PAPER

Experience With 208 Resections for Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Hypothesis: Intraductal papillary mucinous neoplasm (IPMN) is an increasingly recognized disease of the pancreas. We report our experience with pancreatic resection for IPMN.

Design: Retrospective review from 1992 through 2005 with additional independent histopathologic confirmation.

Setting: Mayo Clinic Rochester, a tertiary care center.

Patients: All patients who underwent primary resection for pancreatic IPMN.

Main Outcome Measures: Disease-specific operative outcomes, survival, and recurrence patterns.

Results: Of 208 patients (mean age, 66 years) with IPMN of the pancreas, 168 underwent partial pancreatectomy, and 40 underwent total pancreatectomy; 88 were classified as having adenoma, 38 as having borderline neoplasm, 19 as having carcinoma in situ, and 63 as having invasive carcinoma. The prevalence of a malignant neoplasm was 64% in patients with main duct IPMN compared with 18% in patients with branch duct IPMN. Reresection of the initial pancreatic margin was necessary in 21% of patients. Final negative margins were achieved in 89% of patients. Five-year survival with noninvasive IPMN was 94%. Patients with invasive IPMN had a similar 5-year survival compared with a matched cohort with ductal adenocarcinoma (31% vs 24%; $P=.26$). In patients with invasive IPMN, 58% experienced disease recurrence. In patients with noninvasive IPMN, 10% experienced disease recurrence after partial pancreatectomy and 0% experienced disease recurrence after total pancreatectomy.

Conclusions: Patients with main duct IPMN or high-risk branch duct IPMN should be considered for targeted pancreatectomy. Invasive IPMN behaves as aggressively as ductal adenocarcinoma, but resection seems to provide the only potential for cure. Even with negative resection margins, the pancreatic remnant harbors a risk of recurrence and, thus, careful long-term surveillance is warranted.

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INTRADUCTAL PAPILLARY MUCINOUS neoplasm (IPMN) is an increasingly recognized disease of the pancreas[1,2] that can present in various degrees of invasiveness. The decision to recommend pancreatectomy is based on patients' symptoms, overall health, and clinical features that correlate with the risk of malignancy. However, the true nature of the disease and the long-term outcome after pancreatectomy are insufficiently understood. The extent of resection typically includes all gross detectable neoplasms, accepting the theory that the entire pancreatic duct is potentially at risk of developing into a neoplasm. Long-term follow-up of the pancreatic remnant after resection is recommended[3]; however, the absolute risk of recurrence and the identification of patients at risk are poorly established. This study reports a large, single-center experience with patients who underwent primary resections for IPMN of the pancreas.

METHODS

The study was approved by the Mayo Clinic Rochester institutional review board. All patients who underwent primary resection for pancreatic IPMN at the Mayo Clinic Rochester from January 1, 1992, to December 31, 2005, were identified. Clinical records were reviewed retrospectively. All operative specimens were reevaluated by a pancreatic pathologist (L.Z. or T.C.S.) not blinded to the original report. Histopathologic reevaluation included assessment of the IPMN category according to the criteria of the World Health Organization classification,[1] differentiation of neoplasm, invasion patterns, presence of neu-

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Table 1. Morphologic Classification of IPMN According to Preoperative Radiographic Findings

IPMN Type	No. of Patients (N = 208)	Age, Mean (SEM), y	Malignant Neoplasm, %[a]
Main duct	76	69 (1)	64
Mixed type			
Predominantly main duct	23	65 (3)	43
Predominantly branch duct	25	64 (3)	32
Branch duct	84	65 (1)	18

Abbreviation: IPMN, intraductal papillary mucinous neoplasm.
[a] Malignant neoplasm included carcinoma in situ and invasive carcinoma.

ral and vascular invasion, and degree of desmoplastic reaction. Patients with IPMN originating from the common bile duct or patients with a synchronous malignant neoplasm (unrelated to IPMN) within the pancreas, ampulla, duodenum, or distal common bile duct were excluded. Patients who underwent prior resection for IPMN at other institutions were also excluded. Patient follow-up was obtained through outpatient and hospital records, documents of communication with health care professionals, the Mayo Tumor Registry, and retrieval of death certificates of patients living within the United States. The mean follow-up was 3.2 years (range, 0-15 years).

For group comparison, 541 patients who underwent pancreatectomy for pancreatic or ampullary ductal adenocarcinoma during the same observation period at Mayo Clinic Rochester were studied. Patients with ductal adenocarcinoma were matched in a 1:1 ratio with patients with an invasive IPMN. Exact matching was performed according to the International Union Against Cancer stage[4] and location of the neoplasm (pancreatic vs ampullary), whereas frequency matching was performed according to age.

Descriptive statistics were reported as percentage or mean (SEM) unless specified otherwise. Two-sample t test, χ^2 test (or Fisher exact test), and log-rank test were used for univariate analyses. Survival and time to recurrence were calculated using Kaplan-Meier estimates. $P < .05$ was considered statistically significant. All statistical analyses were performed with SAS statistical software, version 9.0 (SAS Institute Inc, Cary, North Carolina).

RESULTS

During the study period, 443 patients were examined for documented or clinically apparent IPMN of the pancreas at Mayo Clinic Rochester, including 250 patients who underwent pancreatectomy. Of the 250 patients, 23 were excluded after further review of medical records. The histopathologic specimen was available in all the remaining 227 patients and was reevaluated by a pancreatic pathologist. After review, 19 patients were excluded because of change in diagnosis. The 208 remaining patients were subject to further analysis.

PATIENT CHARACTERISTICS AND CLINICAL FINDINGS

The study group included 106 men and 102 women. The age of the study group was 66 (1) years (range, 30-90 years). The most common symptoms at presentation were abdominal pain (56%), weight loss (14%), and jaundice (12%); 23% of all patients had clinical evidence of acute or chronic pancreatitis at diagnosis. Of the patients, 22% were asymptomatic and had an incidental radiographic finding of IPMN. Interestingly, 52% of patients were diagnosed as having another primary malignant neoplasm either before operation or during follow-up.

Before operation, all patients underwent cross-sectional imaging. To further evaluate findings, endoscopic retrograde pancreatography or endoscopic ultrasonography was used in 55% and 64% of patients, respectively, with a tendency to prefer endoscopic ultrasonography in recent years. On imaging, the neoplasm involved the head, body, or tail of the pancreas in 75%, 37%, and 32% of patients, respectively, including 16% who had involvement of the entire pancreas. Forty-two patients (20%) had evidence of a mass on cross-sectional imaging, and 24 additional patients (12%) had at least 1 mural nodule seen only on endoscopic ultrasonography. The prevalence of a malignant neoplasm within the operative specimen in these 66 patients was 74%. Of the 178 patients who underwent endoscopy (including gastroduodenoscopy only), only 33 (19%) had gross evidence of mucin issuing from the pancreatic papilla.

Radiographically, patients were classified as having main duct IPMN, branch duct IPMN, or mixed-type IPMN (**Table 1**). The prevalence of a malignant neoplasm within the operative specimen (including carcinoma in situ and invasive IPMN) in patients with main duct IPMN was 64% compared with 38% in mixed-type IPMN and 18% in branch duct IPMN ($P < .001$). Predictors of malignant neoplasm in patients with branch duct IPMN were the preoperative presence of a mass or mural nodule within the cyst, jaundice, or weight loss or the presence of mucin emanating from the ampulla on endoscopy (**Table 2**). Cyst size was important but not significant in predicting the risk of malignancy. In the 15 patients with a malignant neoplasm and branch duct IPMN, the radiographic diameter of the IPMN lesion was between 1.1 and 8.0 cm. All of these patients had IPMN-related symptoms (n=14), a solid mass or mural nodule (n=12), or main pancreatic duct or common bile duct dilation (n=9) that prompted operative intervention.

Ninety patients underwent fine-needle aspiration biopsy before operation. Eight biopsy specimens were nondiagnostic. Of the remaining 82 biopsy specimens, 51 were consistent with benign disease (including low-grade dysplasia) and 31 were suggestive or diagnostic of malignant disease (including high-grade dysplasia). When compared with the histopathologic review of the operative resection specimen, the accuracy of preoperative fine-needle aspiration was 84% (sensitivity, 78%; specificity, 88%; positive predictive value, 81%).

IPMN-SPECIFIC OPERATIVE FINDINGS

Targeted partial pancreatectomy was performed in 168 patients, including pancreatoduodenectomy in 115 (77% pylorus preservation), distal pancreatectomy in 51 (96% splenectomy), and central pancreatectomy

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Table 2. Univariate Analysis of Preoperative Clinical Factors Associated With a Malignant Neoplasm (Including Carcinoma In Situ and Invasive Carcinoma) in 84 Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm

Factor	Odds Ratio (95% Confidence Interval)	*P* Value	Sensitivity, %	Specificity, %	Positive Predictive Value, %
Cyst size ≥3 cm	2.4 (0.8-7.6)	.12	53	68	27
Mass or mural nodule within cyst	35.4 (8.0-156.7)	<.001	80	90	63
Jaundice	17.0 (1.6-177.3)	.02	20	99	75
Weight loss	7.0 (1.9-26.5)	.002	40	91	50
Ampullary mucin present on endoscopy	0	<.001	0	95	0

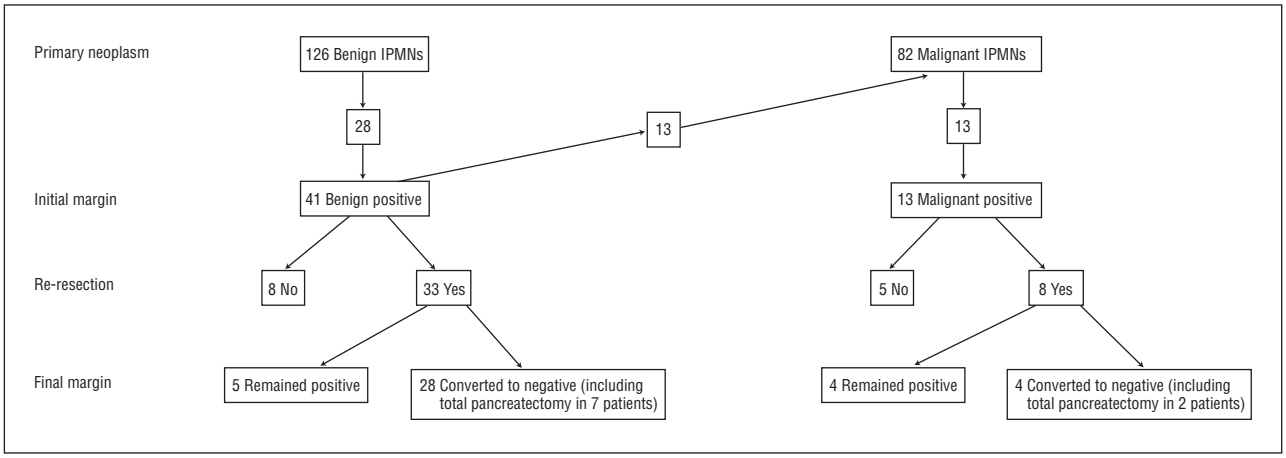

Figure 1. Management of operative margins in the 208 study patients with intraductal papillary mucinous neoplasm (IPMN).

or local excision in 1 each. The remaining 40 patients underwent total pancreatectomy, including conversion from partial resection after persistent microscopically positive margins in 9 patients.

Initial operative margins after partial pancreatectomy were positive in 54 patients (32%), whereas none of the initial margins were positive after total pancreatectomy. Our general approach to findings of positive margins was dependent on the presence of a malignant neoplasm at the margin and the patients' overall health status. Revision of the initial pancreatic margin was performed in 41 of these 54 patients (76%) with 1 to 2 subsequent resections (**Figure 1**). Final negative margins (R0) were achieved in 186 patients (89%). Microscopically positive margins (R1) and gross positive margins (R2) were encountered in 10% and 1% of patients, respectively, with 59% of positive margins harboring benign disease. The most common site for a positive margin was the pancreatic remnant (n=17), uncinate or superior mesenteric artery margin (n=6), and portal vein (n=2). In-hospital morbidity was 37%, and in-hospital mortality was 1.4%. The duration of hospital stay was 12 (1) days. We generally offer adjuvant treatment to all fit patients; however, adjuvant treatment was performed in only 44% of patients with invasive IPMN, including chemotherapy in 44% and external beam radiation therapy in 37%. Several of the patients who did not receive adjuvant therapy were followed up at other institutions.

HISTOPATHOLOGIC FACTORS

Eighty-eight patients were classified as having adenoma, 38 as having a borderline neoplasm, 19 as having carcinoma in situ, and 63 as having invasive carcinoma. The greatest diameter or length of the neoplasm was 4.2 (0.3) cm (range, 0.6-29.0 cm). In noninvasive and invasive IPMN, the neoplasms were 3.9 (0.3) cm and 4.9 (0.6) cm, respectively (*P* = .12). In the 63 patients with invasive IPMN, the invasive component alone was 2.9 (0.3) cm (range, 0.3-9.0 cm). This difference in size was attributable to the coexistence of benign and malignant neoplasms in patients with invasive IPMN. Multifocal disease was present in 15%, 13%, 11%, and 5% of patients with adenoma, borderline neoplasm, carcinoma in situ, and invasive carcinoma, respectively. Oncocytic IPMN was present in 4% of patients. Of the 63 patients with invasive carcinoma, neoplasms most commonly had moderate or poor differentiation (well, 3%; moderate, 49%; poor, 41%; dedifferentiated, 6%). A desmoplastic reaction was often present (none, 0%; mild, 1%; moderate, 43%; marked, 55%). Perineural and vascular invasion were identified in 56% and 16% of patients, respectively. Of the 63 patients, 16 (25%) had a small carcinoma component (stage IA), whereas 28 (44%) had invasive IPMN with direct invasion into peripancreatic structures. Metastatic spread to regional lymph nodes was present in 24 patients (38%) with invasive IPMN. When comparing the 63 patients with invasive IPMN with the 541 patients who

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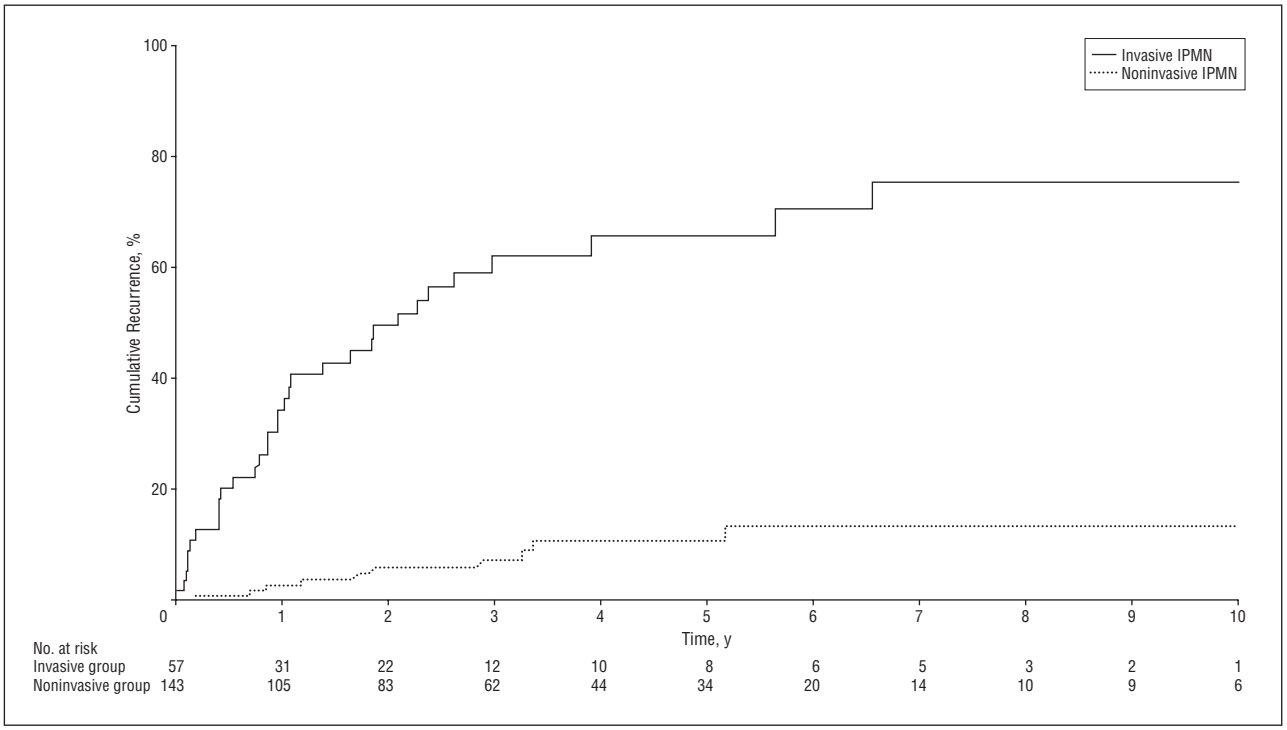

Figure 2. Time to recurrence after pancreatectomy in 143 patients with noninvasive intraductal papillary mucinous neoplasm (IPMN) and 57 patients with invasive IPMN (log-rank test, $P<.001$).

underwent pancreatectomy for ductal adenocarcinoma during the same observation period, a greater prevalence of stage IA carcinoma was found in the IPMN group (stage IA, 25% vs 6%; stage IB, 8% vs 14%; stage IIA, 27% vs 28%; and stage IIB, 38% vs 49% [$P<.001$]).

LOCOREGIONAL AND DISTANT RECURRENCE OF IPMN

Data on radiographic disease recurrence were available in 200 patients. In 33 of 57 patients (58%) with invasive IPMN, cross-sectional imaging suggested disease recurrence during follow-up, including progression of disease in 5 patients with a positive operative margin (malignant positive, 4; benign positive, 1). The median disease-free interval in this group was 25 months, and the 5-year disease-free rate was 66% (**Figure 2**). The initial sites of recurrence were the liver (n=12), the peritoneum (n=7), locoregional areas (n=7), the lung (n=2), and miscellaneous areas (n=5). The 46 patients who underwent partial pancreatectomy (overall recurrence, 54%; distant recurrence, 39%) had an overall recurrence rate not significantly different compared with the 11 patients who underwent total pancreatectomy (overall recurrence, 73%; distant recurrence, 73%). Of the 33 patients with recurrence, 16 received chemotherapy for recurrent disease, including 2 who received external beam radiation. Two additional patients underwent completion pancreatectomy for locoregional recurrence.

In contrast, of 143 patients with noninvasive IPMN, 11 (8%) had recurrence within the pancreatic remnant after resection of carcinoma in situ (3 patients, all with transformation to invasive IPMN) or adenoma (8 patients, none with transformation to invasive IPMN) up to 11 years after the initial operation (5-year recurrence rate, 11%) (Figure 2). This recurrence pattern included progression of IPMN in 1 of 10 patients (10%) with positive margins at operation and pathologic recurrence in 10 of 131 patients (8%) with negative margins at operation. All 11 patients had radiographic disease recurrence after partial pancreatectomy, whereas no patient had recurrence after total pancreatectomy. Management of recurrent disease depended on the suggestion of a malignant neoplasm. Of the 11 patients, 7 had a recurrence in the form of a small branch duct IPMN classified within the international consensus guidelines and were observed clinically; none developed a malignant neoplasm during the 31 (3) months of observation (range, 10-60 months). Of the 11 patients, 3 presented with metastatic (n=1) or locally advanced (n=2) disease 34, 39, and 40 months after pancreatectomy. Fine-needle aspiration biopsy confirmed invasive IPMN. All 3 patients had undergone an R0 resection for carcinoma in situ initially. The recurrence was treated with chemotherapy. Of the 11 patients, 1 was diagnosed as having locoregional recurrence at another institution and underwent completion pancreatectomy, which revealed adenoma.

SURVIVAL

Overall survival depended on histopathologic classification ($P<.001$) (**Figure 3**); 5-year survival rates after resection for adenoma, borderline neoplasm, carcinoma in situ, and invasive carcinoma were 96%, 90%, 94%, and 31%, respectively.

The 5-year survival rate in patients with noninvasive IPMN was 94%. Of the 145 patients with noninvasive IPMN, 15 died during follow-up. The cause of death was

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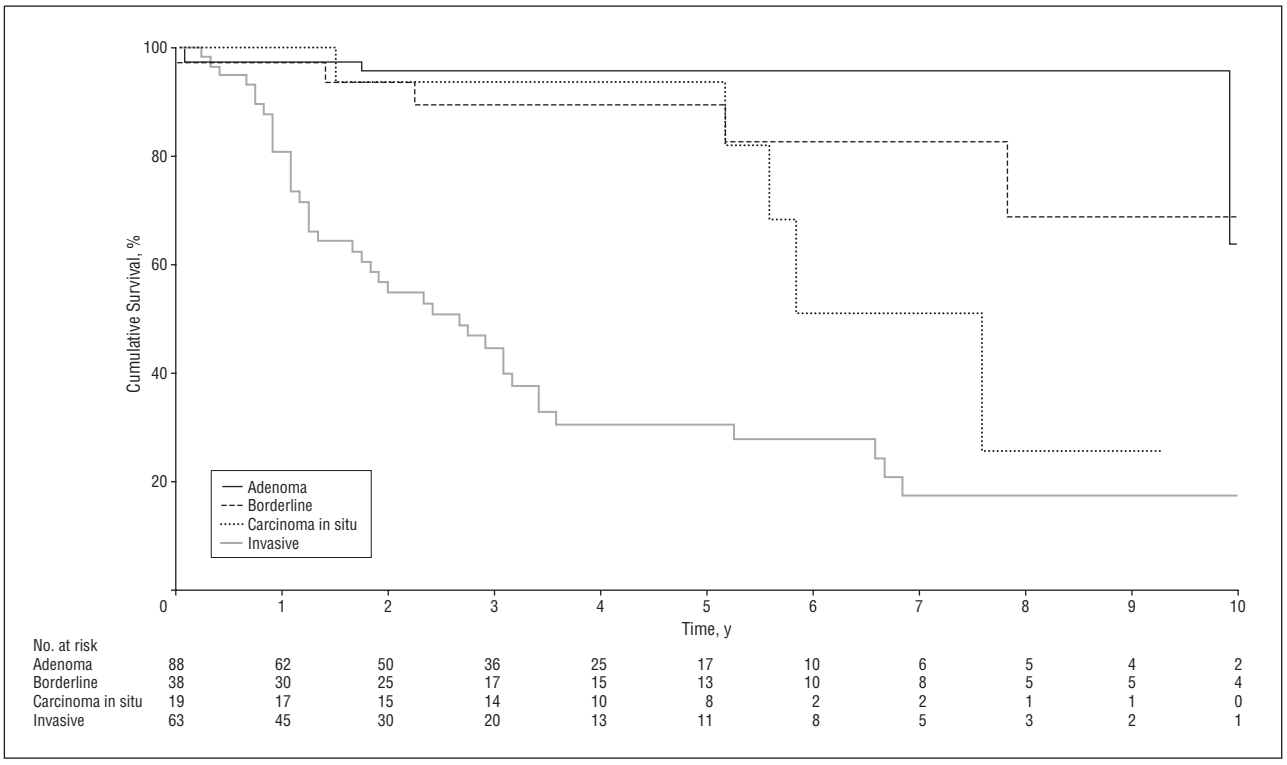

Figure 3. Overall survival after pancreatectomy for patients with intraductal papillary mucinous neoplasm according to the World Health Organization pathologic classification (log-rank test, $P<.001$).

unrelated to the pancreas in 10 patients and unknown in 3 patients. Two patients died of IPMN adenocarcinoma, whereas 1 additional patient was alive and had a malignant recurrence.

In contrast, the 5-year survival rate in patients with invasive IPMN was 31%, which was less than in patients with noninvasive IPMN ($P<.001$). Of the 41 patients with invasive IPMN who died during follow-up, 33 died of progression from IPMN carcinoma and 3 died of unknown causes. The 5 remaining patients who died of causes unrelated to the pancreas all had no evidence of recurrence of IPMN. Patients with invasive IPMN had no significant difference in survival compared with a matched cohort of patients who underwent pancreatectomy for ductal adenocarcinoma (median survival, 32 vs 21 months; 5-year survival rate, 31% vs 24%; $P=.26$) (**Figure 4**). Factors that influenced survival in patients with invasive IPMN are listed in **Table 3**. The use of adjuvant treatment in patients with invasive IPMN did not seem to result in a survival benefit. This somewhat lesser survival in patients given adjuvant chemoradiation therapy might be explained by the observation that adjuvant treatment was given more frequently to patients with advanced International Union Against Cancer stage (adjuvant treatment, 59% stage IIB; no adjuvant treatment, 20% stage IIB).

Of the 186 patients with a negative pathologic margin at operation, the median survival was 119 months, and the 5-year survival rate was 77%. Survival of patients who underwent an R0 resection was greater but not statistically significantly different compared with patients with benign positive margins (median survival, 119 vs 62 months; 5-year survival rate, 77% vs 52%; $P=.14$), whereas patients with malignant positive margins had worse survival compared with patients with negative margins (median survival, 119 vs 11 months; 5-year survival rate, 77% vs 0%; $P<.001$). The lower 5-year survival rate in patients with a benign positive margin can be explained partially by the observation that 11 of the 28 patients had underlying invasive IPMN at resection.

COMMENT

At our institution and many others, IPMN has been diagnosed with an increasing frequency during the past decade.[5,6] Malignancy affects many of these patients. Because of the overall limited accuracy in detection of a malignant neoplasm during routine noninvasive diagnostic evaluation, the focus has been on identifying risk factors with adequate specificity to exclude malignant neoplasm with the intent to observe low-risk patients. Like others, we found a much greater prevalence of malignancy with IPMN that involved the main duct compared with the branch duct.[2,7] We also identified the presence of nodules and symptoms of jaundice and weight loss as predictors of malignancy in the overall group, as well as in those with branch duct IPMN. Fine-needle aspiration cytology had limited efficacy in differentiating benign from malignant IPMN.

With the increasing recognition of risk factors for malignanny, the management of IPMN is evolving. The indication for operation has changed from resection in all fit patients to selective observation of patients with IPMN at low risk of malignancy.[8] This selective approach has found broad acceptance and was incorporated into the

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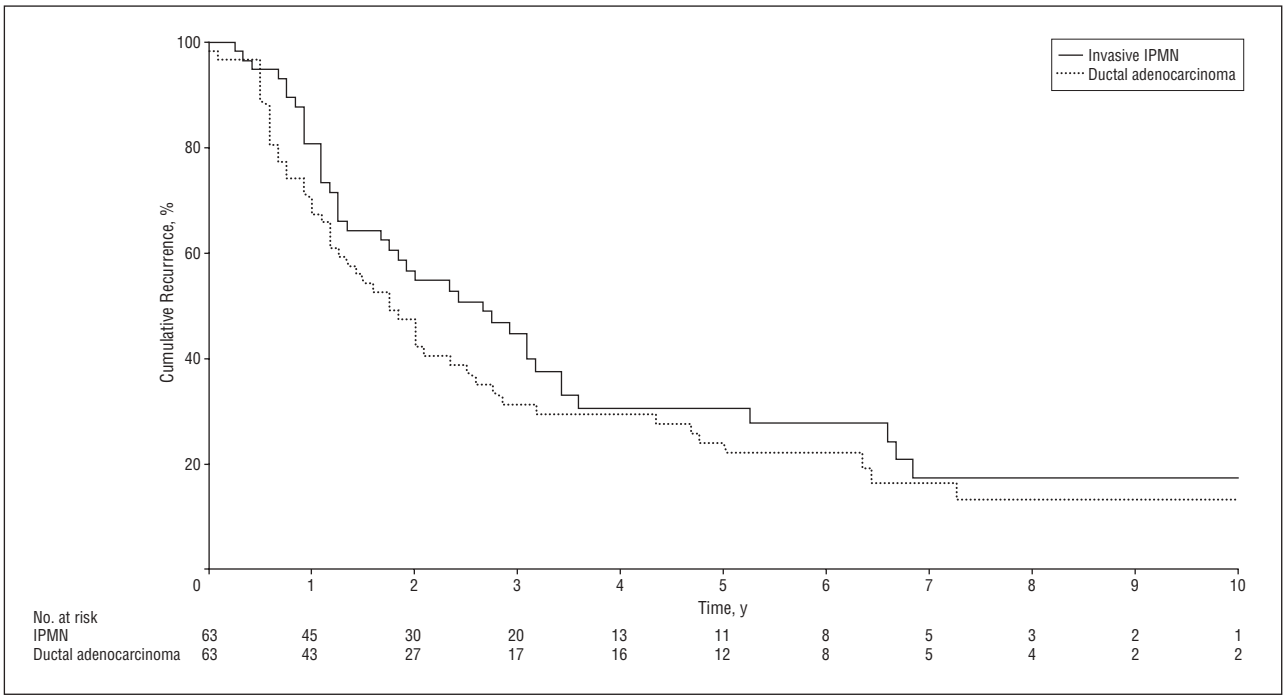

Figure 4. Overall survival after pancreatectomy in 63 patients with invasive intraductal papillary mucinous neoplasm (IPMN) compared with 63 matched patients with ductal adenocarcinoma (log-rank test, *P*=.26).

Table 3. Survival After Pancreatectomy for 63 Patients With Invasive Intraductal Papillary Mucinous Neoplasm[a]

Variable	No. of Patients	5-y Survival, %	Length of Survival, Median, mo	*P* Value
Tumor stage (UICC)				
T1	16	78	81	.005
T2	19	0	29	
T3	28	19	28	
Lymph node status				
N0	39	40	41	.02
N1	24	17	16	
Margin status				
Negative	45	42	42	<.001
Positive[b]	18	0	15	
Differentiation grade[c]				
1 or 2	33	48	43	.007
3 or 4	30	14	15	
Vascular invasion				
Absent	53	36	37	.007
Present	10	10	13	
Perineural invasion				
Absent	28	38	41	.06
Present	35	26	15	
Adjuvant chemoradiation				
Absent	35	34	37	.48
Present	28	27	23	

Abbreviation: UICC, International Union Against Cancer.
[a] The overall 5-year survival for the 63 patients was 31%, and the median length of survival was 32 months.
[b] Includes benign positive margins.
[c] Grade 1 indicates well differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated; and grade 4, dedifferentiated.

international consensus guidelines while being validated recently in larger series.[2,8-10] Our study was not designed to address these guidelines because it is our current practice to observe asymptomatic branch duct IPMN of less than 3 cm in diameter without other evidence for malignancy. In the group of patients who underwent resection, we found that all branch duct IPMNs with malignancy had either mural nodules or a mass and/or caused aggressive symptoms. In our study, cyst size alone was not a significant predictor of a malignant neoplasm. Similar findings have been described recently in a large study by Schmidt et al[7]; however, similar to the report by Schmidt et al, we did not include patients with small branch duct IPMN who were managed with observation. We presume that if observed patients are included in the analysis, cyst size would reveal itself as an important statistical factor. Whether cyst size is an independent clinical marker and, therefore, of additive value is undetermined. In the absence of strong evidence, for now, we still use cyst size for operative patient selection. In general, patients with main duct or mixed-type IPMN or those with disease suggestive of a malignant neoplasm should be considered for pancreatectomy if deemed fit enough for an operation. For these patients, we maintain that the risk of finding malignant IPMN after pancreatic resection seems to outweigh the risks of the operation that can be achieved with a low mortality rate and acceptable morbidity.

Our approach has been to resect all gross disease and to obtain frozen section histology of margins. For most patients, a targeted partial pancreatectomy is sufficient, but a localized resection such as enucleation is not recommended, even in branch duct IPMN. Whenever possible, operative margins that are positive for malignant IPMN should be re-resected in fit patients; in contrast,

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the treatment of patients with margins positive for benign IPMN is controversial. Overall radiographic recurrence in patients with noninvasive IPMN was 8%, with most locoregional recurrences representing what seem to be true recurrences rather than progression of margin-positive disease. Because recurrence can occur even 10 years or more after resection, long-term follow-up with surveillance imaging in all patients after resection of IPMN seems imperative. Invasive transformation of recurrent IPMN after resection for noninvasive IPMN was seen in only 3 patients with carcinoma in situ. Because these recurrences occurred after an apparent R0 resection, one might assume that the transformation developed in the remnant gland rather than at the resection margin. An alternative explanation could be misdiagnosis of an underlying invasive IPMN. Sohn et al[5] reported recurrence in 7 of 84 patients (8%) with noninvasive IPMN, including 5 patients with invasive transformation. White et al[11] found recurrence in 6 of 78 patients (8%) with noninvasive IPMN, including 4 patients with invasive transformation after pancreatectomy for carcinoma in situ and 1 with transformation of adenoma to carcinoma in situ. Although both of these studies reported re-resection for benign, locoregional recurrence, we believe that benign recurrences should be treated in a manner similar to the approach for initially diagnosed IPMN by applying the international consensus criteria to assess the risk for presence of malignant neoplasm.

The risk of developing a metachronous IPMN in the remnant pancreas from a field defect is poorly elucidated but might not differ between invasive and noninvasive IPMN.[12] In our study, such as in many others, we encountered diagnostic difficulty in differentiating local progression and development of a metachronous IPMN in the remnant gland. Because of the retrospective nature of our study, we did not attempt this differentiation because of the potential for bias and, therefore, we reported a combined recurrence rate. Hence, it is not clear whether patients with IPMN are at risk of developing a separate metachronous neoplasm in the pancreatic remnant that differs from local progression at the margin. The present study raises the question of whether patients with invasive IPMN or carcinoma in situ IPMN represent a subgroup that would benefit from total pancreatectomy. The risk of isolated, locoregional progression and transformation to invasive disease after resection of invasive IPMN and carcinoma in situ was 12% and 16%, respectively, which seems greater than the 3% long-term mortality for metabolic complications after total pancreatectomy.[13] Nevertheless, we believe this potential survival benefit in a minority of patients does not justify a recommendation of total pancreatectomy with its associated change in quality of life for all patients with malignant IPMN. Hence, a final answer cannot be provided, and the decision to perform total pancreatectomy needs to be determined on an individual basis.

Survival in patients with noninvasive disease was significantly better than in patients with invasive disease. Patients with IPMN that contained carcinoma in situ had similar 5-year survival rates compared with those with benign disease; however, a risk of malignant recurrence remained within the pancreatic remnant, reflected by poor long-term survival. Overall, unmatched patients with invasive IPMN seem to have a better prognosis for long-term survival compared with patients with ductal adenocarcinoma, likely because of a greater prevalence of early-stage carcinoma in the presence of a potentially symptomatic, coexisting, benign component. When matched by disease stage, however, patients with invasive IPMN and ductal adenocarcinoma had similar survival rates. We believe that the management of invasive IPMN should not differ from that for ductal adenocarcinoma.

In conclusion, our approach to patients with IPMN has evolved over time from recommending resection in all fit patients to a more selective approach with observation of low-risk, branch duct IPMN. The recommended operative approach changed from predominant use of total pancreatectomy to a targeted, anatomical pancreatectomy, resecting parts of the pancreas involved radiographically by the disease as guided by intraoperative frozen section histology. We have shown the pancreatic remnant to be at risk for recurrence; thus, careful, long-term follow-up with surveillance imaging seems warranted. The frequency and method of surveillance imaging are not defined but are conceivably dependent on the underlying IPMN histologic type. In the presence of recurrence, we usually apply the international consensus guidelines. We believe that our data justify this approach. With further understanding of the biological features and behavior of IPMN of the pancreas, we anticipate that the treatment algorithm for such patients will continue to evolve.

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DISCUSSION

Keith D. Lillemoe, MD, Indianapolis, Indiana: This is a very important contribution to our understanding of this relatively new and still somewhat poorly understood form of pancreatic tumor. The authors' management, in general, has followed the international consensus conference guidelines, choosing to operate only on tumors greater than 3 cm, tumors with evidence of mass or mural nodules, patients with a positive cytology, or symptomatic patients. This study confirms much that has been previously reported but also offers some areas of conflict.

I think an important message is the fact that tumor size was not a significant predictor of malignancy in resected patients, confirming recently published data from our institution.

They also stress the importance of careful analysis of margin status on frozen section, with about 20% of resections being extended and about 5% of patients requiring total pancreatectomy to obtain a negative margin.

Finally, they remind us that these patients remain at risk for recurrent disease in the pancreas after partial pancreatectomy and stress the need for continued surveillance.

On the other hand, they offer a few points that are hard to understand and form the basis for my questions.

First, your survival curve for invasive IPMN is no different than that for ductal adenocarcinoma. You say that this analysis has been limited to disease-matched or stage-matched patients with ductal adenocarcinoma for your presentation; however, this is clearly different than has been reported from other institutions. I would like to give you the opportunity to expand a little bit on this finding.

Next, were any of the distal pancreatectomies performed laparoscopically and do you consider this an adequate cancer operation for patients with an unknown extent of malignant disease?

Next, patients with carcinoma in situ in your series had a marked drop-off in late survival. How much of this survival drop-off was related to recurrent or metastatic disease, or was it new IPMN disease in the remnant gland? If so, do you have the margin status of those patients who have recurrent disease?

Finally, and most importantly in my mind, is the group of patients that were not presented, the 193 patients in your observation group. I believe that the prospective follow-up that you are providing to these patients is most important, as most of us can figure out who to operate on, but who not to operate is the difficult question. Can you tell us how many of the patients that were initially in the observation group eventually went to surgery, and if they did go to surgery, how many actually had invasive cancer of the resected specimen?

Dr Schnelldorfer: To address your first question concerning the survival in patients with invasive IPMN compared to patients with ductal adenocarcinoma, when we just look at unmatched survival, there is a better survival rate in the invasive IPMN group compared to ductal adenocarcinoma. However, we believe this difference is due to a greater prevalence of early-stage disease in the invasive IPMN group. When matched according to age, stage, and type of operation performed, this survival benefit fades away. We, therefore, believe both diseases are similarly aggressive. The reason for IPMN presenting at an earlier stage is presumably due to a larger benign component associated with a smaller invasive portion, which causes symptoms, resulting in earlier presentation of the patient.

Concerning the second question about laparoscopic distal pancreatectomy, our current series only included patients up to 2005. We have started performing laparoscopic procedures for this kind of disease in very selected patients since. It is not a good cancer operation if you have a high suspicion of malignancy. But for patients who have a small symptomatic lesion that is thought to be benign, laparoscopic distal pancreatectomy is an option.

Concerning the third question in terms of patients with carcinoma in situ and what the cause of death was after 5 years, there were 2 patients who died of natural cause and 3 patients who died due to recurrence within the pancreatic remnant. This is out of a group of only 19 patients with carcinoma in situ. We are not entirely sure of the cause of malignant recurrence in those 3 patients, simply because the carcinoma in situ was completely excised and there were negative margins. Although the pathologic specimens were reevaluated by our pancreatic pathologists, there is still a remote possibility that we underdiagnosed these patients and they indeed might have had invasive IPMN. However, we are not certain of that.

Concerning our experience on patients who were observed, we recently presented a manuscript from our institution that reported 70 patients who were observed with low-risk branch duct IPMN and compared them to 77 patients who underwent pancreatectomy for branch duct IPMN. This study revealed that all the patients who had malignant disease were captured by the international consensus guidelines.

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