinence; and the possible requirement of temporary or even definitive stomas associated with radical surgery may not be justified. On the other hand, CRT alone may lead to clinically significant sequelae, such as radiation proctitis, fecal incontinence, and urinary or sexual dysfunction. Even though these were not objectively measured in our study we are currently prospectively studying objective physiological data through manometric studies and quality of life before and after CRT in these patients. In terms of urinary and sexual dysfunction, pretreatment status may be significantly impaired in these patients due to their advanced age and therefore, determination of actual or significant worsening may be extremely difficult. In our series, none of the patients required surgery for the management of functional disorders or morbidity directly related to CRT.

However, before "throwing away the scalpel" several issues in the management of complete tumor regression following neoadjuvant CRT remain unresolved.[14] First, clinical, radiological, and endoscopic assessment of tumor response is complex and may represent a significant challenge even for experienced colorectal surgeons. The risk of leaving behind deep nests of residual cancer or mesorectal lymph node metastases is a serious drawback for nonoperative management in this setting.[15,16] Reported rates of metastatic lymph nodes for complete primary rectal tumor reponse (pT0) ranges between 0% to 10%.[13,15,16] These rates are lower than those observed for nonirradiated pT1 rectal cancer where local excision, and therefore no lymph node removal, is accepted.[20–22] Furthermore, the clinical relevance of microscopic foci of cancer cells is still undetermined for irradiated and nonirradiated rectal cancer.[23–25] Finally, the variation in the interval period between CRT completion and surgery may have determined these differences in rates of pT0 N+ tumors. It has been suggested that increased interval periods may have an impact on the rates of complete pathological response.[26] In this setting, rectal resections performed at 6 weeks from CRT completion may have interrupted ongoing necrosis, implying that some patients would actually achieve complete tumor regression if longer waiting periods was allowed, such as 8 weeks or longer.[13] Interestingly, this phenomenon was similarly observed for epidermoid anal cancer, where tumor assessment 4 weeks after CRT completion led to significant subestimation of complete response rates when compared to


A
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival
0
100
200
Months


B
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival
0
100
200
Months

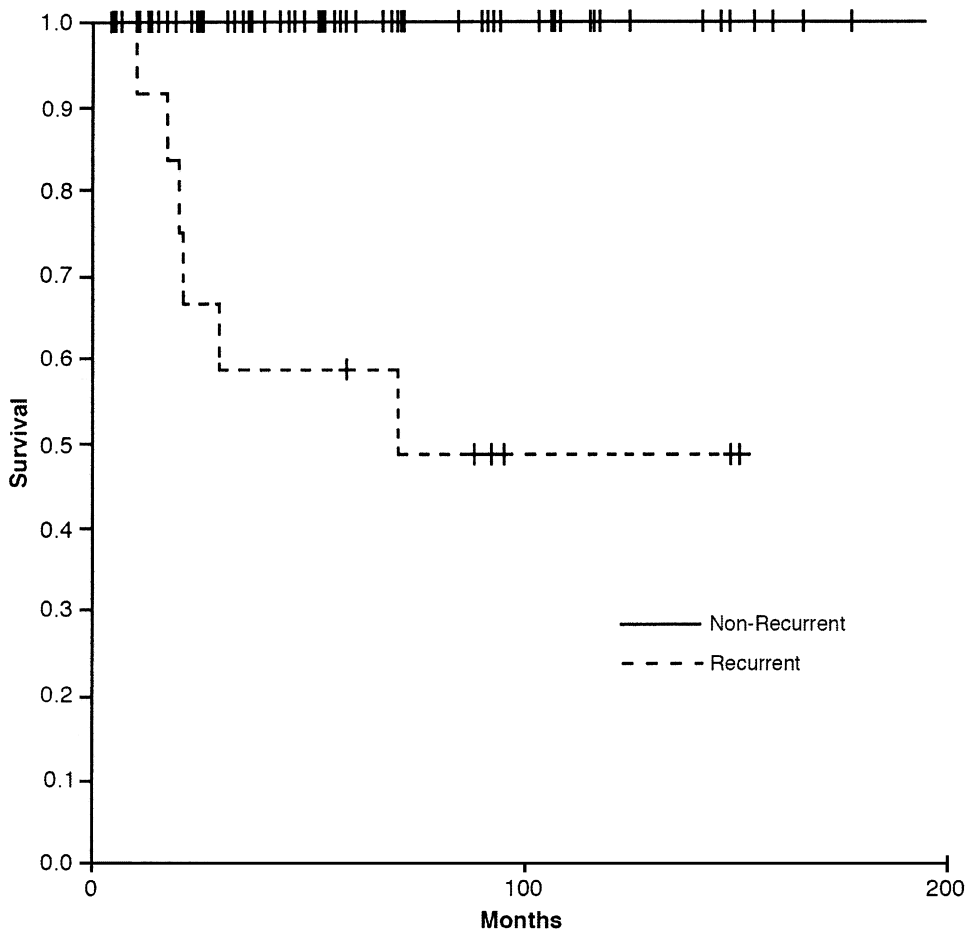


Fig. 2. Overall survival curve according to the presence of recurrence following nonoperative management of a complete clinical response after neoadjuvant therapy for distal rectal cancer. There was a significant difference in overall survival between patients with and without recurrent disease ($P < 0.0001$).

assessment performed at 8 weeks in the same series of patients.[27]

Despite these pathological and theoretical issues, local and distant failure for distal rectal cancer are the most important clinical outcomes to be considered as evidence for the understanding of the results of complete tumor response following neoadjuvant CRT. In fact, despite optimal surgery, distal tumor location has been shown to be an independent risk factor for increased local recurrence.[4,28] When considering rectal cancer following CRT and surgery, final disease stage and the presence of lymph node metastases remain the most significant risk factors associated with disease recurrence.[13,29,30] Local disease recurrence following complete pathological response at surgery has not yet been reported.[12,31,32] These results may be explained by the small series of patients with complete pathological response and by considerably short follow-up of these patients. In fact, it has been suggested that the irradiated rectal cancer may result in decreased but also delayed recurrent disease.[30,32] A recently reported small series of patients followed for at least 9 years, showed that over a third of the patients with recurrent rectal cancer managed initially by preoperative CRT and surgery, developed local recurrences after 5 years of follow-up.[30] On the other hand, over 90% of local recurrences in nonirradiated rectal cancer develops within 3 years of follow-up.[28,33] In an interesting study of patients with rectal cancer treated by surgery alone or associated with postoperative CRT, with a mean follow-up of 10 years, 72% of the local relapses occurred before 18 months of follow-up, considerably earlier than those studies including patients managed by neoadjuvant CRT.[34]

Interestingly, in our series of 99 nonoperated distal rectal cancer patients, local failure consisted of

Fig. 1. Survival curves of patients with nonoperative management of a complete clinical response after neoadjuvant therapy for distal rectal cancer. **A,** Overall survival. **B,** Disease-free survival.

exclusively endorectal recurrences with a surprisingly long mean interval of 52 months for recurrence. First, this observation may reflect a distinct tumor behavior of this highly selected subset of patients. One could argue that these tumors exhibit a slow proliferative ratio and that endorectal tumor regrowth may actually represent undetected residual microscopic tumor foci. Considering that only 5% of our series developed endorectal recurrences or regrowth in a considerably long-term follow-up, clinical, radiological and endoscopic assessment of complete tumor regression turned out to be accurate in 95% of the cases. Moreover, all patients with exclusively local endorectal recurrences could be salvaged by different treatment strategies. Even though longer follow-up for these patients is warranted, local disease control can be considered satisfactory and therefore, even in the group of patients ultimately managed by radical surgery, survival has not been compromised by this initial nonoperative approach. However, delaying surgical resection may ultimately lead to increased perioperative morbidity given the more chronic effects of CRT in pelvic tissues. Even though this could not be determined in our study due to the small number of patients managed by delayed radical resection, it should be considered as an objective outcome when considering patients managed by initially nonoperative approach.

The issue of longer recurrence intervals for the irradiated rectal cancer may actually challenge current concepts in follow-up surveillance and also the initial results of local disease control rates in prospective randomized trials.[5,6] In terms of follow-up surveillance, the observation of a majority of disease recurrence occurring within 3 years of treatment may not be true for patients undergoing neoadjuvant chemoradiation for rectal cancer. In this setting, specific follow-up programs may be required with more intensive surveillance for longer periods of time and consequently increased costs. Also, if later or delayed recurrence may represent a significant issue in irradiated rectal cancer, results from trials with longer follow-up periods should be awaited before definitive conclusions are drawn for the irradiated rectal cancer. Finally, this delayed pattern of local recurrence following nonoperative treatment for distal rectal cancer after neoadjuvant CRT demands prolonged follow-up surveillance of these patients since local disease control may have not been achieved after considerably long periods of time.

Even though local recurrence is considered an important issue in the management of rectal cancer, these rates are significantly higher for distally located tumors even after radical surgery with or without neoadjuvant chemoradiation therapy.[4,28] Interestingly, in our series of patients managed nonoperatively after complete clinical regression, patients who developed recurrences had significantly lower tumors when compared to patients who did not develop recurrent disease (2.8 ± 1.8 versus 4.0 ± 1.7, $P = 0.036$). Moreover, even though pretreatment staging was not associated with recurrent disease, patients with local recurrences had significantly higher rates of radiological evidence of positive lymph nodes and stage cIII (100% LN+ versus 0% LN+, $P = 0.03$ and 100% stage III versus 33.3% stage I and 66.7% stage II, $P = 0.01$, respectively). The small number of patients with recurrences in our series does not allow definitive conclusions, however, these results suggests a possible role of lymph node metastases in local failure in these patients.

One should not expect to significantly decrease systemic disease recurrence with the neoadjuvant CRT approach for distal rectal cancer. In fact, prospective randomized trials have failed to demonstrate definitive survival benefit of this approach, possibly due to distant failure rates.[5,6] However, preoperative CRT has been shown to decrease circulating bone marrow micrometastases, suggesting a possible decrease (or delay) in tumor recurrence.[35] The risk of disseminated microscopic foci of metastatic disease, undetectable by standard staging radiological studies may contribute to a significant proportion of the cases with distant failure. In fact, the observation of significantly shorter recurrence intervals for distant failure when compared to local failure may be explained by these occult metastatic foci.[36] The use of PET scan (and PET-CT scans) may actually decrease the rates of these still undetectable metastatic disease.[37] In our series, systemic recurrences occurred at a shorter interval period compared to local failure; however, this difference was not significant, possibly reflecting this occult metastatic phenomenon. These results are again similar to other reported series with late local relapses and early distant failures, suggesting the possible role of preoperative CRT in delaying local failure onset but not influencing distant relapse.[30] Once again, even though pretreatment staging was not associated with recurrent disease, patients with systemic recurrence had significantly lower rates of radiological evidence of lymph node metastases, suggesting that systemic recurrence may develop due to hematogenic rather than lymphatic spread. Also, the observed overall survival for patients with stage c0 was exclusively affected by systemic recurrence since none of the patients with endorectal recurrence alone died of disease progression. Even so, long-term survival rates were considerably high.

Since disease recurrence in the irradiated rectal cancer can be significantly delayed, overall survival may be significantly affected with a time frame shift. Therefore, disease-free survival may be a more realistic parameter for comparison between stages and treatment strategies even in a series of patients with a considerably long follow-up period. Indeed, in our previously reported series there was no overall or disease-free survival benefit in patients with stage p0 over patients with stage c0. On the other hand, disease-free survival of patients with stage c0 and p0 were significantly better than patients with stage pII and pIII but not than patients with stage pI, possibly requiring longer follow-up in order to obtain a survival benefit.[13] This present series has shown a significant increase in both local and distant disease failure when compared to our previous reports, possibly associated with the increase in the follow-up period and in the number of patients.[12,13]

In conclusion, even though surgery remains the standard of treatment for rectal cancer, nonoperative management for distal rectal cancer after complete clinical response following neoadjuvant CRT is safe and associated with low rates of local failure, frequently amenable to salvage therapy, and resulting in excellent long-term survival rates. The shorter interval recurrence periods for distant failure may be associated with the presence of occult distant metastases undetected by standard staging radiological studies. The surprisingly long mean interval period for local failure suggests that a change in the follow-up surveillance strategy in these patients may be necessary when compared to patients with nonirradiated rectal cancer. Moreover, studies concerning irradiated rectal cancer may warrant increased follow-up before definitive conclusions in terms of local disease control and survival.

REFERENCES

1. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583–596.
2. Tjandra JJ, Kilkenny JW, Buie WD, Hyman N, Simmang C, Anthony T, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2005;48:411–423.
3. Madbouly KM, Remzi FH, Erkek BA, Senagore AJ, Baeslach CM, Khandwala F, et al. Recurrence after transanal excision of T1 rectal cancer: Should we be concerned? Dis Colon Rectum 2005;48:711–719; discussion 719–721.
4. Petersen S, Hellmich G, von Mildenstein K, Porse G, Ludwig K. Is surgery-only the adequate treatment approach for T2N0 rectal cancer? J Surg Oncol 2006; 93:350–354.
5. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–1740.
6. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–646.
7. Janjan NA, Khoo VS, Abbruzzese J, Pazdur R, Dubrow R, Cleary KR, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: The M.D. Anderson Cancer Center experience. Int J Radiat Oncol Biol Phys 1999;44: 1027–1038.
8. Habr-Gama A, Perez RO, Kiss DR, Rawet V, Scanavini A, Santinho PM, et al. Preoperative chemoradiation therapy for low rectal cancer. Impact on downstaging and sphincter-saving operations. Hepatogastroenterology 2004;51: 1703–1707.
9. Medich D, McGinty J, Parda D, Karlovits S, Davis C, Caushaj P, et al. Preoperative chemoradiotherapy and radical surgery for locally advanced distal rectal adenocarcinoma: Pathologic findings and clinical implications. Dis Colon Rectum 2001;44:1123–1128.
10. Habr-Gama A, de Souza PM, Ribeiro U Jr, Nadalin W, Gansl R, Sousa AH Jr., et al. Low rectal cancer: Impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum 1998;41:1087–1096.
11. Guillem JG, Chessin DB, Cohen AM, Shia J, Mazumdar M, Enker W, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005; 241:829–836; discussion 836–838.
12. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. Ann Surg 2004;240:711–717; discussion 717–8.
13. Habr-Gama A, Perez RO, Nadalin W, Nahas SC, Ribeiro U Jr, Silva E Jr, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. J GASTROINTEST SURG 2005; 9:90–99; discussion 99–101.
14. Meyers MO, Tepper JE. Rectal cancer: Can we throw away the scalpel? Ann Surg Oncol 2005;12:95–97.
15. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: An analysis of 488 patients. J Am Coll Surg 2002;194:131–135; discussion 135–136.
16. Stipa F, Zernecke A, Moore HG, Minsky BD, Wong WD, Weiser M, et al. Residual mesorectal lymph node involvement following neoadjuvant combined-modality therapy: Rationale for radical resection? Ann Surg Oncol 2004;11: 187–191.
17. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479–1482.
18. Simunovic M, Sexton R, Rempel E, Moran BJ, Heald RJ. Optimal preoperative assessment and surgery for rectal cancer may greatly limit the need for radiotherapy. Br J Surg 2003;90:999–1003.
19. Colquhoun P, Wexner SD, Cohen A. Adjuvant therapy is valuable in the treatment of rectal cancer despite total mesorectal excision. J Surg Oncol 2003;83:133–139.

20. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 2002;45:200–206.
21. Hahnloser D, Wolff BG, Larson DW, Ping J, Nivatvongs S. Immediate radical resection after local excision of rectal cancer: An oncologic compromise? Dis Colon Rectum 2005;48: 429–437.
22. Floyd ND, Saclarides TJ. Transanal endoscopic microsurgical resection of pT1 rectal tumors. Dis Colon Rectum 2006; 49:164–168.
23. Perez RO, Habr-Gama A, Nishida Arazawa ST, Rawet V, Coelho Siqueira SA, Kiss DR, et al. Lymph node micrometastasis in stage II distal rectal cancer following neoadjuvant chemoradiation therapy. Int J Colorectal Dis 2005;20:434–439.
24. Andreola S, Leo E, Belli F, Gallino G, Sirizzotti G, Sampietro G. Adenocarcinoma of the lower third of the rectum: Metastases in lymph nodes smaller than 5 mm and occult micrometastases;preliminary results on early tumor recurrence. Ann Surg Oncol 2001;8:413–417.
25. Oberg A, Stenling R, Tavelin B, Lindmark G. Are lymph node micrometastases of any clinical significance in Dukes Stages A and B colorectal cancer? Dis Colon Rectum 1998; 41:1244–1249.
26. Moore HG, Gittleman AE, Minsky BD, Wong D, Paty PB, Weiser M, et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 2004;47:279–286.
27. Deniaud-Alexandre E, Touboul E, Tiret E, Sezeur A, Houry S, Gallot D, et al. Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiat Oncol Biol Phys 2003;56:1259–1273.
28. Bonadeo FA, Vaccaro CA, Benati ML, Quintana GM, Garione XE, Telenta MT. Rectal cancer: Local recurrence after surgery without radiotherapy. Dis Colon Rectum 2001;44:374–379.
29. Luna-Perez P, Trejo-Valdivia B, Labastida S, Garcia-Alvarado S, Rodriguez DF, Delgado S. Prognostic factors in patients with locally advanced rectal adenocarcinoma treated with preoperative radiotherapy and surgery. World J Surg 1999;23:1069–1074; discussion 1075.
30. Coco C, Valentini V, Manno A, Mattana C, Verbo A, Cellini N, et al. Long-term results after neoadjuvant radiochemotherapy for locally advanced resectable extraperitoneal rectal cancer. Dis Colon Rectum 2006;49:311–318.
31. Ruo L, Tickoo S, Klimstra DS, Minsky BD, Saltz L, Mazumdar M, et al. Long-term prognostic significance of extent of rectal cancer response to preoperative radiation and chemotherapy. Ann Surg 2002;236:75–81.
32. Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum 2003;46:298–304.
33. Kraemer M, Wiratkapun S, Seow-Choen F, Ho YH, Eu KW, Nyam D. Stratifying risk factors for follow-up: A comparison of recurrent and nonrecurrent colorectal cancer. Dis Colon Rectum 2001;44:815–821.
34. Chmielarz A, Kryj M, Wloch J, Poltorak S, Sacher A, Lasek-Kryj M. Prognostic factors for the time of occurrence and dynamics of distant metastases and local recurrences after radical treatment in patients with rectal cancer. Med Sci Monit 2001;7:1263–1269.
35. Kienle P, Koch M, Autschbach F, Benner A, Treiber M, Wannenmacher M, et al. Decreased detection rate of disseminated tumor cells of rectal cancer patients after preoperative chemoradiation: A first step towards a molecular surrogate marker for neoadjuvant treatment in colorectal cancer. Ann Surg 2003;238:324–330; discussion 330–331.
36. Swayne LC, Goldenberg DM, Diehl WL, Macaulay RD, Derby LA, Trivino JZ. SPECT anti-CEA monoclonal antibody detection of occult colorectal carcinoma metastases. Clin Nucl Med 1991;16:849–852.
37. Chessin DB, Kiran RP, Akhurst T, Guillem JG. The emerging role of 18F-fluorodeoxyglucose positron emission tomography in the management of primary and recurrent rectal cancer. J Am Coll Surg 2005;201:948–956.

Discussion

Andreas M. Kaiser, M. D. (Los Angeles, Calif): Dr. Perez, thank you for the opportunity to comment on your paper. I would like to congratulate you on this next piece of evidence in a series of most important contributions made by the group in Sao Paulo. It is of no doubt that there is no other group that has shaken the foundation of our understanding in regard to the treatment of rectal cancer more than they did in the last couple of years. Not even 10 years ago, nobody would even have considered in good faith not to operate on a patient with an operable rectal cancer, but dr. Habr-Gama and her colleagues were more foreseeing and brave than the rest of the world to try this unconventional approach. They were able to show that neoadjuvant chemoradiation not only results in improved outcomes but that in fact a significant number of patients have a complete clinical response, which may last and obviate the previously thought mandatory need for surgery.

In their 2004 *Annals of Surgery* paper, they were able to show that even patients with clinically visible scars after chemoradiation did equally well being simply followed clinically without surgery when compared to a group who were subjected to the surgery but were found to have no residual tumor on pathology. In that sense, the post-chemoradiation stage appears to be more important than the original tumor stage before initiation of treatment. NO unexpectedly, however, there are patients who seem to be doing all right for a while but after that develop a recurrence, either locally or systemically.

One of the most critical questions to be answered will be whether the delay between finishing the radiation and the eventful needed surgery worsens the final outcome of such a patient group. Dr. Perez showed us that the type of recurrence still allows a salvage operation with eventual good outcome. But they also confirmed what a number of studies have shown before, that in fact the overall survival is generally determined by the systemic disease, not the local control. Another message learned from this paper, however, is that it is unfortunately the most distal cancers in which we would be most inclined to avoid surgery but which also are the ones associated with the highest risk of local failure from the nonoperative management. I have two sets of questions for the authors, and may be we can go through them.

When we look at this study's outcome data, we are surprised how good in fact the results are — 85% disease-free survival and 92% overall survival for a blend for tumor stages is much better than our average outcomes reported in the SEER data. And the author's success does not appear to be the result of a very aggressive chemoradiation protocol but comes from a relatively mild chemoradiation regimen. I would therefore wonder whether the authors have an explanation for their better results? I would also wonder whether they extended the chemotherapy as we would normally do for stage II and III rectal cancer, up to 6 months after a resection. And given the systemic failures, do you see any role for more systemic chemotherapy as you go on?

Rodrigo Perez, M.D. (Sao Paulo, Brazil): To answer the first question, I think there is significant data indicating that local recurrence in irradiated rectal cancer may occur significantly later than in patients with nonirradiated rectal cancer. So we might have to wait a little more before we can say that these results are better than any other reported in the literature. That would be the first issue I would address.

The second is that one could argue that the rates of complete response are too high despite the not so aggressive approach. I would say that the interval period may be a critical issue. There is some data in the literature indicating that the interval between chemoradiation and tumor assessment or surgery may actually affect this rate of complete response, indicating that the more you wait, the more you get. So these are the two issues regarding improved results.

The answer to the second question is; adjuvant chemotherapy is currently offered for our patients based on final pathological staging, and therefore we routinely indicate chemotherapy only for stage III rectal cancer and only those patients with stage II considered to be high-risk patients. There has been a great deal of discussion with the oncologists regarding giving patients with complete clinical response chemotherapy, and we are thinking we are going to end up giving them more chemotherapy not only during the chemoradiation regimen but also extending chemotherapy during the resting period of eight weeks. We are trying to set up trial to study this.

Dr. Kaiser: Thank you for your answer. The second set of questions is about patient selection, if I may. Even if you label the clinically tumor-free patients as C0, the ones who end up developing a recurrence are false negative. In your study, you excluded the 23 patients who developed a "re-growth" within 12 months. However, from a practical stand point, the decision about whether to operate or to wait on a patient is generally made somewhere between 6 and 12 weeks after completion of chemoradiation. I would ask you to comment on this as it seems to me that this 12 month time point definition of C0 is somewhat arbitrary and obviously filters a more favorable subset of patients from the more average cohort. And I would also like to know whether you offered surgery to everybody and whether there were patients who objected to the nonoperative management?

Dr. Perez: As you know, accurate methods of tumor assessment following chemoradiation therapy are lacking, and as a result of that, there are some patients who are actually false negative. In our series, these 23 patients most likely represent a misdiagnosis rather than actual disease recurrence. Interestingly, these patients had a time delay for definitive surgery, and we found that this delay did not have a negative impact on survival in the whole series of patients. We hope to present this data at the ACS meeting.

Dr. Kaiser: Were the patients asking for an operation?

Dr. Perez: Patients are fully informed that the standard of therapy is still radical surgery. When the patient has a complete clinical response and he follows our recommendation of an initial nonoperative approach, we also fully inform them that this situation may be temporary and surgery may be required at any time during follow-up. We did not experience any patient who actually demanded surgery following a complete clinical response. What we did have were some patients coming from abroad who had a complete response and were offered surgery elsewhere, and they wanted to hear Prof. Habr-Gama's second opinion.

Dr. Kaiser: Thank you very much for allowing me to discuss this very stimulating research.

Ileorectal Anastomosis for Slow Transit Constipation: Long-Term Functional and Quality of Life Results

Imran Hassan, M.D., John H. Pemberton, M.D., Tonia M. Young-Fadok, M.D., Y. Nancy You, M.D., Ernesto R. Drelichman, M.D., Doris Rath-Harvey, R.N., Cathy D. Schleck, B.S., Dirk R. Larson, M.S.

The results of colectomy and ileorectal anastomosis (IRA) in patients diagnosed by physiologic testing as having slow transit constipation (STC) have been reported. The durability of functional results and long-term quality of life (QoL) in these patients, however, has not been established. Between 1987 and 2002, 3670 patients were evaluated for constipation at our institution; 110 (3%) fulfilled the criteria for STC and underwent an IRA. Patients were prospectively followed and functional outcomes assessed annually by standardized questionnaires. After a median follow-up of 11 years, 104 eligible patients were mailed validated questionnaires to assess functional outcomes and QoL (Knowles-Eccersley-Scott Symptom [KESS] score, the Irritable Bowel Syndrome Quality of Life [IBS-QOL], and the SF-12 health survey). Prospectively assessed functional data was available on 85 of 104 (82%) eligible patients. At last follow-up, improvement of constipation and satisfaction with bowel function was reported by 98% and 85% of patients, respectively. Performance measures including social activity, household work, sexual life, and family relationships were reported to have improved or were not affected as a result of surgery by 75%, 86%, 81%, and 86% of the patients respectively. Fifty-nine patients (57%) responded to the study questionnaires. All 59 patients reported their constipation to be better since IRA, 83% did not require any medication, and 85% reported being satisfied with bowel function. The KESS scores of patients undergoing IRA for STC (median 6, range 0–35) were lower than reported scores of STC patients not operated upon (median 21, range 11–35, $P < 0.001$) indicating symptomatic improvement after surgery. Mean IBS-QOL scores were similar to reported scores of patients undergoing IRA for other conditions [80 (23) versus 84 (16)], $P = 0.7$). Mean SF-12 physical and mental summary scores were similar to reported SF-12 scores of the normal population (49.5 versus 50 and $P = 0.70$, 48.7 versus 50, $P = 0.42$, respectively). Ileorectal anastomosis in appropriately selected patients with slow transit constipation results in durable symptomatic relief and a long-term quality of life indistinguishable from the general population. (J GASTROINTEST SURG 2006;10:1330–1337)

KEY WORDS: Slow transit constipation, quality of life, ileorectal anastomosis

Chronic constipation is more a constellation of symptoms than a definable disease. Moreover, patients complaining of constipation are a heterogenous group; the various symptoms representing various pathologic processes.[1] Advancements in defining colonic and anorectal physiology have improved the understanding of colonic motility, the process of defection and the factors contributing to chronic constipation.[2,3] Currently, by following an objective evaluation strategy[2] that quantifies colonic, pelvic, and anorectal function, patients are classified into four diagnostic categories depending upon the presence or absence of various underlying physiologic abnormalities: (1) slow transit constipation (STC), (2) pelvic floor dysfunction (PFD), (3) combined slow transit constipation and pelvic floor dysfunction (STC + PFD), and (4) constipation predominant irritable bowel syndrome (IBS-C). We have demonstrated previously that patients with slow transit constipation documented by colonic transit studies with or without pelvic floor dysfunction, benefit from colectomy and ileorectal anastomosis (IRA).[2,3] Subsequent reports have validated this approach by reporting similar improvements in functional outcomes of these patients.[4–9]

In recent years, however, there has been a growing recognition that in order to assess the true efficacy of any operative intervention, the patient's perspective

From the Division of Colon and Rectal Surgery and Section of Biostatistics, Mayo Clinic, Rochester, Minnesota.
Reprint requests: John H. Pemberton, M.D., Division of Colon and Rectal Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

 Published by Elsevier Inc.
1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.006

of the outcome needs to be assessed objectively in the same manner as conventional outcome measures are documented. As a result, standard outcome measures are being increasingly supplemented with studies of quality of life (QOL).[10] QOL is a multidimensional construct that reflects the patient's subjective evaluation of the effects of the treatment on their physical, psychological, social functioning and well-being.[11] It has been previously suggested that QOL is a soft outcome, although this argument no longer is valid as QOL assessments are now performed using standard questionnaires with documented psychometric properties.[12] There are two basic types of QOL questionnaires: generic and disease/treatment specific. Generic questionnaires assess the ability of patients to cope physically, emotionally and socially as well as their general performance at work and in daily life.[13] In contrast, the content of disease- or treatment-specific instruments are limited to areas of consequence to the patients affliction from a particular condition.[14]

The purpose of this study was to assess the long-term functional and QOL outcomes of patients who had undergone an IRA for slow transit constipation using both generic and disease-specific validated QOL instruments.

PATIENTS AND METHODS

Three thousand six hundred seventy patients were evaluated for constipation at our institution's specialist gastrointestinal motility unit between 1987 and 2002. All patients underwent a complete history and physical examination, appropriate laboratory investigations and either a colonoscopy or barium enema to rule out anatomic causes of constipation. Patients were then evaluated with standardized colonic transit and pelvic floor studies that have been described in detail previously.[2] In brief, colonic motility was assessed by either marker[15] or scintigraphic[16] transit, while pelvic floor function studies included anorectal manometry and balloon expulsion. Selected patients underwent defecography. One hundred twelve patients (3%) fulfilled the standardized criteria for slow transit constipation with or without pelvic floor dysfunction. Patients (n = 92) with slow transit constipation alone underwent an IRA, while patients (n = 30) with slow transit constipation and pelvic floor dysfunction underwent IRA after a successful course of pelvic floor retraining. Patients with PFD alone were treated by pelvic floor retraining (biofeedback) and patients with IBS-C were managed medically.

Data was collected in a prospectively maintained computerized database. Bowel function and functional outcomes were assessed yearly by a standard institution-specific questionnaire. Functional aspects evaluated included social activity, sports, housework, recreation, family relationships and sex life. After a median follow up of 11 years (range 1.5–16.5 years), 104 eligible patients were mailed a study-specific questionnaire and three validated questionnaires assessing bowel function and health-related QOL.

Study-specific Questionnaire

The study-specific questionnaire was composed of questions designed to assess bowel function, change in symptoms of constipation, use of constipating or antidiarrheal medications- and patient satisfaction after an IRA.

SF-12

The SF-12[17,18] contains items selected from the SF-36 based on their relative efficiency and psychometric performance across eight dimensions of general overall health.[19] The SF-36 health survey is one of the most widely used generic health status instruments to assess health-related quality of life.[20] Since it contains 36 items and thus places a considerable burden on the respondents and the investigators, a substantially shorter questionnaire, the SF-12, was developed, reducing the number of items to 12.[19] About 80% of adults studied using a pilot test completed the SF-12 in less than 2 minutes. The SF-12 is scored to produce two summary scores, the physical and mental health summaries (PCS and MCS). These summary scores are estimated using a weighted formula for predicting the original SF-36 summary scores. The SF-12 summary scores have reproduced the psychometric performance of the SF-36 and have been found to be good predictors of the original summary scores as they account for approximately 90% of the variation in the SF-36 summary measures.[19,21]

Knoweles-Eccerslley-Scott Symptom (KESS) Questionnaire

The KESS is a structured symptom scoring questionnaire for patients complaining of constipation consisting of 11 items.[22] The questions were designed to incorporate internationally recognized criteria and previously reported relevant symptoms of constipation. The KESS score has been validated against the Cleveland Clinic Score (Pearson r = 0.90 and 95% limits of agreement ±14%), which is itself a validated tool for distinguishing constipated

patients with a proven pathophysiologic abnormality from those in whom physiologic investigations were normal.[22] The KESS score has been shown to be able to discriminate between the pathophysiologic subgroups for the majority of patients with constipation. Discriminant scores predict patients with pure slow transit constipation or PFD better than patients with mixed abnormalities.[22,23] However, the KESS total score clearly differentiates patients with slow transit constipation from healthy controls.[22] The questionnaire can be completed in less than 5 minutes. Each question has four or five possible answers, which are scored on an unweighted linear numeric scale to produce a range of between 0 and 3 or 0 and 4 points. Lower scores represented symptom free states and higher scores, increased symptom severity. The total KESS score is the sum of all scores gained on individual questions with a maximum possible score of 39 points. The answers to each question are phrased in such a manner that any patient who fulfilled the standardized criteria for constipation would likely score at least 1 point per question.[22]

Irritable Bowel Syndrome–Quality of Life Measure (IBS-QOL)

The IBS-QOL is a self-reported QOL measure specific to irritable bowel syndrome (IBS).[24] It is made up of 34 items and takes an average of 10 minutes to complete. The IBS-QOL has 10 subscales: Dysphoria, Interference with activity, Body image, Health Worry, Food Avoidance, Social Reaction, Sexual, Relationships, Symptom Frequency Index, and Symptom Bothersome Index. Responses are based on a 5-point Likert scale (not at all … extremely or a great deal). The individual responses to the 34 items are summed and averaged for a total score that is transformed to a 0–100 scale, with higher scores indicating better QOL.[24]

Data Analysis and Statistics

Statistical analysis was performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). The analysis focused on comparing responders and nonresponders, and patients with and without pelvic floor dysfunction. In addition, limited QOL outcomes from the cohort were compared to the corresponding parameters from previously published cohorts.[22,25] Outcomes comprised of discrete, nominal variables were compared using χ^2 tests or Fisher's exact tests when low expected cell counts were observed. Continuous variables were analyzed using two-sample *t*-tests, or Wilcoxon rank sum tests when the data were not sufficiently Gaussian. The SF-12 mental and physical component summary scores are standardized to have a mean of 50 and standard deviation of 10; comparisons of these scores with an external reference population were performed using a one-sample *t*-test. Significance was assumed at the $P < 0.05$ level.

RESULTS

Between 1987 and 2002, 110 patients (104 females, median age 40 years) after objective preoperative evaluation underwent a colectomy with ileorectal anastomosis (IRA) for slow transit constipation. Six patients were deceased on most recent follow-up. Among the 104 remaining patients, 65 patients had slow transit constipation alone and 39 patients had combined slow transit constipation and pelvic floor dysfunction.

Prospectively assessed functional outcomes were obtained through annual questionnaires for 85 of the 104 (82%) eligible patients. At last follow-up (mean 5.7 years, SD 3.8 years) the median stool frequency was four bowel movements per day and improvement of constipation and satisfaction with bowel function was reported by 98% and 85% of the patients respectively. Performance measures including social activity, household work, family relationships, recreation, and sexual life were reported to have improved or were not affected as result of surgery by 75%, 86%, 86% 80%, and 81% of the patients respectively. Fifty-nine of the 104 (57%) eligible patients with a median follow-up of 11 years (mean 10 years, SD 4) responded to the validated functional and QOL outcome instruments. All 59 respondents reported their constipation to be better since IRA, 83% did not require constipating or antidiarrheal medication and 85% reported being satisfied with their bowel function.

The KESS score of the patients (median 6, range 0–35) undergoing IRA for slow transit constipation were less than the reported scores of patients with slow transit constipation not operated upon[22] (median score 21, range 11–35, $P < 0.001$) suggesting symptomatic improvement after surgery. Mean IBS-QOL scores were similar to reported scores of patients undergoing IRA for other benign conditions[25] [80 (standard deviation 23) versus 84 (standard deviation 16), $P = 0.7$) Mean SF-12 physical and mental summary scores were similar to reported SF-12 scores of the normal population (49.5 versus 50, $P = 0.70$, 48.7 versus 50, $P = 0.42$).

There were no significant differences between the KESS, the IBS-QOL, and SF-12 scores of patients

with slow transit constipation alone and slow transit constipation with pelvic floor dysfunction (Table 1).

Nonresponders

Concerning patients not responding to the functional and QOL outcome questionnaires, we could find no differences between responders and nonresponders in terms of age, gender, length of follow-up, year of surgery, and incidence of PFD. (Table 2). Furthermore, no differences were seen in the yearly assessed functional outcomes. (Table 3).

DISCUSSION

We found that patients diagnosed with slow transit constipation by objective preoperative criteria and who underwent colectomy and ileorectal anastomosis had satisfactory long-term functional results and an excellent quality of life as measured by validated QOL instruments. This is the first report of a large series of patients categorized prospectively using tests of colonic and pelvic floor function and followed for this length of time (median 11 years) documenting QOL outcomes measured by standardized QOL instruments.

Inconsistent functional results have been reported in the literature for surgery for slow transit constipation.[7] This variability may be due to the lack of standardized preoperative physiologic testing in some of these reports.[26–29] We have found that patients with slow transit constipation, documented by colonic motility studies, were the patients most likely to benefit from an IRA.[2,3] Patients with pelvic floor dysfunction alone or constipation-predominant irritable bowel syndrome who are managed surgically do not show the same functional improvement and may account for the poor functional results associated with IRA in these various studies. The group of patients with IBS, which actually forms the great majority of patients evaluated for chronic constipation (>60%), can be reliably diagnosed with physiologic testing and be managed by aggressive medical therapy. Studies using standardized preoperative evaluation to select patients for surgery consistently report superior outcomes as compared to studies in which patients did not undergo formal evaluation.[3,7,9,30]

In our study, we evaluated functional and QOL outcomes using standardized validated instruments at a median of 11 years following IRA. Previous reports evaluating functional results of surgery for slow transit constipation have used instruments which were unreliable and not validated.[1,3,6,8,9,31–33] Knowles et al.[7] suggested that studies evaluating outcomes of surgery for slow transit constipation should be independent, prospective, have long-term follow-up, and use validated questionnaires that assess QOL and gastrointestinal function. We agreed, and thus all patients who underwent surgery for slow transit constipation at our institution were entered into a computerized database and prospectively evaluated through annual questionnaires administered by a nurse not directly involved in their care. Analysis of these prospectively collected data suggests that the majority (85%) of patients report improvement of their bowel function and functional outcomes following surgery. After a median follow-up of 11 years, we then evaluated the functional and QOL outcomes of this cohort in a cross-sectional manner using validated instruments; the data confirmed the long-term benefit of surgery on functional and QOL outcomes.

Table 1. Comparison of functional and QOL outcomes of patients with STC alone and STC and PFD (N = 59)

	STC (N = 42)	STC and PFD (N = 17)	*P*-value
Median KESS score (IQ range)	6 (4–9)	6.5 (3–l3)	0.77
Median IBS-QOL score (IQ range)	93 (80–96)	88 (73–93)	0.19
Median SF-12 (physical scale) (IQ range)	54 (48–56)	50 (40–57)	0.61
Median SF-12 (mental scale) (IQ range)	54 (42–58)	51 (44–57)	0.59

IQ = interquartile range; STC = slow transit constipation; PFD = pelvic floor dysfunction.

Table 2. Comparison of the responders and nonresponders to the study questionnaires (N = 104)

	Responders (N = 59)	Non responders (N = 45)	*P*-value
Gender (females)	97%	91%	0.40
Mean age, yr (SD)	41 (11)	38 (14)	0.13
Follow-up from surgery, in mo (SD)	73 (47)	59 (42)	0.21
STC	75%	63%	0.21
STC and PFD	25%	37%	0.44

SD = standard deviation; STC = slow transit constipation PFD = pelvic floor dysfunction.

Table 3. Comparison of responders and nonresponders to study questionnaires based upon prospectively collected yearly data (N = 85)

Questionnaire issue	Responders (N = 53)	Non responders (N = 32)	*P*-value
Satisfaction with bowel function	87%	75%	0.04
Constipation (better)	100%	94%	0.13
Median stool frequency (IQ range)	4 (2–6)	4 (3–6)	0.73
Social life (not affected/improved)	77%	72%	0.63
Housework (not affected/improved)	87%	84%	1.00
Relationships (not affected/improved)	91%	78%	0.29
Recreation (not affected/improved)	83%	75%	0.56
Sex life (not affected/improved)	85%	75%	0.24

IQ = interquartile range.

The functional results following surgery were assessed using the KESS Questionnaire, which was designed to incorporate standardized criteria and relevant symptoms of constipation. The median KESS score of our patients was significantly better than the median score of patients with slow transit constipation prior to surgery confirming that IRA is beneficial for patients with STC. On the study-specific questionnaire, the majority of the patients reported an improvement of their bowel function and their overall QOL. This improvement in functional outcome is consistent with the results of others that have demonstrated the success of surgery in properly selected patients.[5,7–9,30,34] The definition of "success" for IRA, however, has been nebulous, as successful results have variably been equated to normal bowel frequency,[33] spontaneous passage of stool,[2] or the patient's satisfaction with their outcomes.[30] We agree with Fitzharris and colleagues[5] that these definitions are arbitrary and not reliably reproducible, making comparisons across studies difficult. Although stool frequency is a primary outcome measure, the prevalence of other symptoms like abdominal pain, diarrhea, and incontinence needs to be included in any global outcome assessment. The KESS scores not only assess bowel frequency but also evaluates associated symptoms like pain and bloating. While there were no specific questions regarding incontinence or diarrhea, our study-specific questionnaire had items pertaining to bulking and antidiarrheal agents, which are reasonable markers for incontinence and loose stools. Since the majority of our patients did not require any medications, either to hasten or slow gastrointestinal function, the incidence of these symptoms, we believe, was likely low.

We used the SF-12 and the IBS-QOL health survey instruments to assess QOL outcomes. The SF-12 is a generic health survey instrument which is based on the SF-36, one of the most widely used QOL instruments. Several studies have used the SF-36 to assess QOL after gastrointestinal surgery and has found it to be a reliable method of assessing QOL.[10,35,36] Although the SF-12 has been modified from the SF-36 in order to reduce the number of items and decrease the burden on the respondents, it maintains the psychometric properties of the SF-36 and is a good predictor of the original summary scores.[19]

We are not aware of any validated disease-specific instruments that assess QOL in slow transit constipation patients before or after surgery. Fitzharris et al.[5] used the Gastrointestinal Quality of Life Index (GIQLI) to assess QOL in their surgical cohort of patients with slow transit constipation. Although the GIQLI is a validated QOL instrument, it contains QOL questions that are related to upper and lower gastrointestinal symptoms. The IBS-QOL was designed for patients with irritable bowel syndrome, and because a significant proportion of patients with slow transit constipation also have symptoms such as abdominal pain, nausea, and bloating that are similar to IBS, we believe it to be a suitable instrument for assessing bowel function related QOL. It also has been previously used to assess QOL in patients who have undergone colon surgery.[25,37] Further studies are required to validate these findings and identify a better method of assessing disease-specific QOL in these patients.

A subgroup of patients with slow transit constipation has associated pelvic floor dysfunction, the incidence of which is between 15% and 50%.[38] There is much debate regarding the optimal treatment strategy for these patients, because surgery results in almost uniformly poor functional outcomes.[34,38] In our practice, these patients undergo successful biofeedback training prior to being considered for surgery. Our long-term functional and QOL data support this approach as there was no difference in the outcomes of patients who had slow transit constipation alone or in combination with pelvic floor

dysfunction. Bernini and colleagues[38] have reported that of the16 patients with colonic inertia and nonrelaxing pelvic floor diagnosed on physiologic testing and who underwent preoperative biofeedback, six patients still complained of incomplete evacuation that was severe in two and unresponsive to postoperative biofeedback. Differences in patient selection, duration of follow-up, diagnostic criteria, and outcomes measured could account for this discrepancy in results. We disagree with Lubowski and colleagues,[31] who do not advocate treating patients with pelvic floor function preoperatively with biofeedback; not addressing pelvic floor dysfunction preoperatively may compromise the postoperative functional outcomes of IRA for STC.

One potential limitation of our study was the 57% response rate of patients to validated functional and QOL questionnaires. In order to minimize the chance of a response bias, we compared the demographics and prospectively collected annual functional outcomes of responders and nonresponders; importantly no differences were found. Although not eliminating the possibility that a response bias was present, such an approach minimizes such an outcome.

In conclusion, IRA for STC in patients selected for surgery based on objective preoperative physiologic testing results in excellent long-term outcomes with a high degree of patient satisfaction. Functional results as measured by the KESS score and IBS-QOL documented improved patient outcomes following surgery and SF-12 scores documented that after IRA for STC, patients had a quality of life indistinguishable from the normal population.

The authors would like to thank Mr. Charles Knowles, Senior Lecturer and Honorary Consultant Surgeon, Dr. Mark Scott, Senior Clinical Scientist, and Mr. Peter Lunniss, Senior Lecturer and Honorary Consultant Surgeon, Centre for Academic Surgery, The Royal London Hospital, Whitechapel, London, United Kingdom, for allowing the use of the Knowles-Eccerslley-Scott Symptom (KESS) Questionnaire and its values.

REFERENCES

1. Piccirillo MF, Reissman P, Wexner SD. Colectomy as treatment for constipation in selected patients. Br J Surg 1995;82: 898–901.
2. Pemberton JH, Rath DM, Ilstrup DM. Evaluation and surgical treatment of severe chronic constipation. Ann Surg 1991; 214:403–411; discussion 411–413.
3. Nyam DC, Pemberton JH, Ilstrup DM, Rath DM. Long-term results of surgery for chronic constipation. Dis Colon Rectum 1997;40:273–279.
4. Christiansen J, Rasmussen OO. Colectomy for severe slow-transit constipation in strictly selected patients. Scand J Gastroenterol 1996;31:770–773.
5. FitzHarris GP, Garcia-Aguilar J, Parker SC, et al. Quality of life after subtotal colectomy for slow-transit constipation: both quality and quantity count. [see comment]. Dis Colon Rectum 2003;46:433–440.
6. Hutson JM, Wheatley J, Uemura S, Hurley M. A long-term follow-up of patients undergoing colectomy for chronic idiopathic constipation. Austral N Z J Surg 1997;67:136, author reply 137.
7. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. Ann Surg 1999;230:627–638.
8. Verne GN, Hocking MP, Davis RH, et al. Long-term response to subtotal colectomy in colonic inertia. J GASTROINTEST SURG 2002;6:738–744.
9. Webster C, Dayton M. Results after colectomy for colonic inertia: a sixteen-year experience. Am J Surg 2001;182:639–644.
10. Hassan I, Chua HK, Wolff BG, et al. Quality of life after ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum 2005;48:2032–2037.
11. Sprangers MAG. Quality of life assessment in oncology. Acta Oncol 2002;41:229–237.
12. Frost MH, Sloan JA. Quality of life measurements: A soft outcome—Or is it? Am J Manage Care 2002;8(18 Suppl): S574–S579.
13. Ren XS, Kazis L, Lee A, et al. Comparing generic and disease-specific measures of physical and role functioning: Results from the Veterans Health Study. Med Care 1998;36: 155–166.
14. Wiklund IK, Glise H. Quality of life in different gastrointestinal conditions. Eur J Surg 1998;(Suppl 582):56–61.
15. Metcalf AM, Phillips SF, Zinsmeister AR, et al. Simplified assessment of segmental colonic transit. Gastroenterology 1987;92:40–47.
16. Stivland T, Camilleri M, Vassallo M, et al. Scintigraphic measurement of regional gut transit in idiopathic constipation. Gastroenterology 1991;101:107–115.
17. Ware JE Jr, Kolinski M, Keller SD. How to score the SF-12 physical and mental health summeries: A user's manual. Boston: The Health Institute, New England Medical Center, Boston, MA, 1995.
18. Ware JE Jr, Kosinski M, Keller SD. SF-12: How to score the SF-12 physical and mental health summary scales, 3rd ed. Lincoln: QualityMetric Incorporated, 1998.
19. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.
20. Ware JE Jr. SF-36 health survey update. Spine 2000;25: 3130–3139.
21. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51:1171–1178.
22. Knowles CH, Eccersley AJ, Scott SM, et al. Linear discriminant analysis of symptoms in patients with chronic constipation: Validation of a new scoring system (KESS). Dis Colon Rectum 2000;43:1419–1426.
23. Knowles CH, Scott SM, Legg PE, et al. Level of classification performance of KESS (symptom scoring system for constipation) validated in a prospective series of 105 patients. Dis Colon Rectum 2002;45:842–843.

24. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: A disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999–1007.
25. You NY, Chua HK, Nelson H, et al. Ileosigmoid anastomosis provides superior functional outcomes than ileorectal anastomosis after subtotal colectomy. Colorectal Dis 2005;7(S1).
26. Roe AM, Bartolo DC, Mortensen NJ. Diagnosis and surgical management of intractable constipation. Br J Surg 1986;73: 854–861.
27. Yoshioka K, Keighley MR. Clinical results of colectomy for severe constipation. Br J Surg 1989;76:600–604.
28. Leon SH, Krishnamurthy S, Schuffler MD. Subtotal colectomy for severe idiopathic constipation. A follow-up study of 13 patients. Dig Dis Sci 1987;32:1249–1254.
29. Vasilevsky CA, Nemer FD, Balcos EG, et al. Is subtotal colectomy a viable option in the management of chronic constipation? Dis Colon Rectum 1988;31:679–681.
30. Pikarsky AJ, Singh JJ, Weiss EG, et al. Long-term follow-up of patients undergoing colectomy for colonic inertia. Dis Colon Rectum 2001;44:179–183.
31. Lubowski DZ, Chen FC, Kennedy ML, King DW. Results of colectomy for severe slow transit constipation. Dis Colon Rectum 1996;39:23–29.
32. Pluta H, Bowes KL, Jewell LD. Long-term results of total abdominal colectomy for chronic idiopathic constipation. Value of preoperative assessment. Dis Colon Rectum 1996; 39:160–166.
33. Kamm MA, Hawley PR, Lennard-Jones JE. Outcome of colectomy for severe idiopathic constipation. Gut 1988;29: 969–973.
34. Mollen RM, Kuijpers HC, Claassen AT. Colectomy for slow-transit constipation: preoperative functional evaluation is important but not a guarantee for a successful outcome. Dis Colon Rectum 2001;44:577–580.
35. Ko CY, Rusin LC, Schoetz DJ Jr, et al. Does better functional result equate with better quality of life? Implications for surgical treatment in familial adenomatous polyposis. Dis Colon Rectum 2000;43:829–835; discussion 835–837.
36. Ko CY, Rusin LC, Schoetz DJ Jr, et al. Long-term outcomes of the ileal pouch anal anastomosis: The association of bowel function and quality of life 5 years after surgery. J Surg Res 2001;98:102–107.
37. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol 2005;100:93–101.
38. Bernini A, Madoff RD, Lowry AC, et al. Should patients with combined colonic inertia and nonrelaxing pelvic floor undergo subtotal colectomy? Dis Colon Rectum 1998;41: 1363–1366.

Discussion

Scott A. Strong, M.D. (Cleveland, OH): I would like to congratulate Dr. Hassan, Dr. Pemberton, and their colleagues for this very interesting study that has long been due on this cohort of very difficult to manage patients. What they have been able to show is that with appropriately selected patients, a colectomy with ileorectal anastomosis provides both a durable long-term improvement in functional results as well as an acceptable quality of life. There are a few questions or items I wish to have elaborated on based on both the presentation and review of the manuscript that I appreciated receiving.

The first is obviously selecting the right patient cohort. You only operated on 3% of those patients who were evaluated for constipation, and I would like you to comment specifically on the role of excluding whole gut dysmotility. Are you still using only scintigraphy at this point, or do you still use some type of transit marker study with an evaluation of the more proximal bowel? Second, do you use any type of psychological testing in these patients preoperatively?

Regarding the outcome, my experience is that those patients who have a component of pelvic floor dysfunction with their slow transit constipation will occasionally relapse back into difficulties with pelvic floor dysfunction and require retraining with repeat biofeedback following their operation at varying time intervals.

Lastly, what was indicated from the manuscript is that you have very good follow-up in this cohort of patients with these annual mailings regarding their bowel function and other items. However, this 57% response rate of this particular study seems like it is quite disparate from that, and I wonder if you could speculate on the reason for that disparity and perhaps how that may have impacted the results.

Thank you.

Imran Hassan, M.D. (Rochester, Minn): Thank you, Dr. Strong. for your insightful comments and questions. Regarding the evaluation of patients with chronic constipation, they undergo a medical workup including a history, physical examination and laboratory investigations, a colonic evaluation with either a barium enema or a colonoscopy, and transit studies with either Sitz markers or scintigraphy. They also undergo pelvic floor evaluation that usually includes anorectal manometry and ballon expulsion tests.

Based upon these tests, patients are divided into four categories. Patients in whom both these tests are normal fall in the category of constipation predominant irritable bowel syndrome and are the majority of these patients. The second group is the group of patients who have pelvic floor dysfunction but have normal colonic transit studies; these patients undergo biofeedback and pelvic floor retraining and don't benefit from surgery. The last

two groups include patients with slow transit constipation with or without pelvic floor dysfunction. Patients with slow transit constipation undergo surgery, while patients with pelvic floor dysfunction undergo pelvic floor retraining followed by surgery.

Regarding the possibility of whole gut dusmotlity, that is certainly a concern. Dr. Michael Camelleri from our institution a few years back showed that because of colonic dysomtility, the small bowel and the stomach slow down because the colon acts as a physiologic brake; therefore if we take care of the colon, the motility in the small bowel and the stomach eventually normalize. That at least has been our experience, although there probably is a small subset of patients with actual whole gut dysmotility who probably won't benefit from surgery. If there is any question of that, one can do a temporary loop ileostomy and see if the patient's symptoms significantly improve. Depending on the extent of symptomatic improvement one can decide to take out the colon or not.

The issue of psychologic testing is valid and relevant; definitely the group from Minneapolis has shown that a significant number of patients have significant psychiatric disorders. We did not specifically look into this, but it is certainly something that needs to be kept in the back if the mind, as there may be psychiatric issues that need to be addressed prior to surgery.

Regarding the question about relapse of pelvic floor dysfunction after surgery, this can certainly happen. I don't have the exact number, but about 10% to 20% of the patients do so and redevelop pelvic floor dysfunction. However, if these patients undergo pelvic floor retraining again, their function improves and can return to baseline.

The last question is about the response rate. This is something that everybody who does survey research has had to deal with in recent years. In our experience, some of it is due to HIPAA regulations and some of it is the tertiary referral nature of our practice with patients coming from all over the country, making reliable follow-up difficult; furthermore, this is a young group of patients who at their stage of life tend to move because of personal and/or professional reasons.

Regarding why there was a difference in the response rates to the study questionnaires compared to the annual questionnaire, I think some patients may have initially replied to the annual questionnaires for a few years but did not continue to do so in the long run and therefore may not have answered the study questionnaires that were mailed after a median follow-up of about 120 months. In order to minimize a potential response bias, we compared the available data on responders and nonresponders and were unable to find any significant differences. While this does not necessarily exclude a response bias, it hopefully minimized it.

The other issue is that of patient burden. We tried to minimize the number of questions, yet there were about 50 questions we had to ask. The annual questionnaire has only about five or 10 questions. So it is a balance of what we need to know; and what is nice to know.

Janice F. Rafferty, M.J. (Cincinnati, Ohio): Were any of your patients operated on laparoscopically during that time period, and if so, did it affect their quality of life questionnaires that they completed?

Dr. Hassan: Toward the end, from about 1998 onward, about 80% of them had laparoscopic colectomics. We didn't do a subset analysis because we started getting smaller numbers. Like the previous presentation showed, patient-related outcomes in the long term for laparoscopic and open surgery become equal. I am sure if we tortured the data hard enough we would probably get it to show a difference, but I wasn't very keen on doing that.

A Margin-Negative R0 Resection Accomplished With Minimal Postoperative Complications Is the Surgeon's Contribution to Long-Term Survival in Pancreatic Cancer

Thomas J. Howard, M.D., Joseph E. Krug, M.D., Jian Yu, M.S., Nick J. Zyromski, M.D., C. Max Schmidt, M.D., Lewis E. Jacobson, M.D., James A. Madura, M.D., Eric A. Wiebke, M.D., Keith D. Lillemoe, M.D.

Pancreatic cancer has a poor prognosis with complete surgical resection being the only therapy to offer a realistic chance for long-term survival. The aim of this study is to identify surgery-related variables that influence long-term survival. Between 1990 and 2002, 226 consecutive patients (mean age of 64 ± 11 years) had resection for pancreatic adenocarcinoma. Prognostic variables in these patients were analyzed using univariate and multivariate analysis. Two hundred four patients (90%) had pancreaticoduodenectomy, 13 patients (6%) had distal pancreatectomy, and 9 patients (4%) had a TP. Stage I disease was present in 50 (22%), stage II disease in 170 (75%), and stage III disease in 6 (3%). R0 resections were achieved in 70%. Operative morbidity was 36% and 30-day mortality was 6%. Actual 1-year, 3-year, and 5-year survival rates were 49% (n = 111), 14% (n = 31), and 4% (n = 9). Using multivariate analysis: tumor size, tumor differentiation, obtaining an R0 resection, and lack of postoperative complications were variables associated with long-term survival. Long-term survival in patients with pancreatic cancer after resection remains poor. Achieving a margin negative resection (R0) with no postoperative complications are prognostic variables that can be affected by the surgeon. (J GASTROINTEST SURG 2006;10:1338–1346)

KEY WORDS: Pancreatic adenocarcinoma, pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy, R0 resection, postoperative complications, long-term survival

Pancreatic cancer is lethal and is currently the fourth leading cause of cancer death in the United States with an overall 5-year survival rate of less than 5%.[1] Long-term survival in patients with pancreatic cancer occurs only in patients who can have their tumor completely resected and is influenced by prognostic factors that can be broadly classified as either: tumor-related (TMN stage classification, tumor differentiation), surgery-related (resection margin, blood loss), or treatment-related (systemic disease treatment with adjuvant, neoadjuvant therapy).[2,3] Over the past 20 years, the literature has documented a dramatic decrease in the postoperative morbidity and mortality rates associated with pancreatic resections.[4] Curiously, despite more patients having their tumors safely resected, evidence documenting a corresponding increase in long-term survival rates in patients with pancreatic cancer has been lacking.[5] What are the reasons for this discrepancy? If long-term survival is entirely dependent on tumor stage or differentiation (tumor-related), then improvements in survival will require a breakthrough in achieving an earlier clinical diagnosis of this disease.[6] If survival is predominantly predicated by the presence of occult systemic disease at the time of diagnosis (treatment-related), then progress in long-term survival will require improvements in chemotherapeutic agents or identification of specific molecular tumor targets that can be utilized in adjuvant or neoadjuvant treatment strategies.[7] While progress in methods of early diagnosis and identification of targets for adjuvant therapy are advancing, these developments are slow. Of immediate interest to surgeons is whether any factors related to the performance of a standard pancreatic operation can be manipulated to improve long-term survival.

From the Pancreas Research Group, Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana.
Reprint requests: Thomas J. Howard, M.D., Route 130, 535 Barnhill Drive, Indianapolis, IN 46202. e-mail: tjhoward@iupui.edu

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.008

The aim of this study is to identify independent prognostic variables that influence *actual* long-term (3- and 5-year) survivors in a large, consecutive series of patients from a single institution undergoing resection of pancreatic adenocarcinoma.

METHODS

Between 1990 and 2002, 226 consecutive patients (125 men and 101 women with a mean age of 64 ± 11 years) had operation for histologically confirmed pancreatic adenocarcinoma and were included in a clinical database for review. Cystadenocarcinomas, intraductal papillary mucinous carcinoma, adenosquamous carcinoma, acinar cell carcinoma, undifferentiated carcinoma, islet cell carcinoma, distal bile duct adenocarcinoma, and ampullary adenocarcinomas were excluded from study. Patients underwent a standard preoperative evaluation including contrast-enhanced abdominal computed tomography (CT) (1990–2002); endoscopic ultrasound with fine needle aspiration (FNA) cytology was introduced and used extensively later in the study (1992–2002). Patients with obstructive jaundice and abnormal liver function tests generally underwent preoperative endoscopic biliary stenting. Resectable disease was suggested by cross-sectional imaging and EUS and confirmed at the time of laparotomy. Resection was performed in the absence of liver metastases, carcinomatosis, invasion of the transverse mesocolon, involvement of the superior mesenteric artery or hepatic artery. Retroperitoneal tumor infiltration into the celiac axis or extensive vascular infiltration of the superior mesenteric–portal venous confluence was also considered unresectable disease. Limited involvement of the superior mesenteric–portal vein confluence was not considered a contraindication to resection with curative intent if the surgeon deemed that venous resection and reconstruction could be accomplished while obtaining a margin negative (R0) resection.[8] Operations used in this series consisted of: pancreaticoduodenectomy (PD) (N = 204; pylorus-preserving PD, n = 116 [57%], standard PD, n = 88 [43%]), distal pancreatectomy with splenectomy (DPS) (n = 13), and total pancreatectomy (TP) (n = 9). The specific operations carried out in each patient depended on the anatomic location of the tumor and the goal of achieving negative surgical margins. All operations were performed at Indiana University Medical Center by one of six experienced gastrointestinal surgeons. Thirteen patients (6%) who had PD in this series had concomitant portal–mesenteric venous resection and reconstruction. All operations in this series included only a standard lymphadenectomy as defined by Pedrazzoli et al.[9]

Pancreatic adenocarcinoma was staged following the methods of the American Joint Committee on Cancer.[10] Resected specimens were evaluated for tumor size, histologic grade, lymph node involvement, resection margin, capsule invasion, perineural invasion, or vascular invasion. An R0 resection was defined as no tumor identified on microscopic examination of inked, paraffin-embedded, hematoxylin and eosin–stained margins when reviewed by the surgical pathologist. Bile duct margins, duodenal margins, pancreatic neck margins, and retroperitoneal soft tissue margins were routinely examined. A positive (R1) resection margin in this study was defined as the detection of tumor at the inked margin under microscopic examination. An R2 resection was defined as the surgeon cutting across macroscopically visible tumor which remained at the operative site. All long-term survivors (n = 31) had their pathology independently reviewed by a dedicated gastrointestinal pathologist blinded to the original diagnosis.

Patient charts were retrospectively reviewed, and the following data were collected. Demographic data included patient age, gender, and race. Tumor-related variables included tumor size, location, histologic grade, lymph node involvement, microvascular invasion, and perineural invasion. Surgery-related variables included type of operation, surgeon, length of operation, intraoperative blood loss, blood volume transfused, surgical margin status, hospital length of stay, major postoperative morbidity, and postoperative mortality. Major postoperative complications (morbidity) were defined as pancreatic fistula (>30 ml of amylase-rich fluid [>3× upper limit of normal for serum] out of an operatively placed drain ⩾7 days after operation); intraabdominal abscess (loculated fluid collection with enhancing rim on contrast-enhanced CT scan associated with fever or leukocytosis and culturing bacteria on drainage); postoperative hemorrhage (requirement of more than 4 units of packed red blood cells postoperatively or need to return to the operating room for control of bleeding); reoperation (return to the operating room in the postoperative period [30 days] for an abdominal procedure); pneumonia (fever, leukocytosis, and infiltrate on chest x-ray; acute myocardial infarction (ECG changes and elevation of cardiac enzymes); pulmonary embolism (hypoxemia and defect identified on ventilation-perfusion scan or helical CT scanning of the chest); and sepsis (fever, leukocytosis, and need for systemic antibiotics). Postoperative mortality was defined as death within 30 days of surgery. Treatment-related

variables included the use of adjuvant chemotherapy, chemoradiotherapy, or no adjuvant treatment. Time of last clinical follow-up was recorded using hospital records, outpatient records, or information from the patient's family physician. The Social Security database was used for the exact date of death, if it could not be known precisely by review of the medical record.

All data analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC). The Pearson χ^2 or Fisher's exact test was used as appropriate to compare categorical variables. The Wilcoxon rank-sum test was used to compare the median values of continuous data. Overall survival is reported as actual survival. Kaplan-Meier survival curves were used for univariate and multivariate analysis. Patients who died within 30 days of their surgery were included as postoperative deaths. Variables with a value of $P < 0.10$ identified by univariate analysis were entered into the Cox proportional hazard regression model to determine the effects of multiple factors on long-term survival.[11] A two-tailed P-value of <0.05 was considered statistically significant. This study was carried out following approval and under the regulations set forth by the Institutional Review Board (IRB) at Indiana University Purdue University at Indianapolis (IUPUI) and the Indiana University School of Medicine (Study Number 0503-75).

RESULTS

Demographic data, surgical procedures, postoperative morbidity and mortality rates, and actual 1-, 3-, and 5-year survival rates for the entire cohort of 226 patients are given in Table 1. Stage I disease was present in 50 patients (22%), stage II disease in 170 patients (75%), and stage III disease in 6 patients (3%). Tumors were located overwhelmingly (94%) in the pancreatic head resulting in the vast majority of resections being either PD (90%) or TP (4%). The mean hospital stay for the entire cohort of patients was 11 days: there was a 38% incidence of major postoperative morbidity and a 6% 30-day postoperative mortality. Actual 1-year, 3-year, and 5-year survival rates were: 49% (n = 111), 14% (n = 31), and 4% (n = 9), respectively. For purposes of the remaining analysis, we defined long-term survival in this study as patients who lived 3 or more years.

Tumor-related variables and their relationship to long-term survival are shown in Table 2. Long-term survivors were younger (60 ± 11 versus 65 ± 10 years, $P = 0.04$) and had significantly smaller tumors (2.2 ± 1.2 versus 2.8 ± 1.4 cm, $P = 0.01$) that histologically were found to have better differentiation ($P = 0.0002$). Stage, nodal involvement, or microscopic evidence of perineural or perivascular invasion was not significantly different between groups. Surgery-related variables are given in Table 3. Only the extent of resection, with long-term survivors having more R0 resections, was significantly different between groups ($P = 0.03$). Complete data on the use of adjuvant therapy were available in only 158 (70%) of the 226 patients. Of the 53 patients who received adjuvant chemoradiotherapy, 50 (94%) received combined external-beam radiation therapy (4500–5400 cGy) with systemic 5-fluorouracil (5-FU), while 3 patients (6%) received combined external-beam radiation therapy and gemcitabine (Gemzar). Given this limited data set, we identified no significant differences between short- and long-term survivors and the use of adjuvant therapy. When examining the differences between the three operative procedures used in this series: PD, TP, and DPS, a significantly higher percentage of women were in the DPS group compared to patients who had either PD or TP ($P = 0.003$). While DPS took significantly less time than either PD (218 versus 323 minutes) or TP (218 versus 387 minutes) ($P = 0.009$), more tumors in this group were poorly differentiated ($P = 0.02$), and a margin-negative R0 resection was achieved with this operation only 31% of the time ($P = 0.006$).

Table 1. Demographic and overall clinical characteristics to all 226 patients with pancreatic adenocarcinoma who had pancreatic resection between 1990 and 2002

Characteristic	All pancreatic resections (N = 226)
Age (mean ± SD yr)	64 ± 11
Gender male, n (%)	125 (55%)
AJCC tumor stage, n	
I	50 (22%)
II	170 (75%)
III	6 (3%)
Procedure, n	
Whipple	204 (90%)
Distal pancreatectomy	13 (6%)
Total pancreatectomy	9 (4%)
Median hospital stay (days)	11
Postoperative morbidity, n	82 (36%)
Postoperative mortality, n	14 (6%)
Actual 1-yr survival, n	111 (49%)
Actual 3-yr survival, n	31 (14%)
Actual 5-yr survival, n	9 (4%)

Table 2. Patient-tumor-related prognostic factors in long-term (≥3 years) survivors (n = 31) versus those who did not survive for 3 years (n = 195)

		Long-term survivors (>3 yr)		
Factor	**All resections (n = 226)**	**Yes (n = 31)**	**No (n = 195)**	***P*-value**
Age (mean ± SD yr)	64 ± 11	60 ± 11	65 ± 10	0.04
Gender male (n)	125 (55%)	17 (55%)	108 (55%)	0.95
Race				
Tumor size (cm)	2.7 ± 1.4	2.2 ± 1.2	2.8 ± 1.4	0.01
Differentiation, n				0.0002
Poor	91 (40%)	4 (13%)	87 (45%)	
Moderate	113 (50%)	19 (61%)	94 (48%)	
Well	22 (10%)	8 (26%)	14 (7%)	
AJCC tumor stage, n				0.29
I	50 (22%)	10 (32%)	40 (21%)	
II	170 (75%)	21 (68%)	149 (76%)	
III	6 (3%)	0 (0%)	6 (3%)	
Lymph nodes positive, n	126 (56%)	13 (42%)	113 (58%)	0.09
Perineural invasion, n	116 (51%)	14 (45%)	102 (52%)	0.46
Vascular invasion, n	63 (28%)	8 (26%)	55 (28%)	0.78
Peripancreatic invasion, n	145 (64%)	18 (58%)	127 (65%)	0.45
Median survival, mo	13	50	11	<0.0001

The effects of a surgeon's experience with PD and its impact on surgery-related variables were analyzed. The six surgeons were stratified into those who did less than 5 PDs per year (three surgeons), 5–20 PDs per year (one surgeon), and greater than 20 PDs per year (two surgeons). Operative times were significantly less ($P < 0.0001$) and venous resection and reconstruction was used more by the higher-volume surgeons. No differences were noted in extent of resection (R0 versus R1 versus R2), median postoperative length of stay, postoperative morbidity, or postoperative mortality rates. Median patient survival was significantly longer (28 months) in the intermediate-volume surgeons when compared either the low-volume (13 months) or high-volume (13 months) surgeons ($P = 0.04$).

A comparison of two different time periods during this analysis (1990–1998 versus 1999–2002) was

Table 3. Surgery-related prognostic factors in long-term (≥3 years) survivors (n = 31) versus those who did not survive for 3 years (n = 195)

		Long-term survivors (>3 yr)		
Factor	**All resections (n = 226)**	**Yes (n = 31)**	**No (n = 195)**	***P*-value**
Procedure, n				0.30
Whipple	204 (90%)	26 (84%)	178 (91%)	
Total pancreatectomy	9 (4%)	2 (6%)	7 (4%)	
Distal pancreatectomy	13 (6%)	3 (10%)	10 (5%)	
Operative time, min	320 ± 122	319 ±113	320 ± 124	0.90
Median blood loss, ml	1200	1200	1300	0.63
Median transfusion, ml	750	500	750	0.85
Venous resection, n	13 (6%)	1 (3%)	12 (6%)	1.00
Extent of resection, n				0.03
R0	158 (70%)	27 (87%)	131 (67%)	
R1	63 (28%)	4 (13%)	59 (30%)	
R2	5 (2%)	0 (0%)	5 (3%)	
Postoperative morbidity, n	82 (36%)	7 (22%)	75 (38%)	0.09
Median hospital stay, days	11	10	11	0.17
Hospital readmission, n	52 (23%)	4 (13%)	48 (25%)	0.15

Table 4. Significant risk factors affecting long-term survival after resection for pancreatic adenocarcinoma using the Cox proportional hazards model (N = 212)

Variable	Subgroup	Hazard ratio	*P*-value
Tumor size (cm)	<3, ⩾3	1.38 (1.02, 1.87)	0.03
Tumor differentiation	Poor, moderate, well	0.76 (0.60, 0.95)	0.02
R0 resection	Yes, no	1.39 (1.02, 1.90)	0.03
Postoperative complication	Yes, no	0.68 (0.51, 0.91)	0.009

done to identify any differences in patient characteristics or changes in the surgical technique or perioperative care over time. In the more recent time interval, operations were shorter (290 versus 347 minutes, $P = 0.003$) and were carried out on older patients (66 versus 63 years, $P = 0.02$) who had larger tumors (2.9 ± 1.3 versus 2.5 ± 1.4 cm, $P = 0.003$), and patients spent less time postoperatively in the hospital (median LOS 10 versus 12 days, $P = 0.02$). Extent of resection, histopathologic variables, tumor stage, and postoperative morbidity and mortality rates did not change significantly over these two periods of observation.

Results of a univariate analysis of potential risk factors affecting long-term survival showed that tumor size (<3 cm versus ⩾3 cm), tumor differentiation (poor, moderate, well), lymph node involvement (Y, N), tumor stage (I, II, III), achieving an R0 resection, and lack of postoperative complications were significantly associated with long-term survival. Using a Cox proportional hazards model; tumor size (HR [hazard ratio] = 1.38, $P = 0.03$), tumor differentiation (HR = 0.76, $P = 0.02$), R0 resection (HR = 1.39, $P = 0.003$), and lack of major postoperative complications (HR = 0.68, $P = 0.009$) were identified as factors that were independently associated with long-term survival (Table 4).

DISCUSSION

Tremendous advances in preoperative imaging, anesthetic management, surgical technique, and perioperative care have markedly reduced postoperative morbidity and mortality rates in patients undergoing pancreatic resections for pancreatic cancer.[2,4,12] Skillful tumor removal does not, however, equate to long-term survival as the vast majority of patients, even those who have margin-negative R0 resections, eventually die from recurrent disease.[13–15] Surgeons, in seeking to improve these results for long-term survival, have adopted techniques such as extended lymph node dissections (ELNDs)[16,17] and complex vascular reconstructions.[8,17] Although carried out with only modest increases in postoperative morbidity, the application of these techniques has failed to improve long-term survival. It can be argued, based the presence of metastatic disease in small "early" pancreatic tumors,[18] patterns and timing of tumor recurrence after resection,[19,20] incidence of micrometastatic disease,[21] and autopsy data on the modes of pancreatic cancer spread,[22] that operations beyond obtaining a simple, margin-negative (R0) resection are superfluous.

Evidence has been accumulating to suggest that both perioperative outcomes[23,24] and long-term survival following pancreatic cancer surgery[25] are associated with the volume of these procedures performed in individual hospitals. The majority of this work has been based on large, administrative databases[23–25] with the best studies controlling for patient and provider characteristics.[24] We investigated this association in our relatively small sample size where all procedures were done at the same high-volume institution by board-certified, experienced gastrointestinal surgeons. Outside of a significantly decreased operative time ($P < 0.001$) and a higher percentage of venous resection in the high-volume surgeon group; blood loss, transfusion requirements, extent of resection, perioperative morbidity, perioperative mortality, and median hospital stay were similar between groups. Of considerable interest is our observation that the intermediate volume surgeon group (5–20 PDs per year) had a significantly better median survival time for their patients. Rather than illuminating any specific skill set or characteristics necessary to decipher the volume/outcome association, these data emphasize the complexities associated with tumor heterogeneity, patient selection, and surgical judgment and skill.

In our analysis using multivariate regression, tumor-related variables including tumor size (HR = 1.38, $P = 0.03$) and tumor differentiation (HR = 0.76, $P = 0.02$) were identified as covariates affecting long-term survival. These observations confirm those reported by others.[2,3,12,26] Other covariates affecting long-term survival included achieving a margin negative R0 resection (HR = 1.39, $P = 0.03$) and completing the operation without a major postoperative complication (HR = 0.68, $P = 0.009$), factors that can be significantly

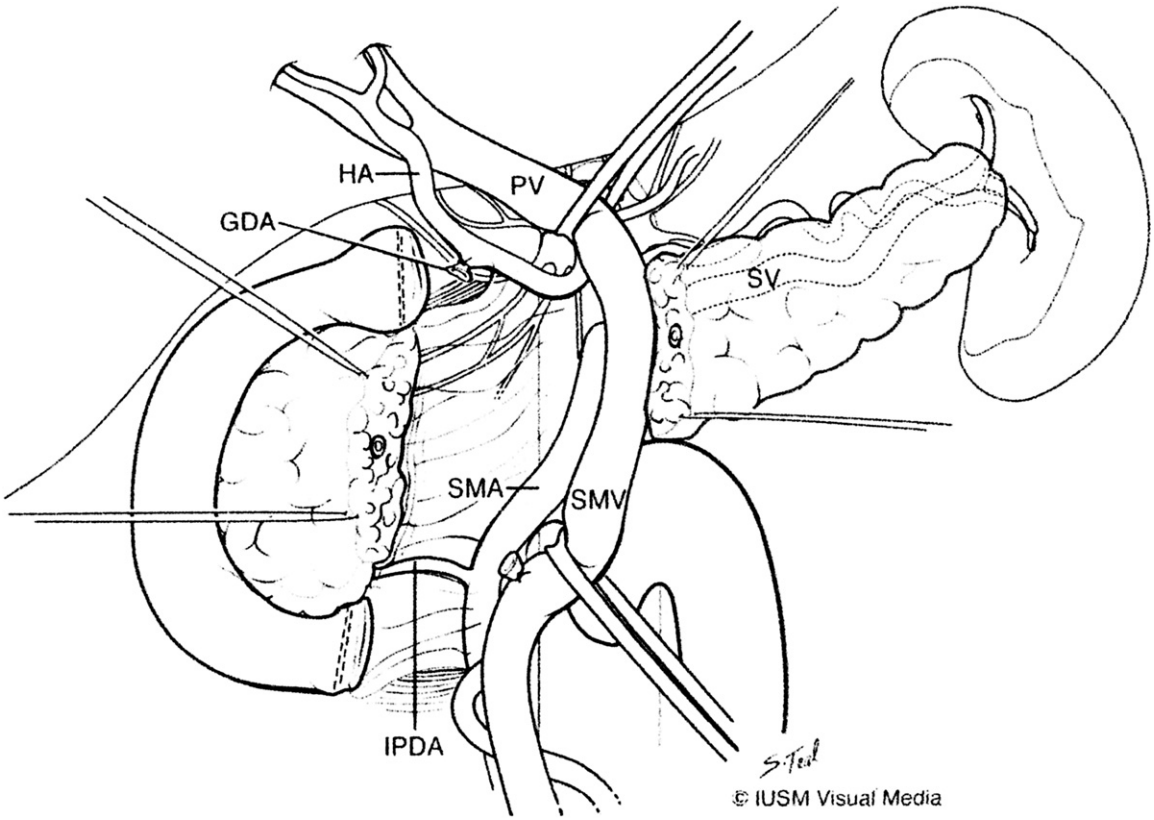


Fig. 1. Technique of retroperitoneal soft tissue dissection emphasizing lateral retraction of the superior mesenteric vein (SMV) portal vein (PV) confluence using vessel loops to ensure a dissection plane of the right lateral aspect of the superior mesenteric artery (SMA). HA = hepatic artery, GDA = gastroduodenal artery, IPDA = inferior pancreaticoduodenal artery, SV = splenic vein.

impacted by surgeons. Achieving a margin-negative (R0) resection in pancreatic adenocarcinoma has been emphasized by others,[3,12] and its importance was highlighted when it was found to be the most powerful independent predictor of long-term survival in 366 consecutive patients with resected pancreatic carcinoma.[2] In this study, the retroperitoneal soft tissue margin was positive in 35 patients (56%), the pancreatic neck margin was positive in 16 patients (25%), and the bile duct margin was positive in 12 patients (19%). Despite this strong correlation with long-term survival, the specific technical aspects of the retroperitoneal soft tissue dissection and the proper pathologic handling and analysis of the retroperitoneal resection margin for accurate, reproducible staging have been emphasized by only a few.[27,28] We would emphasize the importance of complete mobilization of entire superior mesenteric–portal venous confluence from the uncinate process of the pancreas inferiorly by carefully isolating and dividing the one or two uncinate venous branches from the first jejunal branch or, in certain circumstances, sacrifice of the first jejunal branch in order to obtain this mobilization. The entire superior mesenteric–portal venous confluence, using a vein retractor of soft vessel loops, is then retracted laterally toward the left side of the patient to allow exposure of the soft tissue and inferior pancreaticoduodenal artery outside the adventitia of the superior mesenteric artery where the nerves that originate in the superior mesenteric plexus run to the inferior aspect of the pancreas[28,29] (Fig. 1). Similarly, the superior aspect of the retroperitoneal soft tissue dissection should include resection of the posterior hepatic plexus off the celiac ganglion and common hepatic artery plexus.[29]

Our long-term survival data is indeed sobering with actual 1-year survival of 49%, 3-year survival of 14%, and 5-year survival of 4% (n = 9). It must be emphasized that these data are reported as *actual* survival rather than *actuarial* survival using the method of Kaplan-Meier and include postoperative mortality in the long-term survival calculations. Actuarial survival is a calculated number based on projected curves derived to express the rate of mortality per unit time over the course of anticipated

follow-up.[30] These extrapolations can be unduly influenced by a high percentage of patients with short clinical follow-up or a large number of censored observations.[31] While the majority of clinical studies are reported with actuarial survival, a review of 15 recent series representing 2075 resections for pancreatic adenocarcinoma revealed an actual 5-year survival rate of only 4% (2). These observations have been made by other authors reporting actual 5-year survival rates of 6.8%,[13] 10%,[14] and 4%,[15] respectively. We chose this time period (1990–2002) for analysis as it is a time period where our center was considered high volume for pancreatic surgery (>25 cases per year) and to ensure adequate clinical follow-up on long-term survivors. All 31 long-term survivors (≥3 years) reported in this series had their pathology independently reviewed and confirmed by a gastrointestinal pathologist who was blinded to the primary diagnosis, an important component of any long-term survival analysis in pancreatic carcinoma as has been emphasized by others.[30]

Unlike other papers on survival in pancreatic adenocarcinoma that focused solely on PD, this cohort is a consecutive series of resection for pancreatic adenocarcinoma and includes a small group of patients who had either DPS (n = 13, 6%) or TP (n = 9, 4%). Pancreatic adenocarcinoma involving the body and tail of the pancreas (DPS) or extensive and/or multifocal disease throughout the entire pancreas (TP) are tumors known to have an adverse effect on survival.[32,33] While operative time for DPS was significantly shorter than for either PD or TP, our ability to achieve a margin negative R0 resection was limited to only 31% in the DPS group and 67% in the TP group. In addition, a higher percentage of these tumors had characteristics (poorly differentiated, lymph node involvement, and advanced stage) that reflected their biologic aggressiveness. These findings are underscored by the fact that we had no 5-year survivors in either group. Numbers are small, but other groups have reported occasional long-term survival in selected patients with body and tail adenocarcinoma who have had complete surgical resections.[32] Whether anatomic resection techniques for distal pancreatectomy such as the radical antegrade modular pancreatosplenectomy will be able to improve on the margin-negative resection rate or have any influence on long-term survival remains to be seen.[34]

We are entering a phase in the surgical treatment of pancreatic carcinoma where recognition that micrometastatic disease occurs early in its clinical course is paramount.[35] Improvements in long-term survival will come only from adequate treatment of systemic disease.[36,37] The surgeon's role is currently to provide an adequate margin-negative R0 resection with a minimum of postoperative complications to remove macroscopic tumor burden and preserve the patient's physiologic function to ensure they are capable of receiving timely and appropriate adjuvant therapy.[38] Assuming this new clinical paradigm, our energies in the future should focus not on achieving more aggressive locoregional resections, but a commitment to enroll patients in multi-institutional clinical trials using novel adjuvant or neoadjuvant treatment strategies.

CONCLUSIONS

Long-term survival in patients with pancreatic cancer after resection remains poor. Achieving a margin-negative resection (R0) with a minimum of postoperative complications to remove the macroscopic tumor burden and preserve the patient's physiologic function to ensure they are capable of receiving timely, appropriate adjuvant therapy is the surgeon's contribution to long-term survival.

REFERENCES

1. Jemal A, Murray T, Ward E. 2005 Cancer statistics. CA Cancer J Clin 2005;55:10–30.
2. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adencarcinoma. Br J Surg 2004;94:586–594.
3. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of the pancreas. Br J Surg 1996;83:625–631.
4. Shäfer M, Müllhaupt B, Clavien PA. Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. Ann Surg 2002;236:137–148.
5. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999;189:1–7.
6. Manu M, Buckels J, Bramhall S. Molecular technology and pancreatic cancer. Br J Surg 2000;87:840–853.
7. Lockhart AC, Rothenberg ML, Berlin JD. Treatment for pancreatic cancer: Current therapy and continued progress. Gastroenterology 2005;128:1642–1654.
8. Howard TJ, Villanustre N, Moore SA, et al. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. J GASTROINTEST SURG 2003;7:1089–1095.
9. Pedrazzoli S, Beger HG, Obertop H, et al. A surgical and pathological based classification of resective treatment of pancreatic cancer: Summary of an international workshop on surgical procedures in pancreatic cancer. Dig Surg 1999;16:337–345.
10. Exocrine pancreas. In: Greene Fl, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M, eds. AJCC Cancer Staging Manuel, 6th edition. New York: Springer, 2002, pp 157–164.
11. Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187–220.

12. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas: 616 Patients: Results, outcomes, and prognostic indicators. J GASTROINTEST SURG 2000;4:567–579.
13. Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas: Is it really improving? Ann Surg 1995;221: 59–66.
14. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996;223:273–279.
15. Gudjonsson B. Carcinoma of the pancreas: Critical analysis of costs, results of resections, and the need for standardized reporting. J Am Coll Surg 1995;181:483–503.
16. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508–517.
17. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, Foster N, Sargent DJ. A prospective, randomized trial comparing standard pancreaticoduodenectomy with pancreaticoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618–628.
18. Tsuchiya R, Tomioka T, Izawa K, et al. Collective review of small carcinomas of the pancreas. Ann Surg 1986;2003: 77–81.
19. Westerdahl J, Andrén Sandberg Å, Ihse I. Recurrence of exocrine pancreatic cancer: Local or hepatic? Hepatogastroenterology 1993;40:384–387.
20. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. Word J Surg 1997;21:195–200.
21. Bogoeversuski D, Yuekebas EF, Schurr P, et al. Mode of spread in the early phase of lymphatic metastasis in pancreatic ductal adenocarinoma: Prognostic significance of nodal microinvolvement. Ann Surg 2004;240:993–1001.
22. Mao C, Domenico DR, Kim K, Hanson DJ, Howard JM. Observations on the developmental patterns and consequences of pancreatic exocrine adenocarinoma: findings of 154 autopsies. Arch Surg 1995;130:125–134.
23. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998;228:429–438.
24. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349: 2117–2127.
25. Fong Y, Gonen M, Rubin D, Radzymer M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. Ann Surg 2005;242:540–547.
26. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: A population-based, linked database analysis of 396 patients. Ann Surg 2003;237:74–85.
27. Warshaw AL, Thayer SP. Pancreaticoduodenectomy: How I do it. J GASTROINTEST SURG 2004;8:733–741.
28. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J GASTROINTEST SURG 2004;8:935–950.
29. Yi SQ, Miwa K, Ohta T, et al. Innervation of the pancreas from the persective of perineural invasion of pancreatic cancer. Pancreas 2003;27:225–229.
30. Tsiotos GG, Farnell MB, Sarr MG. Are the results of pancreatectomy for pancreatic cancer improving? World J Surg 1999;23:913–919.
31. Gudjonsson B. Survival statistics gone awry: Pancreatic cancer, a case in point. J Clin Gastoenterol 2002;35:180–184.
32. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarinoma of the body or tail of the pancreas justified? J GASTROINTEST SURG 2003;7: 946–952.
33. Baumel H, Huguier M, Manderscheid JC, Fabre JM, Houry S, Fagot H. Results of resection for cancer of the exocrine pancreas: A study from the French Association of Surgery. Br J Surg 1994;81:102–107.
34. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery 2003;133:521–527.
35. Z'graggen K, Centeno BA, Fernandez-del-Castillo C, et al. Biological implications of tumor cells in blood and bone marrow of pancreatic cancer patients. Surgery 2001;129: 537–546.
36. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Eng J Med 2004;350:1200–1210.
37. Picozzi VJ, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am J Surg 2003;183: 476–480.
38. Traverso LW. Pancreatic cancer: Surgery alone is not sufficient. Surg Endosc 2006;S446–S449.

Discussion

John P. Hoffman, M.D. (Philadelphia, Pa): I would like to thank Dr. Howard for the privilege of reviewing this very nice manuscript 2 weeks ago. I will get right to the questions.

As for your use of actual survival, it is fine for those patients with operations done before 2001, but you have no information for the many patients treated since then at your institution. It is also reassuring to see the actual numbers. However, it is really quite difficult to subvert the Kaplan-Meier actuarial method of determining survival probability unless the case mix or therapies vary considerably through time. Have you tried subtracting or adding a year or two of data and then comparing the actuarial to the actual curves?

I would also quibble with your method of determining your 5-year survival. You did not stop entering patients with operations 5 years ago but added another cohort with resections less than 5 years from the end of the study. For the purists, if that extra

year of patients were subtracted from your dataset such that all had their resections greater than 5 years ago, how would that change your actual numbers?

Congratulations for thoroughly examining your surgical margins. Were frozen sections taken of the cut pancreatic and bile duct margins, and if positive, was more tissue taken? Did you look at the relative prognostic influence of the various margins when positive?

Finally, how do your results change your treatment recommendations, particularly for the patients with a borderline resectable lesion where one is unlikely to be able to do a margin-free resection?

Thanks again.

Thomas Howard, M.D. (Indianapolis, Ind): Thank you, John. I appreciated your input in putting the manuscript together.

In terms of actual versus actuarial survival, we go into it a little bit in the manuscript. I think sometimes we are deceiving ourselves with actuarial data, particularly when our follow-up is not very good with a large number of censored observations. Pancreatic cancer is a bad disease and we need to face that fact, which is the reason we chose to present actual survival data. We also did not exclude operative deaths in our survival. I believe much of the data that we hear and see presented at meetings and finding its way into the literature is skewed when you exclude operative deaths and use survival probabilities (Kaplan-Meier). This data represents a view of actual survival in patients who had surgery with curative intent at our institution during this time period.

You questioned our time period for patient accrual. We picked 1990 to 2002 because of one of the senior authors was active during this period and we wanted to include all of his patients as well as patients operated on by others. We didn't try to manipulate this cohort in an attempt to get a better or worse survival rate. This is one snapshot view of our practice and we picked these years for the analysis. I would point out that no patient in this series is censored; all patients are either alive or deceased. There are no patients living besides the 31 patients who are in the long-term survival group.

Frozen sections that we get routinely are the pancreatic neck margin, retroperitoneal soft tissue margin, and the bile duct margin. Seventy-five percent of the positive margins in this series were false negatives on frozen section at the time of operation so no further tissue was resected. The prognostic influence of a positive margin in our experience is similar to yours; we found a shorter survival in patients with positive retroperitoneal soft-tissue margins.

The take-home message from this paper is you need to do good surgery (margin-negative resection), but that is not enough. These patients, even with margin-negative R0 resections, die of recurrent disease. Clearly, effective adjuvant therapy is necessary, whether you give it before or after an operation, if we are to realize a true improvement in long-term survival. Towards this end, our efforts as surgeons should be directed not at larger operations, but at recruiting patients to large, prospective clinical trials investigating adjuvant therapies.

The Influence of Positive Peritoneal Cytology on Survival in Patients With Pancreatic Adenocarcinoma

Cristina R. Ferrone, M.D., Barbara Haas, M.D., Laura Tang, M.D., Daniel G. Coit, M.D., Yuman Fong, M.D., Murray F. Brennan, M.D., Peter J. Allen, M.D.

The American Joint Committee on Cancer (AJCC) staging system for pancreatic adenocarcinoma classifies positive peritoneal cytology as stage IV disease. Data are limited with respect to the prevalence of positive peritoneal cytology and its influence on survival in patients with resectable, locally advanced, and metastatic disease. Four hundred sixty-two patients underwent staging laparoscopy for pancreatic adenocarcinoma between January 1995 and December 2005. Kaplan-Meier survival comparisons were performed to evaluate the significance of positive peritoneal cytology on overall survival (OS) in resected patients and patients with locally advanced and metastatic disease. Of the 462 patients, 47% (217/462) underwent a pancreatic resection. The 21% (95/462) with locally advanced disease and 32% (150/462) with metastatic disease did not undergo resection. Peritoneal cytology was positive in 17% (77/462), and was associated with stage of disease (metastatic, 37%; locally advanced, 11%; resected, 5%; $P = 0.01$). Positive cytology was not associated with OS in patients with metastatic disease or locally advanced disease, but was in resected patients (median, 16 months vs. 8 months; $P < 0.001$). Node-positive disease was present in 8 of 10 patients resected with positive cytology (2 years OS, 12% positive cytology vs. 23% negative; $P = 0.006$). In this study, patients who underwent resection in the presence of positive peritoneal cytology and absence of other identifiable metastatic disease had a similar survival as other patients with stage IV disease. (J GASTROINTEST SURG 2006;10:1347–1353)

KEY WORDS: Pancreatic adenocarcinoma, cytology

Pancreatic adenocarcinoma continues to be a lethal disease, with surgical resection being the only treatment associated with long-term survival. Despite continuous improvements in perioperative management, pancreatic resection continues to be associated with substantial morbidity and mortality. Even at high-volume centers, the morbidity and mortality of pancreatic resection are reported to be approximately 35%-51% and 1%-6%, respectively.[1–3] Pancreatic resection in the setting of identifiable metastatic disease has not been associated with improved survival.[4] Because of this, most surgeons only recommend resection for the setting of disease that seems locoregional.

To determine resectability, accurate staging of pancreatic cancer is essential. Better imaging, including multidetector spiral CT and magnetic resonance imaging scans, as well as endoscopic ultrasound have improved our ability to identify metastatic and locally unresectable disease. In addition, staging laparoscopy has been shown to be a minimally invasive method of identifying radiographically occult disease in up to 24% of patients.[5,6]

The current American Joint Committee on Cancer (AJCC) staging system for pancreatic adenocarcinoma classifies positive peritoneal cytology as stage IV disease.[7] If this is true, patients who are discovered to have positive peritoneal cytology as their only site of distant metastatic disease should behave similarly to other stage IV patients. Data are limited, however, with respect to the prevalence of positive peritoneal cytology and its influence on survival in patients with radiographically resectable, locally advanced, and metastatic disease.

The purpose of this study was to define the prevalence of positive cytology in a modern cohort of patients with pancreatic adenocarcinoma at

Presented at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, California, May 20–24, 2006 (poster presentation).

From the Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York.
Reprint requests: Peter J Allen, M.D., Department of Surgery, Memorial Sloan-Kettering Cancer Center, Howard 1223, 1275 York Avenue, New York, NY 10021. e-mail: allenp@mskcc.org

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.07.013

a tertiary referral center. In addition, we wanted to determine the influence of positive cytology on survival in patients with resectable, locally advanced, and metastatic disease.

METHODS

Between January 1995 and December 2005, 934 patients were operatively explored for pancreatic adenocarcinoma. Staging laparoscopy and peritoneal cytology was obtained in 462 of the 934 patients (49%). Clinical factors including age, gender, weight loss, pain, jaundice, preoperative CA19-9, preoperative carcinoembryonic antigen (CEA), site, date, and status at last follow-up were recorded. Radiologic staging including the type of imaging and the location where imaging was performed (Memorial Sloan-Kettering Cancer Center [MSKCC] vs. outside hospital) was documented. Pathologic factors included TNM stage, margin, and differentiation.

Operative factors examined included the date of operation, cytology (positive, negative), location of cytology (right upper quadrant, left upper quadrant, and pelvis), and the pathology of any intraoperative biopsy (liver, peritoneal, and other). Staging laparoscopy and resection, when appropriate, was generally performed under the same anesthetic. The technique of laparoscopy varied according to surgeon and the site of concern for resectability. Typically, a supraumbilical camera port and two additional 5 mm ports were placed for exploration. Exploration focused on the liver, peritoneal surfaces, and the transverse mesentery. Cytologic washings were obtained from the right upper quadrant, left upper quadrant, and pelvis. When preoperative imaging revealed a concern about local resectability, an additional 10 mm port was often placed for laparoscopic ultrasound of the lesion and mesenteric vasculature.

Cytology results were not available intraoperatively, and patients without ascites found to have resectable disease at laparoscopy underwent laparotomy and attempted resection. Kaplan-Meier survival comparisons were performed to evaluate the significance of positive peritoneal cytology on OS in resected patients and in patients with locally advanced and metastatic disease.

This study was approved by MSKCC's internal review board, and none of the authors have any conflict of interest.

RESULTS

The clinical and pathological characteristics of the 462 patients in this study are presented in Table 1. Median age was 68 years for the entire cohort, and 51% of the patients were female. The majority of the tumors were located in the head of the pancreas, and 35% were poorly differentiated.

Resection was performed in 217 of the 462 patients (47%), and 64% of resected patients had stage IIB disease (node-positive). Approximately half of the resected patients received adjuvant chemotherapy, and one third received adjuvant radiation therapy. Distant metastatic disease was identified in 150 of the patients (32%) who were not resected. Within this group of patients, 73 were identified with liver-only metastases, 62 with disease isolated to the peritoneum, and 11 with both liver and peritoneal disease. Locally advanced disease was identified in 95 patients (21%), two patients were found to have extraregional nodal disease, and two patients were considered medically unfit for resection secondary to advanced cirrhosis. A similar distribution was seen in the 472 patients who did not undergo laparoscopy. Resection was performed in 62% (294/472), with 67% (187/294) of the resected patients diagnosed with stage IIB disease. Distant metastases were identified in 28% (133/472) and locally advanced disease in 10% (45/472).

Review of radiographic reports and surgeons' notes identified 297 patients (64%) who were considered to be radiographically resectable. Within this group of patients, diagnostic laparoscopy identified unresectable disease in 80 patients (27%). Distant metastatic disease was identified in 68 (23%) patients, locally advanced disease was identified in 10 (3%), and two patients were discovered to have advanced cirrhosis. Therefore, 23% (68 /297) of patients who were deemed resectable by preoperative imaging were discovered to have distant metastatic disease by laparoscopy and thus avoided a laparotomy.

The prevalence of positive cytology by the stage of disease is presented in Table 2. The overall positive cytology rate was 17% (77/462). Positive cytology was most common in patients with peritoneal metastasis (35/62, 56.5%) and least common in patients with resectable lesions (10/217, 5%). Cytology was more likely to be positive for lesions within the body and tail of the pancreas as compared with those in the head/neck (body/tail, 30/93 [32%] vs. head/neck, 47/369 [13%]; $P < 0.001$). Cytology was most commonly positive in the right upper quadrant (n = 57, 19%), followed by left upper quadrant (n = 44, 11%).

The median survival for the entire cohort was 11 months (range, 0–122 months), with 85% of patients having died from disease at the time of last follow-up. The median survival was 16 months (range, 0–122 months) for resected patients and 7 months

Table 1. Clininicopathologic factors of patients with pancreatic adenocarcinoma who underwent laparoscopic evaluation with peritoneal washings

Clinicopathologic characteristics	Total N = 462	Resected n = 217	Unresected n = 245
Median (range)	68 (38–100)	71 (38–89)	67 (40–100)
Female	234 (51%)	109 (50%)	126 (51%)
Pain	190 (41%)	124 (57%)	66 (27%)
Weight loss	203 (44%)	80 (37%)	123 (50%)
Jaundice	204 (44%)	93 (43%)	111 (45%)
Median preop CA 19-9	N = 81	N = 32	N = 49
(0–37 ug/mL)	410	218	451
Median pre op CEA	N = 61	N = 23	N = 38
(0–5 ng/ml)	3.3	2.7	4.9
Tumor location			
Head	369 (80%)	196 (90%)	173 (71%)
Body	59 (13%)	7 (3%)	52 (21%)
Tail	34 (7%)	14 (6%)	20 (8%)
Differentiation			
Well	21 (5%)	13 (6%)	8 (3%)
Moderate	138 (30%)	86 (40%)	52 (21%)
Poor	161 (35%)	117 (54%)	44 (18%)
Unknown	142 (31%)	1	141 (58%)
Stage of resected patients			
IA	3 (<1%)	3 (1%)	
IB	22 (5%)	22 (10%)	
IIA	44 (9%)	44 (20%)	
IIB	138 (30%)	138 (64%)	
III	95 (21%)		95 (39%)
IV	160 (35%)	10 (5%)	150 (61%)
Adjuvant chemotherapy			
Yes		107 (49%)	
No		102 (47%)	
Unknown		8 (4%)	
Adjuvant radition			
Yes		68 (31%)	
No		141 (67%)	
Unknown		8 (4%)	
Follow-up			
NED	30 (7%)	30 (14%)	
AWD	38 (8%)	11 (3%)	27 (11%)
DOD	393 (85%)	175 (81%)	218 (89%)
DUK	1	1	

CEA = carcinoembryonic antigen; NED = no evidence of disease; AWD = alive with disease; DOD = dead of disease; DUK = dead of unknown cause.

(range, 0–57 months) for unresected patients ($P < 0.001$). The presence of positive cytology did not significantly alter median survival in those patients with locally advanced or distant metastatic disease (Table 2 and Fig. 1, *A*, *B*). However, the 5% of patients who underwent resection, and had positive cytology, had significantly worse overall survival when compared to resected patients who did not have positive cytology (16 months vs. 8 months, $P = <0.001$; Fig. 1, *C*). Within the group of 10 patients who were resected in the setting of positive cytology, nine died of disease within 11 months, and the remaining patient died at 28 months of follow-up.

Nearly all of the 10 patients who were resected in the setting of positive cytology had advanced primary lesions (Table 3). Positive lymph nodes were present in 8 of the 10 patients, and nine patients had T3 primary tumors. Even amongst patients with node-positive disease, however, positive peritoneal cytology was associated with a decrease in survival. The eight patients with node-positive disease and positive peritoneal cytology had a median survival

Table 2. Prevalence of positive peritoneal washings

	Resected (n = 217)	Locally advanced (n = 95)	Metastatic (n = 150)	Metastatic liver (n = 84)	Metatstatic Pentoneal (n = 66)
Pos cytology	10 (5%)	10 (11%)	56 (37%)	21 (25%)	35 (53%)
Median survival	11 mo	10 mo	7 mo	6 mo	7 mo
Neg cytology	16 mo	10 mo	7 mo	6 mo	8 mo
Pos cytology	8 mo	6 mo	7 mo	6 mo	7 mo
2-yr OS	31%	7%	7%	5%	9.6%
Neg cytology	36%	5%	8%	3%	12%
Pos cytology	10%	20%	6%	5%	4%
	($P < 0.001$)	($P = 0.7$)	($P = 0.9$)	($P = 0.06$)	($P = 0.11$)

Pos = positive; Neg = negative.

of 8 months compared to 16 months for patients (n = 146) with node-positive disease and negative cytology ($P < 0.001$).

Peritoneal cytology is not a factor considered within the MSKCC's pancreatic adenocarcinoma nomogram.[8,9] Positive peritoneal cytology adversely affected survival as compared to the survival predicted by the pancreatic nomogram for the 10 patients with positive cytology. The nomogram predicted a 1-year survival between 38%–80% for the nine patients with positive cytology; however, 9 of these 10 patients died of disease within 12 months of resection.

DISCUSSION

Patients with pancreatic adenocarcinoma have an extremely high likelihood of dying from metastatic disease. Even patients who undergo resection experience 2- and 3-year survival rates between 35%–39% and 20%–27%, respectively.[9] Resection in the setting of identifiable metastatic disease has been advocated by some as a palliative procedure, but results in overall survival rates are identical to patients with metastatic disease (median, 6–9 months) who do not undergo resection.[4,10] Because of this, our approach has been to avoid resection in patients with identifiable metastatic disease.

Improvements in preoperative imaging have allowed the identification of patients with lesser amounts of disease burden. Even with high-quality cross-sectional imaging, we have found diagnostic laparoscopy to be useful in identifying patients with subradiographic, but visible, metastatic disease.[11] Laparoscopy identified distant disease in 23% of patients, sparing them the morbidity of a laparotomy.

The most recent AJCC staging system classifies positive peritoneal cytology as M1 disease.[7] The majority of data regarding the significance of positive peritoneal cytology is in the setting of ascites. It remains unclear whether or not positive cytology in the absence of ascites results in similar survival rates as other patients with stage IV disease. This is important because cytologic results are not available at the time of laparoscopy, and therefore if one is not going to perform resection in the setting of positive cytology (M1) then a separate procedure would have to be performed.

In the current study, 17% of all patients (77/462) had positive cytology, and this was associated with stage of disease. These findings are consistent with reports from other institutions. In a study by Meszoely et al.[12] in the 168 patients who underwent peritoneal cytology there was an overall positivity rate of 16%, with resected patients having a positive cytology rate of 9.6%. Similarly, Fernandez-del Castillo et al.[13] found a cytologic positivity rate of 8% in resected patients.

As expected, and demonstrated by other groups, the highest incidence of positive peritoneal cytology was in patients with metastatic disease.[13,14] Thirty-eight percent of patients with visible and pathologically confirmed metastases had positive cytology, consistent with the 45% seen by Fernandez-del Castillo et al.[13] and the 42% seen by Meszoely et al.[12] Further analysis of our data demonstrated that patients with peritoneal disease had a significantly higher rate of positive cytology than those patients with liver metastases (57% vs. 25%).

Meszoely et al.[12] demonstrated a significantly improved survival for patients with negative cytology regardless of resectability (median, 17 vs. 9 months). However, they found no statistical difference between patients with positive or negative cytology within the unresectable and resectable groups (7 months vs.11 months and 15 months vs. 19 months). Although we did not find a statistically significant

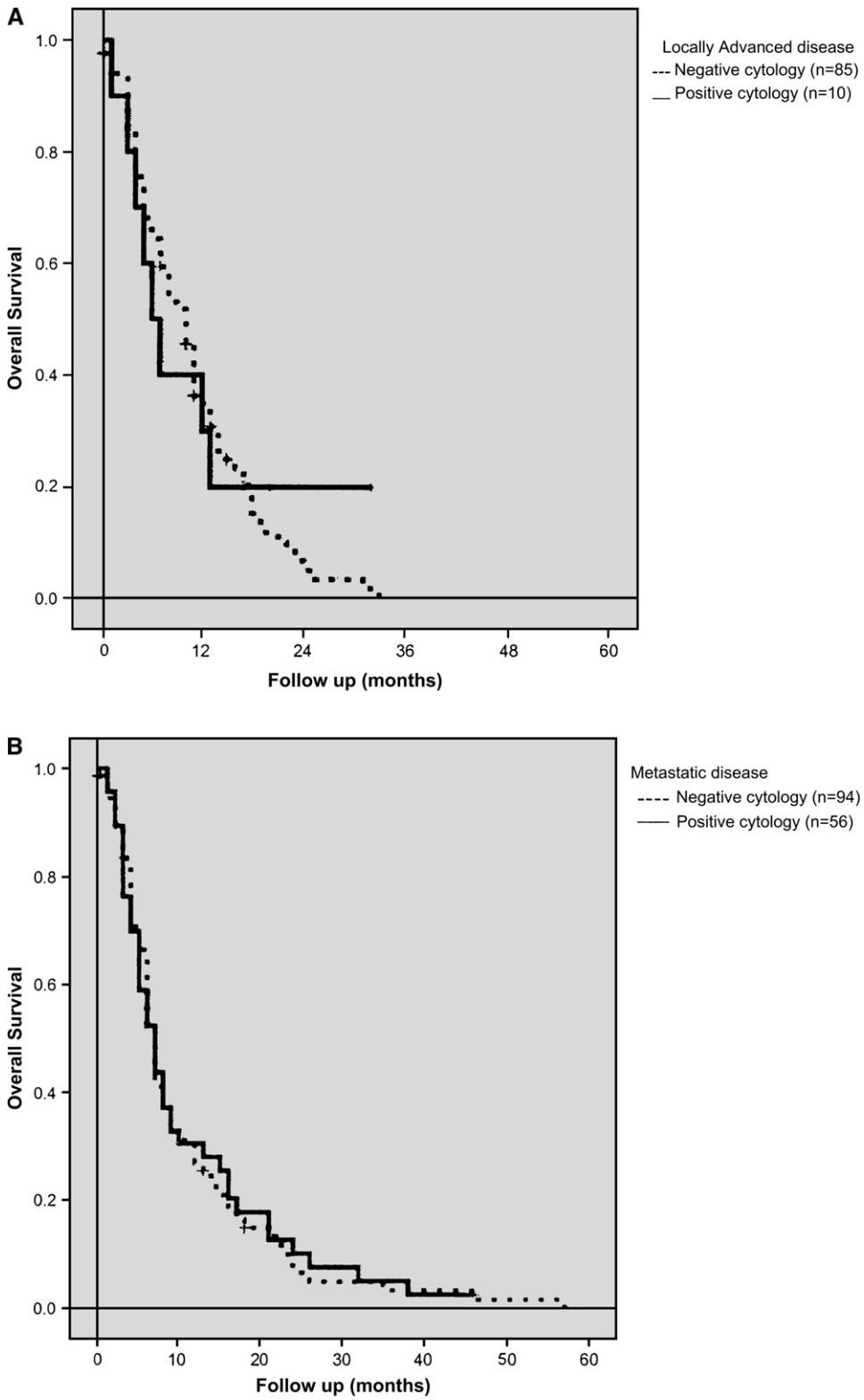


Fig. 1. Kaplan-Meier survival curves for patients with locally advanced (**A**), metastatic (**B**), or resectable (**C**) pancreatic adenocarcinoma, based on cytology.

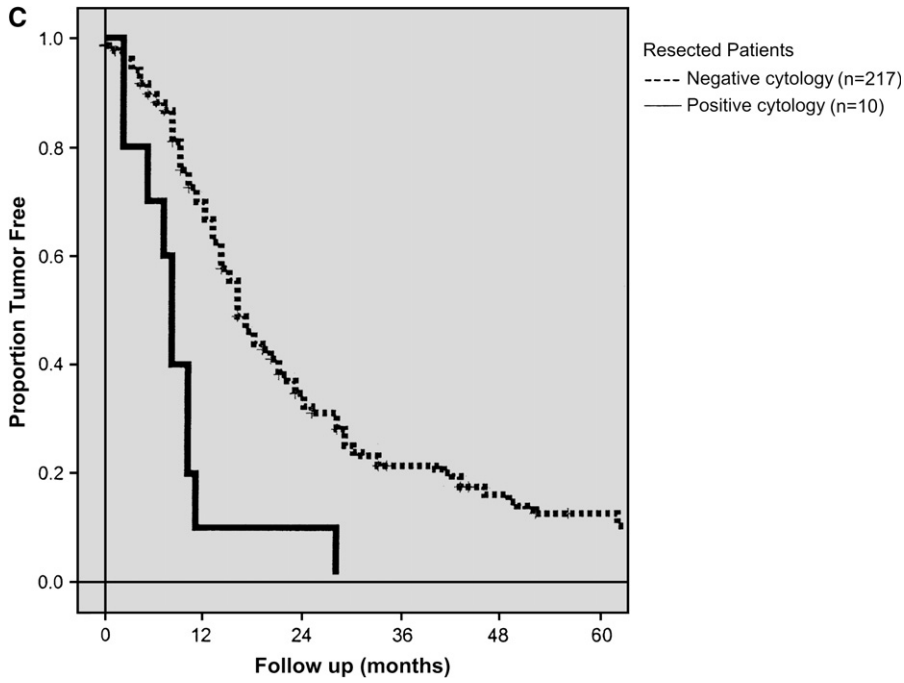


Fig. 1. Continued.

difference in survival of patients with locally advanced disease or visible peritoneal or liver metastases, we did find a significantly worse survival in patients who were resected in the setting of positive cytology. Patients who were resected in the setting of positive cytology had a median survival of 8 months and a 1- and 2-year overall survival of 10%. This is not statistically different from the median survival of 10 months for patients with locally advanced disease or 7 months for patients with metastatic disease. Therefore, cytology results need to be considered when patients are enrolled in clinical trials.

Nomograms are able to evaluate a large number of significant variables to better predict the outcome of individual patients. Patient prognosis is currently estimated on the basis of the AJCC staging system, which does not factor in prognostic determinants other than the T, N, and M stage. However, survival is not uniform due to differing genetic, cellular, and behavioral characteristics. By integrating additional significant prognostic factors, a nomogram can be used to better assess an individual patient's disease-specific survival. Based on findings from the large prospective pancreatic adenocarcinoma database at MSKCC, Brennan et al.[8] developed a nomogram that estimates disease-specific survival probabilities for the 3-year period immediately after surgery. To further evaluate the impact of positive peritoneal cytology on survival, the MSKCC pancreatic adenocarcinoma nomogram was used to predict the overall probability of survival within 3 years of resection for each of the 10 patients.[8,9] The nomogram predicted a 1-year probability of survival between 38%–80%, yet 9 of 10 patients dead of disease within 11 months. This emphasizes not only the significant prognostic effect of positive peritoneal cytology, but also suggests that cytology could be included in prognostic nomograms for pancreatic adenocarcinoma.

Table 3. Cytology predicts survival within stage

	Stage II A (n = 46)		Stage II B n = 146	
	Pos cyto (n = 2)	Neg cyto (n = 44)	Pos cyto (n = 8)	Neg cyto (n = 138)
Median survival	7 mo	21 mo	8 mo	16 mo
2-yr survival	0%	46%	12%	23%
P value	0.002		0.006	

Pos cyto = positive cytology; Neg cyto = negative cytology.

Staging laparoscopy and routine cytology are able to detect M1 disease in approximately 5% of patients with pancreatic adenocarcinoma who are resected. Molecular analysis of peritoneal washing cytology has been shown to be more accurate than routine cytology in gastric cancer.[15–18] To date no study has been published looking at polymerase chain reaction or molecular analysis of peritoneal washing cytology in pancreatic adenocarcinoma patients. We are currently investigating the role of polymerase chain

reaction on peritoneal washings to detect micrometastatic disease.

The results of this study further confirm that cytology from abdominal washings is most frequently positive in patients with peritoneal metastases. In addition, these data did not find that positive cytology was associated with survival in the setting of locally advanced or visible metastatic disease. In resected patients, however, positive cytology was associated with poor survival, which was not significantly different from those patients with metastatic or locally advanced disease. Laparoscopy and cytology as a separate procedure should be considered in high-risk patients. A rapid intraoperative assessment of the cytology would provide useful information that could prevent a patient from undergoing an operation that would not be associated with prolonged survival.

REFERENCES

1. Balcom JH, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: Changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398.
2. Bentrem DJ, Yeh JJ, Brennan MF, et al. Predictors of intensive care unit admission and related outcome for patients after pancreaticoduodenectomy. J GASTROINTEST SURG 2005;9: 1307–1312.
3. Bentrem DJ, Brennan MF. Outcomes in oncologic surgery: does volume make a difference? World J Surg 2005;29: 1210–1216.
4. Lillemoe KD, Cameron JL, Yeo CJ, et al. Pancreaticoduodenectomy and palliation in pancreatic carcinoma. Gastroenterology 1997;112:1046–1048.
5. Jimenez RE, Warshaw AL, Rattner DW, et al. Impact of laparoscopic staging in the treatment of pancreatic cancer. Arch Surg 2000;135:409–414.
6. Warshaw AL, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. Am J Surg 1986;151:76–80.
7. Greene FLPD, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M. AJCC Cancer Staging Handbook, 6th ed. New York: Springer, 2002.
8. Brennan MF, Kattan KM, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg 2004;240:293–298.
9. Ferrone CR, Kattan MW, Tomlinson JS, et al. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. J Clin Oncol 2005;23:7529–7535.
10. Lillemoe KD, Cameron JL, Yeo CJ, et al. Pancreaticoduodenectomy. Does it have a role in the palliation of pancreatic cancer? Ann Surg 1996;223:718–725.
11. Conlon KC. Value of laparoscopic staging for upper gastrointestinal malignancies. J Surg Oncol 1999;71:71–73.
12. Meszoely IM, Lee JS, Watson JC, et al. Peritoneal cytology in patients with potentially resectable adenocarcinoma of the pancreas. Am Surg 2004;70:208–213.
13. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Further experience with laparoscopy and peritoneal cytology in the staging of pancreatic cancer. Br J Surg 1995;82:1127–1129.
14. Merchant NB, Conlon KC, Saigo P, et al. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg 1999;188:421–426.
15. Mori K, Aoyagi K, Ueda T, et al. Highly specific marker genes for detecting minimal gastric cancer cells in cytology negative peritoneal washings. Biochem Biophys Res Commun 2004;313:931–937.
16. Nakanishi H, Kodera Y, Yamamura Y, et al. Molecular diagnostic detection of free cancer cells in the peritoneal cavity of patients with gastrointestinal and gynecologic malignancies. Cancer Chemother Pharmacol 1999;43(Suppl):S32–S36.
17. Kodera Y, Nakanishi H, Ito S, et al. Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: Detection of cytokeratin 20 mRNA in peritoneal washes, in addition to detection of carcinoembryonic antigen. Gastric Cancer 2005;8:142–148.
18. Kodera Y, Nakanishi H, Yamamura Y, et al. Prognostic value and clinical implications of disseminated cancer cells in the peritoneal cavity detected by reverse transcriptase-polymerase chain reaction and cytology. Int J Cancer 1998;79:429–433.

The Utility of F-18 Fluorodeoxyglucose Whole Body PET Imaging for Determining Malignancy in Cystic Lesions of the Pancreas

John C. Mansour, M.D., Lawrence Schwartz, M.D., Neeta Pandit-Taskar, M.D., Michael D'Angelica, M.D., Yuman Fong, M.D., Steven M. Larson, M.D., Murray F. Brennan, M.D., Peter J. Allen, M.D.

Previous studies have suggested that whole body positron-emission tomography (PET) can distinguish between benign and malignant cysts of the pancreas. Patients were identified (n = 68) who had undergone whole body PET imaging for a cystic lesion of the pancreas between Jan. 1997 and May 2005. Cross-sectional imaging studies were reviewed by a single blinded radiologist, and positive PET studies were reviewed by a blinded nuclear medicine physician. Operative resection was performed in 21 patients (31%), and 47 patients were managed with radiographic follow-up. F-18 Fluorodeoxyglucose (FDG)-avid lesions were identified in eight of the 68 patients (12%). Within the resected group of patients (n = 21), four of the seven patients (57%) with either in situ or invasive malignancy (adenocarcinoma: 3 of 5, papillary mucinous carcinoma: 1 of 2) had positive PET imaging (mean SUV, 5.9; range 2.5–8.0), and 2 of the 14 patients (14%) with benign lesions had positive PET imaging (serous cystadenoma, n = 1, SUV = 3.3; pseudocyst n = 1, SUV = 2.7). All lesions proven to be malignant with increased FDG uptake had highly suspicious findings on cross-sectional imaging. Within the group of resected patients, the sensitivity of PET for identifying malignant pathology was 57%, and the specificity was 85%. The sensitivity and specificity of PET for malignancy in this study was lower than previously reported, and PET findings did not identify otherwise occult malignant cysts. We do not believe whole body FDG-PET to be essential in the evaluation of cystic lesions of the pancreas. (J GASTROINTEST SURG 2006;10:1354–1360)

KEY WORDS: Pancreas, cyst, PET scan

A broad spectrum of pathologic entities can present as cystic lesions of the pancreas. These range from non-neoplastic pancreatic pseudocysts, to benign serous cysts, to pancreatic adenocarcinoma.[1–4] Differentiating between these entities has important treatment implications as observation is appropriate for benign lesions, and resection is warranted for selected premalignant or malignant lesions.[2,5]

A variety of tests have been employed to help differentiate between benign and malignant cysts of the pancreas. These include computed tomography (CT), magnetic resonance imaging (MRI), transabdominal ultrasound, endoscopic ultrasound, and cyst aspiration with cytology and/or cyst fluid analysis.[6–11] Cross-sectional imaging has been a useful tool for differentiating between benign and malignant lesions. However, there is still no defined set of patient or imaging characteristics to clearly determine which lesions are concerning for malignancy. The difficulty is that no single test, or combination of tests, has shown high sensitivity and specificity for the identification of malignant cystic lesions of the pancreas.[6,7]

Some authors have proposed that F-18 fluorodeoxyglucose (18-FDG) whole body PET imaging can identify those cystic lesions of the pancreas which may be malignant or pre-malignant. Sperti and colleagues quoted a sensitivity and specificity of PET scan for detecting malignant pancreatic cystic lesions of 94%. Based on these findings, this group has concluded that PET imaging is more accurate than CT in identifying malignant cysts of the pancreas. They conclude that tumors with high FDG uptake require aggressive resection and negative PET scans likely identify tumors amenable to conservative resection or follow-up.[12,13]

From the Departments of Surgery (J.C.M., M.D'A., Y.F. M.F.B., P.J.A.), Nuclear Medicine (N.P-T., S.M.L.), and Radiology (L.S., N.P-T., S.M.L.), Memorial Sloan-Kettering Cancer Center, New York, New York.
Reprint requests: Peter J. Allen, M.D., Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021. e-mail: allenp@mskcc.org

 Published by Elsevier Inc.
1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.08.002

The purpose of this study was to examine our experience with PET imaging for patients with cystic lesions of the pancreas. Our primary aim was to determine the sensitivity and specificity of PET imaging for malignancy in patients who had undergone resection. Our secondary aim was to evaluate whether PET imaging was able to identify malignant cysts that were otherwise without suspicious characteristics on cross-sectional imaging.

METHODS

We reviewed our prospectively maintained database of patients with cystic lesions of the pancreas. Patients are included in this database if they were coded for the *ICD-9* diagnosis of pancreatic cyst or pseudocyst (577.2), had a cystic lesion of the pancreas on imaging studies, and were evaluated by a surgeon or gastroenterologist. This database includes all patients evaluated since 1995, and currently contains over 500 patients. There were 68 patients identified who had undergone an FDG whole body PET scan between January 1997 and January 2005. These patients comprised our study population.

Patient, radiographic, and cyst characteristics were reviewed for each patient. Patient characteristics included age, gender, presence or absence of symptoms from the cyst, presence or absence of diabetes mellitus, and insulin use. Radiographic and cyst characteristics included the presence of septations, a solid component, mural nodularity, pancreatic duct dilation, cyst calcium, cyst size, and the histopathologic diagnosis for resected lesions. If multiple cystic lesions were present within the pancreas, the diameter of the largest lesion was recorded. If multiple cystic lesions were closely clustered with little or no intervening pancreatic parenchyma, the diameter of the cluster of lesions was recorded. The duration of radiographic cyst follow-up was defined as the time from identification of the cyst on imaging to the time of last cross-sectional imaging for which results were available. Any information not already included in the prospectively collected pancreatic cyst database was collected from review of the patient's electronic medical record.

Cross-sectional imaging was reviewed by a single blinded radiologist specializing in abdominal cross-sectional CT and MRI (L.S.). Cross-sectional imaging was available for review in 67 of the 68 cases. The reviewer examined the earliest and most recently performed studies, and had no knowledge of treatment or pathologic related information. The reviewer was unaware of the results of PET imaging. Cross-sectional imaging studies were given a score ranging from 1 (benign findings) to 5 (highly suspicious findings). This score was based on the overall impression of the lesion. Lesions concerning for intraductal papillary mucinous neoplasms with possible malignant features were scored as 3 or "uncertain" (Fig. 1).

Reports from all PET studies were reviewed, and all positive PET studies were reviewed by a single nuclear medicine physician (N.P-T). PET imaging characteristics were recorded including the millicuries of radiation dose received, and the highest area of pathologic FDG uptake measured by standardized uptake value (SUV). The PET reviewer was blinded to any clinical or pathologic information pertaining to the patient including the cyst characteristics identified by cross-sectional imaging. The physician was not blinded to the location of the cyst within the pancreas.

RESULTS

Over the 8-year time period of the study, 68 patients were identified who had undergone whole body PET imaging for a cystic lesion of the pancreas. The demographic data for these 68 patients are presented in Table 1. The average age of patients was 66 years (range 39–84), and there were 23 males (34%) and 45 (66%) females in the study. The majority of patients (66%) had no symptoms attributable to the pancreatic cyst. A minority of patients had a history of pancreatitis (6%) or diabetes mellitus (15%).

All of the patients in this study had a CT scan performed during their diagnostic evaluation. The next most common imaging study was magnetic resonance imaging (MRI or MRCP). MR was performed in 48 patients (71%). Additional studies used in the evaluation of the cystic lesion included upper

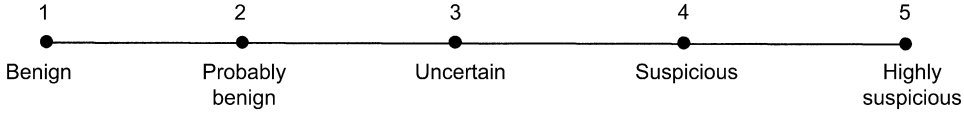


Fig. 1. A Radiology Assessment Score was assigned to each cystic lesion evaluated by a reviewing radiologist. The radiologist assessed the lesion based solely on cross-sectional imaging characteristics.

Table 1. Patient and cyst characteristics for the 68 patients who underwent PET imaging

Characteristic	
Mean age (y)	66
Range	39–84
Gender (n)	
Female	45 (66%)
Male	23 (34%)
Symptomatic (%)	34
History of pancreatitis (%)	6
History of diabetes mellitus (%)	15
Mean lesion size (cm)	2.7 (Range, 0.6–8.5)
No. of Lesions (n)	
1	61 (90%)
2	4 (6%)
⩾3	3 (4%)
Cyst	
Septated (n)	40 (59%)
Solid component (n)	21 (31%)
Mural nodularity (n)	12 (18%)
Pancreatic duct dilation (n)	9 (13%)

Table 2. Histopathologic results of the 21 resected patients

Result	No.	%
Malignant	7	33
Adenocarcinoma	5	
IPMN in situ	2	
Benign	14	67
Serous cystadenoma	5	
Pseudocyst	4	
IPMN	3	
Mucinous cystadenoma	2	

endoscopy (47%), endoscopic ultrasound (46%), and fine-needle aspiration (47%).

The cyst characteristics for all patients in the study are presented in Table 1.

The mean cyst diameter was 2.7 cm (range 0.6 to 8.5 cm), and 90% (n = 61) of the patients had a single cystic lesion identified. The most common location of the cyst was in the head of the pancreas (32%). Septations were identified in the cyst in 40 patients (59%). Forty-seven patients (69%) had lesions with septations, a solid component, mural nodularity, or pancreatic ductal dilation. The mean radiographic cyst follow-up for all lesions was 22 months (range 0 to 102 months; median 17 months). The mean radiographic cyst follow-up for lesions observed without resection was 24 months (median 20 months).

Resection was performed in 21 of the 68 patients (31%). Malignancy was identified in seven of the 21 resected patients (33%). Adenocarcinoma was diagnosed in five patients, and papillary mucinous carcinoma (IPMN with carcinoma) was diagnosed in two patients (Table 2). The remaining 47 patients (69%) were not resected and had a mean radiologic cyst follow-up of 24 months. Within this group of 47 patients the average change in cyst diameter at the time of last follow-up was 0.2 cm (range 0.0−1.6 cm).

The PET imaging was performed at our institution for 61 of the 68 patients (90%). The remaining studies were performed prior to evaluation at our center. PET imaging was reported as positive in eight of the 68 patients (12%). All of these eight patients were reported to have acceptable blood glucose levels at the time of examination. The SUV for the area correlating to the pancreatic cyst ranged from 1.9 to 8.0 (mean 4.6) in positive studies. Resection was performed in six of the eight PET-positive lesions (Table 3). Malignancy (adenocarcinoma, n = 3) was identified in four of these six patients. Cross-sectional imaging revealed benign findings (score 1) in one of the two unresected PET-positive lesions and this patient has been followed for 24 months with no radiologic progression. The other patient with an unresected PET-positive cyst had features concerning for malignancy on cross-sectional imaging and was recommended resection but refused biopsy or surgical intervention (Table 3).

PET imaging was reported as negative in 60 of 68 studies (88%). Resection was performed in 15 patients with negative PET imaging (Table 4). Malignancy was identified in three of the 15 patients with negative PET, and these three patients represent 43% (3 of 7) of the patients found to have malignancy at the time of resection. If only patients who underwent resection are considered, the sensitivity and specificity of PET imaging for distinguishing between benign and malignant cysts of the pancreas in this study were 57% and 85%, respectively. If the single unresected PET-positive patient with worrisome cross-sectional imaging is categorized as malignant, the sensitivity of PET imaging increases to 62%.

Radiology review of cross-sectional imaging was performed in 67 of the 68 patients. The results of this review are presented in Table 5. Suspicious findings (radiology score 4 or 5) were present in 12 of the 21 resected patients, nonsuspicious findings (score 1 or 2) were present in four patients, and indeterminate findings were present in five patients (5 of 21, 24%). If patients scored as 1 or 2 are considered "radiographic negative" and those scored 4 or 5 are considered "radiographic positive," the sensitivity and specificity for cross-sectional imaging in this

Table 3. Patients with positive PET imaging

Age (yr)/ gender	Symptoms	SUV	Cyst size (cm)	Solid	Septated	PD Dilated	Mural nodule	Pathology	Radiology recommendation score
52/M	Yes	5.8	2	Yes	No	No	Yes	Adenoca	4
83/F	Yes	2.5	4.8	No	Yes	No	Yes	Adenoca	4
64/F	Yes	8	2.8	Yes	No	Yes	Yes	Adenoca	5
80/F	No	7.3	4.8	Yes	Yes	Yes	Yes	IPMN in situ	5
73/F	Yes	3.3	7.0	No	Yes	No	Yes	Serous cystadenoma	3
82/F	Yes	2.7	2.3	No	Yes	No	Yes	Pseudocyst	4
76/F	No	1.9	3.9	Yes	Yes	No	No	—	2
76/F	Yes	5	7.4	Yes	Yes	No	Yes	—	5

study were 100% and 40%. Examples of both cross-sectional and PET imaging are included here in Figure 3.

DISCUSSION

Because of the increasing use of high-quality cross-sectional imaging, increasing numbers of patients are being identified with cystic lesions of the pancreas.[2,3] However the ability to differentiate between benign and malignant cysts remains limited. Techniques such as thin-cut CT scans, MRI and MRCP, PET imaging, endoscopic ultrasound, and cyst aspiration have all been evaluated as ways to differentiate between benign and malignant cystic lesions of the pancreas.[2,5–15] The sensitivity and specificity of CT and MR for malignant cystic lesions have been reported as 25–100% and 40–92%.[6–9,14,15]

In 2001 and 2005, Sperti and colleagues published their experience with whole body PET imaging for cystic lesions of the pancreas.[12,13] In their studies, 77 of 105 patients (73%) underwent resection. PET imaging was positive in 35 of the 105 (33%) patients, and malignancy was identified in 34 of the 77 (53%) resected patients. They concluded that the sensitivity and specificity of PET for detecting malignant lesions were greater than or equal to 94%. Following the publication of these studies, our institution saw a sharp increase in the number of PET scans obtained to characterize cystic lesions of the pancreas.

Table 4. Pathology and PET imaging results

No. of patients	PET negative (%)	PET positive (%)
Total (n = 68)	60 (88)	8 (12)
Not resected (n = 47)	45 (96)	2 (4)
Resected (n =21)	15 (71)	6 (29)
Benign (n =14)	12 (86)	2 (14)
Malignant (n = 7)	3 (43)	4 (57)

The objective of this study was to review our experience with PET imaging for cystic lesions of the pancreas. We sought to define whether PET imaging was able to identify malignancy within pancreatic cysts and to assess whether PET results would be additive to the information already obtained from cross-sectional imaging. In other words, did PET imaging identify malignant lesions not identified as suspicious on cross-sectional imaging?

Our results did not find the sensitivity and specificity of PET to be as high as reported in the studies from Italy. In our study, three of seven patients with malignancy were found to be negative by PET imaging (sensitivity, 57%), and 2 of 14 patients with benign lesions were PET positive (specificity, 85%). In addition, six of the seven malignant lesions were found to be suspicious on cross-sectional imaging (sensitivity, 86%). The remaining malignant lesion was scored as uncertain by our radiologist.

The discordance between the high sensitivity and specificity seen in prior studies and our relatively low sensitivity and specificity may be due in part to patient selection. In the studies reported from Italy, as many as 65% of patients had clear CT evidence for malignancy, including encasement of the superior mesenteric vein and intraabdominal metastases. None of the patients in our series demonstrated metastatic or locally advanced disease on cross-sectional imaging. In addition, our incidence of malignancy and rate of resection was much lower than in the studies from Italy (30–34% versus 10%, and 62–82% versus 29%). This is most likely because our series included lesions with more ambiguous cross-sectional imaging characteristics than seen in prior series evaluating PET and pancreatic cystic lesions. Among the 17 patients with a radiology recommendation score of 3 (uncertain), only 4 (24%) patients had positive PET scans. Only one of these

Table 5. Radiology assessment scores, PET results, and known pathology

			Among 21 patients with known pathology	
Radiology score	**PET negative (%)**	**PET positive (%)**	**No. benign (%)**	**No. malignant (%)**
1	8	0	—	—
2	19	1	4 (100)	0
3	16	1	4 (80)	1 (20)
4	14	3	5 (63)	3 (37)
5	2	3	1 (25)	3 (75)

lesions with a positive PET scan harbored malignancy.

Whole body PET imaging identified FDG-avid lesions primarily among those patients with cross-sectional imaging characteristics that would result in resection being recommended, regardless of the PET findings. Only one patient of the 17 with uncertain cross-sectional imaging had an FDG-avid malignancy identified by PET imaging.

We advocate a selective approach to resection of pancreatic cystic lesions at our institution. This approach is reflected in the 31% rate of resection in this series. Admittedly, we do not have a histologic diagnosis in the other 69% of patients in this series. Fortunately, we do have a histologic diagnosis for 75% of the patients with positive PET scans. One of the patients without a diagnosis has a benign-appearing cyst on cross-sectional imaging with no change after 2 years of close follow-up. If we presume that the remaining patient with a positive PET scan had an undiagnosed malignancy, this increases the sensitivity of PET imaging to 62%. The presence of undetected malignancy among the remaining 45 unresected patients with negative PET imaging would result in a calculated sensitivity of PET for detecting malignancy within pancreatic cystic lesions below 57%.

If the five patients with intraductal papillary mucinous carcinoma or mucinous cystadenoma are considered to have premalignant lesions requiring resection, the sensitivity and specificity of PET imaging are altered. The adjusted specificity and

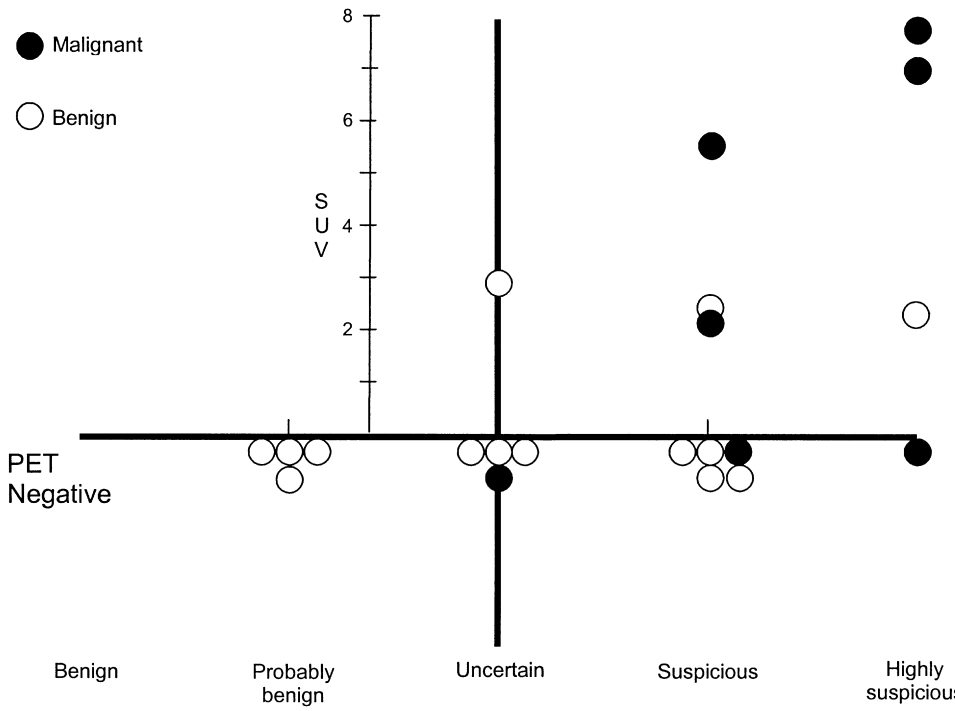


Fig. 2. Distribution of patients with known pathology based on pathology, PET results, and cross-sectional imaging interpretation

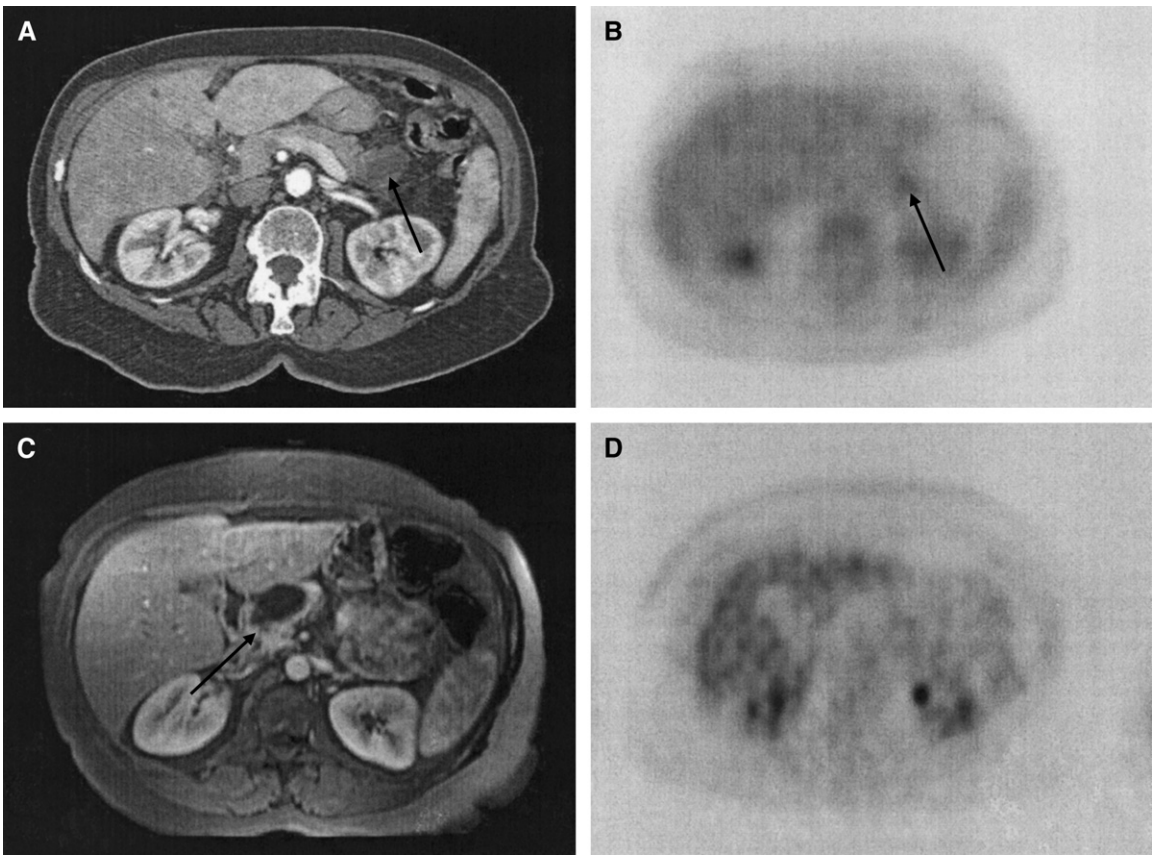


Fig. 3. Panel A and B demonstrate a patient with IPMN in situ found in a pancreatic tail lesion with suspicious CT imaging and abnormal uptake on FDG PET imaging. Panel C and D demonstrate a patient with adenocarcinoma in a pancreatic head mass seen on MRI and no areas of corresponding abnormal FDG avidity seen on PET.

sensitivity for identifying malignant and possibly premalignant lesions become 77% and 33%, respectively.

CONCLUSION

Cystic neoplasms of the pancreas present a difficult diagnostic and treatment problem. These problems stem from our inability to reliably distinguish malignant cystic lesions from benign cystic lesions. In our series we describe 68 patients with cystic neoplasms of the pancreas evaluated with FDG whole body PET imaging. In this series, 10% of patients harbored a malignancy and 12% had a positive PET scan. The sensitivity and specificity for identifying malignant cystic neoplasms of the pancreas in this population of patients were 57% and 85% respectively. Of those lesions with positive PET scans and identified malignancy, all had cross-sectional imaging favoring resection.

Despite previous reports, the role for PET imaging of pancreatic cystic lesions has not been well-defined. We do not believe that the routine use of whole body PET imaging provides any additive benefit to high-quality cross-sectional imaging for identifying pancreatic cystic lesions harboring malignancy. Focused evaluation of the utility of PET in patients with indeterminate lesions, or the use of PET techniques that increase the resolution of PET imaging, may identify a group of patients where PET imaging may be useful.

REFERENCES

1. Fernandez-del Castillo C, Warshaw AL. Cystic tumors of the pancreas. Surg Clin North Am 1995;75:1001–1016.
2. Allen PJ, Jaques DP, D'Angelica M, Bowne WB, Conlon KC, Brennan MF. Cystic lesions of the pancreas: Selection criteria for operative and nonoperative management in 209 patients. J Gastrointest Surg 2003;7:970–977.
3. Sakorafas GH, Sarr MG. Cystic neoplasms of the pancreas: What a clinician should know. Cancer Treat Rev 2005;31: 507–535.
4. Conlon KC. Management of cystic lesions of the pancreas. Clin Adv Hematol Oncol 2005;3:461–463.

5. Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeeb A, Komorowski RA, et al. Cystic pancreatic neoplasms: Observe or operate? Ann Surg 2004;239:651–657.
6. Siech M, Tripp K, Schmidt-Rohlfing B, Mattfeldt T, Widmaier U, Gansauge F, et al. Cystic tumours of the pancreas: Diagnostic accuracy, pathologic observations and surgical consequences. Langenbecks Arch Surg 1998;383:56–61.
7. Lim SJ, Alasadi R, Wayne JD, Rao S, Rademaker A, Bell R, Talamonti MS. Preoperative evaluation of pancreatic cystic lesions: Cost-benefit analysis and proposed management algorithm. Surgery 2005;138:672–679; discussion 679–680.
8. Sahani DV, Kadavigere R, Blake M, Fernandez-del Castillo C, Lauwers GY, Hahn PF. Intraductal papillary mucinous neoplasm of pancreas: Multi-detector row CT with 2D curved reformations-correlation with MRCP. Radiology 2006;238:560–569.
9. Walsh RM, Henderson JM, Vogt DP, Baker ME, O'Malley CM Jr, Herts B, et al. Prospective preoperative determination of mucinous pancreatic cystic neoplasms. Surgery 2002;132:628–633.
10. Pelaez-Luna M, Chari ST. Cyst fluid analysis to diagnose pancreatic cystic lesions: An as yet unfulfilled promise. Gastroenterology 2006;130:1007–1009.
11. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S. International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.
12. Sperti C, Pasquali C, Decet G, Chierichetti F, Liessi G, Pedrazzoli S. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: A prospective study. J GASTROINTEST SURG 2005;9:22–28.
13. Sperti C, Pasquali C, Chierichetti F, Liessi G, Ferlin G, Pedrazzoli S. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumors of the pancreas. Ann Surg 2001;234:675–680.
14. Taouli B, Vilgrain V, Vullierme MP, Terris B, Denys A, Sauvanet A, et al. Intraductal papillary mucinous tumors of the pancreas: Helical CT with histopathologic correlation. Radiology 2000;217:757–764.
15. Curry CA, Eng J, Horton KM, Urban B, Siegelman S, Kuszyk BS, Fishman EK. CT of primary cystic pancreatic neoplasms: Can CT be used for patient triage and treatment? AJR Am J Roentgenol 2001;177:469–470.

Cytoreduction Results in High Perioperative Mortality and Decreased Survival in Patients Undergoing Pancreatectomy for Neuroendocrine Tumors of the Pancreas

Mark Bloomston, M.D., Peter Muscarella, M.D., Manisha H. Shah, M.D., Wendy L. Frankel, M.D., Osama Al-Saif, M.D., Edward W. Martin, M.D., E. Christopher Ellison, M.D.

We reviewed our experience with pancreatectomy for neuroendocrine tumors (NE) to determine outcomes after R0/R1 or R2 resection and compare them to patients in whom resection was not attempted. Data were reviewed for all patients presenting with NE tumors of the pancreas between 1990 and 2005. Kaplan-Meier survival curves were compared by log-rank analysis. Multivariate analysis was completed using Cox proportional hazards to identify risk factors for poor survival after resection. Of 120 patients, 65 (54%) had functional tumors. Resection was undertaken in 83: distal pancreatectomy in 41, pancreaticoduodenectomy in 27, enucleation in 14, and central pancreatectomy in 1. Survival was significantly longer after resection (91 months versus 24, $P < 0.001$). R0/R1 resection was accomplished in 64 (77%) and resulted in lower perioperative mortality (2% versus 21%, $P < 0.01$) and longer survival (112 months versus 24, $P < 0.001$) compared to R2 resection. Survival after R2 resection was no better than after no resection. Factors predictive of decreased survival were moderate/poor differentiation, R2 resection, and high-risk features. Long-term survival is possible following complete resection for NE tumors of the pancreas. However, cytoreduction resulting in incomplete tumor removal carries significant perioperative mortality without long-term survival benefit and should be discouraged. (J GASTROINTEST SURG 2006;10:1361–1370)

KEY WORDS: Neuroendocrine, pancreas, endocrine, islet cell carcinoma, survival

Neuroendocrine tumors of the pancreas, or islet cell tumors, are an exceedingly rare entity, affecting an estimated one to two per 1 million population each year.[1,2] Unlike the more common ductal adenocarcinoma, these pancreatic neoplasms have a more indolent course, with long-term survivals being commonplace, even in the setting of advanced disease.[3,4] Owing to the rarity of these tumors, there are few large studies that report the outcome of surgical management. In addition, there is lack of agreement regarding the surgical management of patients with metastatic or locally advanced disease. Some have advocated an aggressive surgical approach in all patients including cytoreduction and metastastectomy.[5,6] A review of our recent experience with pancreatectomy in patients with neuroendocrine tumors of the pancreas was undertaken to determine predictors of long-term survival and to address the role of palliative and/or cytoreductive surgery.

METHODS

After obtaining approval from the institutional review board at The Ohio State University, 120 patients presenting with primary neuroendocrine tumors of the pancreas between January 1990 and December 2004 inclusive were identified from the neuroendocrine tumor registry. Thirty-seven were considered unresectable due to metastatic (n = 29) or locally advanced (n = 8) disease. The data from

Presented at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, California, May 22, 2006.
From the Departments of Surgery (M.B., P.M., O.A.-S., E.W.M., C.E.), Internal Medicine (M.H.S.), and Pathology (W.L.F.), The Ohio State University Comprehensive Cancer Center, Columbus, Ohio.
Reprint requests: Mark Bloomston, M.D., The Ohio State University, N924 Doan Hall, 410 W. 10th Avenure, Columbus, OH 43210. e-mail: Mark.Bloomston@osumc.edu

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.004

these patients were used for comparison of demographics and survival with the remaining 83 who underwent resection of their primary pancreatic neuroendocrine tumors. Data collected included patient age, gender, comorbidities, presenting symptoms, results of preoperative imaging, intraoperative findings, pathologic findings, and postoperative complications.

Overall survival was calculated from the time of operation or, for patients with unresectable disease, time of determination of unresectable disease until time of death from any cause. Patients with signs or symptoms of hormonal excess appropriate for the accompanying biochemical abnormality for each tumor type were considered as having functional neuroendocrine tumors. Patients without symptoms related to or biochemical evidence of hormone excess were considered as having nonfunctional tumors. Primary tumor location was determined by preoperative imaging reports, operative notes, and pathology reports. Tumors were classified as high risk under the following circumstances: (1) nodal or distant metastasis at the time of operation, (2) pathologic evidence of invasion into or beyond the capsule of the pancreas, or (3) the presence of lymphovascular/neural invasion. Surgical procedures were classified as R0 (no residual tumor), R1 (microscopic residual disease), or R2 (gross residual disease).

Delayed gastric emptying was defined as the need for gastric decompression for more than 10 days.[7] Pancreatic fistula was considered when fluid drainage having an amylase of three times greater than serum occurred any time after the third postoperative day.[8] An abscess was defined as any fluid collection identified with imaging or at surgical exploration in combination with the appropriate signs and symptoms. Any wound that required reopening was considered as a wound infection.

Survival curves were constructed using the Kaplan-Meier method and compared using log-rank analysis. Multivariate regression analysis was undertaken using Cox proportional hazards model to determine risk factors for poor overall survival using patient-related variables (age, gender, comorbidities, MEN1, symptoms), operation-related variables (operation undertaken, extent of resection, perioperative morbidity), and tumor-related variables (function, high-risk features, size, T stage, nodal status, metastases, margins, low- versus high-risk features). Unless otherwise stated, continuous data were compared using two-tailed Student's *t* test, and categorical data were compared using Fisher's exact test. Statistical significance was accepted with 95% confidence.

RESULTS

Patient Demographics

Eighty-three patients underwent resection of primary pancreatic neuroendocrine neoplasms from January 1990 through December 2004. Patients who underwent resection were significantly younger than those who were deemed unresectable with a slight female preponderance (Table 1).

Clinical Presentation

In 18 patients (15%), pancreatic masses were identified incidentally and, as such, were without specific symptoms (Table 1). All of these tumors were found to be hormonally inactive except for one patient with MEN1 found to have a gastrinoma by an elevated gastrin level during screening. The remaining patients presented with symptoms related to hormone excess (n = 59) or local tumor invasion (n = 43). Twelve of 13 (92%) MEN1 patients presented with functional tumors compared to 53 of 107 (50%) with sporadic tumors ($P = 0.003$). The most common presentation in the patients with functional tumors was Zöllinger-Ellison (ZE) syndrome, occurring in all patients with gastrinomas (Table 1). Patients presenting with hypoglycemia were more likely to undergo resection. Otherwise,

Table 1. Demographics and clinical presentation of patients with primary pancreatic neuroendocrine tumors

	Not resected	Resected	*P*
No. of patients	37	83	
Gender	18 M/19 F	36 M/47 F	NS
Mean ± SD age	58 ± 14.8	52 ± 14.8	0.044
Multiple endocrine neoplasia type 1	2 (5%)	11 (13%)	NS
von Hippel-Lindau	0	1 (2%)	NS
Asymptomatic	2 (5%)	16 (19%)	NS
Pain	16 (43)	15 (18%)	0.006
Jaundice	2 (5%)	5 (6%)	NS
Hormone excess	16 (43%)	43 (52%)	NS
Zöllinger-Ellison syndrome	6 (16%)	17 (20%)	NS
Hypoglycemia	1 (3%)	14 (17%)	0.035
Rash	0	3 (4%)	NS
Diarrhea	1 (3%)	0	NS
Carcinoid syndrome	6 (16%)	4 (5%)	NS
WDHA syndrome	1 (3%)	3 (4%)	NS
Cushing's syndrome	0	1 (1%)	NS
Hypercalcemia	1 (3%)	1 (1%)	NS

NS = not significant ($P > 0.05$); WDHA = watery diarrhea, hypokelemia, achlorhydria.

the clinical presentation was similar between both groups of patients.

Gastrinoma and insulinoma were the most common of the 47 functional tumors resected (Fig. 1). All but four of these patients presented with symptoms associated with hormone excess. Two patients with carcinoid and one with pancreatic poly peptide-secreting tumor (PPoma) presented with pain, while an additional patient with carcinoid presented with obstructive jaundice.

Preoperative Localization

The results from 80 preresection computed tomography (CT) and 41 somatostatin scintigraphy (SS) scans were available for review. The primary tumor was successfully located by CT scan in 67 (84%) and by SS in 33 (80%). SS identified two primary tumors not visualized by CT, whereas three primary tumors were evident by CT only. Of 39 patients who had results available for both CT and SS scans, the primary tumors were identified in 36 (92%).

Of 29 patients with metastatic disease found at the time of resection, 26 (90%) had metastases identified prior to operation. Intra-abdominal metastases were identified preoperatively by CT in 26 of 29 (90%) patients compared to 12 of 16 (75%) with metastases who underwent preoperative SS (P = NS). Intra-abdominal metastases were identified by SS in three patients where CT did not show metastatic disease. The converse was true in one patient whose metastases were only seen by CT.

Operation

Neuroendocrine tumors occurred with similar frequency in the head and body/tail of the pancreas (Table 2). Tumors of the uncinate process or neck of the pancreas were much less common. As such, distal pancreatectomy with or without spleen preservation and pancreaticoduodenectomy with or without pylorus preservation were the most common operations undertaken. Three distal pancreatectomies were completed laparoscopically, one with spleen preservation. Tumor enucleation was used most commonly for tumors located in the head of the pancreas (n = 11).

In nearly one-quarter of patients, additional organs were partially or completely resected to remove metastatic or locally advanced disease (Table 2). Liver metastases were resected in 11 (13%), including

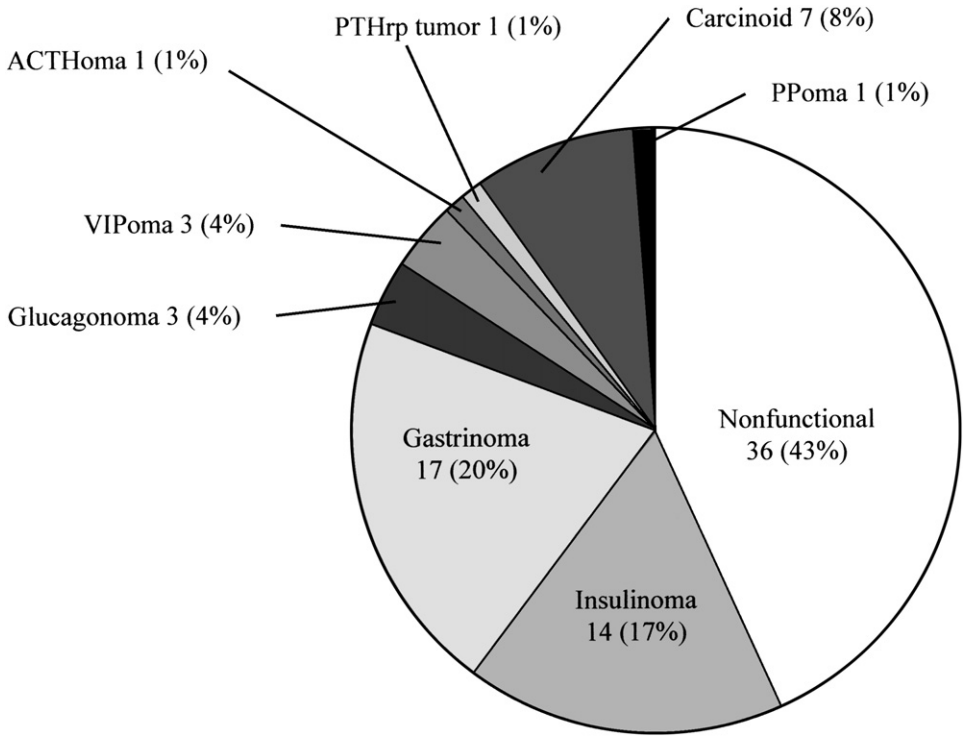


Fig. 1. Distribution of tumor types in patients with neuroendocrine tumors of the pancreas who underwent resection. Total does not add up to 100% due to rounding VIP = vasoactive intestinal peptide, ACTH = adrenocorticotropin hormone, PTHrp = parathyroid hormone-related protein, PP = pancreatic polypeptide.

Table 2. Operative characteristics of patients undergoing resection for neuroendocrine tumors of the pancreas

Tumor location	Head	39 (47%)*
	Uncinate	1 (1%)
	Neck	4 (5%)
	Body/tail	42 (51%)
Primary operation	SPD	13 (16%)
	PPPD	14 (17%)
	Distal pancreatectomy	41 (49%)†
	Enucleation	14 (17%)
	Central pancreatectomy	1 (1%)
Additional organs resected‡	Total patients	20 (24%)
	Liver	11 (13%)
	Stomach	7 (8%)
	Small/large bowel	7 (8%)
	Kidney	2 (1%)
	Adrenal gland(s)	3 (4%)
Extent of resection	R0	58 (70%)
	R1	6 (7%)
	R2	19 (23%)

PPPD = pylorus-preserving pancreaticoduodenectomy; SPD = standard pancreaticoduodenectomy.
*Includes two patients with combined head and tail lesions.
†Includes five patients undergoing spleen preservation and three laparoscopic pancreatectomies.
‡Number do not add up due to some patients having multiple procedures.

major liver resection (i.e., removal of two or more Couinaud segments) in 6 and wedge resection in 5.

Complete (i.e., R0) resection of all known disease was achieved in most patients (Table 2). The likelihood of an R0 resection was more common in patients with functional than in those with nonfunctional tumors (74% versus 64%, $P = 0.045$). Patients with metastatic tumors were less likely to undergo R0 resection (34% versus 89%, $P < 0.0001$) and more likely to have gross residual disease (59% versus 4%, $P < 0.0001$) than those without metastases. Similarly, patients with high-risk tumors were less likely to undergo R0 resection than those with low-risk tumors (63% versus 90%, $P = 0.027$). R0 resection was achieved in 67% of patients with symptomatic tumors compared to 81% of patients with asymptomatic tumors (P = NS). Patients with symptomatic tumors, however, were more likely to undergo R2 resection compared to those without symptoms (28% versus 0%, $P < 0.0001$). There were no significant differences between patients who underwent R2 resection and those in whom resection was not undertaken with respect to age, gender, comorbidities, MEN1, proportion of nonfunctional tumors, poor differentiation, or the presence of metastatic disease.

Pathology

Resected tumor sizes ranged from less than 1 to 14 cm (Table 3). The vast majority of tumors were high risk with nodal or distant metastasis accounting for the high-risk distinction in 48. The remaining 15 tumors were classified as high risk based upon lymphovascular invasion, neural invasion, or invasion into or beyond the capsule of the pancreas. Distant metastases were found in four patients without evidence of lymph node metastases and another five where lymph nodes were not harvested. Metastases were present in 18 (38%) functional tumors compared to 11 (31%) nonfunctional tumors (P = NS). The liver was the most common site for distant metastases. Seventy-four percent of functional tumors and 78% of nonfunctional tumors were classified as high-risk (P = NS).

The vast majority of tumors were well differentiated with only three classified as poorly differentiated (Table 3). Well differentiated tumors were slightly less likely to demonstrate high-risk features (70%) than those that were moderately (89%) or poorly (100%) differentiated, but this was not statistically significant ($P = 0.2$, χ^2 analysis).

Perioperative Morbidity

Fifty-four complications occurred in 36 (43%) patients following resection (Table 4). The most common complications were gastrointestinal and included pancreatic fistula (n = 7), delayed gastric emptying (n = 3), intestinal infarction (n = 2), pancreatic necrosis (n = 1), pancreatic pseudocyst (n = 2), anastomotic leak (n = 3), bile leak (n = 1), enterocutaneous fistula (n = 1), and bowel obstruction (n = 2). All seven pancreatic fistulas were asymptomatic and managed nonoperatively with drains placed at the time of initial operation. Infectious

Table 3. Pathologic features of resected pancreatic neuroendocrine tumors

Mean tumor size (cm)		3.6 ± 2.9 (SD)
Differentiation	Well	61 (73%)
	Moderate	19 (23%)
	Poor	3 (4%)
Histology	Low risk	20 (24%)
	High risk	63 (76%)
Node-positive disease		39 (60%)*
Metastases	Total patients	29 (39%)
	Liver	26
	Regional	2
	Kidney	1
Positive margin		15 (18%)

*Lymph nodes sampled in 65 patients.

Table 4. Complications in patients undergoing resection for neuroendocrine tumors of the pancreas

Total complications	54
Number of patients with complications	36 (43%)
Complication type	
Infectious	13
Cardiovascular	5
Respiratory	3
Gastrointestinal	22
Neurologic	2
Hematologic	8
Other	1
Death	5 (6%)

complications included: pneumonia (n = 5), abscess (n = 5), *Clostridium difficile* colitis (n = 1), central line infection (n = 1), and wound infection (n = 1). Noninfectious respiratory complications were acute respiratory distress syndrome (n = 1), pneumothorax (n = 1), and pleural effusion (n = 1). Hematologic complications included deep venous thrombosis (n = 5), pulmonary embolism (n = 2), and retroperitoneal hematoma (n = 1). Cardiovascular complications were arrhythmia (n = 4) and endocarditis (n = 1). Neurologic complications consisted of cerebral vascular accident (n = 1) and seizures (n = 1). Finally, one patient developed abdominal compartment syndrome. Five patients required reoperation in the early postoperative period; two for intestinal infarction, one for pancreatic necrosis, one for enteric anastamotic leak, and one for bowel obstruction. These patients accounted for four perioperative deaths. A fifth patient died in the perioperative period from a cerebrovascular accident. Perioperative mortality was significantly higher following R2 resection (21% versus 2%, $P = 0.009$).

Follow-up and Survival

Complete clinical data were available for all patients. After median follow-up of 41.8 months (range 0.4–138.8), 29 additional patients died and 49 patients remained alive. During this time, recurrences occurred in 19 patients a median 14 months after operation. Liver was the most common site of recurrence (n = 13), while one patient had local recurrence in the bed of pancreatic resection following R1 resection, one recurred in the pelvis, and two each recurred elsewhere in the pancreas or small bowel mesentery. Two patients underwent resection of their metachronous hepatic metastases, and a third had staged resection of a synchronous liver metastasis. One died of cholangitis related to a biliary stricture 20 months following liver resection and subsequent hepatic artery chemoembolization (33 months after distal pancreatectomy), one is alive with recurrent disease in the liver 47 months after liver resection (79 months after distal pancreatectomy), and one is alive without evidence of disease 12 months after distal pancreatectomy (11 months after hepatectomy). Thirteen others underwent hepatic artery chemoembolization for unresected synchronous metastases (n = 8) or recurrent disease (n = 5); seven died at a median of 38 months after pancreatectomy and seven are alive at median of 50.7 months of follow-up.

Patients who underwent resection had significantly longer survivals than those who did not have resection (Fig. 2). The actuarial overall survival rates following resection at 2, 5, and 10 years were 77%, 62%, and 40%, respectively, with a median survival of 91 months (95% confidence interval 62.8–119.9). In patients not undergoing resection, 2-, 5-, and 10-year survival was 49%, 23%, and 0%, respectively, with median survival of 52.8 months (95% confidence interval 22.2–83.5).

Patients who had complete resection of all gross tumor (i.e., R0/R1) had significantly improved survival compared to those left with gross residual (R2) disease (median 112.1 months versus 24.1, $P = 0.0002$). Patients who had R2 resection had survival similar to those who did not have resection (median 24.0 versus 23.9 months) (Fig. 3A). This lack of difference in survival curves held true when the four postoperative deaths after R2 resection were excluded.

Data concerning the degree of differentiation were available for all resected tumors. Given the limited number of poorly differentiated tumors and the similar survival associated with moderate and poor differentiation (24.1 versus 19.4 months, respectively), these tumors were considered together in comparison to well-differentiated tumors. Well differentiation imparted a survival advantage over those with moderate or poor differentiation (139.7 versus 21.9 months, $P = 0.00004$) (Fig. 3B). Finally, patients with tumors that were deemed low risk based upon lack of nodal or distant metastases, vascular or neural invasion, or local invasion had significantly prolonged survival compared to those with high-risk tumors (median 142.5 versus 69.6 months, $P = 0.003$) (Fig. 3C). Other risk factors predictive of poor outcome by univariate analysis are tumor size greater than 3.0 cm, presence of distant metastases, and positive margins (Table 5). Well-differentiated tumors and complete removal of all gross disease were significant predictors of improved survival by multivariate analysis.

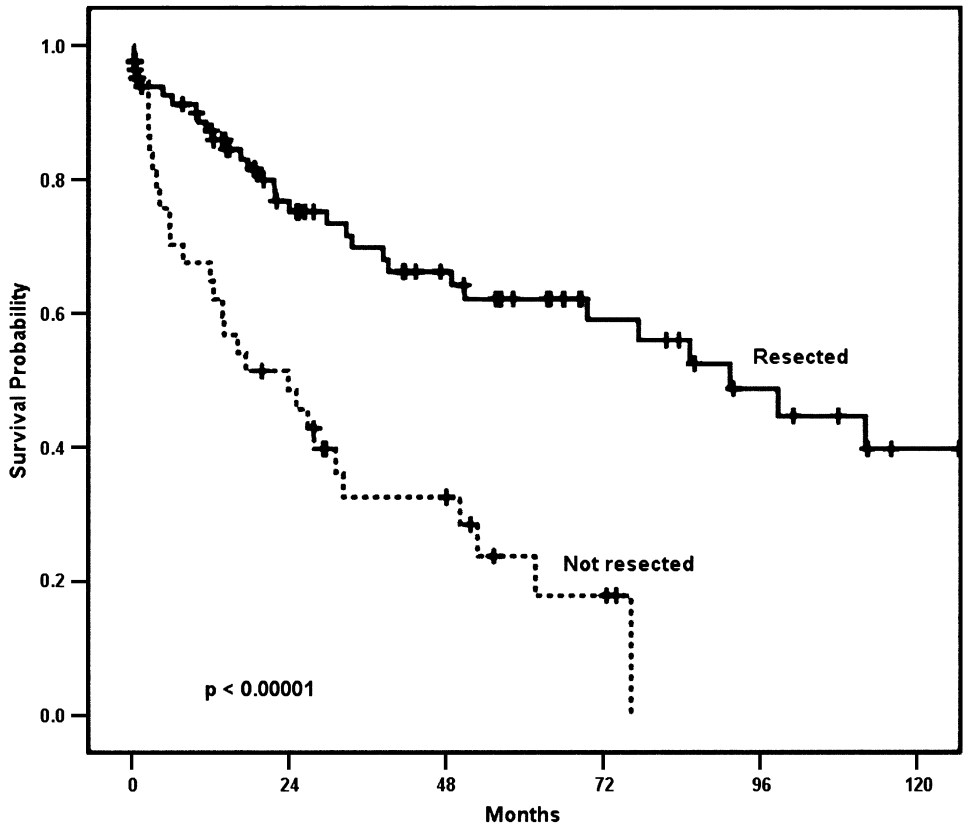


Fig. 2. Kaplan-Meier Curves for overall survival in patients who had resection of pancreatic neuroendocrine tumors compared to those in whom resection was not undertaken.

DISCUSSION

Neuroendocrine tumors of the pancreas were first described over 100 years ago when discovered at autopsy.[9] The first clinical syndrome associated with a neuroendocrine tumor and the first surgical interventions would not be reported until the 1920s.[10,11] With Zöllinger and Ellison's first report of the syndrome of intestinal ulcerations associated with an autonomously functioning gastrin-producing tumor in 1955, the link between hormone dyscrasias and neuroendocrine tumors of the pancreas began to be investigated.[12] Since then, few institutions began to amass experience in the management of these rare pancreatic tumors. In this report, we present our experience with resection of pancreatic neuroendocrine tumors in 83 patients since 1990, representing one of the largest experiences in the modern surgical era.

Our patients who underwent resection of their pancreatic neuroendocrine tumors tended to be in their early 50s with a female preponderance. These patients were younger than patients presenting during the same time period who did not have resection. Hereditary predisposition to pancreatic neuroendocrine tumors was evident in 13% of our resected patients, which is similar to the 5–15% incidence reported previously.[13–15] The majority of tumors were hormonally active (i.e., "functional"). As such, most patients presented with symptoms appropriate for the excess hormone. As expected, gastrinomas and insulinomas composed the vast majority of functional tumors. Nonfunctional tumors tended to present either asymptomatic or with symptoms related to local space-occupying effects (e.g., pain or jaundice). Preoperative imaging consisted of CT scanning in nearly all patients, while somatostatin scintigraphy was obtained in only half. When applied, these imaging modalities were equally sensitive in localizing the primary tumor. When combined, they had a sensitivity of 92% but in no case did preoperative somatostatin scintigraphy alter the course of management. In our hands, the potential benefit of this imaging modality preoperatively is to document tumor avidity allowing for its use in surveillance for recurrent disease following resection.

Most tumors were removed by radical resection commensurate with their location within the

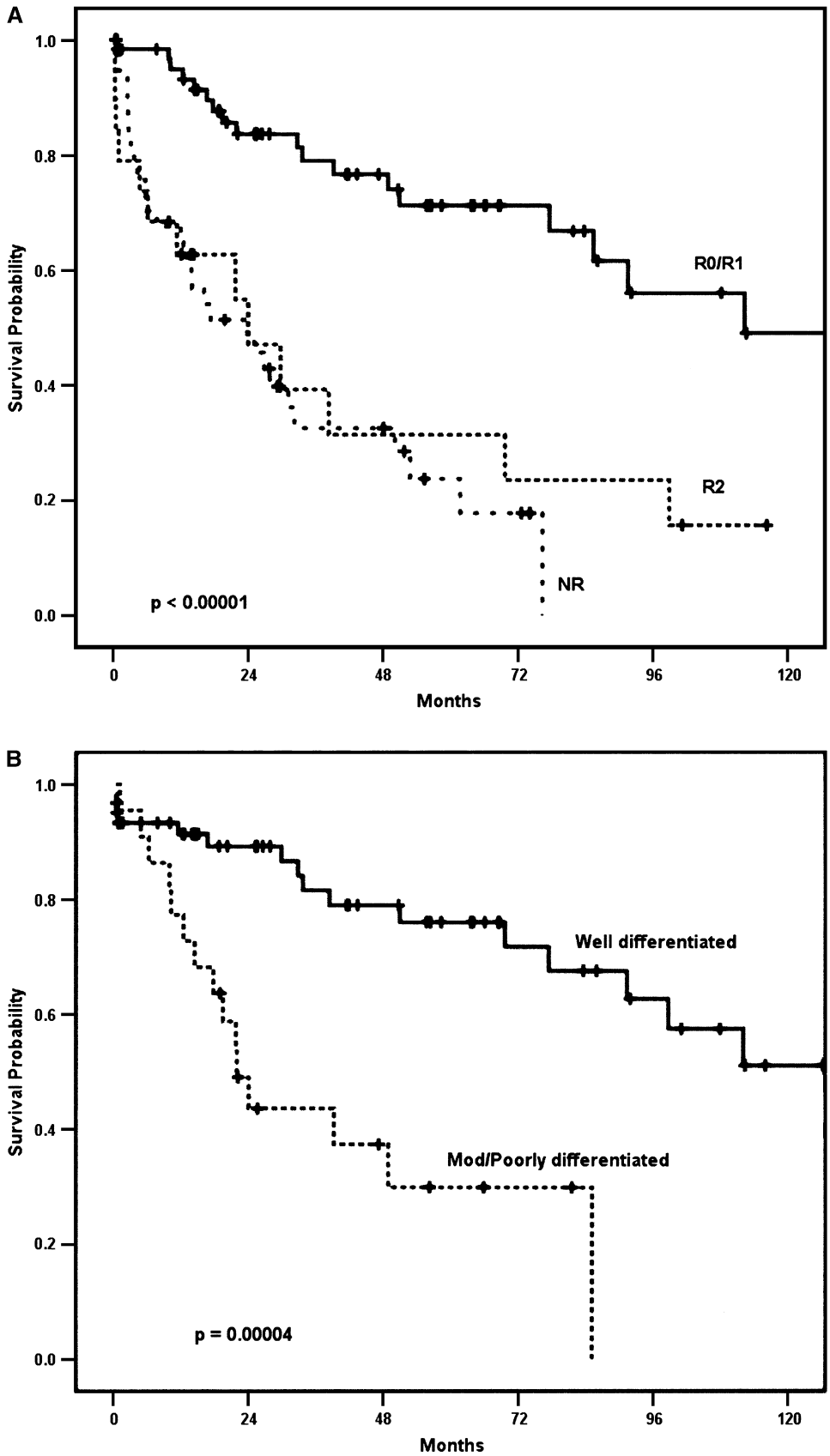


Fig. 3. Kaplan-Meier survival curve comparisons between patients undergoing resection of neuroendocrine tumors of the pancreas based upon (**A**) completeness of resection, (**B**) tumor differentiation, and (**C**) high- versus low-risk tumor.

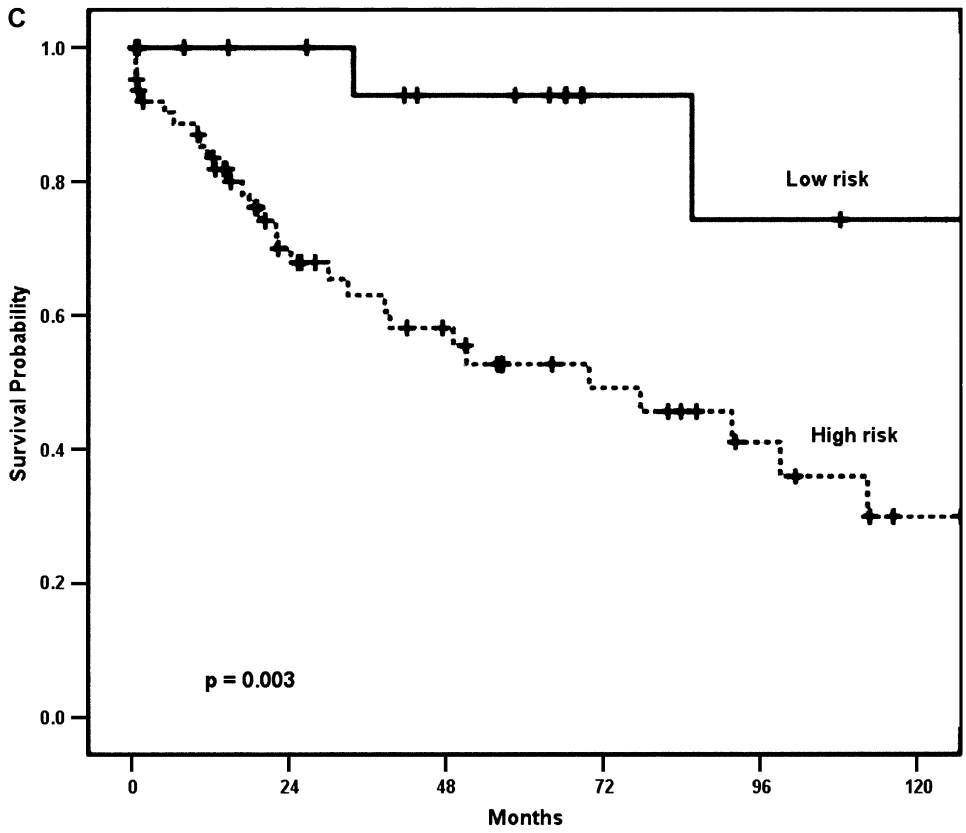


Fig. 3. Continued.

pancreas. Tumor enucleation was reserved for patients in which radical resection seemed excessive given an easily accessible small lesion. Two patients undergoing enucleation recurred in the small bowel mesentery outside of what would have been the confines of a more radical resection and one patient with MEN1 recurred within the pancreas. Tumor enucleation did not significantly reduce postoperative

Table 5. Risk factors for overall survival

	P-value		Hazard ratio	95% Confidence interval
	Univariate	Multivariate		
Age (≤50 yr vs. >50 yr)	NS	NS		
Gender (M vs. F)	NS	NS		
Comorbidities (present vs. absent)	NS	NS		
Family history (MEN1 vs. sporadic)	NS	NS		
Operation (radical vs. enucleation)	NS	NS		
Extent of resection (R2 vs. R0/R1)	<0.001	0.008	3.7	1.4–9.9
Additional organs resected (yes vs. no)	NS	NS		
Tumor differentiation (moderate/poor vs. well)	<0.001	<0.001	7.4	2.7–20.3
Tumor size (≤3 cm vs. >3 cm)	0.011	NS		
Functional (yes vs. no)	NS	NS		
Nodal status (positive vs. negative)	NS	NS		
Metastases (present vs. absent)	0.01	NS		
Margins (positive vs. negative)	0.003	NS		
Complications (yes vs. no)	NS	NS		
Malignant potential (low risk vs. high risk)	0.003	NS		

complications and accounted for a higher pancreatic fistula rate (21%) than radical resection (6%), although none of these fistulas were of clinical significance. However, there were no postoperative deaths following enucleation and, therefore, we continue to use this approach when appropriate in patients who may not otherwise tolerate a more complex resection.

Overall, perioperative mortality was 6%. This is slightly higher than what has been reported in other studies.[3,14,16] This is likely related to our aggressive resection of adjacent organs and metastatic disease. Phan et al.[14] reported 125 resected periampullary neuroendocrine tumors over a 48-year period. In that series, concomitant resection of other organs was undertaken in 9.6% and liver resection was used in 7% with a perioperative mortality of 2.8%. Similarly, Matthews et al.[16] undertook concomitant liver resection in 11% with a perioperative mortality of 3.5%. The extent of liver resection in these two series was not stated. Chu et al.,[3] on the other hand, reported concomitant major hepatectomy in two patients (10%) with a resultant 6% perioperative mortality. In our series, additional organs were resected for disease in 24% with liver resection being applied in 11 (13%), 6 of whom underwent major hepatectomy. When patients with advanced disease were unable to be completely resected (i.e., R2 resection), perioperative mortality was increased (21% versus 2%). This could be explained by these patients being more debilitated due to the chronicity of their disease or heavier tumor burden. Additionally, patients undergoing incomplete resections were forced to recover with a still significant tumor load, usually in the liver. The decision to aggressively resect metastatic disease at the time of primary resection is still made on a case-by-case basis. This limited experience is too small to make any meaningful conclusions on the safety of this approach, but we still consider it in younger healthy patients in whom resection of the primary has gone smoothly with minimal blood loss and removal of all gross disease is anticipated.

The histologic distinction between benign and malignant neuroendocrine tumors is a difficult one that has not been fully defined. It is our belief that all neuroendocrine tumors possess malignant potential and, therefore, we consider them all as carcinomas. Instead, using the criteria of the presence of nodal or distant metastases, invasion of the primary into or through the capsule of the pancreas, or lymphovascular or neural invasion, 76% of tumors were able to be classified as high risk for aggressive behavior. While this classification system has not been tested prospectively and does not always allow for preoperative risk assessment for aggressive behavior, it does allow for postoperative risk stratification and individualization of surveillance. The significant difference in survival between low- and high-risk tumors reiterates the importance of thorough histologic evaluation of the primary tumor, including the determination of lymphvascular/neural invasion, although this distinction was not itself a significant predictor by multivariate analysis. The degree of tumor differentiation, on the other hand, did significantly affect survival by univariate and multivariate analyses, clearly favoring those with well differentiated tumors. Less important for long-term survival were margin status and node negativity, although these statistics were likely influenced by small sample size. Contrary to other reports, tumor function did not affect survival, likely due to the advanced stage of all patients common in our referral practice.

Besides tumor differentiation, the only other factor that was predictive of long-term survival by multivariate analysis was the extent of resection. Patients with gross residual disease after resection of their pancreatic primary were at a distinct disadvantage. In fact, these patients fared no better, and arguably worse given the four postoperative deaths, than those who did not have any resection at all. This did not appear to be a selection bias given the similarity between the two groups of patients with respect to demographic and pathological data measured.

CONCLUSION

The surgical management of patients with neuroendocrine tumors of the pancreas continues to evolve. While systemic chemotherapy is notoriously ineffective against these tumors, liver-directed therapies such as hepatic artery chemoembolization coupled with long-term survival commonly seen in patients with advanced disease has led many toward advocating an aggressive surgical approach, even cytoreduction.[5,17,18] As well, cytoreduction of 90% or greater of tumor volume has been suggested to improve symptom control of endocrinopathies associated with function neuroendocrine tumors.[19,20] We, too, have traditionally approached these patients aggressively. While long-term survival is possible in patients with advanced neuroendocrine tumors of the pancreas, debulking strategies for cytoreduction or symptom palliation resulting in R2 resection are difficult operations resulting in substantial postoperative mortality without any clear survival benefit over no resection. Given the nearly 2-year median survival without resection of advanced neuroendocrine tumors, noncurative operations in these patients should be avoided. The best hope

for long-term survival is a curative surgical approach with anticipation of clearing of all gross disease.

REFERENCES

1. Meko JB, Norton JA. Endocrine tumors of the pancreas. Curr Opin Gen Surg 1994;186–194.
2. Bieligk S, Jaffe BM. Islet cell tumors of the pancreas. Surg Clin North Am 1995;75:1025–1040.
3. Chu QD, Hill HC, Douglass HO Jr, Driscoll D, Smith JL, Nava HR, Gibbs JF. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. Ann Surg Oncol 2002;9:855–862.
4. Evans DB, Skibber JM, Lee JE, Cleary KR, Ajani JA, Gagel RF, Sellin RV, Fenoglio CJ, Merrell RC, Hickey RC. Nonfunctioning islet cell carcinoma of the pancreas. Surgery 1993;114:1175–1181; discussion 1181–1182.
5. Pederzoli P, Falconi M, Bonora A, Salvia R, Sartori N, Contro C, Marcucci S, Bassi C. Cytoreductive surgery in advanced endocrine tumours of the pancreas. Ital J Gastroenterol Hepatol 1999;31(Suppl 2), S207–S112.
6. Sato T, Konishi K, Kimura H, Maeda K, Yabushita K, Tsuji M, Demachi H, Miwa A. Strategy for pancreatic endocrine tumors. Hepatogastroenterology 2000;47:537–539.
7. Yeo CJ. Management of complications following pancreaticoduodenectomy. Surg Clin North Am 1995;75:913–924.
8. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M. Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 2005;138:8–13.
9. Nicholls A. Simple adenoma of the pancreas arising from an island of Langerhans. J Med Res 1902;8:385–395.
10. Howland G, Campbell W, Maltby E, Robinson W. Dysinsulinism: Convulsions and coma due to islet cell tumor of the pancreas, with operation and cure. JAMA 1929;93:674–679.
11. Wilder R, Allan F, Power M, Robertson H. Carcinoma of the islands of the pancreas: Hyperinsulinism and hypoglycemia. JAMA 1927;89:348–355.
12. Zollinger R, Ellison E. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955;142:709–728.
13. Norton JA, Kivlen M, Li M, Schneider D, Chuter T, Jensen RT. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. Arch Surg 2003;138:859–866.
14. Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: Review of 125 patients. J Gastrointest Surg 1998;2:472–482.
15. Jordan PH Jr. A personal experience with pancreatic and duodenal neuroendocrine tumors. J Am Coll Surg 1999;189:470–482.
16. Matthews BD, Heniford BT, Reardon PR, Brunicardi FC, Greene FL. Surgical experience with nonfunctioning neuroendocrine tumors of the pancreas. Am Surg 2000;66:1116–1122; discussion 1122–1123.
17. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, Murthy R, Hicks ME, Ajani JA. Hepatic artery embolization and chemoembolization for treatment of patients with metastatic carcinoid tumors: The M.D. Anderson experience. Cancer J 2003;9:261–267.
18. Yao KA, Talamonti MS, Nemcek A, Angelos P, Chrisman H, Skarda J, Benson AB, Rao S, Joehl RJ. Indications and results of liver resection and hepatic chemoembolization for metastatic gastrointestinal neuroendocrine tumors. Surgery 2001;130:677–682; discussion 682–685.
19. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, Rosemurgy AS, Yeatman TJ, Carey L, Duhaine L, Kvols LK. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol 2006;13:572–581.
20. Sarmiento JM, Que FG, Grant CS, Thompson GB, Farnell MB, Nagorney DM. Concurrent resections of pancreatic islet cell cancers with synchronous hepatic metastases: Outcomes of an aggressive approach. Surgery 2002;132:976–982; discussion 982–983.

Durability of Portal Venous Reconstruction Following Resection During Pancreaticoduodenectomy

Rory L. Smoot, M.D., John D. Christein, M.D., Michael B. Farnell, M.D.

Venous resection and reconstruction is becoming more common during pancreaticoduodenectomy (PD). There are multiple options for reconstruction of the mesenteric venous system ranging from primary repair to grafting with autologous or synthetic material. Few studies report on the patency rates and long-term morbidity of these repairs. We sought to describe our experience with venous reconstruction during PD with specific attention to patency and long-term morbidity and mortality. Thrombosis rates of mesenteric venous reconstruction during PD are low, with low associated morbidity. In this retrospective cohort, clinical, operative, and pathologic data were collected from consecutive patients for 1988 through 2003. Graft patency on follow-up imaging studies was determined, and short- as well as long-term morbidity and mortality were recorded. Sixty-four patients underwent PD with venous resection/reconstruction from 1988 through 2003. Mean patient age was 63 years, with pancreatic ductal adenocarcinoma as the pathology in 88%. Reconstruction consisted of primary lateral venorrhaphy in 29 (45%), PTFE graft in 18 (28%), primary end-to-end repair in 13 (20%), and autologous vein graft in 4 (6%). There was one perioperative death (2%). Follow-up imaging to assess patency was available for a mean of 12.2 months postoperatively. Eleven thromboses were diagnosed at a mean of 11.9 months. Three thromboses (5%) were noted within 30 days and full anticoagulation was chosen. Fifty-three percent of patients received anticoagulation with aspirin, warfarin, or clopidogrel based upon surgeon preference. There was no difference in thrombosis rates between those receiving anticoagulation and those who did not ($P = 0.65$). In those patients with thrombosis outside the acute time period, morbidity was limited to ascites in three patients and splenic vein thrombosis with uncomplicated esophageal varices in another patient. Mesenteric venous resection and reconstruction during PD has a high patency rate, and those reconstructions that do thrombose are associated with a low morbidity. The majority of reconstruction thromboses that occurred late were associated with recurrence. (J GASTROINTEST SURG 2006;10:1371–1375)

KEY WORDS: Pancreaticoduodenectomy, pancreatic cancer, superior mesenteric vein, portal vein, vein resection, thrombosis

Approximately 30,000 cases of pancreatic cancer will be diagnosed each year, with the mortality rate approaching the incidence.[1] Pancreaticoduodenectomy (PD) with complete resection offers the only chance for cure. However, due to the presence of metastatic disease or invasion of local structures, most patients are not operative candidates at presentation. Historically, involvement of regional vasculature by pancreatic carcinoma has been considered a contraindication to resection. In 1973, Fortner[2] described the technique of an en bloc regional pancreatectomy for pancreatic cancer, including arterial and venous resection and reconstruction, but the morbidity and mortality rates proved prohibitive. As operative experience has increased with PD, those cases in which venous resection is performed have become more common, and morbidity and mortality rates have become acceptable. Currently, venous resection has been reported in up to 20% of pancreaticoduodenectomies at high-volume pancreatic surgery centers.[3,4]

Several series have compared PD with and without venous resection, documenting similarities in morbidity, operative mortality, and survival.[5–12] Few have analyzed the durability of venous reconstruction following resection during PD.[4,13] The aim of this study was to evaluate the durability of venous reconstruction during PD with special attention to the type of reconstruction and the associated morbidity.

From the Division of Gastroenterologic and General Surgery, Department of Surgery, Mayo Clinic, Rochester, Minnesota (R.L.S., M.B.F.) and Department of Surgery, Section of Gastrointestinal Surgery, University of Alabama at Birmingham, Birmingham, Alabama (J.D.C.).
Reprint requests: Michael B. Farnell, M.D., Department of Surgery, Division of Gastroenterologic and General Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. e-mail: farnell.michael@mayo.edu

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.001

METHODS

Consecutive patients undergoing PD with venous resection at the Mayo Clinic, Rochester, Minnesota, between 1988 and 2003 were identified. Clinicopathologic factors were analyzed to determine factors affecting durability and to identify morbidity associated with failure of venous reconstruction. Categorical variables were compared using χ^2 analysis.

Operative Technique

Contrast-enhanced computed tomography (CT) has been the most useful imaging study in determining local resectability, the utility of which has been well documented.[14,15] When indicated in fit patients, a PD is undertaken as previously described.[16] Adherence to the lateral or posterior aspect of the portal vein–superior mesenteric vein (PV-SMV) may not be discovered until the pancreatic head has been reflected laterally following transection of the pancreatic neck. At this point, one is committed to resection and the surgeon should have a plan for tangential or segmental excision of the involved venous segment.

Early in our experience, we completed venous resection prior to division of the arterial branches and soft tissue along the right lateral aspect of the superior mesenteric artery (SMA). More recently, we have altered our technique by performing the dissection of the retroperitoneal margin prior to venous resection. The advantages of this are to avoid the need for venous anastomosis prior to removal of the specimen, minimize venous occlusion time, and allow preservation of the splenic vein. This is accomplished by performance of a generous Kocher maneuver and isolation of the superior mesenteric artery both at its origin and caudad to the uncinate process. The Kocher maneuver orients the superior mesenteric artery posterior to the PV-SMV and allows access for completion of the retroperitoneal dissection. Arterial branches coursing into the uncinate are sequentially clamped, divided, and ligated, thereby completely freeing the pancreas from the SMA. The pancreatic head is then rotated back to its normal anatomic orientation and the venous resection performed as the final step prior to specimen removal. Vascular control is always obtained proximally and distally taking care to isolate the SMV, PV, and splenic vein. In addition, we have found in-flow occlusion of the SMA concurrently with venous clamping useful in minimizing bowel edema. Systemic heparinization at the time of resection and reconstruction has not been used routinely. The venous segment is sharply excised to ensure a negative margin. Once the specimen is removed, the venous segment as well as the portal vein groove and uncinate margin should be marked. Communication between the surgical and pathologic teams is imperative to accurately assess the pancreatic and venous specimens for invasion and margin status.

In order to harvest the left renal vein, the Kocher maneuver is extended to the left. The left renal vein is stapled flush with the inferior vena cava and just to the right of the insertion of the left gonadal and adrenal veins (Fig. 1).

In completing the venous reconstruction, the venous segment should be fully mobilized to reduce tension on the anastomosis. Mobilizing the PV and SMV is accomplished by ligating and dividing multiple small venous tributaries. Both the root of the small bowel mesentery and the right colon may be released posteriorly to increase mobility and minimize tension on the anastomosis. Intraoperative ultrasound is used to evaluate the venous reconstruction for patency, and once established; the remainder of the reconstruction (pancreaticojejunostomy, hepaticojejunostomy, and duodenojejunostomy) is completed.

RESULTS

For the years 1988 through 2003, 64 patients were identified who underwent PD with venous resection and reconstruction. Thirty-one men and 33 women had a mean age of 63 years. The dominant pathology was pancreatic ductal adenocarcinoma (n = 56, 88%), with four patients undergoing PD with venous resection for islet cell neoplasms, two with an inflammatory mass, one with distal cholangiocarcinoma, and one with metastatic colon adenocarcinoma.

Thirty-four patients (53%) underwent a pylorus-preserving PD, while 30 patients underwent a standard PD. Venous reconstruction was accomplished with primary lateral venorrhaphy in 29 patients (45%), a PTFE graft (n = 18, 28%), primary end-to-end anastomosis (n = 13, 20%), or an autologous vein graft (n = 4, 6%). Two of the PTFE reconstructions were patches, while 16 were ringed interposition grafts. Total clamp time was recorded for 36 patients (mean, 14 minutes). Patency was routinely assessed with intraoperative ultrasound.

The most common perioperative complication was delayed gastric emptying, occurring in 17 patients (27%). Two patients (3%) experienced anastomotic hemorrhage requiring reoperation. Three patients (5%) were diagnosed with a pancreatic leak, and five (8%) were found to have an

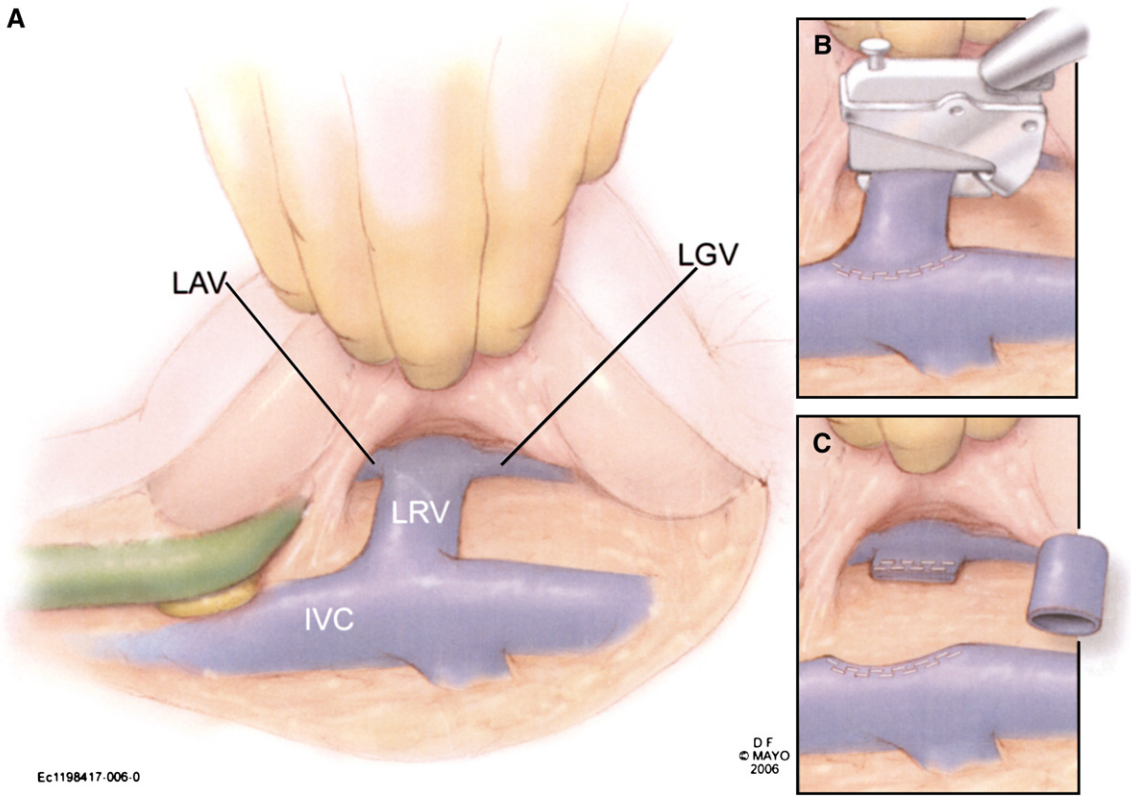


Fig. 1. A, The Kocher maneuver is extended to the left and elevation of the pancreatic head allows exposure of the entire left renal vein (LRV) as well as the left adrenal (LAV) and gonadal veins (LGV). B, The vein is transected with a linear stapling device distal to the insertion of the left adrenal and gonadal veins and again flush with the inferior vena cava (IVC). C, The left renal vein is used as an interposition graft to restore continuity to the mesenteric venous system. (Permission granted by the Mayo Foundation for Medical Education and Research.)

intra-abdominal abscess. Two patients had evidence of hepatic ischemia at the time of reperfusion, which was documented by transient transaminase elevation. Additionally, three patients undergoing autologous vein grafting with the left renal vein experienced a transient increase in serum creatinine levels. There was one perioperative death (2%), secondary to acute thrombosis. Hepatic failure ensued and hemorrhage complicated by coagulopathy led to death. Two additional patients received therapeutic anticoagulation secondary to acute thrombosis following a PTFE interposition graft in one patient and primary end-to-end repair in the other.

Thirty-four patients (53%) were anticoagulated following the reconstruction, based on attending surgeon preference. Nineteen patients were treated with aspirin, 11 with warfarin, and 4 with clopidogrel. There was no difference in thrombosis rates in those patients receiving anticoagulation compared to those who did not ($P = 0.65$).

Follow-up imaging was performed in 61 patients (95%) and available a mean of 12.2 months postoperatively. Eleven (17%) thromboses were diagnosed, and mean time to thrombosis was 11.9 months (range, 0.1–38.7 months). Three of the thromboses were noted within the first 30 days, while the remaining were found at a mean of 16.2 months. Of the 11 thromboses, the reconstructions consisted of a PTFE interposition graft (n = 6), lateral venorrhaphy (n = 3), and primary end-to-end anastomosis (n = 2). A higher percentage of patients with a PTFE interposition graft had documented thromboses when compared to those who underwent other types of reconstruction (33% versus 12%); however, this difference was not significant ($P = 0.16$). Ascites was diagnosed in three patients, and one patient developed splenic vein thrombosis and uncomplicated esophageal varices.

DISCUSSION

Although PD offers the only chance for cure in patients with pancreatic head adenocarcinoma, questions have arisen regarding the indications, safety,

and outcomes of patients undergoing extended resections for locally advanced disease. While previous studies have focused on margin status and comparisons of overall survival, few have analyzed the durability of the venous reconstruction or reported on the morbidity associated with graft thrombosis.[6,7]

In this series, PD with venous resection was most commonly performed for ductal adenocarcinoma of the pancreatic head. The majority of patients underwent a tangential venous resection with reconstruction completed by primary lateral venorrhaphy. Primary end-to-end anastomoses and interposition grafting were performed less frequently early in our experience but are now the two techniques we prefer. Importantly, the conduit selection for interposition grafting in this series differs from that in the literature. Early in the series, PTFE interposition grafts were used, while our current practice is to use the left renal vein as an interposition graft if possible. Previous reports describe the saphenous vein[10] or internal jugular vein[4] for autologous grafting. Access to the left renal vein is relatively straightforward and is gained through the same operative field. The caliber of the graft is similar to the PV, and although the number included in this series is low, no thromboses of the left renal vein grafts were observed. Following reconstruction with the left renal vein, all patients were evaluated with contrast-enhanced CT demonstrating renal blood flow and patent reconstruction. Renal function was preserved in all four left renal vein graft patients in this series.

Of the 11 thromboses observed (17%), only 3 (5%) were in the acute setting (less than 30 days). One of these three patients died secondary to the acute thrombosis. At the time of PD in this patient, access to the PV demonstrated involvement of the portal vein lumen with extension into the liver. Potentially curative resection was not possible; thus, tangential excision of the portal vein was performed with primary lateral venorrhaphy in order to complete removal of the specimen. On postoperative day (POD) 2, thrombosis was noted with hepatic insufficiency. Progressive hepatic failure with coagulopathy and bleeding led to death on POD 13. Acute thrombosis was also noted on POD 8 in a patient who had undergone PTFE interposition grafting. The thrombosis resolved with intravenous heparin therapy. This patient had metastatic colonic adenocarcinoma and was subsequently found to be heterozygous for factor V Leiden and continued on warfarin therapy. The third patient with an acute thrombosis had undergone primary end-to-end reconstruction and had thrombosis noted on POD 6, which resolved with intravenous heparin and outpatient warfarin therapy. Importantly, the remaining eight thromboses were documented late (mean, 16.2 months) and were noted at the time of, or following identification of, locoregional recurrence. In these patients, the long-term morbidity attributable to thrombosis was limited. Three of these patients with late thrombosis developed ascites. An additional patient with splenic vein thrombosis went on to develop uncomplicated esophageal varices.

The literature documenting portal vein graft thrombosis rates is sparse. DiPerna et al.[13] observed patency rates of 93% and 90% at 12 and 24 months, respectively. Unfortunately, this series included multiple different vascular reconstructions, of which only eight were portal vein resections with reconstruction. More specifically, Tseng et al.[4] noted occlusion in 6.9% of portal vein grafts, but specific timing and morbidity were not discussed. The thrombosis rate (17%) in this series is higher than those previously reported, but acute thrombosis occurred in only 5% of reconstructions. Importantly, in this series graft thrombosis appears to be a late event in the majority of patients, is associated with recurrence, and has a low morbidity.

Recommendations for anticoagulation following major venous reconstruction for malignancy have varied. In this experience, patients received a variety of agents including aspirin, warfarin, and clopidogrel. No difference was observed in thrombosis rates when comparing patients receiving therapy and those who did not ($P = 0.65$). There is a paucity of literature regarding anticoagulation following portal venous reconstruction, although as previously mentioned, the use of PTFE interposition grafts is not a widespread practice. The literature available regarding anticoagulation and abdominal venous reconstructions involving synthetic grafts focuses on inferior vena cava repair and the use of warfarin. Sarmiento et al.[17] reported 19 inferior vena cava reconstructions, following en bloc resection for malignancy, after which all patients were initially anticoagulated with heparin and then transitioned to warfarin. Two patients experienced late graft thromboses, with a 91% patency rate at 3 years. The question remains whether anticoagulation with warfarin should follow PTFE interposition grafting of the SMV-PV after PD, and if this recommendation can be extrapolated from experiences with the inferior vena cava reconstructions. While a higher percentage of PTFE grafts thrombosed in our series, this was not statistically different, and the majority of thromboses were diagnosed following recurrence.

Currently, our approach to patients with SMV-PV involvement is to perform lateral venorrhaphy

only if possible without compromising luminal diameter. Primary end-to-end anastomosis is performed in those patients requiring segmental resection if it can be accomplished without tension. In those patients who cannot be reconstructed with primary end-to-end anastomosis, an interposition graft is used, with the left renal vein being our first preference due to ease of harvest and its handling properties. Following interposition grafting, a daily aspirin in instituted. If perioperative imaging reveals evidence of thrombosis, therapeutic anticoagulation is recommended.

CONCLUSIONS

The decreased morbidity and mortality of PD with venous resection and reconstruction have made this operation a reasonable option in patients with locally advanced disease. The durability of venous reconstruction is good, and although thrombosis occurs, in the majority of patients it is following recurrence and is associated with limited morbidity. The left renal vein offers an alternative to synthetic interposition grafting and may decrease thrombosis rates. Overall, the ability to identify those patients appropriate for venous resection and reconstruction will remain paramount, and the operation should only be attempted by surgeons at high-volume pancreatic centers with experience in venous resection and reconstruction.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Fortner JG. Regional resection of cancer of the pancreas: A new surgical approach. Surgery 1973;73:307–320.
3. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996;223:273–279.
4. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: Margin status and survival duration. J Gastrointest Surg 2004;8:935–950.
5. van Geenen RC, ten Kate FJ, de Wit LT, van Gulik TM, Obertop H, Gouma DJ. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129:158–163.
6. Bachellier P, Nakano H, Oussoultzoglou PD, et al. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 2001;182:120–129.
7. Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003;186:149–153.
8. Kawada M, Kondo S, Okushiba S, Morikawa T, Katoh H. Reevaluation of the indications for radical pancreatectomy to treat pancreatic carcinoma: Is portal vein infiltration a contraindication? Surg Today 2002;32:598–601.
9. Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996; 223:154–162.
10. Howard TJ, Villanustre N, Moore SA, et al. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. J Gastrointest Surg 2003;7:1089–1095.
11. Poon RT, Fan ST, Lo CM, et al. Pancreaticoduodenectomy with en bloc portal vein resection for pancreatic carcinoma with suspected portal vein involvement. World J Surg 2004;28:602–608.
12. Shibata C, Kobari M, Tsuchiya T, et al. Pancreatectomy combined with superior mesenteric-portal vein resection for adenocarcinoma in pancreas. World J Surg 2001;25: 1002–1005.
13. DiPerna CA, Bowdish ME, Weaver FA, et al. Concomitant vascular procedures for malignancies with vascular invasion. Arch Surg 2002;137:901–906; discussion 6–7.
14. Bold RJ, Charnsangavej C, Cleary KR, et al. Major vascular resection as part of pancreaticoduodenectomy for cancer: Radiologic, intraoperative, and pathologic analysis. J Gastrointest Surg 1999;3:233–243.
15. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: Prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol 2004;99:492–501.
16. Heywood G, Farnell MB. Pancreatic and periampullary carcinoma. In: Kelly KA, Sarr MG, Hinder RA, eds. Mayo Clinic Gastrointestinal Surgery. Philadelphia: Saunders, 2004, pp 271–297.
17. Sarmiento JM, Bower TC, Cherry KJ, Farnell MB, Nagorney DM. Is combined partial hepatectomy with segmental resection of inferior vena cava justified for malignancy? Arch Surg 2003;138:624–630; discussion 30–31.

In Vitro Evidence for Role of ERK, p38, and JNK in Exocrine Pancreatic Cytokine Production

Isaac Samuel, M.D., F.R.C.S., F.A.C.S., Asgar Zaheer, Ph.D., Rory A. Fisher, Ph.D.

Elucidation of mechanisms of acinar cell cytokine production is essential for a better understanding of acute pancreatitis pathogenesis. We hypothesize that the stress kinases ERK, p38, and JNK play an important role in acinar cell cytokine production. Rat pancreatic fragments were incubated with 100 nM concentration of the cholecystokinin analog caerulein or 100 nM caerulein and specific ERK inhibitor (100 μM PD98059), specific p38 inhibitor (10 μM SB203580), or specific JNK inhibitor (20 μM SP600125). After 3 hours of caerulein treatment, pancreatic fragments were homogenized and assayed for total and phosphorylated ERK, p38, and JNK, and for tumor necrosis factor-α or interleukin-1β concentrations (ELISA). Pancreatic fragments stimulated with caerulein showed activation of ERK, p38, and JNK and increased cytokine concentrations (ANOVA, $P < 0.05$). Specific stress kinase inhibitors significantly attenuated caerulein-induced activation of the corresponding stress kinase and cytokine production; however, the effect of the JNK inhibitor was comparatively less convincing. Increased activation of ERK, p38, and JNK in pancreatic fragments was not associated with significant increases in total ERK, total p38, or total JNK concentrations. The stress kinases ERK and p38 play an important role in caerulein-stimulated exocrine pancreatic overproduction of cytokines. The role of JNK needs further evaluation in this experimental model. (J GASTROINTEST SURG 2006;10:1376–1383)

KEY WORDS: Acute pancreatitis, stress kinase, MAP kinase, cytokines, rat

Pancreatic acinar cells overproduce cytokines following CCK-A receptor hyperstimulation.[1,2] Elucidation of mechanisms of acinar cell cytokine production facilitiates better understanding of early events in acute pancreatitis pathogenesis. Tumor necrosis factor-α (TNF) and interleukin-1β (IL-1) are key cytokines that initiate and propagate acute pancreatic inflammation.[1] The role of stress kinases in pancreatic acinar cell cytokine production is not completely understood. We have previously shown that the early phase of bile–pancreatic duct ligation–induced acute pancreatitis in rats is associated with stress kinase activation and increased cytokine production.[2–4] We have also shown that bile–pancreatic juice exclusion from gut increases pancreatic $p38^{MAPK}$ activation and cytokine production after duct ligation.[2] We hypothesize that the stress-activated protein kinases ERK, p38, and JNK play a significant role in acinar cell TNF and IL-1 production. To test this hypothesis, we performed in vitro experiments to evaluate the effect of specific stress kinase inhibitors on pancreatic acinar cell cytokine production following hyperstimulation with the CCK-A receptor agonist caerulein.

MATERIAL AND METHODS

The University of Iowa Institutional Animal Care and Use Committee approved the experimental protocols used in this study, satisfying the guidelines of the U.S. Public Health Service. Male Sprague-Dawley rats weighing 250–325 g were purchased from Harlan Sprague-Dawley (Indianapolis, IN).

This work was presented at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, CA, May 22, 2006.

Dr. Samuel was supported for this research by an American College of Surgeons Faculty Research Fellowship (2003-2005) and a National Institutes of Health NIDDK Career Development Award (grant K08-DK062805).

From the Departments of Surgery (I.S.), Neurology (A.Z.), and Pharmacology (R.A.F.), University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City, Iowa, and Veterans Affairs Medical Center, Iowa City, IA (I.S., A.Z.).

Reprint requests: Isaac Samuel, M.D., F.R.C.S., F.A.C.S., Department of Surgery, VAMC and University of Iowa Carver College of Medicine, 200 Hawkins Drive, 4625 JCP, Iowa City, IA 52242. e-mail: Isaac-samuel@uiowa.edu

 Published by Elsevier Inc.

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.003

Caerulein was purchased from Sigma Chemical (St. Louis, MO). PD98059, SB203580, and SP600125 were purchased from Calbiochem (San Diego, CA; www.calbiochem.com).

Midline laparotomy was performed under general anesthesia induced with ketamine hydrochloride (87 mg/kg) and xylazine hydrochloride (13 mg/kg). The pancreas was excised with aseptic precautions and gently rinsed with Dulbecco's modified Eagle medium (DMEM/F12; Invitrogen, Grand Island, NY) containing 5% FBS. Preparation and culture of rat pancreatic fragments were essentially as described by the Saluja group[5] and the Norman group,[6] with the following modifications. The fresh pancreas was diced into pieces less than 1.0 mm in size, seeded onto 24-well tissue culture plates, and incubated in 1 ml of DMEM/F12 for 3 hours at 23°C in a tissue culture incubator with humidified atmosphere of 95% air and 5% CO_2.[5–7] In selected experimental groups (see later), stress kinase inhibitors were added at the beginning of the equilibration period. At the end of the 3-hour equilibration period, the pancreatic fragments were gently rinsed with DMEM/F12 containing 5% FBS and finally suspended in 1 ml of DMEM/F12 containing 20% FBS. Groups that received stress kinase inhibitors were replenished with the same dose of the respective inhibitor after the rinse. The experiment was then begun by adding 10 μl of saline vehicle alone in the control group or 10 μl of the CCK-A receptor agonist caerulein in the groups described below to achieve a final concentration of 100 nM.

In part 1 of the study, the pancreatic fragments were studied in the following experimental groups (five wells per group):

1. Saline-treated control group
2. Diseased control group: 100 nM caerulein
3. Diseased treated group: 100 nM caerulein after 3-hour preincubation with 10 μM specific p38 inhibitor SB203580
4. Diseased treated group: 100 nM caerulein after 3-hour preincubation with 100 μM specific ERK inhibitor PD98059
5. Additional control group: 10 μM specific p38 inhibitor SB203580 alone (without caerulein)
6. Additional control group: 100 μM specific ERK inhibitor PD98059 alone (without caerulein) (in groups 5 and 6, the inhibitors alone were added the same time as in groups 3 and 4)

Doses of ERK inhibitor and p38 inhibitor used were as recommended by the manufacturer. Three hours after addition of caerulein, pancreatic fragments were harvested, separated from the medium by centrifugation, and homogenized in 10 mM HEPES buffer (pH 7.5). The soluble fraction was assayed for total and phosphorylated ERK and p38 and for TNF and IL-1 concentrations, using commercial ELISA kits according to the manufacturer's instructions (Biosource, Inc., Camarillo, CA). Prior to ELISA, the homogenate was assayed for protein using the Bradford assay, and each sample was diluted with the same buffer to a protein concentration of 1 mg/ml.

In part 2 of the study, the following experiment was performed after data from part 1 was analyzed. After successfully demonstrating that the specific ERK and p38 inhibitors attenuate caerulein-stimulated cytokine production in pancreatic fragments (see Results), we began experiments to evaluate the role of JNK in cytokine production in the same in vitro model. We used the specific JNK inhibitor SP600125 and measured IL-1 production by pancreatic fragments stimulated by 100 nM caerulein for 3 hours, as described in part 1. However, initial studies using the dose of SP600125 recommended by the manufacturer (20 nM with 3-hour preincubation) and even a much higher dose (10 μM with 3-hour preincubation) failed to significantly attenuate IL-1 production or JNK activation in response to caerulein (data not shown). Therefore, we used a longer preincubation period and incubated the pancreatic fragments with 10 μM SP600125 overnight prior to 100 nM caerulein hyperstimulation for 3 hours. DMSO was used as the solvent for SP600125 and was diluted in DMEM before adding to the well. All other details of the experiment were as in part 1.

Statistical Analysis

SigmaStat software (Version 2.03; www.spss.com) was used for statistical analysis. One-way ANOVA was used for analysis of data. Five wells were studied in each experimental group, and results are expressed as mean ± SEM. A *P*-value below 0.05 was considered statistically significant.

RESULTS

Part 1

Pancreatic fragments stimulated with caerulein showed significant increases in phospho-ERK and phospho-p38, without increases in total ERK or total p38 concentrations (Figs. 1 and 2). Specific ERK and p38 inhibitors significantly attenuated caerulein-induced increases in the corresponding phospho-stress kinase and attenuated caerulein-induced IL-1 and TNF production by an impressive margin (Figs. 1–3). The ERK inhibitor did not significantly inhibit p38 activation, and the p38 inhibitor did not

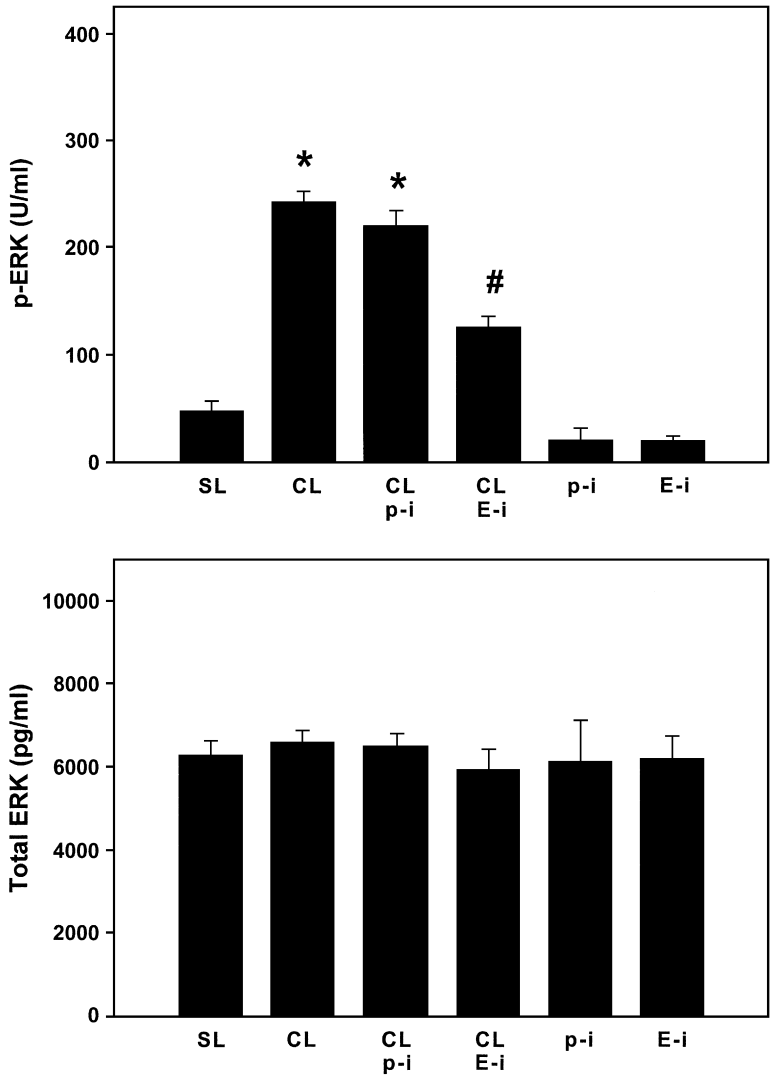


Fig. 1. Caerulein (CL) activates ERK in pancreatic fragments without increasing total ERK concentrations. ERK inhibitor (E-i) attenuates CL-induced ERK activation. The stress kinase inhibitors alone showed no significant effect. Results are mean ± SEM; n = 5 wells per group. *Significant difference from the saline-treated control group (SL); pound sign (#) indicates significant difference from the SL and diseased-control group that received CL; one-way ANOVA, $P < 0.05$. p-i =p38 inhibitor.

significantly inhibit ERK activation, corroborating the specificity of the respective inhibitor. In control groups, the individual stress kinase inhibitors used alone (without caerulein) showed no significant effect.

Part 2

ELISA of IL-1 and phosphorylated JNK in pancreatic homogenates showed significant increases in IL-1 production and JNK activation in pancreatic fragments stimulated with caerulein (Fig. 4). As in the case of ERK and p38, total JNK concentration was not increased after caerulein treatment (data not shown). The specific JNK inhibitor SP600125 (10 μM with overnight preincubation) was associated with a marginal but statistically significant attenuation of both phospho-JNK concentration and IL-1 overproduction associated with caerulein hyperstimulation. As the effect of SP600125 on JNK activation was not as convincing as that of the ERK or p38 inhibitors, we were not encouraged to measure TNF in these samples.

DISCUSSION

Using novel quantitative methods (ELISA) for measuring total and activated stress kinase concentrations, we provide new evidence that ERK, p38,

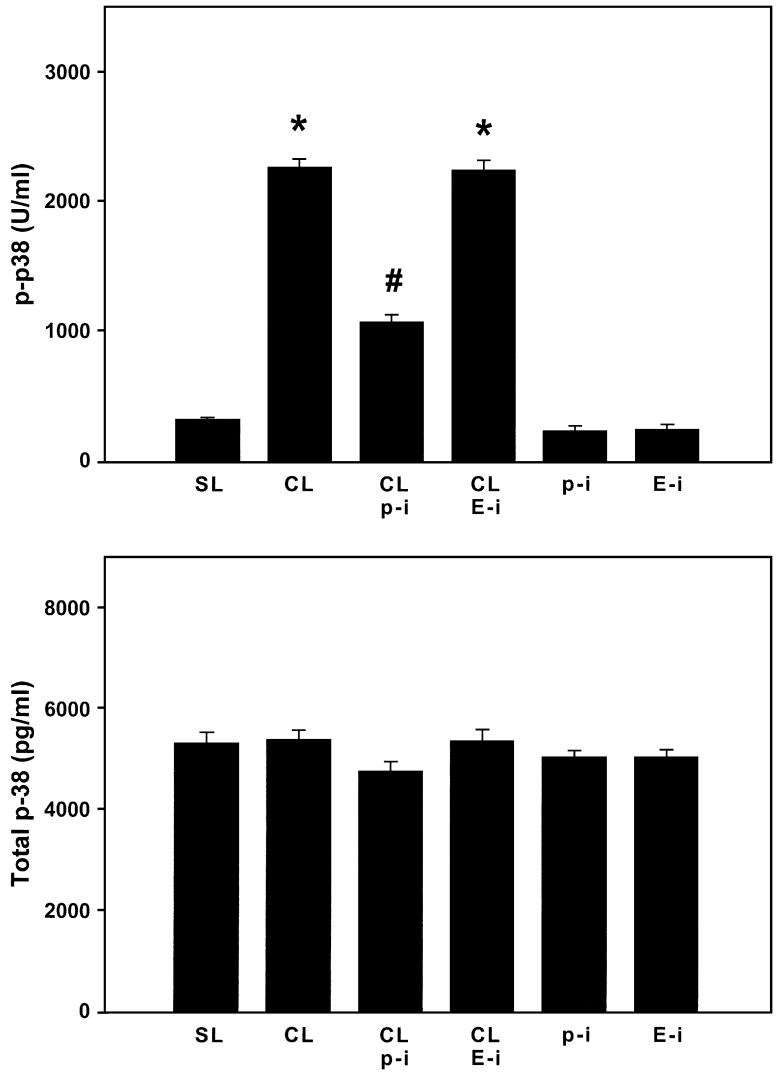


Fig. 2. Caerulein (CL) activates p38 in pancreatic fragments without increasing total p38 concentrations. p38 inhibitor (p-i) attenuates CL-induced p38 activation. The stress kinase inhibitors alone showed no significant effect. Results are mean ± SEM; n = 5 wells per group. *Significant difference from the saline-treated control group (SL); pound sign (#) indicates significant difference from the SL and diseased control group that received CL; one-way ANOVA, $P < 0.05$. E-i = ERK inhibitor.

and JNK play a role in caerulein-stimulated exocrine pancreatic production of cytokines. Increased stress kinase activation in pancreatic fragments was not associated with significant increases in total ERK, total p38, or total JNK concentrations, indicating that stress kinase activation following caerulein hyperstimulation is not a mere consequence of stress kinase induction but rather the result of true activation of preexisting ERK, p38, and JNK. Furthermore, the inability of the p38 inhibitor SB203580 to inhibit activation of ERK following caerulein hyperstimulation does not support the recent view that SB203580 may cross-react and antagonize the CCK-A receptor.[8] As tissue macrophages do not have CCK-A receptors, it is reasonable to suggest that pancreatic acinar cells may be the source of caerulein-stimulated IL-1 and TNF production in this experimental model.[5,6] However, stimulated acinar cells plausibly could produce molecular messengers that induce macrophage cytokine production.

Compared to the magnitude of attenuation of ERK and p38 activation and cytokine production achieved by ERK inhibitor or p38 inhibitor, SP600125 was less efficient in attenuating JNK activation and IL-1 production in our experiments. We speculate that this reflects the relative inefficiency of phospho-JNK inhibition in our experimental system, rather than a lesser role for JNK in acinar cell IL-1

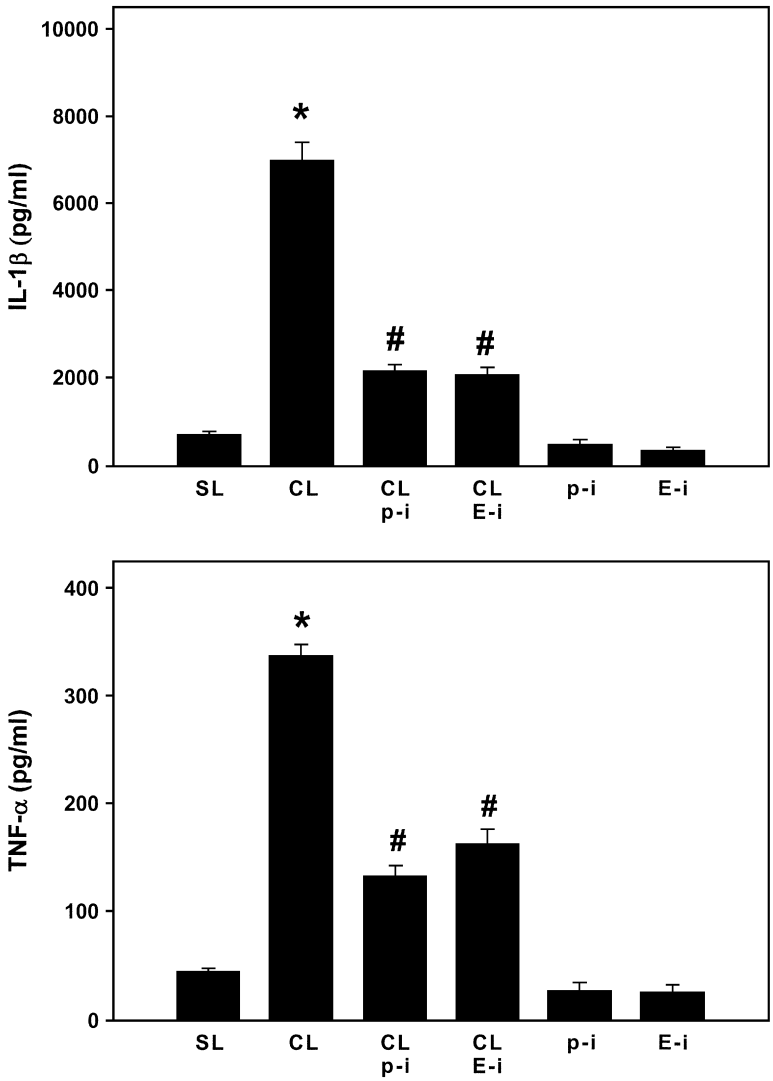


Fig. 3. Caerulein (CL) increases IL-1 and TNF production by pancreatic fragments. The ERK inhibitor (E-i) and the p38 inhibitor (p-i) attenuate CL-induced IL-1 and TNF production. The stress kinase inhibitors alone showed no significant effect. Results are mean ± SEM; n = 5 wells per group. *Significant difference from the saline-treated control group (SL); pound sign (#) indicates significant difference from the SL and diseased control group that received CL; one-way ANOVA, $P < 0.05$.

production, probably due to inadequate intracellular penetration of SP600125. Of note, Wagner et al.[9] have shown that the JNK pathway inhibitor CEP-1347 dose-dependently inhibits caerulein-induced JNK activation in isolated rat pancreatic acini. We selected SP600125 instead of CEP-1347 for our studies as the former is a direct inhibitor of JNK while the latter acts upstream of JNK.[10] Alternative reagents such as small interfering RNA to JNK may be better suited to evaluate the role of JNK in future experiments.

Acute pancreatitis is a common condition associated with significant morbidity and mortality.[1,11] Cytokine cascade activation initiated within the pancreas may lead to a systemic inflammatory response with potentially fatal multiorgan failure.[12–14] However, the early events in pancreatic cytokine cascade activation are poorly understood.[12–15] The stress-activated protein kinases ERK (extracellular signal-regulated kinase 1/2), p38 (p38 MAP kinase), and JNK (cJun N-terminal kinase 1/2) are novel signaling cascades in mammalian cells activated by cell stress and capable of inducing cytokine production.[16] Following cell surface receptor hyperstimulation, each stress kinase is activated by phosphorylation via an upstream kinase cascade and then activates

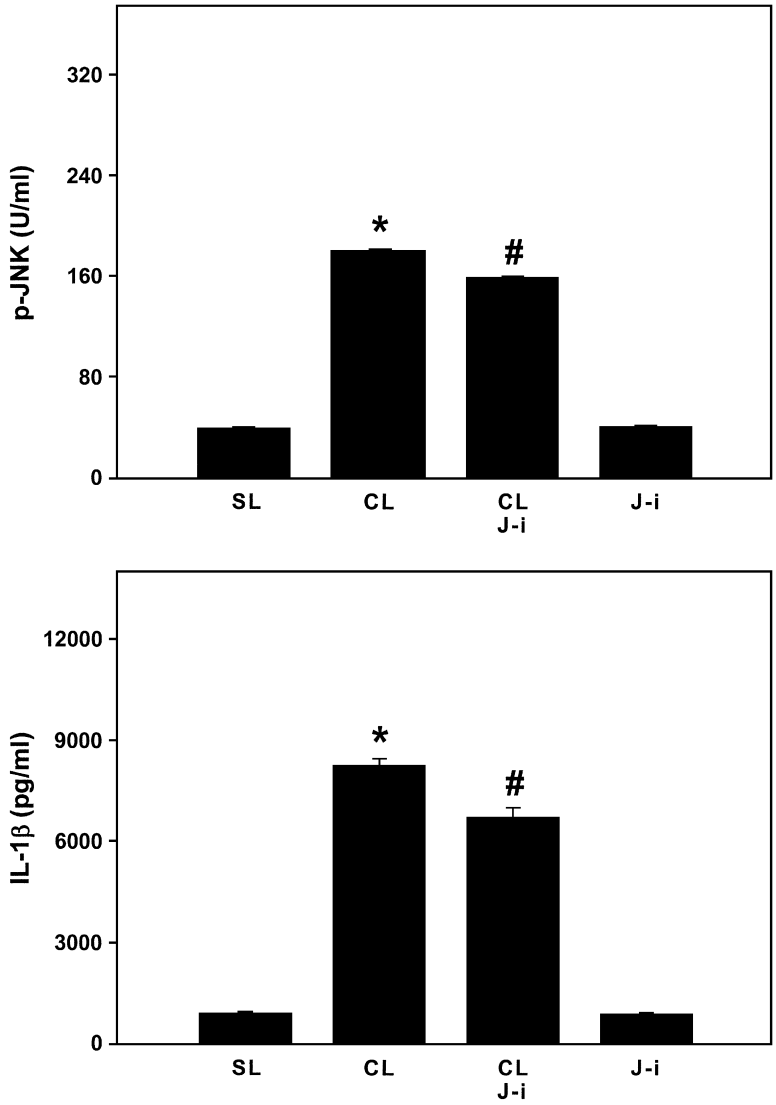


Fig. 4. Caerulein (CL) activates JNK and increases IL-1 production in pancreatic fragments. JNK inhibitor (J-i) marginally attenuates CL-induced JNK activation and IL-1 production. The J-i alone showed no significant effect. Results are mean ± SEM; n = 5 wells per group, asterisk (*) indicates significant difference from the saline-treated control group (SL); pound sign (#) indicates significant difference from the SL and diseased-control group that received CL; one-way ANOVA, $P < 0.05$.

a downstream nuclear transcription factor that regulates gene expression.[17] Using an original surgical model, the Donor Rat Model, we have previously shown that duodenal bile–pancreatic juice replacement attenuates p38 activation and TNF overproduction in the early stages after duct ligation.[2] These results suggest that bile–pancreatic juice exclusion from gut, which causes feedback hyperstimulation of the exocrine pancreas via neurohormonal pathways (e.g., CCK), increases pancreatic stress kinase activation and cytokine production after duct ligation. We performed the present study to evaluate in vitro a mechanistic relationship between the concurrent events of stress kinase activation and cytokine production seen with our in vivo studies. The dispersed pancreatic acini and isolated acinar cell preparations often used for in vitro investigations are not ideal for studies of cytokine- and stress-activated pathways, as the collagenase digestion and mechanical agitation of the preparatory procedure itself induces activation of the pathways under study.[7] Therefore, we preferred to use the pancreatic fragment model in the present study.

Recent work has provided supporting evidence for the role of stress kinases in acute pancreatitis pathogenesis.[3,9,11,16,18–23] The specific JNK inhibitor CEP 1347 and specific ERK inhibitors (U0126, PD98059) ameliorate acute pancreatitis in rats induced by supramaximal doses of caerulein.[9,21,22] Although one report indicates that p38 inhibition exacerbates caerulein-induced acute pancreatitis in rats,[21] other reports indicate that p38 activation exacerbates acute inflammation in experimental models of acute pancreatitis.[18,19,23,24] In caerulein-induced and CDE diet-induced acute pancreatitis in mice, the p38 and JNK inhibitor CNI-1493 reduces pancreatic necrosis and downregulates the TNF gene.[25] CNI-1493 also attenuates pulmonary TNF production and parenchymal injury induced by intravenous administration of pancreatic ascites in rats.[11] In acute pancreatitis induced by retrograde injection of bile salts, CNI-1493 reduces pancreatic and pulmonary injury, limits increases in circulating TNF concentrations, and improves survival.[23] In the same model, CNI-1493 also reduces hepatic TNF levels and parenchymal injury.[18] The p38 inhibitor SB203580 attenuates hepatic TNF overproduction induced by elastase perfusion.[24] The unique aspects of our present study are (1) the use of pancreatic fragments rather than dispersed acini, (2) the use of novel reagents (ELISA) to quantitate pancreatic stress kinases, (3) the demonstration of changes in stress kinase phosphorylation in relation to total stress kinase concentration, and (4) the measurement of exocrine pancreatic IL-1 and TNF, both of which are downstream products of stress kinase activation.

CONCLUSION

The stress kinases ERK and p38 play an important role in caerulein-stimulated exocrine pancreatic overproduction of cytokines. The role of JNK needs further evaluation in this experimental model.

REFERENCES

1. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg 1998;175:76–83.
2. Samuel I, Zaheer S, Zaheer A. Bile-pancreatic juice exclusion increases p38MAPK activation and TNF-alpha production in ligation-induced acute pancreatitis in rats. Pancreatology 2005;5:20–26.
3. Samuel I, Zaheer S, Fisher RA, Zaheer A. Cholinergic receptor induction and JNK activation in acute pancreatitis. Am J Surg 2003;186:569–574.
4. Samuel I, Zaheer S, Nelson JJ, Yorek MA, Zaheer A. CCK-A receptor induction and P38 and NF-kappaB activation in acute pancreatitis. Pancreatology 2004;4:49–56.
5. Bhagat L, Singh VP, Hietaranta AJ, Agrawal S, Steer ML, Saluja AK. Heat shock protein 70 prevents secretagogue-induced cell injury in the pancreas by preventing intracellular trypsinogen activation. J Clin Invest 2000;106:81–89.
6. Jaffrey C, Eichenbaum D, Denham DW, Norman J. A novel pancreatic model: The snip method of pancreatic isolation for in vitro study. Pancreas 1999;19:377–381.
7. Blinman TA, Gukovsky I, Mouria M, Zaninovic V, Livingston E, Pandol SJ, Gukovskaya AS. Activation of pancreatic acinar cells on isolation from tissue: cytokine upregulation via p38 MAP kinase. Am J Physiol Cell Physiol 2000; 279:C1993–C2003.
8. Morel C, Ibarz G, Oiry C, Carnazzi E, Berge G, Gagne D, Galleyrand JC, Martinez J. Cross-interactions of two p38 mitogen-activated protein (MAP) kinase inhibitors and two cholecystokinin (CCK) receptor antagonists with the CCK1 receptor and p38 MAP kinase. J Biol Chem 2005; 280:21384–21393.
9. Wagner AC, Mazzucchelli L, Miller M, Camoratto AM, Goke B. CEP-1347 inhibits caerulein-induced rat pancreatic JNK activation and ameliorates caerulein pancreatitis. Am J Physiol Gastrointest Liver Physiol 2000;278:G165–G172.
10. Bogoyevitch MA, Boehm I, Oakley A, Ketterman AJ, Barr RK. Targeting the JNK MAPK cascade for inhibition: Basic science and therapeutic potential. Biochim Biophys Acta 2004;1697:89–101.
11. Denham W, Yang J, Norman J. Evidence for an unknown component of pancreatic ascites that induces adult respiratory distress syndrome through an interleukin-1 and tumor necrosis factor-dependent mechanism. Surgery 1997;122: 295–301; discussion.
12. Samuel I, Toriumi Y, Wilcockson DP, Turkelson CM, Solomon TE, Joehl RJ. Bile and pancreatic juice replacement ameliorates early ligation- induced acute pancreatitis in rats. Am J Surg 1995;169:391–399.
13. Samuel I, Joehl RJ. Bile-pancreatic juice replacement, not cholinergic and cholecystokinin-receptor blockade, reverses acinar cell hyperstimulation after bile-pancreatic duct ligation. Am J Surg 1996;171:207–211.
14. Cameron JL, Mehigan D, Zuidema GD. Evaluation of atropine in acute pancreatitis. Surg Gynecol Obstet 1979;148: 206–208.
15. Steer ML. Pathobiology of experimental acute pancreatitis. Yale J Biol Med 1992;65:421–430.
16. Schafer C, Williams JA. Stress kinases and heat shock proteins in the pancreas: Possible roles in normal function and disease. J Gastroenterol 2000;35:1–9.
17. Karne S, Gorelick F. Etiopathogenesis of acute pancreatitis. Surg Clin North Am 1999;79:699–710.
18. Yang J, Denham W, Carter G, Tracey KJ, Norman J. Macrophage pacification reduces rodent pancreatitis-induced hepatocellular injury through down-regulation of hepatic tumor necrosis factor alpha and interleukin-1beta. Hepatology 1998;28:1282–1288.
19. Yang J, Murphy C, Denham W, Botchkina G, Tracey KJ, Norman J. Evidence of a central role for p38 map kinase induction of tumor necrosis factor alpha in pancreatitis-associated pulmonary injury. Surgery 1999;126:216–222.
20. Samuel I, Zaheer S, Nelson J, Yorek M, Zaheer A. CCK-A receptor induction and P38(MAPK) and NF-kappaB activation in acute pancreatitis. Pancreatology 2004;4:49–56.
21. Fleischer F, Dabew R, Goke B, Wagner AC. Stress kinase inhibition modulates acute experimental pancreatitis. World J Gastroenterol 2001;7:259–265.
22. Clemons AP, Holstein DM, Galli A, Saunders C. Caerulein-induced acute pancreatitis in the rat is significantly

ameliorated by treatment with MEK1/2 inhibitors U0126 and PD98059. Pancreas 2002;25:251–259.
23. Yang J, Denham W, Tracey KJ, Wang H, Kramer AA, Salhab KF, Norman J. The physiologic consequences of macrophage pacification during severe acute pancreatitis. Shock 1998;10:169–175.
24. Murr MM, Yang J, Fier A, Gallagher SF, Carter G, Gower WR, Norman JG. Regulation of Kupffer cell TNF gene expression during experimental acute pancreatitis: The role of p38-MAPK, ERK1/2, SAPK/JNK, and NF-kappa B. J GASTROINTEST SURG 2003;7:20–25.
25. Fink G, Yang J, Carter G, Ward K, Ulrich P, Tracey K, Norman J. A low molecular weight macrophage inhibitor decreases severity of pancreatitis through inhibition of IL-1 and TNF production. Surg Forum 1996;47: 137–140.

Mechanism of Gastric Bypass–Induced Body Weight Loss: One-Year Follow-up After Micro–Gastric Bypass in Rats

Björn Stenström, M.D., Marianne W. Furnes, D.V.M., Karin Tømmerås, Ph.D., Unni Syversen, M.D., Ph.D., Chun-Mei Zhao, Ph.D., Duan Chen, M.D., Ph.D.

Bariatric surgery (Roux-en-Y or mini–gastric bypass) is designed to limit food intake by creating a small gastric pouch and to reduce nutrient absorption by bypassing the long limb of the intestine. We report 1-year follow-up results after micro–gastric bypass in rats. Micro–gastric bypass was performed by anastomosis of the esophagus and the proximal jejunum. Body weight, body composition, bone mineral density, food intake, and serum levels of ghrelin and obestatin were measured. Growing rats had a 40% weight reduction 2 months after micro–gastric bypass surgery compared to 20% after gastrectomy and 30% after stomach bypass (anastomosis of the esophagus and duodenal bulb). Six months after micro–gastric bypass surgery, the rats stopped growing compared to controls that gained continuously due to expansion of the fat compartment. Adult rats (600 g) lost 30% of their body weight 5 months after the micro–gastric bypass, while food intake was not reduced. Serum levels of obestatin (but not ghrelin) were reduced in rats with micro–gastric bypass. The results suggest that micro–gastric bypass efficiently reduced body weight, particularly fat mass; loss of the weight after micro–gastric bypass was not due to reduced food intake; and lean tissue and bone development were impaired in growing subjects after gastric bypass. (J GASTROINTEST SURG 2006;10:1384–1391)

KEY WORDS: Micro–gastric bypass, body weight, food intake, ghrelin, obestatin, rats

Overweight and obesity are plaguing our society in epidemic proportions. In a recent report from the HUNT study in Norway, the prevalence of overweight and obese persons was about 20% higher than that 10 years ago, especially in the younger age groups.[1] The health benefits of weight reduction are well recognized. However, weight loss through diet and exercise fails in most patients, and the current weight-loss drugs have had limited success. Gastric bypass surgery, where the stomach is circumvented by linking the esophagus to the intestine, is believed to diminish hunger and result in long-term maintenance of reduced body weight, and is thus becoming a common treatment for obesity.[2–4] The common surgical procedures include (1) restrictive operations such as vertical banded gastroplasty, silastic ring gastroplasty, and gastric banding, (2) malabsorptive operations including variations of the intestinal bypass, and (3) combined operations that use both restriction and malabsorption including variations of short-limb, long-limb, or distal gastric bypass and biliopancreatic diversion.[5,6] The current standard for bariatric surgery is the Roux-en-Y gastric bypass[2,7,8] (Fig. 1A). In addition, the so-called mini–gastric bypass has been recently recommended[9,10] (Fig. 1B). The average loss of excess weight after surgery was found to be about 60% after 2-year follow-up.[11] Because some weight is gradually regained over time, and thus what happens in the long term is considered crucial. In fact, a clinical study after 10-year follow-up reported persistent benefits in terms of body weight and associated metabolic abnormalities after the surgery.[12] Although gastric bypass surgery is generally believed to be a safe and effective option with well-defined risks,[2,13,14] very little information has been published

Supported by a grant from The Cancer Foundation of St. Olav's Hospital (University Hospital of Trondheim), Norway. Dr. Stenström is recipient of a Ph.D. fellowship from the Central Norway Regional Health Authority.
From the Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. Reprint requests: Prof. Duan Chen, Laboratory Centre of St. Olav's Hospital (3rd Floor, East Side), Erling Skjalgssons Gate 1, NO-7006 Trondheim, Norway. e-mail: duan.chen@ntnu.no

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.07.005

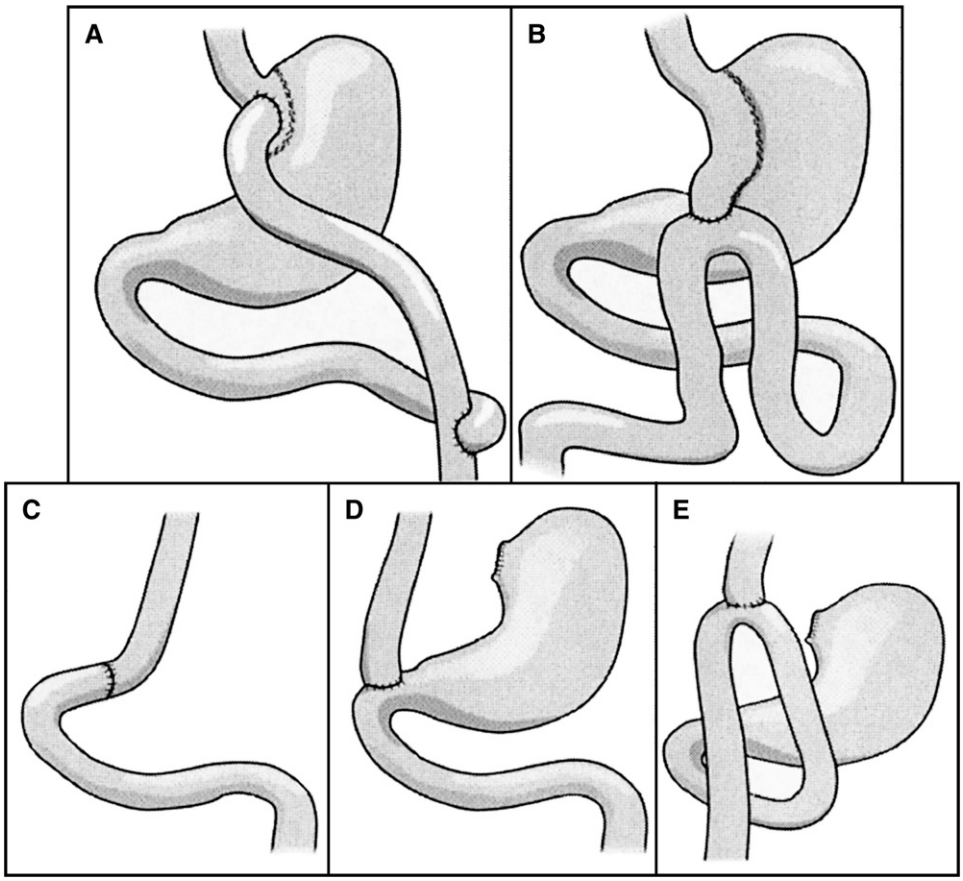


Fig. 1. Surgical procedures. **A,** Roux-en-Y gastric bypass. **B,** Mini–gastric bypass. **C,** Total gastrectomy. **D,** Stomach bypass. **E,** Micro–gastric bypass.

with respect to the effects of these surgeries on metabolism and development in adolescents. Morbid obesity is also becoming more frequent among children, and bariatric surgery is advocated as a potential pediatric intervention.[15,16] It is therefore important to investigate both the long-term benefits and potential postoperative complications of gastric bypass surgery in a broad context.[16] The aims of the present study were to develop models of bariatric surgery in rats and to study the mechanism behind the body weight reduction after the surgery. Herein, we performed micro–gastric bypass surgery in 2-month-old male rats and followed their growth up to 1 year by monitoring body weight, serum levels of ghrelin and obestatin, fat and fat-free compartments, bone mineral density (by dual-energy X-ray absorptiometry [DXA]), and stomach adaptation.

MATERIAL AND METHODS

Animals and Study Groups

Male rats (Sprague-Dawley at 2 months of age from Taconic, Lille Skensved, Denmark; and Long-Evans at 12–15 months of age from Taconic Farm, Inc., Germantown, NY) were used. They were housed in Makrolon cages at 20 °C, with 40–45% relative humidity on a 12-hour light/dark cycle, with four or five rats in each cage. The animals had free access to standard rat food pellets (B&K Universal, Hull, UK) and tap water ad libitum throughout the study. Four experimental groups were included, namely total gastrectomy (Fig. 1C), stomach bypass (Fig. 1D), and micro–gastric bypass (Fig. 1E) (Table 1). Each experimental group was paired with a control group that received a sham operation. Additional data were collected for fat mass and fat-free mass, bone mineral density of whole body and femur, ghrelin and obestatin levels at different time points in young rats that underwent micro–gastric bypass or sham operations. Each micro–gastric bypass group included 10 rats (total = 50 rats). Four animals died preoperatively, and four died at various time points pre-DXA. The sham-operated group included 10 animals at each postoperative time point, except the 12-month group (6 rats) and 1-month group (9 rats) (total = 45 rats). The micro–gastric bypass and the control sham operation was performed at four different time points, beginning with

Table 1. Experimental groups

Group	Surgery	No. of rats	Age of rats (mo)	Follow-up (mo)
I	Total gastrectomy	14	2–2.5	2
	Sham operation	9	2–2.5	2
II	Stomach bypass	6	2–2.5	2
	Sham operation	6	2–2.5	2
III	Microgastric bypass	50	2–2.5	1–12
	Sham operation	45	2–2.5	1–12
IV	Microgastric bypass	4	12–15	5
	Sham operation	4	12–15	5

the 12-month group. The 9- and 6-month groups were operated on 3 months later. After an additional 3 months, the 3-month group received operations, and the 1-month group followed 2 months later. Animals were killed after DXA analysis was performed at two time points. At the first time point, the 1-, 3-, and 6-month postoperative groups were killed. Three months later, the remaining 9- and 12-month postoperative groups were killed.

The experiments were approved by the Norwegian Animal Welfare Committee (Forsøksdyrutvalget, FDU).

Anesthesia and Surgery

All animals (except group IV) were operated on, analyzed with DXA, or killed under anesthesia with 0.02 ml/kg of a solution containing fluanison and fentanyl (2.5 mg/ml and 0.05 mg/ml, Hypnorm; Janssen Animal Health, Buckinghamshire, England) and midazolam (1.25 mg/ml, Dormicum; Alpharma AS, Oslo, Norway) or 0.04 ml/kg of a mixture of 2 ml of haloperidol (Haldol, 5 mg/ml; Janssen-Cilag, Beerse, Belgia), 3 ml of fentanyl (Fentanyl, 50 μg/ml; Alpharma AS, Oslo, Norway), 3 ml of midazolam (Dormicum, 5 mg/ml; Alpharma AS, Oslo, Norway), and 4 ml of H_2O for subcutaneous injection. The rats in group IV were anesthetized with isoflurane by U-400 Anesthesia Unit (Univentor Limited, Zejtun, Malta).

All operations were performed through a short upper midline incision. Total gastrectomy was performed by removing the whole stomach followed by joining the esophagus and duodenum end-to-end (Fig. 1C). The stomach bypass was performed by anastomosizing the esophagus to the first segment (bulb) of the duodenum end-to-side, leaving the stomach connected to the duodenum (Fig. 1D). The micro-gastric bypass was performed by anastomosizing the easophagus to the proximal jejunum about 2–3 cm distal to the Treitz ligament in an end-to-side fashion (Fig. 1E). The sham operation (performed on controls) was laparotomy only.

Follow-up (Body Weight, Body Composition, and Bone Measurements)

In all groups, body weight was recorded on the same balance before death. DXA was performed before death on a Hologic QDR 4500A with Small Animal software (Hologic Inc., Bedford, MA). Whole body fat mass and fat-free mass, whole body bone mineral density (BMD), and femur BMD were included. The femur length was measured at death after dissection the femur free of any loose tissue. The length is represented as the average of the left and right femurs.

Food Intake, Energy Expenditure, and Activity

The food intake, energy expenditure, and activity were recorded only in group IV, that is, adult Long-Evan rats, by indirect calorimetry using metabolic measuring system (Comprehensive Laboratory Animal Monitoring Systems [CLAMS], Oxymax; Columbus Instruments International, Columbus, OH). This monitoring system is composed of a four-chamber indirect calorimeter designed for continuous monitoring of up to four rats simultaneously, obtaining measurements of $V\dot{O}_2$ and $V\dot{C}O_2$ from each chamber. An air sample was withdrawn every 6 minutes from each cage. Energy expenditure (kcal/hr) was calculated from the following equation: $(3.815 + 1.232\ RER) \times V\dot{O}_2$, where *RER* is the respiratory exchange ratio (volume of CO_2 produced per volume of O_2 consumed [both ml/kg/h]) and $V\dot{O}_2$ is the volume of O_2 consumed per hour per kilogram of mass of animal. Rats were gradually acclimatized to the system over a period of 2 weeks before data collection. Rats were placed in calorimeter chambers for 72 hours (data from the first 48 hours were not used in the analysis) with ad libitum access to their normal diet in ground-up form and tap water.

Serum Ghrelin and Obestatin Levels and Histology of Ghrelin/Obestatin-Producing A-Like Cells in the Stomach

After the animals were killed, serum samples from each rat were collected for measurements of ghrelin and obestatin levels using commercial radioimmunoassay kits (RK-031-30 for ghrelin and RK-031-92 for obestatin; Phoenix Pharmaceuticals, Belmont, CA). Ghrelin and obestatin are known to be produced in the same A-like cells in the stomach, which can be visualized by immunohistochemistry. Tissue specimens (including stomach, esophagus, duodenum,

jejunum, and pancreas) were fixed for 8–12 hours at 4 °C in 4% paraformaldehyde (Pharmacia, Trondheim, Norway) and embedded in paraffin. Then 4-μm-thick sections were cut and mounted onto super-frost glass slides. Primary antibodies (rabbit anti-ghrelin and anti-preproghrelin) were applied at final dilutions of 1:7000 or 1:6000 (code no. H031-031, H-031-034; Phoenix Pharmaceuticals). The thickness of the oxyntic mucosa was measured using transverse sections, and the density of immunoreactive A-like cells in the oxyntic mucosa (number of cells per millimeters of mucosa along the submucosa) was assessed. Histology of the tissues was evaluated after routine hematoxylin and eosin staining.

Data Analysis

The values are expressed as mean ± SEM. Statistical analyses were performed using the Student's *t*-test, ANOVA, Kruskal-Wallis, or Mann-Whitney, as appropriate. Bonferroni correction for multiple comparisons was used where relevant. Analysis was performed either in SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) or GraphPad Prism version 4.03 (GraphPad Software, Inc., San Diego, CA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Body Weight, Body Composition, and Bone Density

In comparison with the age-matched sham-operated controls, the postoperative body weight at 2 months was reduced 20% after gastrectomy, 30% after stomach bypass, and 40% after micro–gastric bypass. One-year follow-up showed that body weight (Fig. 2), fat mass and fat-free mass (Fig. 3), whole body BMD and femur BMD (Fig. 4), and lean and fat mass (Fig. 4) were significantly lower in rats subjected to micro–gastric bypass than those subjected to sham operation. The young rats that had micro–gastric bypass stopped growing after 6 months, in contrast to the controls, which gained weight continuously mainly as a result of continuous expansion of the fat compartment. Femur length at 6 months postoperatively was shorter in rats subjected to micro–gastric bypass than in controls (39.5 ± 2.6 mm versus 43.1 ± 0.6 mm, $P < 0.0001$). It was noted during the cleaning of the femurs that the bones from young rats that had micro–gastric bypass were very fragile and brittle.

Adult rats (about 600 g body weight at the time of surgery) lost about 30% of their body weight 5 months after micro–gastric bypass, whereas sham-operated adult rats maintained weight or gained a little weight (Fig. 5). Moreover, the fat mass (but not fat-free mass) was lower in rats subjected to micro–gastric bypass than in controls (72.1 ± 6.6 g versus 196.4 ± 25.4 g, $P < 0.005$).

Food Intake, Energy Expenditure, and Activity Level

The adult rats (n = 4) subjected to micro–gastric bypass ate 22.5 ± 2.4 g/day, while the age-matched controls (n = 4) ate 15.7 ± 1.9 g/day ($P = 0.071$). Four months after surgery, total energy expenditure was similar in rats subjected either to micro–gastric bypass or a sham operation (112.6 ± 4.8 kcal/day versus 120.2 ± 10.5 kcal/day, $P > 0.05$). *RER* ($V\dot{C}O_2/V\dot{O}_2$) is higher when the animals burn

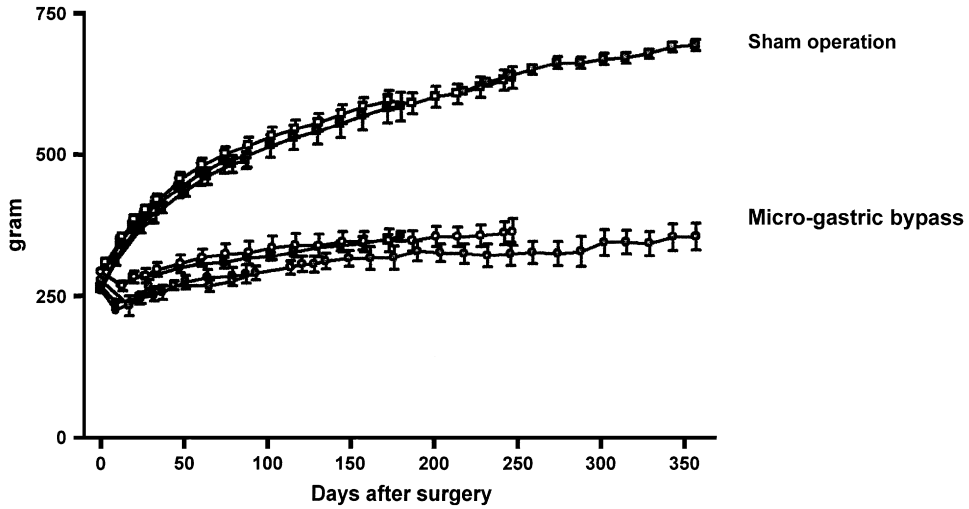


Fig. 2. Body weight changes over time after 1 year of follow up after micro–gastric bypass or sham operation in young rats.

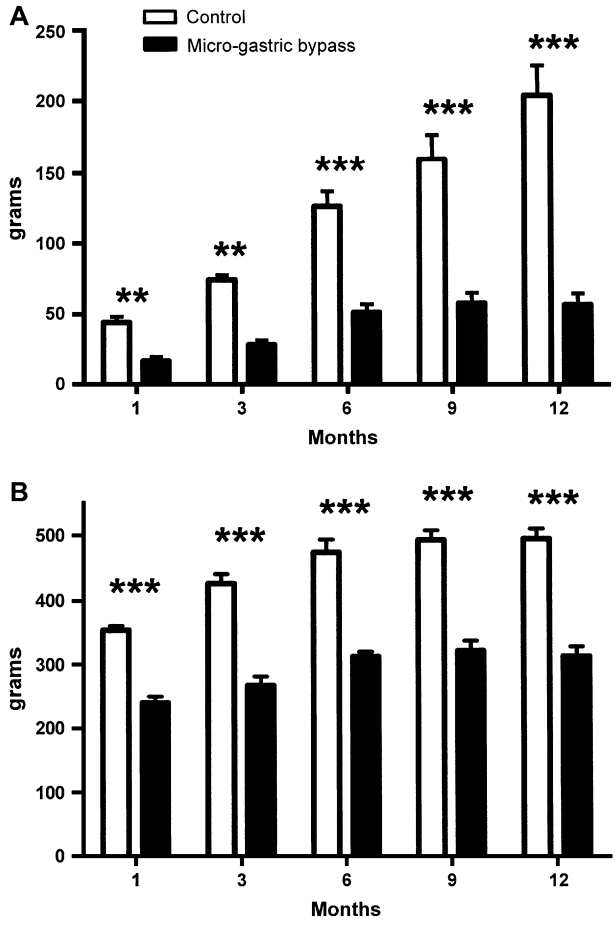


Fig. 3. Changes in fat mass (**A**) and fat-free mass (**B**) over a 12-month period after micro–gastric bypass or sham operation in young rats. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with age-matched sham-operated controls.

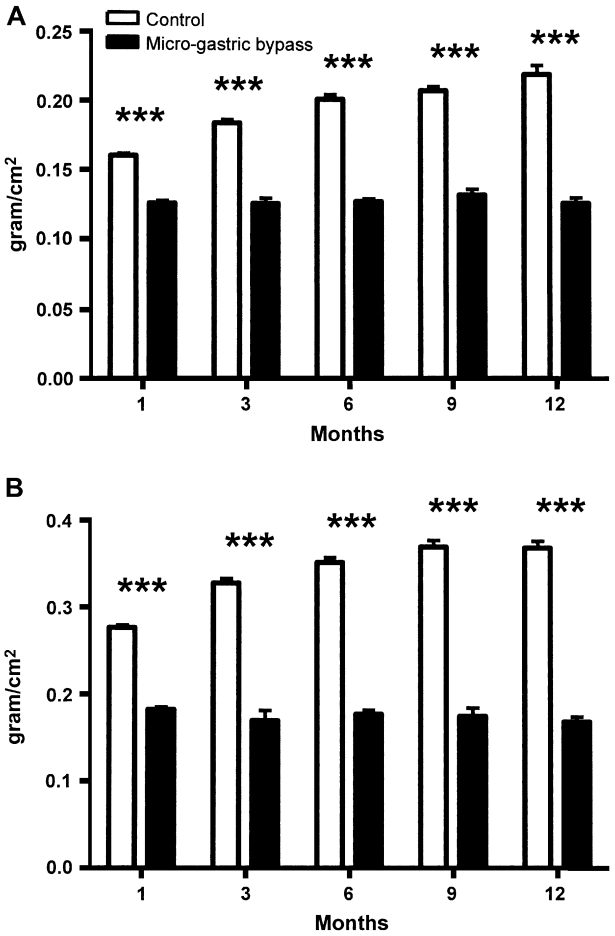


Fig. 4. Bone mineral density of whole body (**A**) and the femur (**B**) changes over a 12-month period after micro–gastric bypass or sham operation in young rats. $^{***}P < 0.001$ compared with age-matched sham-operated controls.

carbohydrates and lower during fat utilization and fasting. *RER* was 1.03 ± 0.04 in the micro–gastric bypass group versus 0.92 ± 0.03 in controls ($P = 0.0795$). Spontaneous locomoter activity appeared unchanged in rats with gastric bypass.

Ghrelin, Obestatin, A-Like Cells, and Other Organs

While the serum levels of ghrelin were not changed after micro–gastric bypass (except the reduction after 1 month) (Fig. 6A), the serum levels of obestatin were reduced significantly at and beyond 3 months postoperatively (Fig. 6B). There was no significant difference in the A-like cell density between rats subjected to either micro–gastric bypass or sham operations 12 months after surgery (micro–gastric bypass 25.2 ± 1.6 ghrelin-immunoreactive cells/mm versus controls 30.3 ± 1.7 cells/mm, $P > 0.05$; micro–gastric bypass 34.5 ± 1.3 preproghrelin-immunoreactive cells/mm versus controls 40.8 ± 2.2 cells/mm, $P > 0.05$). The thickness of the oxyntic mucosa was greatly reduced in rats subjected to micro–gastric bypass (micro–gastric bypass 348 ± 13 μm versus control 622 ± 27 μm, $P < 0.001$; 12 months after surgery). There were no obvious pathological postoperative changes in the tissues of the stomach, esophagus, duodenum, jejunum, and pancreas after 9 and 12 months in rats that had micro-gastric bypass.

DISCUSSION

In the present study, we tested our hypothesis that weight loss after gastric bypass (e.g., Roux-en-Y) surgery used clinically is due to neither reduced food intake nor impaired nutrient absorption as a result of a long bypass of the small bowel.[2,8,17] It has been well demonstrated that the Roux-en-Y gastric bypass reduces body weight in rats.[18,19] In the present study, the body weight was reduced following total

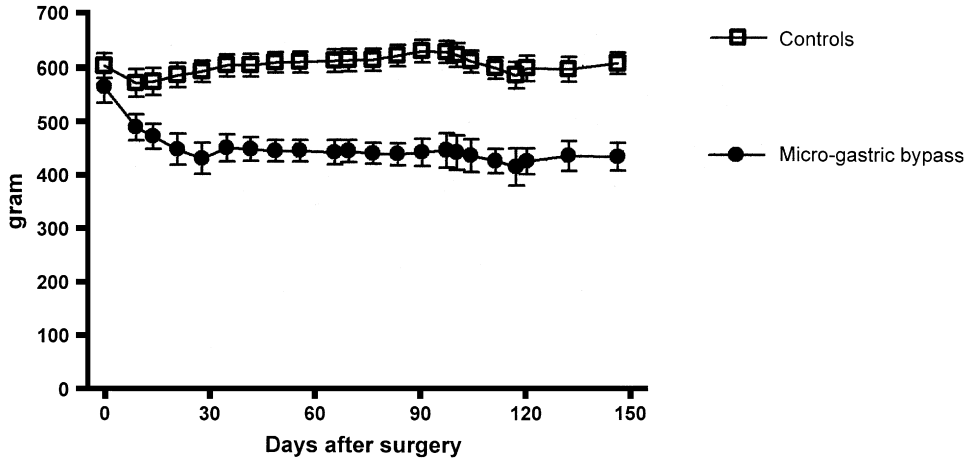


Fig. 5. Body weight changes over the course of 5 months after micro–gastric bypass or sham operation in 1-year-old adult rats.

gastrectomy, stomach bypass, and micro–gastric bypass, suggesting that the stomach per se seems to be responsible for weight loss after the various gastric bypass procedures (see also Stenström et al.[20]). The micro–gastric bypass reported in the present study is similar to the clinically performed mini–gastric bypass procedure (Fig. 1). The rationale for such procedure(s) is that they are simpler and safer than other gastric bypass operations and they avoid exposing the gastric mucosa to biliopancreatic secretions, which may have potentially carcinogenic effects with longer-term exposure and was a major criticism of the original technique. As a result of this micro–gastric bypass, body weight (mainly fat mass) was promptly lost in growing rats as well as adult (and obese) rats. Six months postoperatively, the rats subjected to gastric bypass stopped gaining weight, which was due to a lack of expansion of the fat compartment. Although the underlying mechanism is unknown, the clinical significance is obvious. Moreover, it should be noted that surprisingly and interestingly, food intake was not reduced (actually it was probably increased) and the total energy expenditure was unchanged after the micro–gastric bypass, although these results have to be interpreted with caution as the number of animals is small (four rats per group). The tendency for increased food intake in the rats with micro–gastric bypasses could be because of less fat and smaller energy stores, thus leading them to eat more. If the weight loss in this model is not due to the restriction of food intake and general malabsorption, a selective malabsorption of fat and/or a shift in preferred fuel substrate may be a plausible explanation.

The present study including 1 year of follow up after micro–gastric bypass might suggest that

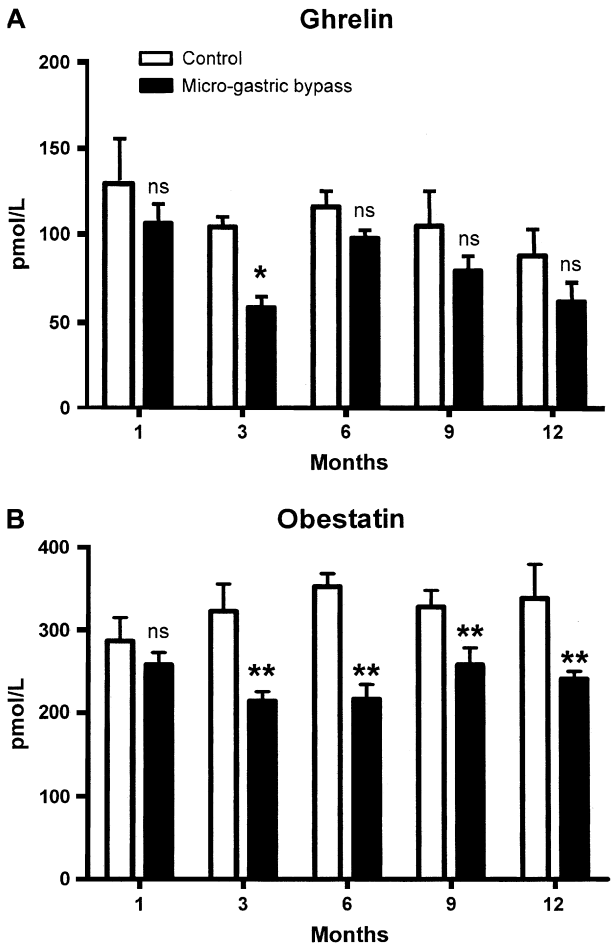


Fig. 6. Changes in serum ghrelin (**A**) and obestatin (**B**) levels over a 12-month period following micro–gastric bypass or sham operations in young rats. *$P < 0.05$. ns, not significant compared with age-matched sham-operated controls.

although the gastric bypass could effectively reduce body weight, particularly the fat compartment in growing rats, the bariatric surgery may not be a good choice for treating obesity in young individuals that are still growing, because not only fat mass accumulation was reduced, but the growth of lean tissue and bone formation could also be impaired. Thus, the growth of a young patient receiving such an operation might be permanently stunted. The present study also shows that the pronounced weight loss was accompanied by a significant reduction of BMD in the rats with gastric bypass, as seen in gastrectomized rats or patients that have had gastrectomy or gastric bypass.[21–29] Possible mechanisms may include general nutritional deficiency, calcium deficiency (little or lack of gastric acid), vitamin D deficiency (impaired absorption of vitamin D precursors), and gastric hormone deficiency (e.g., gastrin, ECL-cell hormone, ghrelin). In fact, it has been shown by a series of studies that the bone loss observed after gastrectomy reflects the loss of the oxyntic mucosa per se and that perhaps the ECL cells in the stomach manufacture a hormone that controls bone metabolism.[20,30]

The stomach is known to be the main source of circulating ghrelin,[31,32] and is most likely the main source for obestatin, because both are produced from the preproghrelin peptide in the stomach.[33] Treatment with ghrelin increased food intake and body weight in rats, while obestatin had the opposite effects.[33] In the present study, the reduction in the serum levels of obestatin but not ghrelin after the micro–gastric bypass do not support the view that either or both peptides are responsible for the reduced body weight after the surgery in rats.[20,34,35]

In conclusion, the micro–gastric bypass efficiently reduced body weight, particularly the fat mass. This procedure is simple and may have a low complication and mortality rate. Second, the loss of body weight after micro–gastric bypass appeared to be neither due to reduced food intake nor associated with productions of ghrelin and/or obestatin. Third, gastric bypass surgery for obese children (and adolescents) is not recommended, because the development of lean tissue and bone may be impaired after the surgery. Fourth, an increased risk of developing of osteopenia (osteoporosis or osteomalacia) seems to be a common outcome of gastric bypass.

The authors thank Shahnaz Rahimipoor (Sør-Trøndelag University College, Norway), Trine Skoglund, Sture Falkmer and Carl-Jørgen Arum (Norwegian University of Science and Technology) for their assistance and comments.

REFERENCES

1. Droyvold WB, Nilsen TI, Kruger O, Holmen TL, Krokstad S, Midthjell K, et al. Change in height, weight and body mass index: Longitudinal data from the HUNT Study in Norway. Int J Obes (Lond) 2006;1–5.
2. Mun EC, Blackburn GL, Matthews JB. Current status of medical and surgical therapy for obesity. Gastroenterology 2001;120:669–681.
3. Solomon C, Dluhy RG. Bariatric surgery: Quick fix or long-term solution? N Engl J Med 2004;351:2751–2753.
4. Wolfe BM, Austrheim-Smith IT, Ghaderi N. Surgical treatment of obesity: Pyloric electrical stimulation. Gastroenterology 2005;128:225–228.
5. Martin LF. The evolution of surgery for morbid obesity. In: Martin LF, ed. Obesity Surgery. New York: McGraw-Hill, Medical Publishing Division, 2004, pp 15–48.
6. Pories WJ, Roth JS. Gastric bypass. In: Martin LF, ed. Obesity Surgery. New York: McGraw-Hill, Medical Publishing Division, 2004, pp 213–225.
7. Barrow CJ. Roux-en-Y gastric bypass for morbid obesity. AORN J 2002;76(590):593–604.
8. Xu Y, Ramos EJ, Middleton F, Romanova I, Quinn R, Chen C, et al. Gene expression profiles post Roux-en-Y gastric bypass. Surgery 2004;136:246–252.
9. Rutledge R. The mini-gastric bypass: Experience with the first 1,274 cases. Obes Surg 2001;11:276–280.
10. Rutledge R, Walsh TR. Continued excellent results with the mini-gastric bypass: Six-year study in 2,410 patients. Obes Surg 2005;15:1304–1308.
11. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: A systematic review and meta-analysis. JAMA 2004;292:1724–1737.
12. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004; 351:2683–2693.
13. Bronlin RE. Bariatric surgery and long-term control of morbid obesity. JAMA 2002;288:2793–2796.
14. Christou NV, MacLean LD. Effect of bariatric surgery on long-term mortality. Adv Surg 2005;39:165–179.
15. Sugerman HJ, Sugerman EL, DeMaria EJ, Kellum JM, Kennedy C, Mowery Y, et al. Bariatric surgery for severely obese adolescents. J GASTROINTEST SURG 2003;7: 102–107.
16. Apovian CM, Baker C, Ludwig DS, Hoppin AG, Hsu G, Lenders C, et al. Best practice guidelines in pediatric/adolescent weight loss surgery. Obes Res 2005;13:274–282.
17. Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. Curr Opin Clin Nutr Metab Care 2004;7: 569–575.
18. Houghton AD, Liepins P, Clarke SM, Mason RC. Effect of gastric resection, Roux-en-Y diversion and vagotomy on gastric emptying in the rat. Br J Surg 1994;81:75–80.
19. Meguid MM, Ramos EJ, Suzuki S, Xu Y, George ZM, Das UN, et al. A surgical rat model of human Roux-en-Y gastric bypass. J GASTROINTEST SURG 2004;8:621–630.
20. Stenström B, Zhao CM, Tømmerås K, Arum CJ, Chen D. Is gastrin partially responsible for body weight reduction after gastric bypass? Eur Surg Res 2006;38:94–101.
21. Persson P, Gagnemo-Persson R, Chen D, Axelson J, Nylander AG, Johnell O, et al. Gastrectomy causes bone loss in the rat: Is lack of gastric acid responsible? Scand J Gastroenterol 1993;28:301–306.

22. Muhlbauer RC, Schenk RK, Chen D, Lehto-Axtelius D, Håkanson R. Morphometric analysis of gastrectomy-evoked osteopenia. Calcif Tissue Int 1998;62:323–326.
23. Lehto-Axtelius D, Chen D, Surve VV, Håkanson R. Post-gastrectomy osteopenia in the rat: Bone structure is preserved by retaining 10%-30% of the oxyntic gland area. Scand J Gastroenterol 2002;37:437–443.
24. Aukee S, Alhava EM, Karjalainen P. Bone mineral after partial gastrectomy II. Scand J Gastroenterol 1975;10:165–169.
25. Tovey FI, Hall ML, Ell PJ, Hobsley M. A review of postgastrectomy bone disease. J Gastroenterol Hepatol 1992;7:639–645.
26. Glatzle J, Piert M, Meile T, Besenthal I, Schafer JF, Konigsrainer A, et al. Prevalence of vertebral alterations and the effects of calcium and vitamin D supplementation on calcium metabolism and bone mineral density after gastrectomy. Br J Surg 2005;92:579–585.
27. Bell NH. Bone loss and gastric bypass surgery for morbid obesity. J Clin Endocrinol Metab 2004;89:1059–1060.
28. Coates PS, Fernstrom JD, Fernstrom MH, Schauer PR, Greenspan SL. Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. J Clin Endocrinol Metab 2004;89:1061–1065.
29. Johnson JM, Maher JW, Samuel I, Heitshusen D, Doherty C, Downs RW. Effects of gastric bypass procedures on bone mineral density, calcium, parathyroid hormone, and vitamin D. J GASTROINTEST SURG 2005;9:1106–1111.
30. Håkanson R, Chen D, Lindstrom E, Norlen P, Bjorkqvist M, Lehto-Axtelius D. Physiology of the ECL cells. Yale J Biol Med 1998;71:163–171.
31. Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, et al. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab 2001;86:4753–4758.
32. Dornonville de la Cour C, Björkqvist M, Sandvik AK, Bakke I, Zhao CM, Chen D, et al. A-like cells in the rat stomach contain ghrelin and do not operate under gastrin control. Regul Pept 2001;99:141–150.
33. Zhang JV, Ren PG, Avsian-Kretchmer O, Luo CW, Rauch R, Klein C, et al. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science 2005;310:996–999.
34. Cummings DE, Shannon MH. Ghrelin and gastric bypass: Is there a hormonal contribution to surgical weight loss? J Clin Endocrinol Metab 2003;88:2999–3002.
35. Fruhbeck G, Diez Caballero A, Gil MJ. Fundus functionality and ghrelin concentrations after bariatric surgery. N Engl J Med 2004;350:308–309.

Bariatric Surgery at the Extremes of Age

J. Fatima, M.D., S.G. Houghton, M.D., C.W. Iqbal, M.D., G.B. Thompson, M.D., F.L. Que, M.D., M.L. Kendrick, M.D., J.L. Mai, M.D., B.S., R.N., M.L. Collazo-Clavel, M.D., M.G. Sarr, M.D.

The safety and efficacy of bariatric surgery in adolescents and especially in Medicare population have been challenged. Our aim was to determine short-term (30-day) and long-term outcomes of bariatric surgery in patients ≥60 years and ≤18 years old. Query of our 20-year bariatric surgery database identified 155 patients ≥60 years and 12 patients ≤18 years. We determined morbidity and mortality rates and sent a questionnaire to all surviving patients; 127 of 139 survivors ≥60 years and all 12 adolescents returned the questionnaire (92%) at a mean of 5 years (range 1–19 years). For patients ≥60 years, 30-day mortality was 0.7%, serious morbidity delaying discharge was 14%, and 5-year mortality was 5%. At a mean of 5 years, body mass index (BMI in kg/m^2) decreased from a mean (±SEM) of 46 ± 1 to 33 ± 1 with a 51% resolution of weight-related comorbidities and an 89% subjective overall satisfaction rate. In patients ≤18 years, all with serious comorbidities, there were no deaths and no serious complications. BMI decreased from 55 (range 39–74) to 36 (range 27–53) at 4 years (range 1–8 years). Resolution of weight-related comorbidities was 82%, and satisfaction with outcome was 83%. Thirty-day hospital mortality (<1%) and 5-year mortality (5%) were much lower than reported previously in the senior population, with acceptable morbidity and importantly, with satisfactory outcomes. Bariatric surgery is safe and effective at high volume centers for patients with morbid obesity at both extremes of age. (J GASTROINTEST SURG 2006;10:1392–1396)

KEY WORDS: Bariatric surgery, gastric bypass, morbid obesity, Medicare population, adolescents

Morbid obesity is a rapidly increasing health care crisis in the developed and the developing world. Inability of nonoperative therapies to achieve and maintain adequate weight loss that reverses direct, weight-related comorbidities has singled out surgical therapy as the most effective treatment for such patients. Its safety and efficacy in the population at the extremes of age, however, are questioned by many involved parties, both physicians and third party insurance providers. Indeed, a recent article by Flum and colleagues[1] questioned the safety of bariatric surgery in the Medicare population, reporting a 30-day postoperative mortality of 4.8%. Such a high mortality rate has not been our experience with over 1800 bariatric operations in the last 20 years that included many patients over 60 years of age and 44 patients over 65 years of age. Comorbid conditions, poor quality of life, and social stigmatization associated with obesity exist over the entire age spectrum, including the Medicare population as well as the adolescent population, who often really suffer from psychosocial retardation. These considerations warrant further investigation to establish the outcomes of bariatric procedures in these specific groups.

As a high-volume center for bariatric surgery, we believed that the previously quoted article by Flum et al.[1] addressing older patients is not representative of bariatric procedures at experienced centers. Therefore, the aim of our study was to analyze the impact of bariatric surgery at both extremes of age in terms of perioperative morbidity and mortality, as well as weight loss, effect on weight-related comorbidities, and patient satisfaction in a high-volume, experienced, multidisciplinary center.

METHODS

After approval from the Institutional Review Board (IRB) of the Mayo Clinic, we queried our bariatric surgery database and identified 1834

Presented at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, May 20–25, 2005.
From the Departments of Surgery and Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota.
Reprint requests: Michael G. Sarr, M.D., Mayo Clinic (AL 2-435), 200 First Street S.W., Rochester, MN 55905. e-mail: frank.deborah@mayo.edu

 Published by Elsevier Inc.
1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.08.014

patients who had undergone bariatric surgery at the Mayo Clinic over the last 20 years from 1985 to 2004. Our inclusion criteria included all consecutive patients either ⩾60 years of age or ⩽18 years of age at the time of the bariatric procedure. We identified 167 patients: 155 patients in the ⩾60-year group (44 were >65 years old) and 12 patients in the ⩽18-year (adolescent) group.

We reviewed medical records to gather information regarding patient demographics, preoperative weight-related comorbidities, type of bariatric operation performed, number of the bariatric procedures that were operative revisions, postoperative morbidities, 30-day operative mortality, and overall 5-year mortality. A questionnaire was mailed to each surviving patient to acquire data on current weight, bowel habits, medications, resolution or persistence of weight-related comorbidities, and overall subjective satisfaction. In addition, patients were evaluated for late complications that required medical or operative management outside of our institution. Nonresponders were mailed a follow-up reminder with the questionnaire. Those who still failed to respond were contacted by telephone. All patients contacted through mail or by phone, were also requested to sign a HIPAA consent form to allow use of their long-term information for this study.

Analysis of Data

Data were grouped separately into the older and the younger age groups. Continuous data are expressed as a mean ± SEM and/or as a range.

RESULTS

A total of 1834 bariatric operations were performed at our institution from 1985 to 2004, of which 167 patients fulfilled the inclusion criteria for our study. Although seven patients underwent vertical banded gastroplasty (from 1985 to 1988), the majority (137 patients) were managed by Roux-en-Y gastric bypass (RYGB) with a standard Roux length of 150 cm or by our selective malabsorptive modification of the RYGB (which we call the very, very long limb RYGB) in 23 patients; this latter procedure establishes a 100-cm common channel of distal ileum and a Roux limb length of 300–500 cm.[2,3] A laparoscopic approach was used in 20 patients in the >60-year group and in one adolescent. Forty operations (23%) in the present series were operative revisions of a previous bariatric procedure.

Fully 92% of the evaluable patients completed the survey including 127 of the surviving patients in the ⩾60-year group and all 12 adolescents. Sixteen patients from the ⩾60-year group were deceased; 12 were lost to follow-up; however, follow-up to at least 1 year was available in all patients. Median ages of the patients in the ⩾60-year group and adolescents at the time of operation were 63 years (range 60–76 years) and 18 years (range 12–18 years), respectively. All adolescents undergoing bariatric surgery were screened carefully by pediatricians and psychologists as well as by our multidisciplinary team prior to bariatric surgery. A detailed discussion took place between the health care providers, the parents, and the patient to ensure appropriate insight and support for this intervention. Family support was deemed absolutely crucial in this adolescent group. Similar preoperative screening and counseling is our standard of care for our adult patients as well.

Postoperative hospital stay for the ⩾60-year group was 8 ± 1 days; mean follow-up was 5 years (1–19 years) with 35% having a follow-up of ⩾5 years. Hospital stay and duration of follow-up in the adolescents were 6 ± 1 days, and 4 years (range 1–8 years).

Morbidity and Mortality

In the ⩾60-year-old group, the 30-day mortality was 0.7% (1 of 155 patients). This female patient had an otherwise uncomplicated operation followed by sudden death on the second postoperative day, presumed secondary to a cardiopulmonary event. The overall 5-year mortality rate in this group was 5%. Serious, postoperative, in-hospital complications developed in 22 patients (14%), including six wound infections and one seroma prolonging hospital stay to a mean of 25 days (range 12–64 days), four small bowel obstructions with a mean hospital stay of 18 days (range 12–30 days), and three anastomotic leaks (two of which required reoperation extending hospital stay to a mean of 17 days (range 15–18 days). Two small bowel obstructions required reoperation on postoperative days 6 and 13, while the other two obstructions were managed conservatively with nasogastric decompression and nutritional support. Other in-hospital complications included pneumonia (n = 4), and one each of myocardial infarction, renal failure, gastric stasis, and gastrointestinal bleeding. Hematemesis from anastomotic ulceration occurred in three patients after discharge. Other delayed complications included hernia in 6% (n = 8) and stricture formation at the cardiojejunostomy managed with endoscopic dilatation in 2% (n = 3).

In the adolescent group, no deaths occurred during the follow-up period, and no in-hospital or

delayed complications were identified in these 12 patients.

Comorbidities

In the ⩾60-year group, 91% of the surviving patients responded to the survey. At the time of operation, BMI was 46 ± 1 kg/m^2, and 51 patients (40%) had documented diabetes, 65 (51%) had HTN requiring at least one antihypertensive medication, and 50 (39%) required CPAP or BiPAP to treat obstructive sleep apnea. Symptoms of gastroesophageal reflux disease (GERD) were present in 53 patients (42%), 19 (15%) were asthmatic, and 61 (48%) had some form of joint arthropathy limiting markedly their mobility and overall quality of life.

At a mean postoperative follow-up of 5 years (range 1–19 years) in the ⩾60-year group, BMI had decreased to 33 ± 1 kg/m^2. On average, patients had an excess body weight loss (%EBWL of 71%) and maintained 61% EBWL at 5 years; 82% of patients maintained >50% EBWL. Complete resolution of diabetes occurred in 59% of patients treated with insulin preoperatively, and 61% were able to discontinue insulin therapy postoperatively. Similarly, 33% of patients who required an antihypertensive medication(s) to control blood pressure, no longer required any medications postoperatively. Forty percent of patients on CPAP or BiPAP preoperatively were independent of this therapy at follow-up. Fifty-nine percent of patients with symptoms of GERD had no symptoms postoperatively, and 53% of asthmatics had complete resolution of asthma. Thirty-five patients with debilitating joint arthropathy preoperatively underwent hip arthroplasty (n = 5), knee arthroplasty (n = 24), or both (n = 6) postoperatively; indeed, overall, 48% of patients with arthropathy preoperatively felt that the bariatric operation helped relieve joint symptoms, and 30% required no further pain medications for joint pain.

In the adolescent group, the response rate to our questionnaire was a 100%. Over the follow-up period of 4 years (range 1–8 years), BMI decreased from 55 kg/m^2 (range 39–74) to 36 kg/m^2 (range 27–53). Weight loss was maintained at 83% EBWL at 4 years of follow-up. All but two patients maintained >50% EBWL. In one patient with a preoperative BMI of 66 kg/m^2, weight loss was clearly unsatisfactory (postoperative BMI = 53) despite construction of a very, very long limb RYGB; this patient had no family history of obesity, yet, despite her facial features suggesting a genetic syndrome, no definitive syndrome could be identified by our geneticists. Indications for bariatric intervention in this group included current or impending medical complications due to morbid obesity, a well-established family history of morbid obesity, and/or severe psychosocial trauma/ retardation and ostracization by peers.

Of the 12 adolescents, all 3 who were both diabetic and hypertensive and the 2 with severe symptoms of GERD, reported complete resolution of these problems with discontinuation of medications at follow-up. One of the three asthmatics has had no symptoms of asthma postoperatively. All seven patients with notable joint arthropathy experienced marked improvement in discomfort and mobility after the bariatric operation.

Bowel Habits and Dietary Changes

Ninety-one percent of patients (n = 116) in the ⩾60-year-old population reported postprandial fullness at the time of follow-up, while 11% (n = 14) had four or more bowel movements on a daily basis; 51% (n = 65) stated that they had intermittent loose stools. Infrequent abdominal cramps occurred in 28% (n = 36).

The majority of patients (85%) reported a persistent decrease in their overall appetite, and 59% stated they had continued a reduced daily food consumption since their operation. Assessment of specific nutrient intake identified reduced fat intake in 33%, monitoring of carbohydrate intake in 17%, and adequate protein intake in 91%. Mild intolerance to certain foods such as red meat, dairy products, and fatty food was present in 43% of this population, but was not incapacitating in any patient.

In adolescents, postprandial fullness was noted in all but two patients. Five of the 12 patients underwent a malabsorptive, very, very long limb RYGB. While only one patient reported more than four bowel movements per day, half had mostly loose stools. Occasional abdominal cramping was experienced by three. Only three adolescents claim to maintain reduced fat and carbohydrate content in their diets.

Satisfaction

The majority of patients in both groups were satisfied with the result of their operation. The percentage of patients who reported satisfaction in the ⩾60-year group was 89%, while all but two patients in the ⩽18-year group were content with their outcome. Twenty-two percent of the ⩾60-year group had been successful in keeping themselves employed, which they attribute to their improved health. Six adolescents are currently in college, while five have completed college and successfully sought employment. All adolescents except one reported

improvement in their overall health in addition to greater social involvement with their peers. Moreover, 87% in the ⩾60-year group would recommend a bariatric procedure to a friend, and 92% (all but one) of the adolescents thought it was a good option for the morbidly obese adolescent.

DISCUSSION

Bariatric procedures in the Medicare and adolescent population afflicted with morbid obesity are safe and effective when performed in high volume, multidisciplinary, experienced centers like Mayo Clinic. Our patients at both extremes of ages benefited from the operation in terms of weight loss and reduction or resolution of comorbidities; the 30-day mortality rate in patients ⩾60 years old was low at 0.7%, and 5-year mortality rate was 5%. These complication and mortality rates were no higher than that amongst the average adult population who undergo this operation. The impact of bariatric surgery on improvement of weight-related morbidity and lifestyle of most patients has been very satisfying.

Our experience in the older patient population contrasts clearly with the results stated in a recent article by Flum and colleagues[1] in 2005. The mortality rate reported in the study by Flum et al.[1] in the Medicare population is much higher than ours at both 30 days (4.8% versus 0.7%) and at 5 years (11.1% versus 5%). The most reasonable explanation for this discordance is the differential surgeon experience, procedural volume, and experienced multidisciplinary approach. In our experience, and that of others,[4] bariatric operations performed at high-volume centers by experienced surgeons experienced in patient selection, operative therapy, and postoperative care is associated with low morbidity and mortality. Bariatric surgery in this patient population does not obligate an inordinate risk of an adverse outcome if performed in appropriately selected patients in the Medicare population at high-volume centers with an experienced, multidisciplinary approach.[2,4–7] The report of Flum and colleagues[1] did demonstrate this differential in outcomes based on surgeon experience with 30-day mortality rates of 9.0% versus 1.1% for surgeons in the lowest versus highest volume quartiles, respectively. In our practice, all surgeons performing bariatric procedures currently have a minimum annual volume of 50 procedures. Our mortality of 0.7% in this older population (>60 years old) compares favorably with the 1.1% reported by Flum and colleagues[1] for surgeons with high volumes, again underscoring the importance of surgeon volume in bariatric surgery. Compared to our overall results for RYGB in patients of all age groups, our data in the older population showed similar hospital mortality, complication rate, hospital stay, weight loss, and patient satisfaction.[8] The benefits reaped postoperatively appear to outweigh the risks, making this an excellent therapeutic option in this population subset as well. Weight loss is accompanied by an impressive decrease in the direct weight-related comorbidities including diabetes, hypertension, sleep apnea, asthma, and GERD. In addition, the resultant weight loss allowed these patients to be acceptable candidates for joint arthroplasties, allowing greater mobility and, hence, capability of managing independently their personal daily life activities.[9]

Similarly, apart from the negative health consequences and physical deconditioning related to their obesity,[10] adolescents with severe obesity fall far behind their peers in active lifestyles. This social retardation may result in social stigmatization, discrimination, and ostracization causing detrimental long-term psychosocial sequelae.[11] These very real hazards of the severely obese youth get translated into psychosocial retardation as they grow into adulthood, with an additional heavy economic impact because of development of medical comorbidities. Addressing this issue at an early stage via a multidisciplinary approach involving pediatricians, psychiatrists, endocrinologists, dieticians, and surgeons, complemented with strong family support to modify behavior and lifestyle, appears to be the most effective therapeutic approach in these unfortunate children/adolescents.[12] While the need for weight loss in these young individuals is well established, there are insufficient data to support the success of bariatric intervention because of a generalized reluctance on the part of the medical profession to intervene surgically.[13–15] Our experience with these 12 adolescents urges us to strongly recommend this approach in selected adolescents, based on success with weight loss, reduction and/or resolution of comorbidities, absence of any complications, and improved social life.

Indeed, an analysis of bariatric procedures for morbid obesity done in patients at extremes of age showed a decrease in use of medical facilities and medical claims, reducing the economic burden of obesity.[16–18] In essence, bariatric surgery and consequent successful weight loss helps both groups of patients to be independent, active members of society and, hence, improves dramatically the quality of life and impacts their medical health substantially.

REFERENCES

1. Flum DR, Salem L, Elrod JB, Dellinger EP, Cheadle A, Chan L. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. JAMA 2005;294: 1903–1908.
2. Murr MM, Balsiger BM, Kennedy FP, Mai JL, Sarr MG. Malabsorptive procedures for severe obesity: comparison of pancreaticobiliary bypass and very very long limb Roux-en-Y gastric bypass. J GASTROINTEST SURG 1999;3: 607–612.
3. Nelson WK, Fatima J, Houghton SG, Thompson GB, Kendrick ML, Mai JL, et al. The malabsorptive very, very long limb Roux-en-Y gastric bypass for super obesity: results in 257 patients. Surgery 2006;140:517–523.
4. Nguyen NT, Paya M, Stevens M, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. Ann Surg 2004;240:586–594.
5. Livingston EH, Huerta S, Arthur D, Lee S, Shields SD, Heber D. Male gender is a predictor of morbidity and age a predictor of mortality for patients undergoing gastric bypass surgery. Ann Surg 2002;236:576–582.
6. Nguyen NT, Rivers R, Wolfe BM. Factors associated with operative outcomes in laparoscopic gastric bypass. J Am Coll Surg 2003;197:548–555; discussion 555–557.
7. Sugerman HJ, DeMaria EJ, Kellum JM, Sugerman EL, Meador JG, Wolfe LG. Effects of bariatric surgery in older patients. Ann Surg 2004;240:243–247.
8. Balsiger BM, Kennedy FP, Abu-Lebdeh HS, Collazo-Clavell M, Jensen MD, O'Brien T, et al. Prospective evaluation of Roux-en-Y gastric bypass as primary operation for medically complicated obesity. Mayo Clin Proc 2000;75: 673–680.
9. Macgregor AMC, Rand CSW. Gastric surgery in morbid obesity, outcome in patients aged 55 years and older. Arch Surg 1993;128:1153–1157.
10. Gidding SS, Nehgme R, Heise C, Muscar C, Linton A, Hassink S. Severe obesity associated with cardiovascular deconditioning, high prevalence of cardiovascular risk factors, diabetes mellitus/hyperinsulinemia, and respiratory compromise. J Pediatr 2004;144:766–769.
11. Durant N, Cox J. Current treatment approaches to overweight in adolescents. Curr Opin Pediatr 2005;17:454–459.
12. Rodgers BM. American Pediatric Surgical Association. Bariatric surgery for adolescents: A view from the American Pediatric Surgical Association. Pediatrics 2004;114:255–256.
13. Stanford A, Glascock JM, Eid GM, Kane T, Ford HR, Ikramuddin S, Schaumuer P. Laparoscopic Roux-en-Y gastric bypass in morbidly obese adolescents. J Pediatr Surg 2003;38:430–433.
14. Abu-Abeid S, Gavert N, Klausner JM, Szold A. Bariatric surgery in adolescence. J Pediatr Surg 2003;38:1379–1382.
15. Sugerman HJ, Sugerman EL, DeMaria EJ, Kellum JM, Kennedy C, Mowery Y, Wolfe LG. Bariatric surgery for severely obese adolescents. J GASTROINTEST SURG 2003;7: 102–107.
16. St. Peter SD, Craft RO, Tiede JL, Swain JM. Impact of advanced age on weight loss and health benefits after laparoscopic gastric bypass. Arch Surg 2005;140:165–168.
17. Papasavas PK, Gagne DJ, Kelly J, Caushaj PF. Laparoscopic Roux-en-Y gastric bypass is a safe and effective operation for the treatment of morbid obesity in patients older than 55 years. Obes Surg 2004;14:1056–1061.
18. Ponce J, Haynes B, Paynter S, Fromm R, Lindsey B, Shafer A, Manahan E, Sutterfield C. Effect of LapBand induced weight loss on type 2 diabetes mellitus and hypertension. Obes Surg 2004;14:1335–1342.

Does the Position of the Alimentary Limb in Roux-en-Y Gastric Bypass Surgery Make a Difference?

Jerome D. Taylor, M.D., I. Michael Leitman, M.D., James ("Butch") Rosser, M.D., Brian Davis, M.D., Elliot Goodman, M.D.

Intestinal obstruction and other complications have been reported following Roux-en-Y gastric bypass (RYGB) surgery. There is controversy of whether the alimentary limb should be placed in the retrocolic or antecolic position. A retrospective analysis was performed on 444 patients undergoing RYGB surgery for morbid obesity during a six year period. During operation, the surgeon chose the positioning of the 75-cm alimentary limb based upon technical consideration (the presence of adhesions from prior surgical procedures, thickness of the transverse mesocolon and mobility of the small bowel mesentery). Group A (216) patients had placement of the Roux limb anterior to the transverse colon, and group B (228) patients had placement of the limb through an opening created in the transverse mesocolon. The average age was 40 years (range 19–64) and the body mass index ranged from 40 to 75 kg/m^2. Patients were followed for 24–86 months (mean 36 months). Any patients lost to follow-up were excluded. The average age of patients in the study was 40 years (range 19–64 years). Patients in both groups were similar in their body mass index and demographic characteristics. Group A had 16 patients (7.4%) that had early intolerance to enteral intake, compared to 13 patients in group B (5.7%, $P > 0.05$). Thirteen patients required reoperation for intestinal obstruction (seven patients in group A and six patients in group B ($P > 0.05$). Development of anastomotic stricture occurred in one patient (0.5%) in group A and three patients (1%, $P > 0.05$) in group B. There were no differences in mean operating room times, hospital length of stay, and excess weight lost. No other complications during the follow-up period were attributed to the position of the alimentary limb. Placement of the Roux limb in the antecolic position is may be technically more feasible in some patients and does not appear to be associated with more complications. It avoids the risk of an internal hernia through the transverse and does not appear to be associated with feeding difficulties in the early or late postoperative period. (J GASTROINTEST SURG 2006;10:1397–1399)

The benefits of Roux-en-Y gastric bypass (RYGB) surgery have been well established for the treatment of morbid obesity. As the number of patients who have undergone this surgery has accumulated over the past several years, long-term complications, previously underappreciated have been increasing in frequency. Intestinal obstruction can occur anytime after abdominal surgery. The complicated anatomy and the effect of massive weight loss present special circumstances in patients who have had gastric bypass surgery more than several years before. This may result in one cause of intestinal obstruction (Petersen's hernia), usually occurring when the alimentary limb is brought through a rent, created in the transverse mesocolon, at the time of RYGB surgery.[1,2]

The diagnosis of Petersen's hernia may be difficult as the physical findings of internal hernias are often vague, clinical laboratory examinations are frequently unreliable and nondiagnostic, and plain radiographs are usually unremarkable, even in the presence of a complete intestinal obstruction. Contrast-enhanced CT, laparoscopy, or even laparotomy may be necessary to accurately diagnose this condition.[3]

Because the development of internal hernias could be related to the method of construction of the

Presented at the Plenary Session at the Forty-Seventh Annual Meeting of The Society for Surgery of the Alimentary Tract, Los Angeles, May 20–25, 2005.

From the Department of Surgery, Beth Israel Medical Center, New York, New York.

Reprint requests: I. Michael Leitman, M.D., Department of Surgery, Beth Israel Medical Center, 10 Union Square East, Suite 2M, New York, NY 10003. e-mail: mleitman@chpnet.org

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.09.007

Roux-en-Y, the present study evaluates whether placement of the alimentary limb in front of the colon (antecolic), instead of through the transverse mesocolon (retrocolic), might reduce the incidence of this complication. This may arise because increased mobility may allow the small bowel to enter a surgically created hernia defect more frequently.[4] Some have argued that meticulous closure of this anatomical defect with nonabsorbable sutures will reduce the formation of a potential space.[5] Others have suggested that by eliminating the transmesenteric defect with antecolic placement of the Roux limb the incidence of internal hernias would be reduced.[6] This complication has been reported in laparoscopic and open RYGB procedures.[7]

PATIENTS AND METHODS

Four hundred fouty-four patients with an indication for gastric bypass surgery according to the National Institutes of Health and American Society for Bariatric Surgery criteria were evaluated over a 6-year period. The patients were closely followed and were similar in comorbidities and any patients lost to follow-up were not included. The minimum follow-up on all patients analyzed was 2 years. The medical records of these patients were analyzed to document outcomes and complications to include intolerance to enteral intake, intestinal obstruction, stricture formation, and reoperation for internal hernia formation. The patients all had the open RYGB performed by the same surgeon. The biliopancreatic limb was created at least 100 cm distal to the ligament of Trietz and the alimentary limb was approximately 75 cm in length in all patients. In patients with a retrocolic anastomosis, the mesenteric defect was approximated with nonabsorbable sutures.

Patients were divided into two groups: group A (216 patients) had the alimentary limb placed anterior to the transverse limb, and group B (228 patients) had the alimentary placed through an opening created in the transverse mesocolon. The body mass index (BMI) ranged from 40 to 75 kg/m^2. Patients were followed for 24–86 months (mean 36 months). Data were subjected to univariate and multivariate analysis. A P-value of less than 0.05 was considered statistically significant.

RESULTS

The two groups were similar in age, BMI, and history of prior surgery. Group A (Table 1) had 16 patients (7.4%) who had early intolerance to enteral intake, compared to 13 patients in group B (5.7%, $P > 0.05$). Intolerance to enteral intake was defined as severe nausea and vomiting that required readmission to the hospital and producing severe symptoms of dehydration. The average operating time was 114 minutes and not statistically different between groups. The average lengthy of stay was 4.3 days and the average excess weight loss was 41% of excess at an average follow-up of 32 months. There were no statistical differences between patients with an antecolic or retrocolic anastomosis.

There were 13 patients who required reoperation for intestinal obstruction (7 patients in group A and 6 patients in group B ($P > 0.05$). All of the patients who developed intestinal obstruction were diagnosed by history, physical examination, and a comprehensive imaging workup to include plain films, CT scan, and/or UGI series. Many of these patients presented with same symptoms of nausea and emesis that started out as intermittent but later became constant and unrelenting. Also, many developed postprandial abdominal pain and discomfort that intensified. Three patients in group A and 2 in group B developed intestinal obstruction on the basis of incarcerated incisional hernias. Four patients in group A and one in group B developed small bowel obstruction due to adhesions. There were three patients (in group B only) who developed an obstruction on the basis of internal (Peterson's) hernia.

Table 1. Comparison of patients with retrocolic and antecolic limb placement

RYGB patients	Early intolerance to enteral intake	Intestinal obstruction requiring surgery	Anastomotic stricture development
Group A, antecolic limb placement (n =216)	16 (7.4%)	7 (3.2%)	1 (0.5%)
Group B, retrocolic limb placement (n = 228)	13 (5.7%)	6 (2.6%)	3 (1%)

$P > 0.05$.

The development of anastomotic stricture was one patient (0.5%) in group A and three patients (1%, $P > 0.05$) in group B. The patients who developed stricture were diagnosed by a complete and through history, physical examination, and an upper gastrointestinal study and/or endoscopy. No other complications during the follow-up period were attributed to the position of the alimentary limb.

DISCUSSION

Reports of long-term complications following RYGB, including the effects of calcium and iron deficiency, marginal ulceration, and intestinal obstruction, are increasing in frequency as the familiarity of these conditions have increased. Intestinal obstruction from any cause may be especially dangerous for the gastric bypass surgery patient due to the alternation of their gastrointestinal anatomy. The incidence of intestinal obstruction following RYGB requiring surgical intervention has been reported to be as high as 8%. There are several factors that could lead to intestinal obstruction, including adhesions. This includes intra-peritoneal and massive weight loss. This may permit more rotation of the small intestinal mesentery and internal hernias, particularly through the defect in the transverse mesocolon. The placement of the olimentary limb in the retrocolic position may further predispose patients to this complication.[3,8–10] However, proponents of this claim that the retrocolic anastomosis protects the small bowel limb and promote drainage from the stomach. The present study did not show any benefit from the retrocolic anastomosis in any patient's ability to tolerate oral feeding.

Intestinal obstruction following RYGB surgery can be difficult to diagnose and result in severe morbidity and mortality if not recognized and treated in a timely fashion.[11–15] Even if the mesocolonic defect is surgically closed, it still allows the potential for the development of Petersen's hernia.[16] The incidence of herniation through the mesocolon has continued to be an issue as the number of procedures performed has increased, but this problem is one that can be addressed if the created defect is avoided.

Small bowel obstruction in the postoperative RYGB patient population continues to be an issue that can be blamed on several factors, including adhesion formation, hernia formation, and narrowing, kinking, and/or stenosis in the alimentary limb. Also, because many of these problems develop later in the postoperative period and many of the patients may be unavoidably lost to follow-up, it is more incumbent for the operating surgeon to eliminate and or minimize as many postoperative issues as possible.

The present study clearly demonstrates that the incidence of internal hernia complications continue to present a problem in the postoperative period is similar in patients with retrocolic and antecolic anastomosis but that Petersen's hernia did not occur in any patient with an antecolic anastomosis.

REFERENCES

1. Macgregor AMC. Small bowel obstruction following gastric bypass. Obes Surg 1992;2:333–339.
2. Duane TM, Wohlgemuth S, Ruffin K. Intussusception after Roux-en-Y gastric bypass. Am Surg 2000;66:82–84.
3. Higa KD, Ho T, Boone KB. Internal hernias after laparoscopic Roux-en-Y gastric bypass: Incidence, treatment and prevention. Obes Surg 2003;13:350–354.
4. Garza E, Kuhn J, Arnold D, Nicholsan W, Reddy S, McCarty T. Internal hernias after laparoscopic Roux-en-Y gastric bypass. Am J Surg 2004;188:796–800.
5. Blachar A, Federle MP. Gastrointestinal complications of laparoscopic Roux-en-Y gastric bypass surgery in patients who are morbidly obese: Findings on radiography and CT. AJR Am J Roentgenol 2002;179:1437–1442.
6. Higa KD, Boone KB, Ho T. Complications of Roux-en-Y gastric bypass: 1040 Patients: What have we learned? Obes Surg 2000;10:509–513.
7. Grundy SM, et al. Gastrointestinal Surgery for Severe Obesity. National Institutes of Health Consensus Development Conference Statement, March 25-27, 1991, Bethesda, MD. Am J Clin Nutr 1992;55(2 Suppl):487S–619S.
8. Champion JK, Williams M. Small bowel obstruction and internal hernias after laparoscopic Roux-en-Y gastric bypass. Ober Surg 2003;13:596–600.
9. Sandrasegaran K, Rajesh A, Lall C, Gomez GA, Lappas JC, Maglinte DD. Gastrointestinal complications of bariatric Roux-en-Y gastric bypass surgery. Eur Radiol 2005;15:254–262.
10. Filip JE, Mattar SG, Bowers SP, Smith CD. Internal hernia formation after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Am Surg 2002;68:640–643.
11. Onopchenko A. Radiological diagnosis of internal hernia after Roux-en-Y gastric bypass. Obes Surg 2005;15:606–611.
12. Fleser PS, Villalba M. Afferent limb volvulus and perforation of the bypassed stomach as a complication of Roux-en-Y gastric bypass. Obes Surg 2003;13:453–456.
13. Quebbemann BB, Dallal RM. The orientation of the antecolic Roux limb markedly affects the incidence of internal hernias after laparoscopic gastric bypass. Obes Surg 2005;15:766–770.
14. Goverman J, Greenwald M, Gellman L, Gadaleta D. Antiperistaltic (retrograde) intussusception after Roux-en-Y gastric bypass. Am Surg 2004;70:67–70.
15. Esmailzadeh H, Powell W, Lourie D. Use of computed tomography in diagnosis of major postoperative gastrointestinal complications of laparoscopic Roux-en-Y gastric bypass surgery. Am Surg 2004;70:964–966.
16. Carmody B, DeMaria EJ, Jamal M, Johnson J, Carbonell A, Kellum J, Maher J. Internal hernia after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2005;1:511–516.

Long-term Results of Conventional Myotomy in Patients With Achalasia: A Prospective 20-Year Analysis

Ines Gockel, M.D., Theodor Junginger, M.D., Volker F. Eckardt, M.D.

Myotomy has proved to be an efficient primary therapy in patients with achalasia, especially in younger patients (<40 years of age). The results of laparoscopic myotomy cannot be finally assessed, on account of the shorter postoperative follow-up. Thus, there are considerable data regarding intermediate-term outcomes after laparoscopic myotomy. The aim of our study was a 20-year analysis of the conventional cardiomyotomy as the underlying basis assessing the results of minimal-invasive surgery. Within 20 years (September 1985 through September 2005), 161 operations for achalasia were performed in our clinic. Enrolled in this study were 108 patients with a conventional, transabdominal myotomy in combination with an anterior semifundoplication (Dor procedure) and a minimal follow-up of 6 months. All patients were prospectively followed and, in addition to radiologic and manometric examinations of the esophagus, the patients were asked for their clinical symptoms by structured interviews in 2-year intervals. The median age at the time of surgery was 44.5 (range, 14–78) years, and 72.2% of the patients were males. The median length of the preoperative symptoms was 3 years (3 months to 50 years), and the postoperative follow-up was 55 (range, 6–206) months. In 70 (64.8%) patients, a pneumatic dilation had been performed. The preoperative Eckardt score of 6 (range, 2–12) could be reduced to 1 (range, 0–4) after myotomy ($P < 0.0001$). Consequently, with 97.2% of all patients, a good-to-excellent result was achieved in the long-term follow-up, corresponding to a clinical stage I-II. Postoperatively, 69 patients (63.9%) gained weight. The radiologically measured maximum diameter of the esophagus decreased from preoperatively 45 (range, 20–75) mm to postoperatively 30 (range, 20–60) mm, while the minimum diameter of the cardia increased from 3.4 (range, 1–10) mm to 10 (range, 5–15) mm. The resting pressure of the lower esophageal sphincter could be reduced from 28.4 (range, 9.4–56.0) mm Hg to 8.6 (range, 3.0–22.5) mm Hg. Conventional myotomy leads in the long run with high efficiency to an improvement of the symptoms evident in achalasia. These results may be regarded as the basis for assessment of the minimal-invasive procedure. (J GASTROINTEST SURG 2006;10:1400–1408)

KEY WORDS: Achalasia, conventional myotomy, prospective 20-year analysis, basis for assessing the laparoscopic procedure

Currently, only two therapeutic options—pneumatic dilation and cardiomyotomy—are known to yield a lasting improvement of symptoms in patients with achalasia. Myotomy has emerged as the primary surgical treatment, particularly in younger patients (<40 years). Although laparoscopic myotomy is increasingly being used, an accurate assessment of the results after this surgical technique is not yet possible, due to the still relatively short follow-up periods. An evaluation of the surgical outcome and postoperative symptoms after laparoscopic myotomy reported in the literature is further complicated by the absence of a uniform scoring system used by different studies to determine the severity degree of achalasia, in particular also with regard to the relationship between the development of postoperative reflux and the achieved resting pressure of the lower esophageal sphincter (LES).

The long-term findings after conventional open cardiomyotomy documented by this study, carried out at a single institution over a 20-year period using a standardized score, as well as radiographic and

From the Department of General and Abdominal Surgery, Johannes Gutenberg-University of Mainz, Germany (I.G., T.J.); and the Department of Gastroenterology, German Diagnostic Clinic, Wiesbaden, Germany (V.F.E.).
Reprint requests: Ines Gockel, M.D., Department of General and Abdominal Surgery, Johannes Gutenberg-University, Langenbeckstr. 1, 55101 Mainz, Germany. e-mail: gockel@ach.klinik.uni-mainz.de

 Published by Elsevier Inc.
1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.07.006

manometric follow-up studies, may therefore be regarded as a basis for the assessment of the minimal invasive procedure.

PATIENTS AND METHODS

Patients

Over a period of 20 years (September 1985 through September 2005), 161 surgical interventions were performed in patients with achalasia at the Department of General and Abdominal Surgery of the Johannes Gutenberg-University Mainz. The diagnosis was established on the basis of manometric, endoscopic, and radiographic findings. Enrolled in the present study, which included a minimum follow-up period of 6 months postoperatively, were 108 patients scheduled to undergo conventional open transabdominal myotomy in combination with an anterior Dor semifundoplication performed by the same surgeon (T.J.). Also considered were re-operations after prior myotomy with an inadequate therapeutic result and persistent high resting pressure of the LES (re-myotomy in 12 patients corresponding to 13 prior interventions: 12 laparoscopic and 1 open procedure). Excluded from the study were patients with esophagectomy for decompensated end-stage achalasia and patients with laparoscopic myotomy. The patients were followed prospectively and queried at 6 months postoperatively as well as at 24-month intervals thereafter by the treating gastroenterologist (V.F.E.) on the basis of a structured interview regarding their clinical symptoms, in addition to undergoing manometric and radiographic follow-up examinations at these time points. The patients were followed until the time of their death or up to the end of the study period; a final checkup was carried out in 2005. At this time, six of the patients were lost to follow-up because they had moved and their place of residence was unknown. Ten patients died during the follow-up period from extraesophageal disorders.

Median age of the patients at the time of operation ranged at 44.5 (range, 14–78) years, and 72.2% of the patients were males.

METHODS

Specific individual patient consent was obtained for this study, for the administration of questionnaires as well as for the technical studies performed preoperatively and postoperatively.

Symptoms

The Eckardt symptom score was used for the documentation of clinical symptoms at the time of the initial examination and in the course of the follow-up period.[1] In addition to the symptom score, the patients were queried postoperatively regarding the presence of gastroesophageal reflux. An endoscopic examination was carried out in patients with clinical suspicion of reflux esophagitis. A symptom score of 3 or fewer points over a minimum period of 6 months was regarded as clinical remission.

Manometric Studies

All patients were examined using a capillary perfusion system according to the method described earlier.[1] Further to the initial resting pressure and relaxation of the LES, contraction amplitudes of the tubular esophageal body were determined after 10 wet swallows. The absence of peristalsis in the esophageal body, a hypertensive, nonrelaxing LES, and simultaneous or repetitive contractions served as the manometric criteria in the diagnosis of achalasia. Patients with constriction or tortuous configuration of the distal esophagus that did not permit insertion of the manometry catheter were excluded from further evaluation, due to the fact that only data on esophageal body motility were available.

Radiographic Studies

Radiographic studies were carried out with the patient in a lying, semiupright, or upright position. Measurements of the maximum diameter of the esophageal body and the narrowest point of the gastroesophageal junction were thus obtained.

Pneumatic Dilation

Pneumatic dilations were performed by the treating gastroenterologist (V.F.E.) using a Browne-McHardy dilator. The balloon tip of the dilator was placed at the gastroesophageal junction and then filled to maximum capacity of the balloon. The pressure thus achieved ranged from 6 to 12 psi and was maintained for approximately 2 minutes, depending upon the tolerance level of the patient.

Surgical Therapy

The surgical procedures (conventional open, transabdominal myotomy in combination with an anterior Dor semifundoplication) were performed in all patients by the same surgeon (T.J.).[2] The minimum length of the myotomy was 6 to 7 cm and extended distally approximately 1.5 to 2 cm onto the anterior gastric wall. The wrap was fixed by a two-row suture line laterally to the myotomy, and its length corresponded to the length of the myotomy in order to cover the whole myotomy.

Statistical Analysis

The SPSS software package was used for statistical data analysis (2001 SPSS 11.0; SPSS, Chicago, IL). Continuous variables are expressed as median values and ranges (minimum to maximum), as well as in percentages. Statistical comparisons of preoperative and postoperative variables were carried out with a nonparametric instrument (Mann-Whitney *U*-test). A linear regression model was used to evaluate the influence of different variables on the postoperative symptom score.

P-values of <0.005 were considered significant for all procedures.

RESULTS

The median time of the preoperative medical history in the 108 patients with open myotomy and a minimum follow-up period of 6 months was 3 years (range, 3 months to 50 years). The follow-up was 94.4%. A pneumatic dilation had been carried out preoperatively in 70 of the 108 patients (64.8%). These patients had a median number of 1 (range, 0–35) dilation. Six patients had received botulinum toxin therapy preoperatively; a maximum number of five injections were administered in one of the patients of this group.

The median operative time was 90 (range, 60–185) minutes; concomitant surgical procedures (e.g., cholecystectomy) were performed in 11 patients (10.2%). The median postoperative hospital stay was 8 days. Intraoperative complications occurred in 7 (6.5%) patients due to perforation of the gastric mucosa, which was repaired with an interrupted suture and covered with the fundoplication. Postoperative complications were observed in two patients (1.8%) (gastrointestinal bleeding and pulmonary embolism); no patient died in the postoperative course. The surgical therapy was unsuccessful in one patient, who presented with recurrent achalasia after an initial improvement of the symptoms in the preoperative course and was treated with a conventional posterior re-myotomy.

The median follow-up period was 55 (range, 6–206) months.

Symptoms

A median preoperative score of 6 (range, 2–12) was calculated using the Eckardt symptom score. It was significantly ($P < 0.0001$) reduced after myotomy and semifundoplication to a median of 1 (range, 0–7) in the long-term course (Fig. 1). In the group of three patients with a postoperative score of 5 (n = 2)

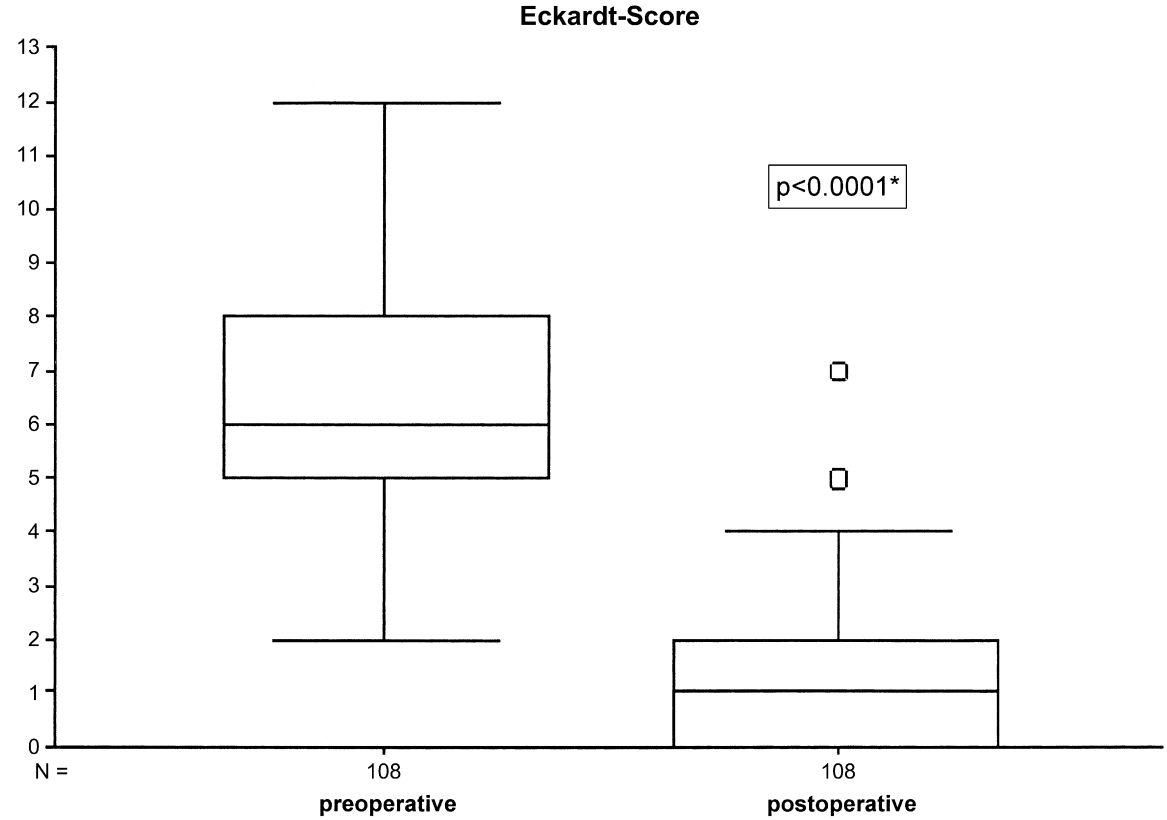


Fig. 1. Preoperative and postoperative Eckardt Score

and 7 (n = 1), respectively, a female patient who developed dolichomegaesophagus is scheduled to undergo esophagectomy in the further course; in another of these patients, a posterior re-myotomy was performed with good success after failed primary surgical therapy. The 5-year remission rate thus was 93% compared with 90% for the 10-year remission rate. An examination of each symptom of the Eckardt score separately shows that, preoperatively, 73.1% of patients reported dysphagia at each meal, 16.7% indicated the daily and 10.2% the occasional occurrence thereof, which corresponds to a median score of 3 (range, 1–3). After myotomy, 89.8% of patients indicated having no or only occasional difficulty in swallowing, resulting a median score of 0 (range, 0–3) ($P < 0.0001$).

Prior to surgical therapy, 55.6% of patients complained of regurgitation occurring daily or at each meal, and 28.7% reported occasional regurgitation (median preoperative score, 2; range, 0–3). Postoperatively, this symptom was absent or occurred only occasionally in 97.2%, corresponding to a score of 0 (0–2) ($P < 0.0001$). The presence of retrosternal pain prior to surgery was indicated by 65.7% of patients, and 27.7% described the pain as occurring daily or several times during the day. The most recent postoperative assessment of the collected data showed that 96.3% of patients experienced no or only occasional spasmodic retrosternal pain. There was thus a significant ($P < 0.0001$) decrease in the median score from 1 (0–3) to 0 (0–2).

While 32.4% of patients indicated a weight loss of up to 10 kg and 13.0% of less than 10 kg prior to surgery, 98.1% reported no or a maximum weight loss of 5 kg postoperatively. The preoperative and postoperative score ranged at 0 (range, 0–3 versus range, 0–2) points, with a statistically significant difference ($P < 0.0001$).

The preoperative body mass index (BMI) of 23.7 (15.7–37.9) kg/m^2 prior to myotomy was therefore significantly ($P < 0.0001$) increased to 25.0 (19.8–35.8) kg/m^2 postoperatively ($P < 0.0001$) (Fig. 2), and a weight gain was documented in 63.9% of all patients. Pyrosis occurred in 22.2% of patients after myotomy, and a total number of 17 (15.7%) patients showed reflux esophagitis on endoscopy. Thus, esophagitis revealed stages I-II according to Savary and Miller only. All of these patients underwent drug therapy for the described conditions. Postoperatively, the resting pressure of the LES recorded in patients with reflux esophagitis was 9.7 (3.0–17.0) mm Hg (n = 10), which did not differ significantly from the median pressure of 8.6 (3.3–22.5) mm Hg (n = 41) noted in patients without reflux esophagitis ($P = 0.6954$).

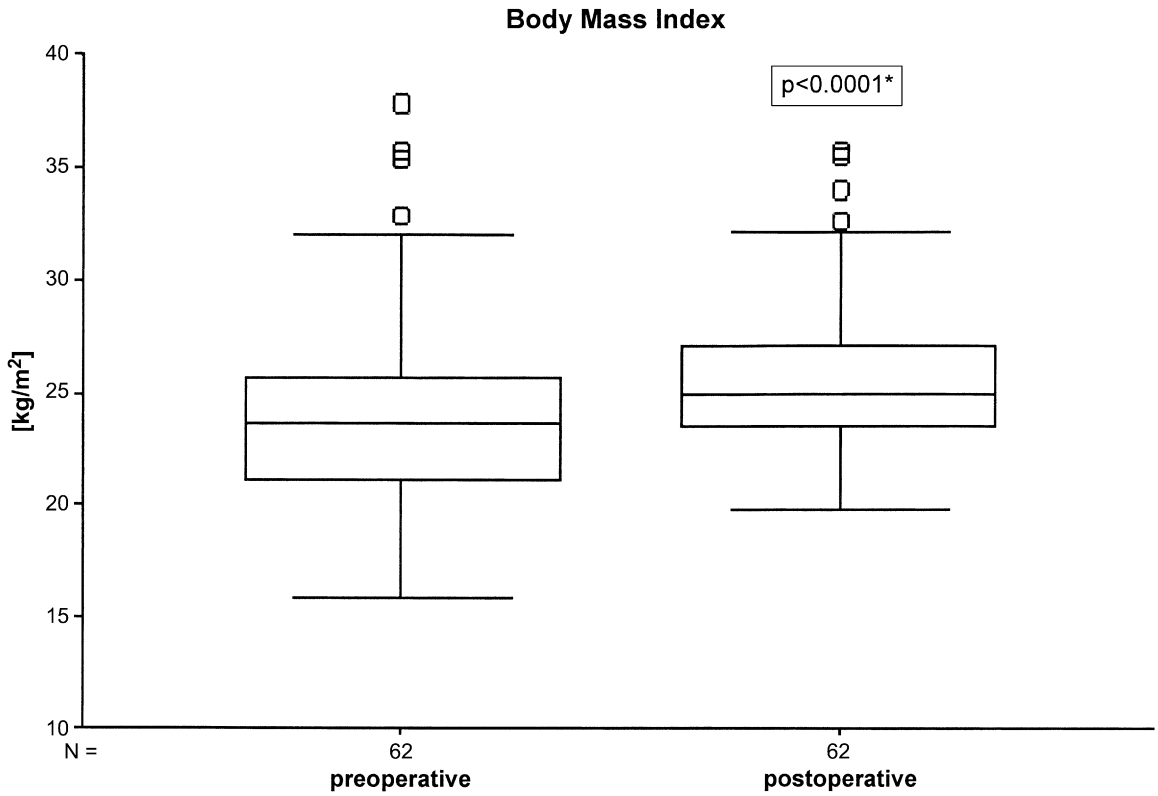


Fig. 2. Preoperative and postoperative body mass index.

Radiographic Findings

Radiographs after barium swallows were obtained in 88 patients prior to and in 76 patients after surgical therapy. However, subjected to analysis were only the data recorded for the maximum esophageal diameter (n = 68) and the minimum diameter of the esophagogastric junction (n = 69). Measurements of these diameters were obtained both preoperatively and postoperatively.

An epiphrenic diverticulum was diagnosed preoperatively and subsequently resected in two patients.

The maximum esophageal diameter of 45 (20–100) mm measured preoperatively was reduced to 28.5 (20–80) mm at the time of the last examination ($P < 0.0001$) (Fig. 3). Conversely, after myotomy there was a significant increase in the diameter of the esophagogastric junction measured at the narrowest point of the structure from an initial median diameter of 3 (1–10) mm to 10 (5–15) mm ($P < 0.0001$) (Fig. 4).

Manometric Findings

Manometric studies of the esophagus prior to myotomy were carried out in 78 and postoperatively in 51 patients. Selected for the present analysis were only the findings documented in patients with preoperative and postoperative manometry (n = 46). Although the preoperative median resting pressure of the lower esophageal sphincter ranged at 27.9 (11.3–56.0) mm Hg, there was a significant reduction in this measurement to 8.6 (3–22.5) mm Hg postoperatively ($P < 0.0001$) (Fig. 5).

Prognostic Factors

The parameters of patient age, gender, duration of medial history, previous pneumatic dilations (independent of the number of dilations), or length of follow-up period were found to exert no influence on clinical long-term outcome after myotomy ($P > 0.05$). Linear regression analysis of the radiographic (maximum diameter of the esophageal body, minimum diameter of the esophagogastric junction) and manometric parameters (resting pressure of the lower esophageal sphincter) prior to surgical therapy did not demonstrate an influence of these factors on the symptom score postoperatively ($P > 0.05$).

DISCUSSION

Myotomy is widely recognized as the most effective therapeutic option for the treatment of achalasia.[3] The results of the present prospective 20-year

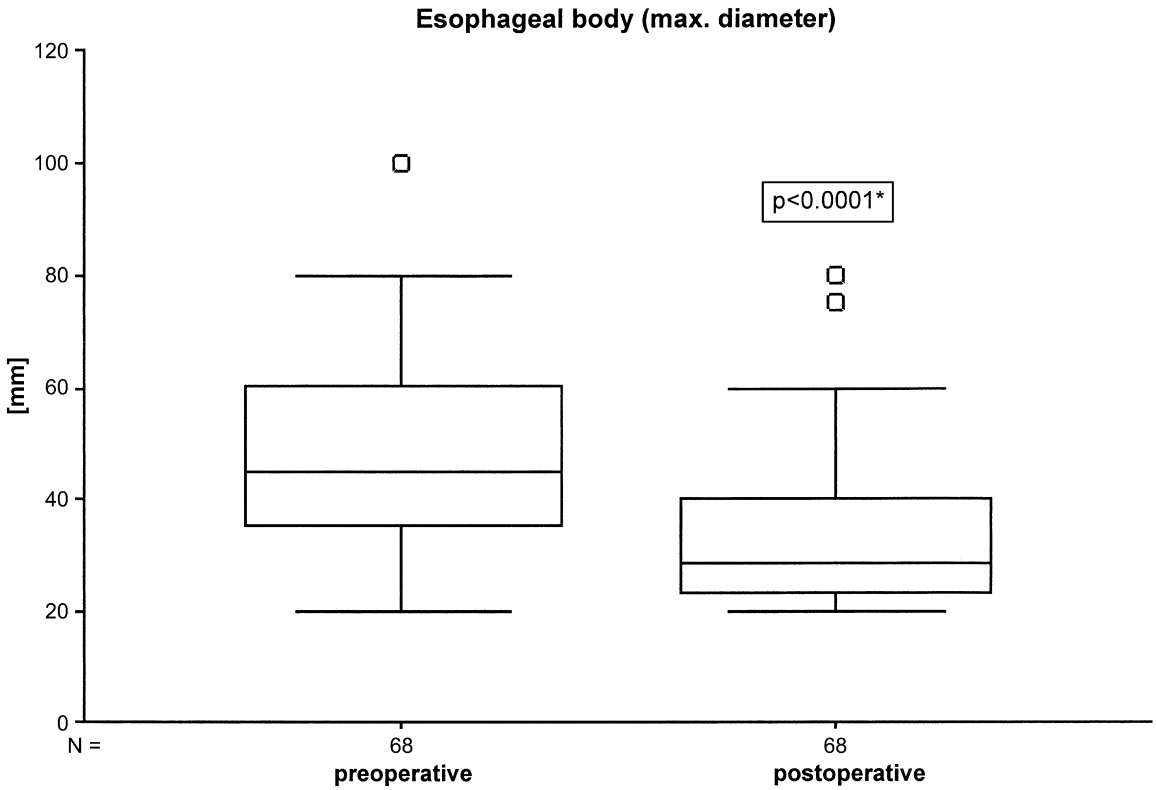


Fig. 3. Preoperative and postoperative maximum diameter of the esophageal body.

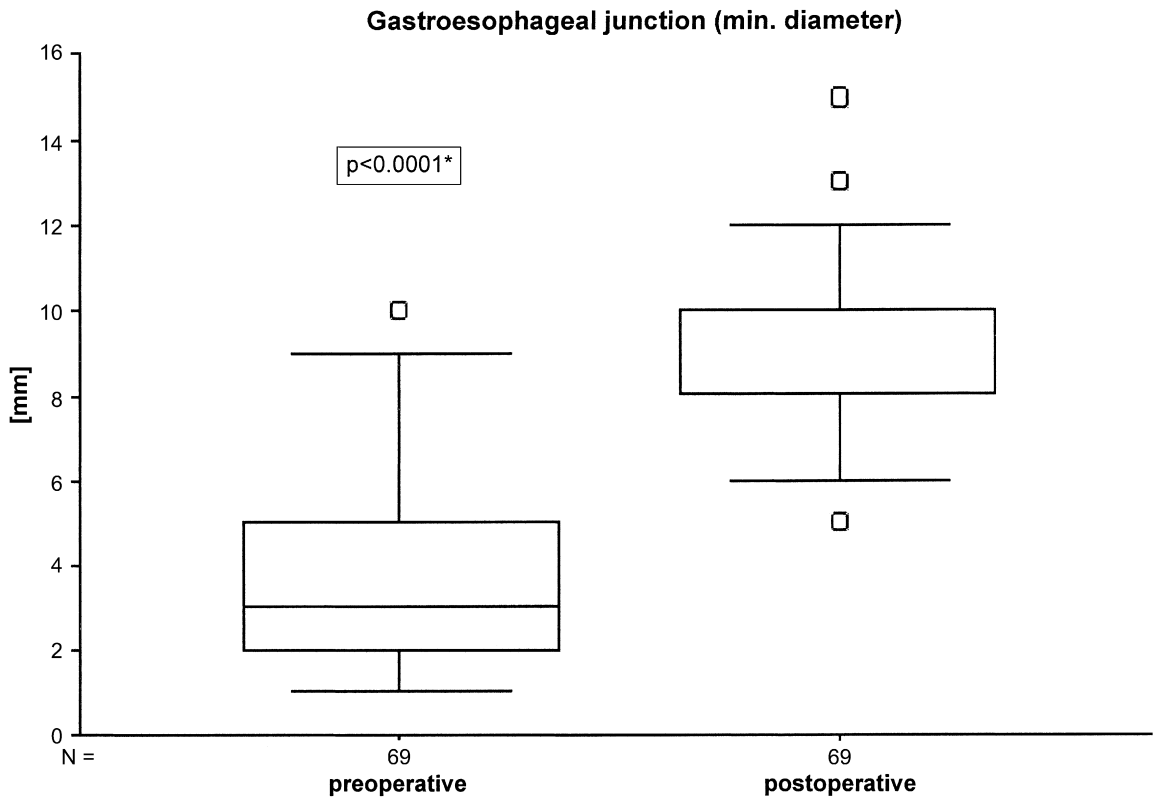


Fig. 4. Preoperative and postoperative minimum diameter of the gastroesophageal junction.

analysis confirm the good long-term prognosis observed by other studies with considerably shorter follow-up periods for open transabdominal myotomy and may be regarded as a basis for the assessment of the minimal-invasive procedure with its considerably shorter follow-up. In view of the favorable results obtained with this surgical procedure, in particular, in patients younger than 40 years, myotomy has established itself as the primary surgical option before pneumatic dilation at the majority of centers.

For both the conventional open and the laparoscopic approach, there is no generalized agreement on the length of the myotomy, and this is still a controversial point. It should ideally be continued beyond a proximal length of 6–7 cm to 3 cm distally to the gastroesophageal junction. The "extended myotomy" is known to lead to a significant reduction in the development of dysphagia in the absence of increased gastroesophageal reflux frequently observed after a "standard myotomy."[4] The aim of extending the length of the myotomy is to decrease the lower esophageal sphincter resting pressure to <10 mm Hg, which has been found by previous studies using pneumatic dilation[5] to be associated with a decrease in the recurrence rate of dysphagia, in addition to being identified as the most important predictor of a good long-term outcome.[1,6] This can without reservation be extended to the surgical intervention itself, which yielded a median resting pressure value of 8.6 mm Hg in the present patient population. Conversely, Zaninotto et al. described an incomplete myotomy and an excessively tight fundoplication or stenosis due to scarring processes as the leading etiologies of persistent dysphagia after laparoscopic myotomy.[7]

A further cause of an unsuccessful cardiomyotomy described by Ellis et al. is the development of a sigmoid-shaped megaesophagus,[8] although this was not attributable to an inadequate length of the myotomy, but to an irreversible progress of the disease. In a study conducted by Patti et al., myotomy has further resulted in favorable long-term outcomes in patients with a large diameter of the esophageal body, or a dolichomegaesophagus.[9] Although in the present study good results were achieved after cardiomyotomy in patients with a markedly dilated esophageal body, transhiatal esophagectomy with gastric tube pull-up was the therapeutic option of choice leading to successful elimination of dysphagia in patients with end-stage achalasia in the long-term course, particularly in the presence of the co-factor peptic stenosis of the lower esophagus.[10]

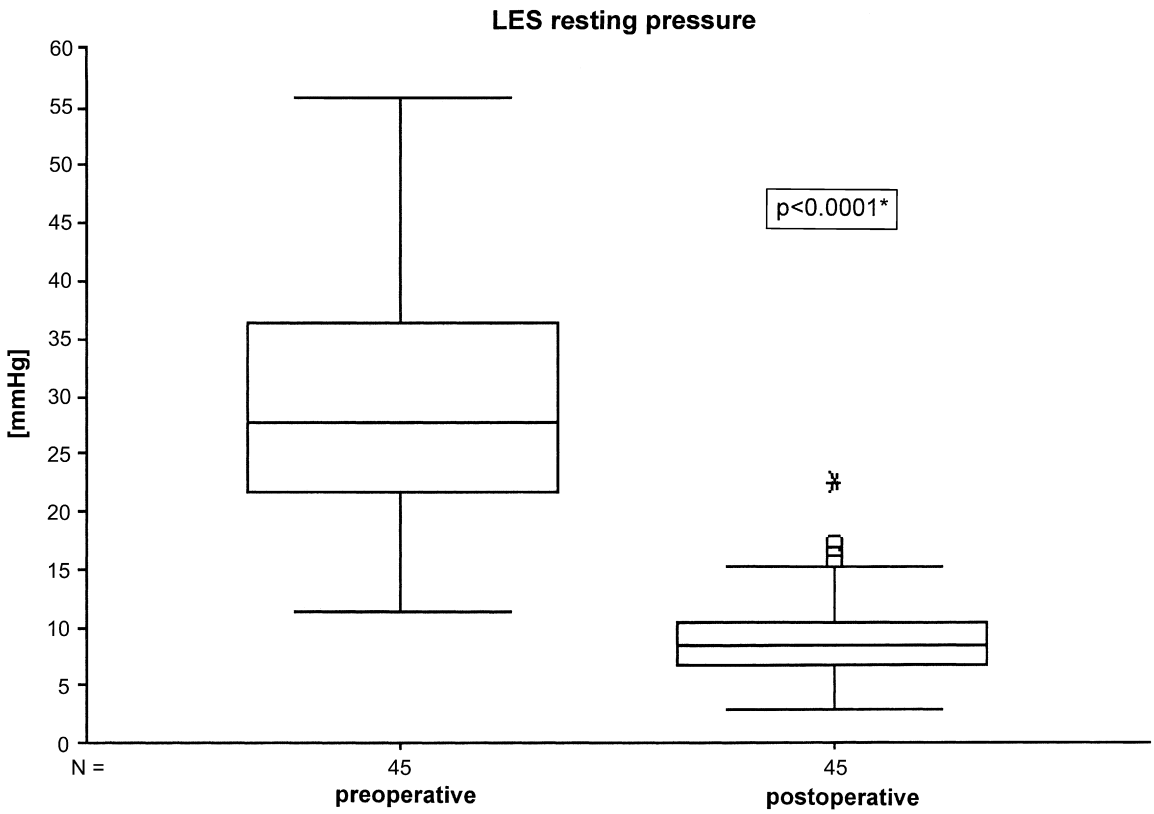


Fig. 5. Preoperative and postoperative LES resting pressure.

The issue of the most appropriate antireflux technique continues to be the subject of controversy: various authors have advocated the performance of a cardiomyotomy without the addition of a fundic wrap both for the conventional open[8,11,12] and the minimally invasive (13–15) procedure. The rationale behind this is to prevent the possible occurrence of resistance in the lower esophageal sphincter with the associated risk of postoperative dysphagia. There are only a small number of proponents of the 360-degree Nissen fundoplication due to the potentiality of recurrent hypertension of the lower esophageal sphincter.[16] Our long-term results confirm the efficacy of the Dor anterior semifundoplication, which covers the myotomy and is incorporated into the lateral pillars of the esophageal and fundic musculature with a two-row suture. Advocates of the Dor semifundoplication emphasize that this technique is more readily performed than the posterior 270° partial wrap according to Toupet, because of the lower technical expense with the structures of the dorsal esophagus and the short gastric vessels not involved. Conversely, authors who support the Toupet fundoplication place emphasis on the additional benefit derived from leaving the two cut muscular edges of the myotomy 'open'. In conclusion, currently available evidence does not suffice to define the 'ideal' antireflux procedure, and a prospective randomized study needs to be conducted to clarify this issue. The incidence of postoperative reflux esophagitis found on endoscopic examination ranged at 15.7% in the present patient population and is thus slightly higher compared to that reported by other studies. The higher rate may be attributable to the short intervals of the follow-up period at which patients of this study routinely underwent an endoscopic examination; this was either not carried out prospectively by other studies, or gastroesophageal reflux was defined or diagnosed differently. All patients described had gastroesophageal reflux Stage I-II according to Savary and Miller and were managed conservatively with medical therapy. There was, however, no significant difference in the postoperative resting pressure of the lower esophageal sphincter between the groups with and without reflux esophagitis.

A comparison of available data published on the outcome after conventional open myotomy using the transabdominal or transthoracic approach showed significantly poorer long-term results in patients treated with the thoracic technique (Table 1).

Table 1. Long-term results of *conventional* myotomy in patients with achalasia

Author/year	No. of patients	Follow-up (yr)	Procedure	Approach	Good results (%)
Parrilla Paricio/1990[17]	48	5.4 (±2.8)	Heller-Toupet	Laparotomy	92
Bonavina/1992[18]	193	5.5 (1–12)	Heller-Dor	Laparotomy	93.8
Ellis/1993[8]	179	9 (1–20)	Heller	Thoracotomy	89
Malthaner/1994[19]	22	Minimum 10	Heller-Belsey	Thoracotomy	68
Mattioli/1996[11]	30	11.5	Heller	Thoracotomy	53.4
Liu/1998[12]	145	Not mentioned	Heller	Thoracotomy	53.3
Chen/2002[20]	32	7.2 (2–16)	Heller-Belsey	Thoracotomy	87
Liu/2004[21]	58	14 (1–22)	Heller*	Laparotomy	84.5
Junginger/2006	108†	4.6 (0.5–17.2)	Heller-Dor	Laparotomy	97.2

*Includes 30 patients with Dor semifundoplication.
†Includes only patients with a minimum follow-up of 6 months.

While European and Latin American researchers were found to give preference to the transabdominal route, the transthoracic procedure emerged as the surgical therapy of choice in North America and the United Kingdom. A notable finding of the literature analysis was the poorer results reported in particular for patients undergoing the open thoracic surgical procedure without establishment of an antireflux-plasty,[8,11,12] which may account for the less favorable long-term effect independent of the surgical approach.

The good results obtained in 81–100% of patients after laparoscopic myotomy have not only heightened the primary surgical interest in the disorder, but also induced a paradigm change among gastroenterologists. The meaningfulness of the results obtained by published trials is limited by the nonuniform use of scores in the assessment of symptoms and, in contrast to conventional surgical procedures, shorter follow-up periods (Table 2). It is therefore currently not possible to draw any firm conclusions about the results of laparoscopic myotomy. Only the good long-term outcomes in 81.7% of patients reported by a recent study including 71 consecutive patients who were followed for a minimum of 6 years permit comparison with results obtained after conventional surgical procedures.[30]

CONCLUSION

The prospectively assessed results documented over a 20-year follow-up period for patients after conventional open myotomy demonstrate that this procedure represents a highly effective therapy for the symptoms of achalasia. The described results may therefore be regarded as a basis for the assessment of the minimal invasive procedure. There are

Table 2. Long-term results of *laparoscopic* myotomy in patients with achalasia

Author/year	No. of patients	Follow-up (mo)	Procedure	Good results (%)	GERD (%)
Raiser/1996[22]	35	11–46	Heller-Dor/Toupet	97	Not mentioned
Boulez/1997[13]	27	17	Heller	100	4
Graham/1997[23]	26	4	Heller-Dor	90	11.1
Hunter/1997[24]	40	12.5	Heller-Dor/Toupet	90	2.5
Wang/1998[14]	27	18	Heller	89	11
Rosati/1998[25]	61	12	Heller-Dor	98.2	7
Patti/1999[26]	133	28	Heller-Dor*	89	17
Hunt/2000[27]	70	34	Heller-Nissen†	81	4.5
Bloomston/2000[15]	67	18	Heller	91	18
Zaninotto/2000[28]	100	24	Heller-Dor	92	6.9
Frantzides/2004[29]	53	36	Heller-Nissen‡	92	9

*Includes eight patients with Toupet-antireflux plasty.
†Includes 13 patients with Dor semifundoplicationi.
‡Includes four patients with Toupet-antireflux plasty.

considerable data regarding intermediate term outcomes after laparoscopic myotomy and considerable conclusions might be drawn regarding this procedure.

REFERENCES

1. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology 1992;103:1732–1738.
2. Dor J, Humbert P, Dor V, Figarella J. L'interet de la technique de Nissen modifiée dans la prevention du reflux après cardiomyotomie extramuquese de Heller. Mem Acad Chir (Paris) 1962;88:877–884.
3. Csendes A, Braghetto I, Henriquez A, Cortes C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. Gut 1989;30:299–304.
4. Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003;138:490–497.
5. Spiess AE, Kahrilas PJ. Treating achalasia: From whalebone to laparoscope. JAMA 1998;280:638–642.
6. Eckardt VF, Gockel I, Bernhard G. Pneumatic dilation for achalasia: Late results of a prospective follow-up investigation. Gut 2004;53:629–633.
7. Zaninotto G, Costantini M, Portale G, Battaglia G, Molena D, Carta A, et al. Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg 2002;235:186–192.
8. Ellis EH. Oesophagomyotomy for achalasia: A 22-year experience. Br J Surg 1993;80:882–885.
9. Patti MG, Feo CV, Diener U, Tamburini A, Arcerito M, Safadi B, et al. Laparoscopic Heller myotomy relieves dysphagia in achalasia when the esophagus is dilated. Surg Endosc 1999;13:843–847.
10. Gockel I, Kneist W, Eckardt VF, Oberholzer K, Junginger T. Subtotal esophageal resection in motility disorders of the esophagus. Dig Dis 2004;22:396–401.
11. Mattioli S, Di Simone M, Bassi F, Pilotti V, Felice V, Pastina M, et al. Surgery for achalasia: Long-term results with three different techniques. Hepatogastroenterology 1996;43:492–500.
12. Liu HC, Huang BS, Hsu WH, Huang CJ, Hou SH, Huang MH. Surgery for achalasia: Long-term results in operated achalasic patients. Ann Thorac Cardiovasc Surg 1998; 4:312–320.
13. Boulez J, Meeus P, Espalieu PH. Oesophagocardiomyotomie de Heller sans anti-reflux par voie laparoscopique. Analyse d'une serie de 27 cas. Ann Chir 1997;51:232–236.
14. Wang PC, Sharp KW, Holzman MD, Clements RH, Holcomb GW, Richards WO. The outcome of laparoscopic Heller myotomy without antireflux procedure in patients with achalasia. Am Surg 1998;64:515–521.
15. Bloomston M, Boyce W, Mamel J, Albrink M, Murr M, Durkin A, et al. Videoscopic Heller myotomy for achalasia: Results beyond short-term follow-up. J Surg Res 2000;92: 150–156.
16. Willis VL, Hunt DR. Functional outcome after Heller myotomy and fundoplication for achalasia. J GASTROINTEST SURG 2001;5:408–413.
17. Parrilla Paricio P, Martinez Haro E, Ortiz A, Aguayo JL. Achalasia of the cardia: long-term results of oesophgomyotomy and posterior partial fundoplication. Br J Surg 1990;77: 1371–1374.
18. Bonavina L, Nosadini A, Bardini R, Baessato M, Peracchia A. Primary treatment of esophageal achalasia: long-term results of myotomy and Dor fundoplication. Arch Surg 1992;127:222–227.
19. Malthaner RA, Todd I, Miller E, Pearson FG. Long-term results in surgically managed esophageal achalasia. Ann Thorac Surg 1994;58:1343–1347.
20. Chen LQ, Chughtai I, Sideris L, Nastos D, Taillefer R, Ferraro P, Duranceau A. Long-term effects of myotomy and partial fundoplication for esophageal achalasia. Dis Esophagus 2002;15:171–179.
21. Liu JF, Zhang J, Tian ZQ, Wang QZ, Li BQ, Wang FS, Cao FM. Long-term outcome of esophageal myotomy for achalasia. World J Gastroenterol 2004;15:287–291.
22. Raiser F, Perdikis G, Hinder RA, Swanstrom LL, Filipi CJ, McBride PJ, Katada N, Neary PJ. Heller Myotomy via minimal-access surgery. An evaluation of antireflux procedures. Arch Surg 1996;131:593–598.
23. Graham AJ, Finley RJ, Worsley DF, Dong SR, Clifton JC, Storseth C. Laparoscopic oesophageal myotomy and anterior partial fundoplication for the treatment of achalasia. Ann Thorac Surg 1997;64:785–789.
24. Hunter JG, Trus TE, Branum GD, Waring P. Laparoscopic Heller myotomy and fundoplication for achalasia. Ann Surg 1997;225:655–665.
25. Rosati R, Fumagalli U, Bona S, Bonavina L, Pagani M, Peracchia A. Evaluating results of laparoscopic surgery for esophageal achalasia. Surg Endosc 1998;12:270–273.
26. Patti MG, Pellegrini CA, Horgan S, Arcerito M, Omelanczuk P, Tamburrini A, Diener U. Minimally invasive surgery for achalasia: an 8-year experience with 168 patients. Ann Surg 1999;230:587–594.
27. Hunt DR, Willis VL. Laparoscopic Heller myotomy for achalasia. Aust NZ J Surg 2000;70:582–586.
28. Zaninotto G, Costantini M, Molena D, Buin F, Carta A, Nicoletti E, Ancona E. Treatment of esophageal achalasia with laparoscopic Heller myotomy and Dor partial anterior fundoplication: prospective evaluation of 100 consecutive patients. J GASTROINTEST SURG 2000;4:282–289.
29. Frantzides CT, Moore RE, Carlson MA, Madan AK, Zografakis JG, Keshavarzian A, et al. Minimally invasive surgery for achalasia: a 10-year experience. J GASTROINTEST SURG 204;8:18–23.
30. Costantini M, Zaninotto G, Guirroli E, Rizzetto C, Portale G, Ruol A, et al. The laparoscopic Heller-Dor operation remains an effective treatment for esophageal achalasia at a minimum 6-year follow-up. Surg Endosc 2005;19:345–351.

Gender Disparities in Colorectal Cancer Screening: True or False?

Rachel A. Callcut, M.D., M.S., Stephanie Kaufman, M.S., Robert Stone-Newsom, Ph.D., Patrick Remington, M.D., M.P.H., David Mahvi, M.D.

To date, nearly all studies examining gender disparities in colorectal cancer screening report a lower endoscopic screening rate in women. Using a statewide claims database, gender differences in screening rates were analyzed in an attempt to validate gender disparities reported in prior survey-based studies. Procedural-level dataset containing all patient encounters for 2003 in which a colonoscopy or flexible sigmoidoscopy were performed was created. Procedures were selected using CPT codes and univariate analysis was performed using SAS v 8.0. Statewide for average-risk individuals 50 years or older, 65,232 endoscopic procedures were performed in 2003. The majority (83%) of endoscopic screening procedures were colonoscopies. Overall, the rate of screening in average-risk women 50 years or older (38 procedures/1000 people) was slightly lower than in men (42/1000) but not statistically significant. The rates of screening were higher in women before the age of 60 years and lower after the age of 60 years. No clinically significant difference was found in the type of screening procedure performed. Gender disparities in rates and types of colorectal cancer screening reported in prior survey studies are not validated in this patient encounter data study. (J GASTROINTEST SURG 2006;10:1409–1417)

KEY WORDS: Colon cancer, screening, gender

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the United States with an estimated 145,290 cases occurring in 2005.[1] CRC accounts for approximately 10% (71,820 cases) of all incident male cancer cases and falls behind only prostate cancer (232,090 or 33% of cases) and lung cancer (93,010 or 13% of cases) in frequency.[1] For women, breast cancer (211,240 or 32% of cases) and lung cancer (79,560 or 12% of cases) are more commonly diagnosed, but CRC still accounts for 11% (73,470) of all female cancers.[1] Unfortunately, the ratio of new cancer cases to deaths is very high resulting in CRC being the overall second leading cause of cancer death (56,290 deaths estimated in 2005) in the nation second to only lung cancer (163,510 estimated deaths).[1] In both men and women, CRC accounts for 10% of all U.S. cancer deaths.

For the average-risk individual, the goal of screening is to select a screening modality with a high sensitivity and specificity but one that is also safe and cost-effective.[2] Currently, the American Cancer Society (ACS), American College of Gastroenterology (ACG), the Agency for Healthcare Research and Quality (AHRQ), and the American Gastroenterological Association (AGA) concur that screening should begin at the age of 50 years.[2–5] The ACS, ACG, and AHRQ recommend annual 3-day at-home kit fecal occult blood testing (FOBT) paired with flexible sigmoidoscopy every 5 years, or double contrast barium enema (DCBE) every 5 years, or colonoscopy every 10 years.[2,3,5] In 2003, the AGA began advocating for colonoscopy as the preferred initial screening modality in average-risk individuals.[4] All agree that any positive FOBT, FS, or DCBE warrants a full colon evaluation using colonoscopy.[2–5]

Although the natural history of the disease provides ample opportunity for screening, a number of recent studies have confirmed that less than 50% of average-risk men and women 50 years or older receive any screening at all.[6–10] In fact, rates of CRC screening lag far behind rates of other cancer screening in the United States. Seeff et al.[6] recently

From the Departments of Surgery (R.A.C., D.M.) and Population Health Sciences (S.K., R.S.-N., P.R.), University of Wisconsin-Madison School of Medicine and Public Health, Madison, Wisconsin.
Reprint requests: David Mahvi, M.D., H4/724 Clinical Sciences Center, 600 Highland Ave., Madison, WI 53792.

1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2006.06.006

estimated that in the United States, 41.8 million average-risk adults aged 50 years and older (50+) have *never been screened* and that 6.7 (9.6%) million more had only ever received FOBT. Using a prediction model based on one of the most widely used public health survey data sources, the National Health Interview Survey (NHIS), they concluded that only 15.7 million of the 70.1 million (22.4%) average-risk individuals had ever received any endoscopic screening and only 5.9 million (8.4%) had undergone FOBT plus endoscopic screening.[6] In stark contrast, cancer screening rates are generally 70–80% for average-risk individuals for other conditions like breast cancer.[8] The ACS is campaigning to increase the proportion of person screened for CRC to 75% of at risk individuals by 2015, whereas the *Healthy People 2010* objective is to increase the proportion to 50%.[9] In addition, decreasing screening disparities have been a focus of the *Healthy People 2010* campaign.

To date, nearly all studies including gender variables report a lower CRC screening rate in women compared with in men.[1,7–9,11–15] In fact, the ACS reports 27% of women have had a recent endoscopic procedure compared with almost 34% of men.[1] Despite being a frequent finding, the contributing factors are largely uninvestigated. Using survey data, researchers have identified an increased fear and more embarrassment with the procedure in women[11,12]; however, this likely does not fully account for all of the reported screening disparity. In fact, one recent study suggested provider factors may be responsible with women being offered screening less often[11] and women being less likely (OR 0.66, 95% CI 0.44–0.97) to have a complete colonic evaluation following a positive FOBT.[15] However, these explanations remain largely speculative as to the underlying etiology and may be reflective of survey biases. In this study, using a statewide claims database with nearly full capture of patient encounters, we analyzed gender differences in rates and diagnosis in an attempt to validate gender disparities reported in prior survey-based studies.

METHODS

Data Source

A procedural-level dataset was created using two statewide databases maintained by the state of Wisconsin: (1) Physician Outpatient Visit Database (POVD) and (2) Ambulatory Surgery Database (ASURG).

Physician Outpatient Visit Database (POVD)

The State of Wisconsin Bureau of Health Information and Policy (BHIP), Department of Health and Family began mandated collection of physician office visit data in 2002. Participation is currently voluntary with the 13 largest health care systems in the state participating. All reportable visits (defined as any visit with a licensed physician in which procedures or services were rendered in either an office or outpatient setting) are compiled into a service level claims database. Records are routinely audited and attempt is made to correct obvious errors including coding errors and missing data. During service year 2003, more than 16 million patient encounters were reported to POVD including records from all 72 Wisconsin counties.

Ambulatory Surgery Discharge Database (ASURG)

All ambulatory surgery centers in the state are mandated to report all patient encounters to the BHIP. Due to mandatory reporting, the ASURG dataset contains 100% of procedures performed in any given service year in the ambulatory surgery setting. Each record reflects a single billable patient encounter and may include multiple reportable codes (or procedures) in one record. Data are routinely reviewed by BHIP and corrected for invalid codes, missing items, and inconsistent data (such as a procedure–sex mismatch).

Combining Data Sets

Using CPT codes, records containing colorectal cancer screening or surveillance procedures of interest were identified in each data set. CPT codes were used to select records in which sigmoidoscopies (45330, 45300, 45331, 45305, 45308, 45309, 45315, 45320, 45333, 45338, 45339) and colonoscopies (45355, 45378, 45380, 45383, 45384, 45385) were performed. Each record contained the following information: patient age group in 5-year intervals, gender, patient county of residence, CPT codes for primary procedure and secondary procedures, primary diagnosis code (*ICD-9-CM*), complication or modifier codes (*ICD-9-CM*), and provider license number. Provider license numbers were then utilized to link specialty information to each individual record. Any procedures performed in a patient residing outside the state were excluded.

To allow merging of the two data sets into one procedural-level statewide database, a county level-weighting factor was applied to the POVD records reflecting the percentage of visits (estimated by

BHIP) reported during 2003 in the county of patient residence. The factor was applied as the inverse of this reporting percentage to account for variation in reporting across the state. If county of residence was unknown, the POVD record was weighted according to the state average percent reporting. The weighted combined database is an approximation of the total procedures performed in service year 2003 in Wisconsin.

Determination of Surveillance Versus Screening Procedures

High-risk patients were identified using *ICD-9-CM* codes corresponding to high-risk conditions including a family history of CRC (V16.0), a personal history of a colon (10.05) or rectal (10.06) cancer, a personal history of polyps (V12.72), or a history of inflammatory bowel disease (Crohn's disease: 555.0–555.9; Ulcerative Colitis: 556.0–556.3, 556.8–556.9). If one or more of the high-risk codes appeared in the record, the procedure was considered to be for surveillance. All other records were assumed to represent screening.

Inclusion Criteria

All records containing a CPT code of interest were included in the data analysis if done in a patient residing in Wisconsin. Relevant CPT codes appearing in any of the procedure fields (principle procedure, secondary procedure, etc…) were selected. For analysis of total procedures, all procedures performed (surveillance and screening) in any age group were selected. Average-risk patients aged 50 years and older were selected for all other analysis.

Diagnosis Codes

Diagnosis and complications were determined using *ICD-9-CM* codes. These codes may appear in either the primary diagnosis code field or in any of the modifier code fields. Any occurrence (in any one of the diagnostic fields) of a relevant diagnosis or complication code warranted assignment of the relevant condition to the patient record. Polyps were identified by codes 211.3, 211.4, and 569.0. Cancers were found using codes 153.0–154.9.

Statistical Analysis

All analysis was performed using SAS for Windows Version 8.0. Descriptive statistics were determined statewide for all procedures and separately for procedures done in average-risk patients. Univariate analysis was done for age group, gender, and provider specialty. Data are reported stratified by gender. Analysis was also stratified by procedure type (FS and colonoscopy) and reported as the percent of colonoscopy done compared with total procedures. Diagnosis was evaluated statewide for all procedures and for procedures done in average-risk patients reported by age group and gender.

Rates were calculated per 1000 people where the population at risk was obtained from U.S. Census Bureau 2003 population estimates statewide, by gender and by age group. Confidence intervals for percent colonoscopies were calculated; all were statistically significant (due to large sample sizes) and therefore, not reported in the Results section. Relative risks reflect the risk compared to an appropriate reference group. For age group analysis, 50+ represented the reference group. For gender, males were the reference category. Confidence intervals (CI) were reported for relative risks with $\alpha = .05$ (95% CI).

RESULTS

Total Procedures

Statewide 103,580 endoscopic procedures were performed in patients of all risk groups, all ages in service year 2003 (Table 1). Procedures performed in average-risk individuals accounted for 81% (83,646 procedures), while procedures performed in average-risk persons 50 years or older (50+) constituted 63% (65,232/103,580) of the total procedures and 78% (65,232/83,646) of the procedures performed in average-risk persons (Table 1). Colonoscopies accounted for 83% of the procedures done in average-risk, 50+ individuals. The overall rate of endoscopic screening for average-risk 50+ was 40 procedures per 1000 people, with 7 FS/1000 people and 33 colonoscopies/1000 people in 2003 (Table 1).

Of all procedures done in average-risk persons, 50+ years old, 51% were done in females (Table 2).

Table 1. Total endoscopic procedures performed in all patients, all average risk [AR], and all AR patients 50 years and older [50+]

	All ages		AR		50+ years old	
Procedure type	n	rate	n	rate	n	rate
FS	15,351	3	14,360	3	11,266	7
COL	88,229	16	69,286	13	53,966	33
Total	103,580	19	83,646	15	65,232	40

Rates are No./1000 population.
COL = colonoscopy; FS = flexible sigmoidoscopy.

Table 2. Gender stratification for average-risk, 50+-year-old patients

	n	%	Rate	RR	95% CI	nCOL	% COL
Men	31,752	49	42.5	1.00		25,721	81
Women	33,480	51	38.5	0.91	0.63–1.18	28,245	84
Total	65,232	100	40.3			53,966	83

COL = colonoscopy.

Although the overall rate of endoscopic screening is slightly lower in average-risk, 50+-year-old women (38.5 procedures/1000 people) compared with men (42.5/1000), there is no statistical difference (Table 2). Women were equally as likely to undergo screening (RR 0.91; 95% CI 0.63–1.18). By age group, the overall rates of screening were higher for women than men until the age of 59 years, after which the rates of screening in men were higher in all subsequent age groups (Fig. 1).

In addition, there was no clinically significant difference in the type of screening women have compared with those in men. In men, 81% of the procedures were colonoscopies compared with 84% of the procedures in women (Table 2). When stratified by age group, the percentage colonoscopies (versus total procedures) for each gender is slightly higher in women (compared with men) before the age of 65 years, and then is virtually identical until after the age of 84 years when colonoscopy is used more frequently in men (Fig. 2). Using rate calculations, women have a slightly higher rate of colonoscopy at ages 50–59 years than men (50–54 years old: 34 versus 36, 55–59 years old: 33 versus 36), but this trend is reversed after the age of 60 years (Fig. 3). However, the gender disparity in the rate of colonoscopy is relatively small until after the age of 75 years.

Diagnosis Rates

For average-risk, 50+-year-olds, lesions were found on 38% (24,580/65,232) of all endoscopic procedures. The vast majority (97%) of these lesions were coded as polyps and the overall lesion detection rate was 15.2 lesions per 1000 people (Table 3). Lesion detection was higher among men than women (18.6/1000 versus 12.3/1000) (Table 3). Likewise, the cancer detection rate was lower in women than in men (4.6/10,000 versus 6.8/10,000). The RR of finding any lesion on endoscopy was 0.66 (95% CI 0.36–0.96) and for cancer 0.67 (95% CI 0.58–0.77) for women compared with men. In men, 44% of procedures done had a lesion found compared with 32% of procedures in women. When stratified by age and gender, lesion detection rates are lower in women in every age group beyond

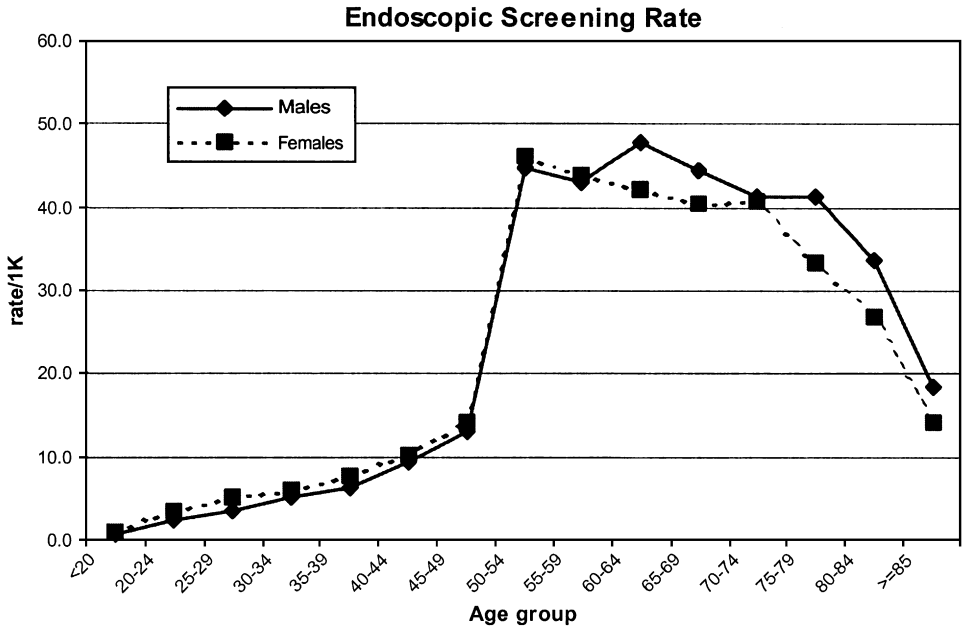


Fig. 1. Endoscopic screening rate.

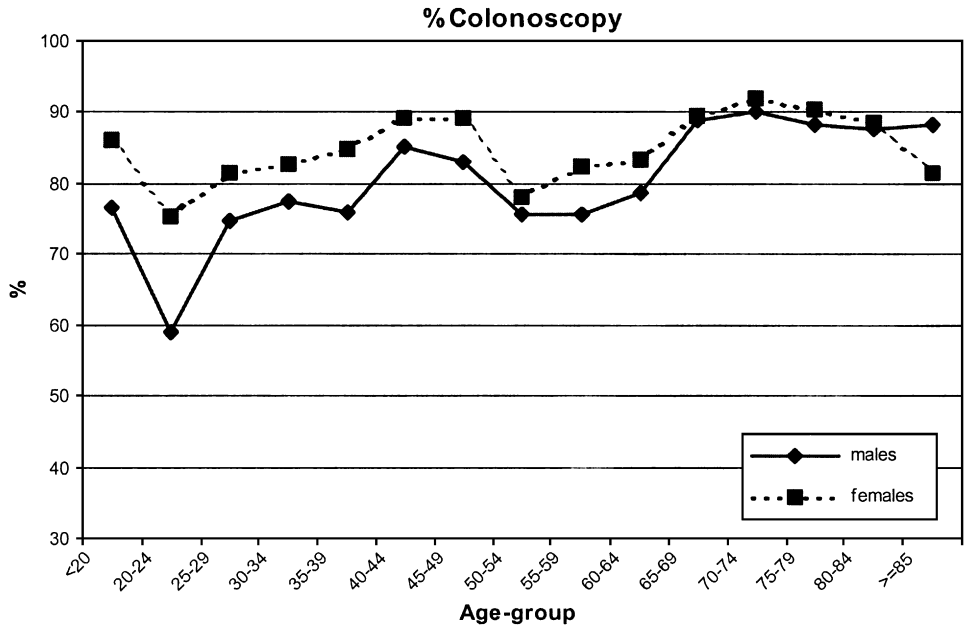


Fig. 2. Percent undergoing colonoscopy.

50 years with the greatest relative gender disparity between ages 65 and 79 years (Fig. 4). For invasive cancer, the disparity is largest between ages 65 and 84 years. When stratified by endoscopic procedure type, men and women receive relatively similar rates of colonoscopy until age 75 (Fig. 5).

DISCUSSION

Using a statewide claims database, 4% (rate 40/1000 people) of the average-risk, 50 years of age and older (50+) population was estimated screened with endoscopy in service year 2003. Ko et al.[16] demonstrated an equivalent annual screening rate

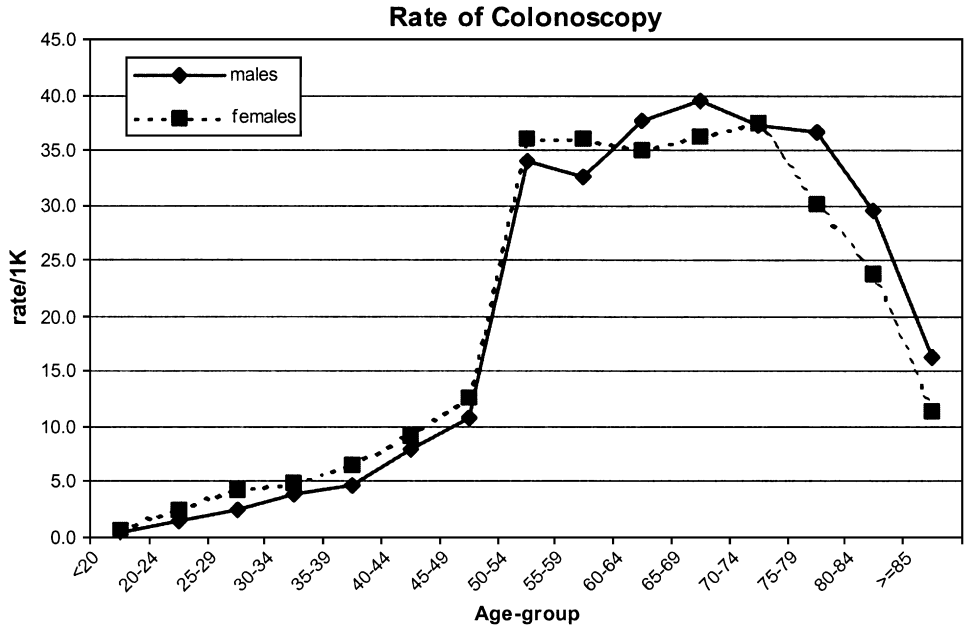


Fig. 3. Colonoscopy rate.

Table 3. Lesion and cancer detection rates by gender in average-risk, 50-year-old patients

	Any lesion detected					Cancer detected			
	n	%	rate	RR	95% CI	n	rate	RR	95% CI
Men	13,889	44	18.6	1.00		412	6.8	1.00	
Women	10,691	32	12.3	0.66	0.36–0.96	313	4.6	0.67	0.58–0.77
Total	24,580	38	15.2						

(4%) using claims data from a health care organization in the state of Washington. Assuming the pattern of screening remained constant over time and that these patients would not be screened again for 5–10 years, approximately 20–40% of the average-risk population has been screened using endoscopic techniques. The upper limit (40%) likely reflects closer to the real percentage considering this study involved a large majority of colonoscopies (83%), which are performed only once every 10 years for screening. This was remarkably similar to results from the National Health Information Survey (NHIS) and the Behavioral Risk Factor Surveillance Survey (BRFSS), which placed the rate (of endoscopic screening in average-risk, 50+ years old) at about 44%.[8,10] Our results were lower than the 2005 ACS estimated rate of recent endoscopic examination for Wisconsinites (47%).[1] In addition, after accounting for procedures in high-risk patients, a similar proportion of procedures were determined to be for screening compared with smaller prior survey, case-control, and cohort studies distinguishing between risk groups (78% in this study versus 61–73% in other studies).[10,14]

Moreover, lesions (polyp plus cancer) were classified using *ICD* codes in 38% of procedures; cancers were coded in 3% of procedures. These detection rates were comparable to estimates from prior non-claims data studies. For example, Lieberman et al.[17] found polyps in 38% of patients and invasive cancers in 1% at endoscopy. Using medical records review, Ker et al.[18] also found 37% of patients had undergone polypectomy with colonoscopic screening. Likewise, Thiis et al.[19] reported 30% of patients undergoing endoscopic screening had a clinically important lesion. Avidan[20] described slightly higher polyp detection rates in a VA study (55%), however, most of the patients were older compared with the present study. Similar occult cancer detection rates for cancers found at the time of endoscopy (not after pathologic exam of polyps or biopsies) have also been shown in work by Mehran et al. (4% cancers), Harewood et al. (4% cancers), and Gorard (4% cancer).[21–23] It is important to note that diagnosis of

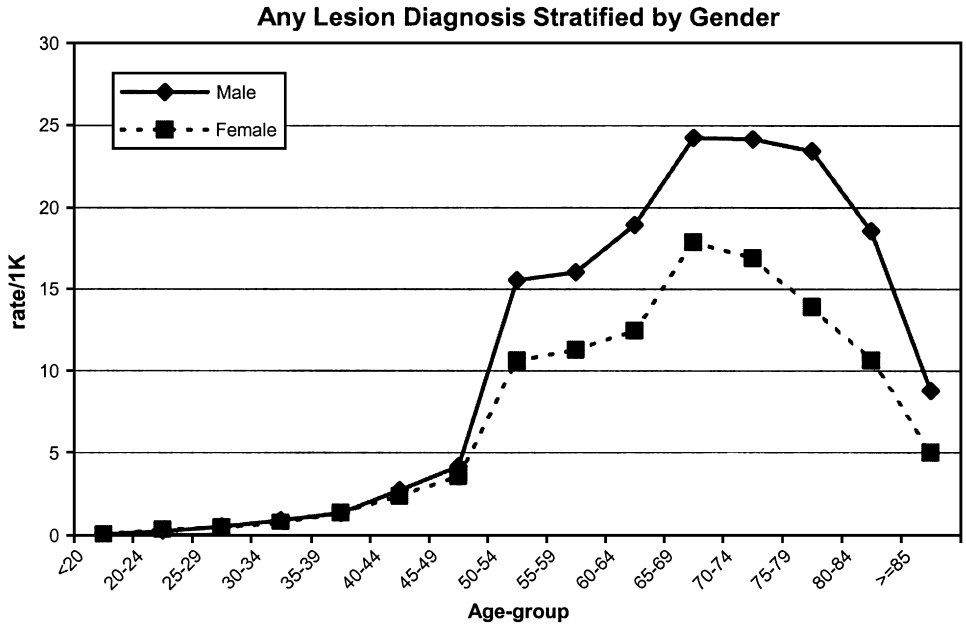


Fig. 4. Any lesion diagnosis stratified by gender.

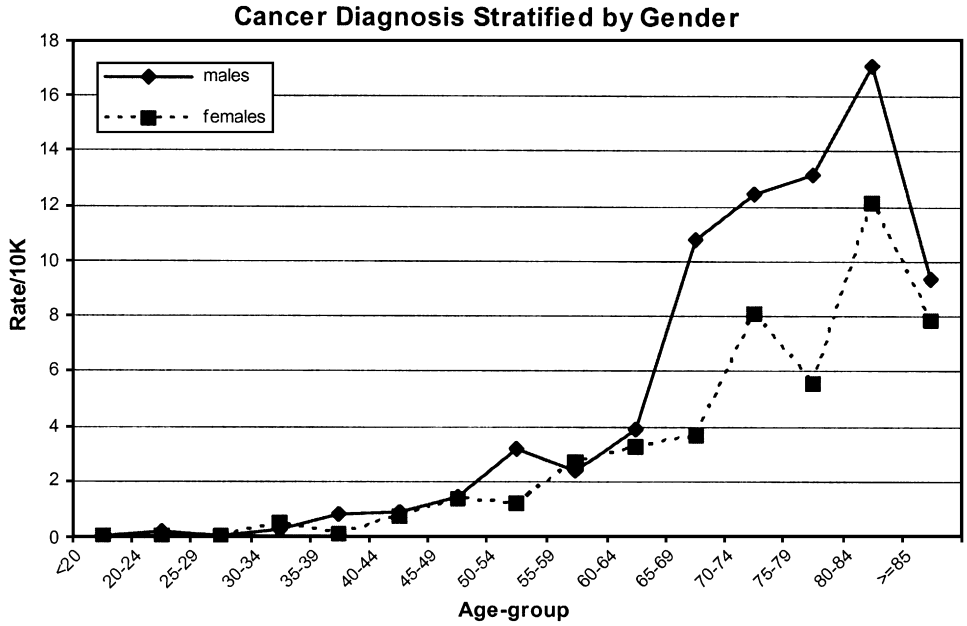


Fig. 5. Cancer diagnosis stratified by gender.

invasive cancer at the time of endoscopic screening reflects only a proportion of total cancers diagnosed once pathologic analysis is performed on polypectomy samples. For example, in this study a total of 856 cancers (all risk groups) were diagnosed at the time of endoscopic screening compared with about 1600 cases of invasive cancer reported each year to the Wisconsin Cancer Reporting System. These analogous results for both screening and diagnosis rates compared with survey, case-control, and cohort studies strengthen the validity of using claims data.

Survey data have traditionally been the primary method for estimating colorectal cancer screening rates. Although widely used, it remains largely unknown if survey data reflects true disparities in screening for many patient characteristics including gender. The overall gender disparity reported in previous survey-based, case-control, cohort studies was not demonstrated in the present study using such patient encounter claims data.[1,7–9,11–15] Only a statistically insignificant decrease in overall screening rates of women compared with men was found. This has also been reported in a recent study by Hawley et al.[10] using medical records review where they concluded there was no difference in overall endoscopic screening rates between men and women. However, in the present study, when stratifying by age groups, women do have lower screening rates after the age of 60 years with the largest difference in rates between the ages of 75–79 years (41 procedures/1000 people for men versus 33/1000 for women). One advantage of the present study over previous survey studies is the ability to account for changes in screening patterns over the spectrum of age ranges. The gender disparity reported in other studies involving groups aged 65 years and older may reflect age confounding as we have demonstrated that screening patterns do not appear stable over the age groups.

In addition, women have been shown to express more fear and embarrassment about undergoing CRC screening especially with colonoscopy.[11,12] Thus, it is plausible that women may be less likely to participate in survey, case-control, and cohort studies regarding testing they find embarrassing. Consequently, the discrepancy in results between the present study and other research may also reflect participation and recall bias in prior work. Using a statewide claims database eliminates recall and participation bias issues, and therefore may represent a more appropriate modality for further study of the influence of gender and other patient factors on screening rates.

Interestingly, we were unable to demonstrate any clinically significant difference in the overall type of endoscopic screening (FS versus colonoscopy) women receive compared with men suggesting that concerns over fear and embarrassment with screening may not be the etiology of disparities in prior studies. However, as with screening rates, usage of colonoscopy did vary across age groups. When stratified by age, colonoscopy rates are fairly constant in women between 50 and 74 years old and then begin

to decline after age 75 years; however, in men, the rates of colonoscopy peaks at age 65 years. Thus, the rates of colonoscopy in men exceed women in all groups older than 65 years old. Both the differences in rates of colonoscopy usage between genders and the rate decline after the age of 75 years could reflect the lower overall rate of any type of screening in women and in those older than 75 years; therefore, the data were also analyzed looking at the percent of total endoscopic exams that were colonoscopies across ages and gender.

Using this strategy, colonoscopy was overall less frequently used at ages 50–64 years. Interestingly, after the age of 65 years, there is virtually no difference across age groups in the proportion of colonoscopies within and across genders until age 85+ where it is more commonly used in men. In summary, although overall rates of endoscopic screening are not different between men and women, with increasing age, women are screened less often. Also, there is no clinically significant difference in the use of colonoscopy across genders (calling in to question prior explanations of gender disparities), however, colonoscopy is more frequently used for screening at advanced ages.

Diagnosis

For average-risk, 50+-year-olds, any lesion was detected in 38% of all endoscopic procedures. Interestingly, women were statistically less likely to have any lesion or cancer detected at the time of endoscopic screening. Overall, 25% less endoscopic exams were positive in women than in men (32% positive endoscopic screen in women versus 44% positive screens in men). Furthermore, the lesion detection rate of women for any lesion was lower in each age group beyond 50 years old. Imperiale et al. and Schoenfeld et al. have also found using age-adjusted detection rates with endoscopic screening women have statistically fewer positive screens than men. In the VA cooperative endoscopic study of average-risk men and women, men had twice as many advanced lesions detected during screening. In addition, 20.4% of women had any lesion detected. In our study, we demonstrate a similar positivity rate with endoscopic screens in women (32%) and a slightly lower difference in overall detection rate difference between men and women (men 18.6 lesions/1000 screens, women 12.3 lesions/1000 screens).

The etiology of the lower rate of lesion detection and advanced neoplasia found at endoscopic screening in women remains largely uninvestigated. Prior studies demonstrating similar disparities in diagnosis speculate that biologic or behavioral differences between men and women are ultimately responsible. If biologic or behavioral differences truly exist and considering the lower detection rates of women in this study and several other recent publications, this would suggest that women develop adenomas and CRC at a differentially lower rate than men. In essence, women are less likely to develop lesions/CRC. However, the overall incidence of new cancer cases has remained relatively equal between men and women over the last several years according to ACS estimates. Importantly, even when screening rates were not statistically different as in this study, diagnosis rates were still significantly lower in women making a biological or behavioral etiology plausible. Further investigation is clearly warranted to determine if female gender has a protective role in development of CRC.

CONCLUSION

Gender disparities in rates and types of colorectal cancer screening reported in prior survey studies are not validated in this patient encounter data study. There is no overall statistically significant difference in rates of screening or type of screening. However, screening rates of men and women do vary across age groups with more women being screened at younger ages compared with men. Diagnosis rates are lower in women compared with men for any lesion or cancer despite similar screening rates.

REFERENCES

1. American Cancer Society. Cancer facts and figures 2005. American Cancer Society, 2005.
2. Swaroop VS, Larson MV. Colonoscopy as a screening test for colorectal cancer in average-risk individuals. Mayo Clin Proc 2002;77:951–956.
3. Rex DK, Johnson DA, Lieberman DA, Burt RW, Sonnenberg A. ACG Recommendations on colorectal cancer screening for average and higher risk patients in clinical practice, April 2000. Am Coll Gastroenterol, 2000.
4. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale—Update based on new evidence. Gastroenterology 2003;124:544–560.
5. American Cancer Society. ACS cancer detection guidelines. American Cancer Society, 2004, 4-11-0005. www.cancer.org.
6. Seeff LC, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, Molinari NA. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? Gastroenterology 2004;127:1661–1669.
7. Rao RS, Graubard BI, Breen N, Gastwirth JL. Understanding the factors underlying disparities in cancer screening rates using the Peters-Belson approach: Results from the

1998 National Health Interview Survey. Med Care 2004;42: 789–800.
8. Straus WL, Mansley EC, Gold KF, Wang Q, Reddy P, Pashos CL. Colorectal cancer screening attitudes and practices in the general population: A risk-adjusted survey. J Public Health Manage Pract 2005;11:244–251.
9. Chao A, Connell CJ, Cokkinides V, Jacobs EJ, Calle EE, Thun MJ. Underuse of screening sigmoidoscopy and colonoscopy in a large cohort of US adults. Am J Public Health 2004;94:1775–1781.
10. Hawley ST, Vernon SW, Levin B, Vallejo B. Prevalence of colorectal cancer screening in a large medical organization. Cancer Epidemiol Biomarkers Prevent 2004;13:314–319.
11. Etzioni DA, Ponce NA, Babey SH, Spencer BA, Brown ER, Ko CY, et al. A population-based study of colorectal cancer test use: results from the 2001 California Health Interview Survey. Cancer 2004;101:2523–2532.
12. Farraye FA, Wong M, Hurwitz S, Puleo E, Emmons K, Wallace MB, Fletcher RH. Barriers to endoscopic colorectal cancer screening: Are women different than men? Am J Gastroenterol 2004;99:341–349.
13. Bressler B, Lo C, Amar J, Whittaker S, Chaun H, Halparin L, Enns R. Prospective evaluation of screening colonoscopy: Who is being screened? Gastrointest Endosc 2004;60:921–926.
14. Slattery ML, Kinney AY, Levin TR. Factors associated with colorectal cancer screening in a population-based study: The impact of gender, health care source, and time. Prev Med 2004;38:276–283.
15. Turner B, Myers RE, Hyslop T, Hauck WW, Weinberg D, Brigham T, et al. Physician and patient factors associated with ordering a colon evaluation after a positive fecal occult blood test. J Gen Intern Med 2003;18:357–363.
16. Ko CW, Kreuter W, Baldwin LM. Effect of Medicare coverage on use of invasive colorectal cancer screening tests. Arch Intern Med 2002;162:2581–2586.
17. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380 (erratum appears in N Engl J Med 2000;343:1204). N Engl J Med 2000;343:162–168.
18. Ker TS, Wasserberg N, Beart RW Jr. Colonoscopic perforation and bleeding of the colon can be treated safely without surgery. Am Surg 2004;70:922–924.
19. Thiis-Evensen E, Hoff GS, Sauar J, Majak BM, Vatn MH. Flexible sigmoidoscopy or colonoscopy as a screening modality for colorectal adenomas in older age groups? Findings in a cohort of the normal population aged 63-72 years. Gut 1999;45:834–839.
20. Avidan B, Sonnenberg A, Schnell TG, Leya J, Metz A, Sontag SJ. New occurrence and recurrence of neoplasms within 5 years of a screening colonoscopy. Am J Gastroenterol 2002;97:1524–1529.
21. Harewood GC, Lieberman DA. Colonoscopy practice patterns since introduction of medicare coverage for average-risk screening. Clin Gastroenterol Hepatol 2004;2:72–77.
22. Mehran A, Jaffe P, Efron J, Vernava A, Liberman A. Screening colonoscopy in the asymptomatic 50- to 59-year-old population (erratum appears in Surg Endosc 2004;18:353 [Vernavay A corrected to Vernava A]). Surg Endosc 2003;17:1974–1977.
23. Gorard DA, McIntyre AS. Completion rate to caecum as a quality measure of colonoscopy in a district general hospital. Colorectal Dis 2004;6:243–249.