Cystic Lesions of the Pancreas: Changes in the Presentation and Management of 1,424 Patients at a Single Institution over a 15-Year Time Period

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BACKGROUND: Cystic lesions of the pancreas are being identified more frequently, and a selective approach to resection is now recommended. The aim of this study was to assess the change in presentation and management of pancreatic cystic lesions evaluated at a single institution over 15 years.

STUDY DESIGN: A prospectively maintained registry of patients evaluated between 1995 and 2010 for the ICD-9 diagnosis of pancreatic cyst was reviewed. The 539 patients managed from 1995 to 2005 were compared with the 885 patients managed from 2005 to 2010.

RESULTS: A total of 1,424 patients were evaluated, including 1,141 with follow-up >6 months. Initial management (within 6 months of first assessment) was operative in 422 patients (37%) and nonoperative in 719 patients (63%). Operative mortality in patients initially submitted to resection was 0.7% (n = 3). Median radiographic follow-up in patients initially managed nonoperatively was 28 months (range 6 to 175 months). Patients followed radiographically were more likely to have cysts that were asymptomatic (72% versus 49%, $p < 0.001$), smaller (1.5 versus 3 cm, $p < 0.001$), without solid component (94% versus 68%, $p < 0.001$), and without main pancreatic duct dilation (88% versus 61%, $p < 0.001$). Changes prompting subsequent operative treatment occurred in 47 patients (6.5%), with adenocarcinoma identified in 8 (17%) and pancreatic endocrine neoplasm in 4 (8.5%). Thus, of the 719 patients initially managed nonoperatively, invasive malignancy was identified in 12 (1.7%), with adenocarcinoma seen in 1.1%.

CONCLUSION: Cystic lesions of the pancreas are being identified more frequently, yet are less likely to present with concerning features of malignancy. Carefully selected patients managed nonoperatively had a risk of malignancy that was equivalent to the risk of operative mortality in those patients who initially underwent resection. (J Am Coll Surg 2011;212:590–600. © 2011 by the American College of Surgeons)

With widespread use of high-quality cross-sectional imaging, cystic lesions of the pancreas are being identified with increasing frequency. The prevalence of incidentally detected cystic lesions of the pancreas is approximately 10%[1] and may reach as high as 30% in patients older than 70 years.[2] Management of these lesions remains controversial for several reasons: 1) the underlying causal pathology ranges from benign to premalignant to malignant, 2) nonoperative histologic diagnosis is inaccurate in approximately 25% of patients, and 3) pancreatic resection is associated with a substantial risk of morbidity and measurable mortality.

Over the last decade, substantial progress has been made concerning the selection of patients for resection, and rou-

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Abbreviations and Acronyms

CEA = carcinoembryonic antigen
EUS = endoscopic ultrasonography
FNA = fine-needle aspiration
IPMN = intraductal papillary mucinous neoplasms
MSKCC = Memorial Sloan-Kettering Cancer Center

tine resection of all cystic lesions of the pancreas is no longer advocated.[3,4] A more selective approach to resection is now widely recommended,[5-7] with resection advocated for symptoms, larger lesions,[8] presence of mural nodules or solid component,[9] presence of septations,[7] or the setting of suspicious fluid cytology[10] or serum marker analysis.[11,12] Selection criteria have been directed toward identifying groups of patients who have an extremely low risk of malignancy (<2%)—when the risk of malignancy approximates the risk of mortality from pancreatic resection—and those patients who have high-risk lesions that are likely to have high-grade dysplasia or invasive disease.

Our group previously reported (2006) the results of a selective surgical approach to patients with cystic neoplasms of the pancreas.[9] This study identified the presence of a solid component, cyst size larger than 2.5 cm, and symptoms as criteria associated with the recommendation for resection. Since this report, we have continued to see increasing numbers of patients with cystic lesions of the pancreas. The aim of this study was to update and expand upon this prior reported experience, now over 15 years and including more than 1,400 patients, with particular attention to changes in presentation and management.

METHODS

Data collection

Memorial Sloan-Kettering Cancer Center's (MSKCC's) pancreatic cyst registry was designed to identify all patients (both operative and nonoperative) evaluated at MSKCC by a surgeon or gastroenterologist for a cystic lesion of the pancreas. This registry includes patients evaluated since 1995. Patients are included in this database if they are coded by the evaluating physician for the ICD-9 diagnosis of pancreatic cyst (577.2) and had a cystic lesion of the pancreas on review of imaging studies. Patients within this database who were evaluated between January 1995 and January 2010 were reviewed and included in this study. Approval for this review was obtained from MSKCC's IRB.

A previous report on this registry was published in 2006[9] and included 539 patients evaluated during the initial 10-year time period (1995 to 2005). In the current study, patient, radiographic, and treatment-related variables were collected as previously described and were also reviewed. Comparisons were made between those patients presented in our previous publication (January 1995 to January 2005) and those evaluated in the most recent 5 years (January 2005 to January 2010).

Statistical analysis

Values are expressed as median, range, or percentage, as appropriate. Chi-square or Fisher exact test was used to compare differences in discrete or categoric variables, respectively, and the *t*-test or Wilcoxon rank-sum test was used for continuous variables. For time-related probability to undergo operative resection analysis, patients' follow-up was censored if the patient was still alive without operative intervention at last follow-up. Time-related probability to undergo surgery was estimated by the method of Kaplan-Meier, and the log-rank test was used to compare survival curves. All tests were 2 sided. For all tests, statistical significance was defined by $p < 0.05$. Data were analyzed with STATA statistical software (release 11, StataCorp LP). Recursive partitioning was used to determine homogeneous subgroups with respect to the likelihood of initial resection. A decision tree was used to display the results of recursive partitioning. The optimal tree was chosen based on 10-fold cross-validation and cost-complexity pruning. Recursive partitioning was implemented using the "rpart" function in R (http://www.r-project.org).[13]

RESULTS

Patient and cyst characteristics and imaging modalities

Between January 1995 and January 2010, 1,424 patients were evaluated for a cystic lesion of the pancreas. During this 15-year period, an increasing number of patients were evaluated each year. During the initial 10 years of the study (1995 to 2005), 539 patients (38%) were evaluated compared with 885 (62%) during the last 5 years of the study. The percent increase in the number of patients evaluated annually was almost linear ($y = 12/653x$, $R^2 = 0.9118$), with an approximate 8% annual increase in the number of patients evaluated for a cystic lesion of the pancreas (Fig. 1). During the study period, the median diameter of the lesions decreased, with a median diameter of 2.4 cm (range 0.3 to 18 cm) in 1995 to 2005 and 1.6 cm (range 0.3 to 14 cm) in 2005 to 2010 ($p = <0.0001$) (Fig. 1).

The patient and cyst characteristics of the 1,424 patients are presented in Table 1. The median age at the time of diagnosis was 67 years (range 15 to 95 years), one-third of the patients were male (n = 497 [35%]), and 92% (n = 1,284) were white. Upper gastrointestinal symptoms were the complaint resulting in identification of the lesion in 38% of patients (n = 542), and 8% had a documented

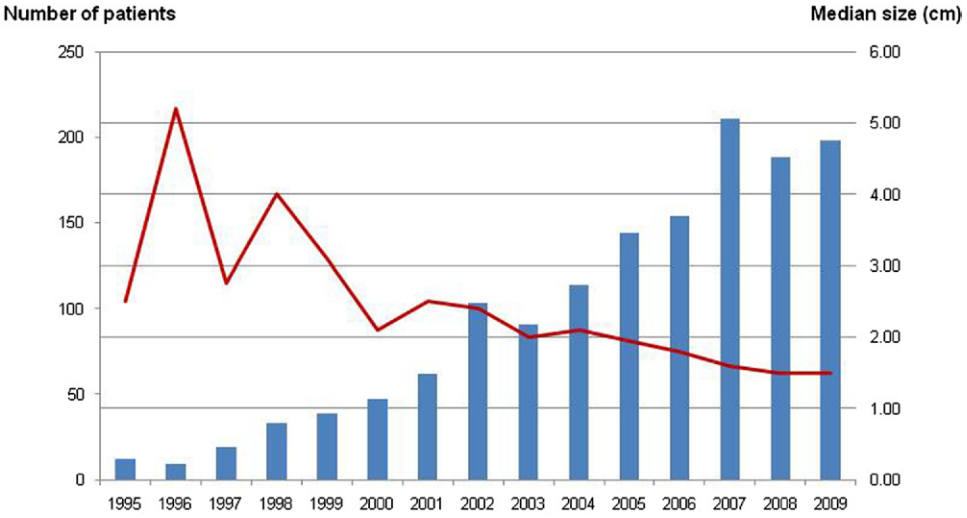

Figure 1. The number of patients evaluated each year for a cystic lesion of the pancreas (blue bars) and the median size (red line) of the lesion at initial visit (1995 to 2010, N = 1,424).

history of pancreatitis. At the time of presentation, the median cyst size was 2 cm (range 0.3 to 18 cm), lesions were most often located in the head of the pancreas (n = 614 [62%]), and the majority of patients (n = 1,025 [72%]) were found to have a solitary cystic lesion (range 0 to >10). Septations were identified in 42% (n = 491), and 14% (n = 164) had a solid component.

Comparisons were made between patients initially reported in 1995 to 2005 and patients from the last 5 years of the study period (2005 to 2010). The median age, race, and gender of the patients did not significantly differ between time periods; however, patients from the more recent time period were less likely to present with symptomatic lesions (1995 to 2005 44% versus 2005 to 2010 35%, p < 0.0001). The location of the lesions did not change significantly over time, (head location: 1995 to 2005 47% versus 2005 to 2010 48%, p = 0.4); however, the median diameter of the lesions was smaller during the second part of our experience (2.4 versus 1.6 cm, p < 0.0001). The radiographic findings of septations (50% versus 36%, p < 0.0001) and solid component (23% versus 9%, p < 0.0001) were also significantly decreased.

During the diagnostic evaluation, CT was the most frequently used imaging modality (n = 1,384 [97%]), and 67% of patients (n = 963) underwent MRI (Fig. 2). PET was used in 11% of patients; however, in 2009, only 5% (11 of 198) of patients underwent PET imaging. Endoscopic evaluation was performed in roughly one-half of

Table 1. Patient and Cyst Characteristics of the 1,424 Patients Evaluated for a Cystic Lesion of the Pancreas between 1995 and 2010

	1995–2010 (N = 1,424)	1995–2005 (n = 539)	2005–2010 (n = 885)	p Value*
Median age at presentation, y (range)	67 (15–95)	67 (19–92)	67 (15–95)	0.6
Sex, male, n (%)	497 (35)	192 (36)	305 (34)	0.3
Race, white, n (%)	1284 (92)	494 (93)	790 (91)	0.1
Symptomatic at diagnosis, yes, n (%)	542 (38)	235 (44)	307 (35)	<0.001
Personal history of pancreatitis, yes, n (%)	114 (8)	59 (11)	55 (6)	0.001
Median initial diameter, mm (range)	20 (3–180)	24 (3–180)	16 (3–140)	<0.001
Location of the cyst, n (%)				
Head	676 (47)	252 (47)	424 (48)	0.4
Body	384 (27)	138 (26)	246 (28)	
Tail	363 (25)	148 (27)	215 (24)	
Septations at initial visit, yes, n (%)	491 (42)	242 (50)	249 (36)	<0.001
Solid component at initial visit, yes, n (%)	164 (14)	106 (23)	58 (9)	<0.001
Calcium at initial visit, yes, n (%)	128 (13)	60 (15)	68 (11)	0.05

*Comparison was between the 2 periods, only in patients with available data.

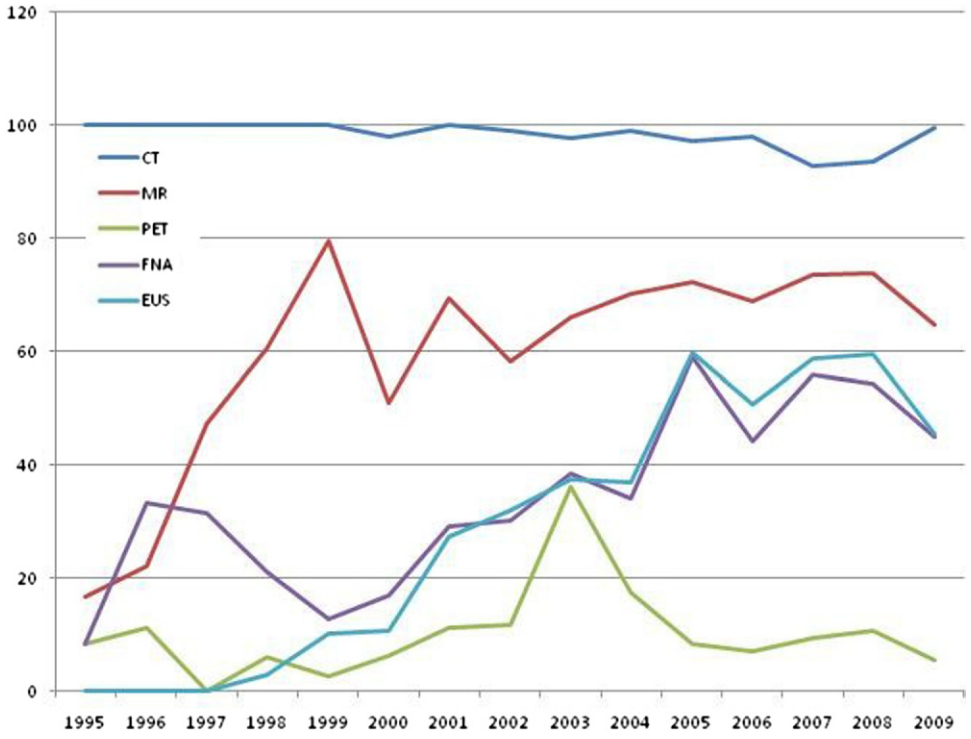

Figure 2. Diagnostic tests used in evaluating 1,424 patients with cystic lesions of the pancreas (1995 to 2010, N = 1,424). EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; MR, magnetic resonance.

patients, with 44% (n = 626) undergoing endoscopic ultrasonography (EUS) and the majority of these patients undergoing fine-needle aspiration (FNA) of the identified lesion (n = 615).

Surgical management and pathology of patients initially resected

Resection was performed in 469 patients (41%), including 422 (37%) within 6 months of their initial visit (initial resection) and 47 patients (47 of 719 [6.5%]) following an initial (>6 months) period of radiographic surveillance (Table 2). In patients who were initially resected (n = 422), the most common procedures were pancreaticoduodenectomy (n = 150 [36%]), distal pancreatectomy with splenectomy (n = 145 [34%]), and distal pancreatectomy (n = 58 [14%]). Comparison between patients from 1995 to 2005 and 2005 to 2010 revealed no significant difference in operative approach; however, significantly fewer patients were selected for initial resection during the more recent time period (initial resection 1995 to 2005 43% versus 2005 to 2010 33%, p = 0.001). The overall grade III complication rate was 36%, and the 30-day mortality rate was between 0.5% and 1% without significant change over time. The median length of stay was 8 days in 1995 to 2005 and 7 days in 2005 to 2010 ($p < 0.001$).

The histopathology of the 422 patients who underwent initial operative resection is presented in Table 3. The most common lesions resected were intraductal papillary mucinous neoplasms (IPMN) (n = 114 [27%]), serous cystadenoma (n = 98 [23%]), adenocarcinoma (n = 60 [14%]), mucinous cystadenoma (n = 45 [11%]), and cystic pancreatic endocrine tumors (n = 30 [7%]). Resection of lesions with carcinoma or high-grade dysplasia represented 23% of the resected lesions (n = 94).

During the second part of the study period, the pathology of the resected lesions evolved. The most commonly resected lesion within the first 10 years of the study was serous cystadenoma, and this frequency significantly decreased during the last 5 years (34% versus 13%, $p < 0.001$). The percentage of patients who underwent resection for noninvasive IPMN increased in the last 5 years of the study (1995 to 2005 17% versus 2005 to 2010 36%, $p < 0.001$). Resection for pseudocyst also decreased in the second period of study (8% versus 1%, p = 0.001). Overall, resection for carcinoma or high-grade dysplasia was more frequent in the recent period (17% versus 28%, p = 0.01), as well as for lesions known to be at risk of malignant progression (ie, IPMN, mucinous cystadenoma, pancreatic endocrine tumor, or solid pseudopapillary tumor 40% versus serous cystadenoma, pseudocyst, or simple cyst 64%, $p < 0.001$).

Table 2. Detail of Patients Undergoing Initial Operative Resection (n = 422)

	1995–2010 (n = 422)	1995–2005 (n = 199)	2005–2010 (n = 223)	p Value*
Initial resection	422 of 1,141 (37%)	199 of 465 (43%)	223 of 676 (33%)	0.001
Procedures, n (%)				
Whipple	150 (36)	63 (32)	87 (39)	0.13
Central pancreatectomy	10 (2.4)	5 (3)	5 (2)	1
Distal pancreatectomy	58 (14)	37 (17)	24 (11)	0.3
Distal pancreatectomy + splenectomy	145 (34)	63 (32)	82 (37)	0.3
Total pancreatectomy	2 (0.5)	0 (0)	2 (1)	0.5
Enucleation	21 (5)	15 (8)	8 (3)	0.2
Exploration/biopsy/bypass	36 (9)	19 (10)	17 (8)	0.5
Laparoscopy, yes	55 (13)	11 (66)	44 (20)	<0.001
Postoperative course				
Length of stay, d (range)	7 (1–144)	8 (1–42)	7 (1–144)	<0.001
Grade ≥III morbidity, yes, n (%)	148 (36)	67 (34)	81 (37)	0.5
Mortality, yes, n (%)	3 (1)	1 (0.5)	2 (1)	1

*Comparison was between the 2 periods, only in patients with available data.

Characteristics and management of patients initially managed nonoperatively

Characteristics of the 719 patients who were initially managed nonoperatively and had more than 6 months of radiographic follow-up are presented in Table 4. The median radiographic follow-up in this group of patients was 28 months (range 6 to 176 months), with 39% (n = 283) having more than 3 years of radiographic follow-up, 27% (n = 190) having more than 4 years, and 17% (n = 125) having more than 5 years. Compared with patients who were initially resected, patients followed radiographically were older at presentation (69 versus 63 years, $p < 0.001$), more likely to have a personal history of malignancy (45% versus 26%, $p < 0.001$), and less likely to have symptomatic lesions (symptomatic 28% versus 51%, $p < 0.001$). They had smaller lesions (median diameter 1.5 versus 3 cm, $p < 0.001$), without solid component (solid 32% versus 7%, $p < 0.001$) and without main pancreatic duct dilation (12% versus 40%, $p < 0.001$).

Operative approach and pathology of patients who underwent resection after having an initial radiographic surveillance period of more than 6 months

A total of 47 patients (47 of 719 [6.5%]) underwent resection after having an initial radiographic surveillance period of more than 6 months. The details of the operative procedure and pathologic examination of the resected lesions are summarized in Table 5. The median follow-up between initial visit and resection within this group of patients was 14 months (range 6 to 121 months). Characteristics of the patients and lesions that underwent delayed resection are

Table 3. Pathologic Examination of Lesions Resected Within 6 Months of Initial Visit (n = 422)

	1995–2010 (n = 422)	1995–2005 (n = 199)	2005–2010 (n = 223)	p Value*
Noninvasive IPMN, n (%)	114 (27)	33 (17)	81 (36)	<0.001
Serous cystadenoma, n (%)	98 (23)	68 (34)	30 (13)	<0.001
Adenocarcinoma, n (%)	60 (14)	25 (13)	35 (16)	0.4
Mucinous cystadenoma, n (%)	45 (11)	25 (13)	20 (9)	0.3
Pancreatic endocrine tumor, n (%)	27 (7)	11 (5)	16 (8)	0.4
Pseudocyst, n (%)	18 (4)	16 (8)	2 (1)	0.001
Solid pseudopapillary tumor, n (%)	8 (2)	4 (2)	4 (2)	1
Simple cyst, n (%)	28 (7)	11 (5)	18 (8)	0.6
Other, n (%)	24 (6)	7 (3)	17 (7)	0.1
Lesion at risk of malignant progression, yes, n (%)†	169 (52)	66 (40)	103 (64)	<0.001
Carcinoma including CIS, yes, n (%)	94 (23)	33 (17)	61 (28)	0.01

*Comparison was between the 2 periods, only in patients with available data.
†Excluding carcinoma and carcinoma in situ.
CIS, carcinoma in situ; IPMN, intraductal papillary mucinous neoplasm.

Table 4. Patient and Cyst Characteristics According to Initial Management

	Initially resected (n = 422)	Initially observed (n = 719)	p Value*
Male, n (%)	161 (38)	241 (34)	0.12
White, n (%)	371 (89)	655 (92)	0.056
Age at first presentation, y (range)	63 (15–90)	69 (21–95)	<0.001
Active smoker, yes, n (%)	52 (13)	38 (5)	<0.001
Personal history of malignancy, yes, n (%)	108 (26)	318 (45)	<0.001
Symptomatic, yes, n (%)	213 (51)	205 (28)	<0.001
Personal history of pancreatitis, yes, n (%)	47 (11)	37 (5)	<0.001
First presentation before 2005, n (%)	199 (47)	266 (37)	0.001
Initial visit size, mm (range)	30 (5–180)	15 (3–120)	<0.001
Location of the cyst, n (%)			
Head	182 (42)	358 (50)	<0.001
Body	102 (24)	205 (22)	
Tail	138 (33)	155 (22)	
Septation at initial visit, yes, n (%)	212 (60)	202 (38)	<0.001
Solid component at initial visit, yes, n (%)	110 (32)	36 (6)	<0.001
Calcium at initial visit, yes, n (%)	54 (18)	54 (11)	0.01
Radiologic evidence of main pancreatic duct dilation, yes, n (%)	71 (39)	45 (12)	<0.001
Radiologic evidence of main bile duct dilatation, yes, n (%)	20 (11)	17 (5)	0.006
Cyst fluid CEA >200 ng/mL*, n (%)	62 (61)	53 (35)	<0.001
Invasive test, FNA, and/or ultrasound endoscopy, n (%)	246 (58)	312 (43)	<0.001

CEA, carcinoembryonic antigen; FNA, fine-needle aspiration.
*Comparison was between the 2 periods, only in patients with available data.

presented in Table 6. Resection was performed for increasing cyst size (n = 35 [74%]), and/or suspicious cytology/fluid (n = 14 [30%]), and/or appearance of a solid component (n = 16 [35%]), and/or main pancreatic duct dilation (n = 4 [8.5%]). In 32% of patients (15 of 47) who underwent resection following initial surveillance, the operation occurred more than 24 months after the initial visit, in 23% (11 of 47) after 36 months, in 17% (8 of 47) after 48 months, and in 10% (5 of 47) after 60 months. Within the group of 15 patients with operations more than 2 years after initial visit, 2 had adenocarcinoma (lost to follow-up before surgery; operations 63 and 102 months after initial visit) and 9 had IPMN, including 3 with carcinoma in situ (operations 30, 39, and 67 months after initial follow-up). Within the group of 8 patients who had invasive carcinoma (8 of 719 [1.1%]), 6 underwent resection within 24 months of the initial visit except for the 2 patients who were lost to follow-up (operations at 63 and 102 months).

Recursive partitioning

Recursive partitioning was performed on the 885 patients who were evaluated for a pancreatic cyst during the last 5 years of the study period (2005 to 2010). The presence of a cyst smaller than 2 cm was the strongest predictor of initial nonoperative management (Fig. 3). Previously published recursive partitioning performed on the group of patients between 1995 and 2005 identified the presence of a solid component as the strongest predictor of initial operative management. The difference between the decision tree analyses over the 2 periods reflects the changing characteristics of the evaluated lesions. Over the last 5 years of the study, large numbers of patients were evaluated for very small lesions (<1 cm, n = 168 and <2 cm, n = 505), which were unlikely to have a solid component (2009, 16 of 198 [8%]; if cyst <2 cm, 6 of 121 [5%]; if cyst <1 cm, 1 of 51 [2%]). Because the characteristics that are of concern for malignancy (solid component, dilated duct, symptoms) were distinctly uncommon, size has become the only feature associated with treatment decision for the group as a whole.

Radiographic surveillance was recommended for 89% of all patients with lesions smaller than 2 cm. The likelihood that operative intervention would be recommended for a cyst smaller than 2 cm that had been initially selected for radiographic follow-up was 1.2% at 12 months, 4% at 36 months, and 6.3% at 60 months (Fig. 4). The risk of death from causes other than pancreatic cancer within the entire group of patients initially managed nonoperatively was approximately 20% at 5 years and 60% at 10 years (Fig. 4). The risk of death from pancreatic cancer within the entire group of patients initially managed nonoperatively was 2.5% at 5 years and 10% at 10 years. Within this group of

Table 5. Detail of Operative Procedure and Pathologic Examination for Patients Resected after Initial Surveillance (n = 47)

	n	%
Procedures		
Whipple	18	38
Distal pancreatectomy	5	11
Distal pancreatectomy with splenectomy	15	32
Enucleation	3	6
Derivation	2	0.5
Exploration/biopsy	2	0.5
Laparoscopy, yes	5	11
Pathologic examination		
Intraductal papillary mucinous neoplasm, noninvasive	21	45
Adenocarcinoma	8	17
Serous cystadenoma	5	11
Pancreatic endocrine tumor	4	8
Mucinous cystadenoma	3	6
Pseudocyst	2	4
Other	4	8
Malignant not including CIS, yes	12	25

CIS, carcinoma in situ.

patients initially managed nonoperatively, 14 died of pancreatic adenocarcinoma. These 14 patients included 9 patients who presented with a cystic lesion and pancreatic cancer that did not undergo exploration because the lesions were unresectable at presentation or because of patient comorbidities. The remaining 5 deaths (5 of 719 [0.7%]) were in patients explored after 6 months of follow-up: 2 underwent pancreaticoduodenectomy and 3 underwent bypass or exploration.

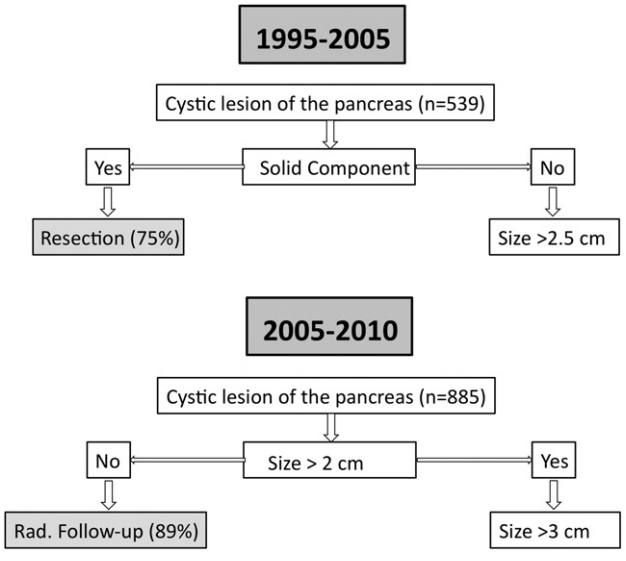

Figure 3. 1995–2005: first and second node of decision tree analysis for the selection of initial operative management in the 539 patients evaluated for a pancreatic cyst. 2005–2010: first and second node of decision tree analysis for the selection of initial operative management in the 885 patients evaluated for a pancreatic cyst from 2005 to 2010. Rad, radiographic.

Table 6. Characteristics of Patients Who Underwent Resection During Surveillance (n = 47)

Characteristic	
Symptomatic, yes, n (%)	21 (45)
Personal history of pancreatitis, yes, n (%)	9 (19)
First presentation before 2005, n (%)	23 (49)
Age at first presentation, y (range)	64 (35–83)
Location of the cyst, n (%)	
Head	25 (53)
Body	10 (21)
Tail	12 (25)
Initial visit cyst size, mm (range)	20 (5–95)
Final visit cyst size, mm (range)	25 (15–125)
Percentage increase in cyst size, % (range)	34 (7–61)
Size increase, yes, n (%)	34 (72)
Solid component at initial visit, yes, n (%)	2 (7)
Solid component at final visit, yes, n (%)	17 (36)
Follow-up, mo (range)	48.1 (8–164)

DISCUSSION

The data presented in this study further demonstrate the challenge facing the medical and surgical community in managing patients with cystic lesions of the pancreas. This report documented a dramatic increase in the annual number of patients evaluated at MSKCC for a pancreatic cyst over the 15-year study period (198 patients evaluated in 2009). As the time period progressed, these lesions were more likely to be incidentally discovered (more than two-thirds incidentally discovered in 2009), smaller in size (median size 1.6 cm in 2009), and less likely to harbor concerning features for malignancy such as a solid component (<10% with solid component in 2009). Initial management of these lesions also evolved over the study period, with fewer patients undergoing initial operative management (1995 to 2005 43% versus 2005 to 2010 33%) and fewer benign lesions being resected (1995 to 2005 34% of resected lesions serous cystadenoma versus 2005 to 2010 13%). Despite these trends, patients with high-risk lesions (carcinoma or high-grade dysplasia) comprised 23% of the lesions initially resected and approximately 2% of those initially observed. Thus, patients with cystic lesions of the pancreas should be considered a *high-risk* group for pancreatic cancer, and careful selection of operative versus nonoperative management is essential.

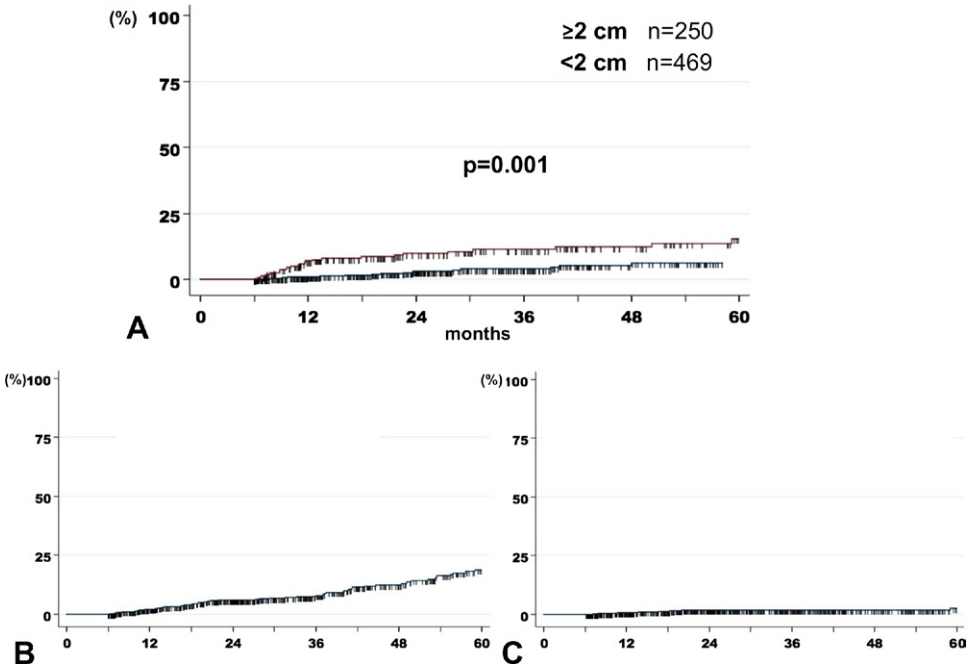

Figure 4. (A) Likelihood of resection in patients initially followed radiographically (n = 719) according to whether the cyst was <2 cm or ≥2 cm at initial presentation (Kaplan-Meier method). (B) Risk of death from causes other than pancreatic cancer. (C) Risk of death from pancreatic cancer in those patients initially selected for nonoperative management (Kaplan-Meier method).

Clinical decision making for these patients has been hampered by the inability to obtain accurate histologic diagnosis without operative resection, and many have recommended routine resection because of this limitation. The imaging characteristics of the most common benign (serous) and premalignant (mucinous) lesions have been described; however, studies have shown that CT is discriminatory in only approximately 40% of cases.[14,15] Even when a cystic lesion can be radiographically defined as mucinous, the ability to discriminate dysplasia within a given lesion is limited to radiographic criteria such main duct dilation or cyst size, which are accurate for high-grade dysplasia or invasive disease in approximately 50% of cases.[16,17] When a radiographically equivocal lesion is identified, EUS with FNA may be performed. EUS provides the ability to obtain detailed ultrasound images of the pancreas and evaluate the cyst fluid. EUS imaging alone, however, has limited accuracy[18] and a high degree of interobserver variability.[19] Cyst fluid analysis and cytology have shown mixed results, with the single best test for discriminating between serous and mucinous lesions being the level of cyst fluid carcinoembryonic antigen (CEA), which is accurate for a mucinous lesion in approximately 80% of cases when higher than 200 ng/mL.[20] Cyst fluid CEA, however, has not been shown to be a reliable marker for dysplasia or carcinoma within the mucinous group.[21]

Because of these diagnostic limitations, there is no consensus as to which tests are necessary to evaluate a cystic lesion of the pancreas. The diagnostic guidelines of the American College of Gastroenterology[22] regarding small cysts (<2 cm) or very small cysts (<5 mm) remain vague. Multidetector CT, which is widely available, remains the primary imaging modality and was performed in nearly every patient evaluated in the present series. CT imaging should be contrast-enhanced triphasic, with thin cuts through the pancreas (2.5-mm section reconstructed to 1.25 mm). MRI may provide improved assessment of communication with the ductal system when compared with multidetector CT,[23,24] but its clinical advantage and cost effectiveness compared with multidetector CT remain unknown. MRI does not expose the patient to radiation, which may be a concern in a young patient who is to be followed radiographically for a prolonged period of time. Invasive procedures such as EUS and FNA are now associated with a very low morbidity[25] and were used in approximately one-half of the patients evaluated in our series. Selective use of EUS has been recommended by others as the most cost-effective strategy in the evaluation of radiographically equivocal and asymptomatic cysts.[26]

We generally use EUS FNA for radiographically equivocal lesions (2 to 3 cm in diameter, some characteristics of serous) when additional information is desired before rec-

ommending a specific treatment approach. We have found the most reliable information from EUS to be for the evaluation of a mass lesion/solid component and the determination of cyst fluid CEA level. When a significant solid lesion or mass component is noted on EUS, and the lesion is not consistent with a serous cyst, then resection is typically recommended. A cyst fluid CEA level >200 ng/mL is highly predictive of a mucinous lesion, and a level of 0 ng/mL is strongly suggestive of a serous lesion when imaging is also consistent.[18] Asymptomatic serous lesions are typically followed, and mucinous lesions of the IPMN subtype are typically resected if the main duct is dilated or if the branch duct lesion is greater than 2.5 to 3.0 cm in diameter.

EUS is not necessary in many cases because a variety of radiographic criteria have been proposed for clinical decision making.[27-29] Some of these criteria have been proposed for cystic lesions in general, and some have been proposed specifically for the premalignant group of mucinous cysts. Regardless, most studies have found that the presence of main duct dilation, a solid component within or adjacent to the lesion, biliary dilation, symptoms, and large cyst (>2.5 to 3 cm) to be factors associated with high-grade dysplasia or invasive disease, and operative resection should be generally recommended.[9,30-33] When these factors are absent, most reports have suggested the risk of an invasive lesion to be less than 1%.[9]

Between 2005 and 2010, the majority of patients evaluated at our institution for a cystic lesion of the pancreas presented with an asymptomatic lesion that was smaller than 2 cm in size, without solid component or main pancreatic ductal dilation. When decision tree analysis was performed, cyst size smaller than 2 cm was the single factor most associated with treatment decision, and 89% of patients with a lesion smaller than 2 cm were followed radiographically. It should be emphasized, however, that size alone was not the only factor associated with treatment recommendations and that 11% of patients with lesions smaller than 2 cm were resected. Factors such as dilation of the pancreatic or bile duct or the presence of a mass component must also be considered and would generally favor resection when present. These latter findings are becoming less common as lesions are identified at a smaller size; in the last 5 years of the study period, a solid component or dilation of the main pancreatic duct was identified in fewer than 10% of all patients evaluated.

In the current study, there were 719 patients who were initially placed into radiographic surveillance and had more than 6 months of radiographic follow-up. With a median follow-up of 28 months, 47 patients (6.5%) underwent resection, and 8 of these patients had pancreatic cancer at the time of resection (8 of 719 [1%]). The risk of developing pancreatic cancer within this group of patients was identical to the risk of operative mortality in the group of 422 patients who underwent initial resection (1%). In addition, within the group of patients initially selected for radiographic follow-up, pancreatic cancer was a minor cause of mortality at both 5 and 10 years from the time of identification of the cyst. The risk of non–pancreatic cancer mortality was 20% at 5 years and 60% at 10 years (risk of death from pancreatic cancer 2.5% at 5 years, 10% at 10 years). We are aware that these findings may be more pronounced within our cohort because they reflect the population of a cancer center. However, the presence of extrapancreatic malignancy in patients with cystic lesions of the pancreas (mainly IPMN) has been reported by others.[34-37] Bose and colleagues[36] reported that 78% of incidental pancreatic cystic lesions were identified during interpretation of a CT scan performed for staging of a nonpancreatic malignancy. Additional patient factors such as age and comorbidity must be considered when one is considering operative resection for an incidentally discovered cystic lesion of the pancreas.

As the evaluated lesions became smaller in size, and more likely to be incidentally detected, the likelihood of resection also decreased. During the last 5 years of the study period, the percentage of patients initially resected decreased from 43% to 33%. The most common histopathologic diagnosis also changed over the 15-year time period. Resection of serous cystadenoma accounted for a minor percentage (1995 to 2005 34% versus 2005 to 2010 13%) of cystic lesions resected over the most recent 5 years, with noninvasive IPMN being the most common histopathology to be resected (1995 to 2005 17% versus 2005 to 2010 38%). This change most likely represents an increased ability to identify serous lesions radiographically as well as a general acknowledgment that these lesions are benign and do not warrant resection, except in the presence of symptoms or possibly when large and/or marginally resectable lesions arise in a young patient. The relative increase in IPMN also likely represents an increased ability to identify these premalignant lesions both radiographically and with cyst fluid CEA, as well as our desire to resect these lesions before the development of invasive disease.

When radiographic surveillance is recommended, our general approach has been to perform imaging every 6 months for 2 years and then to perform annual imaging thereafter. This approach requires long-term commitment from both the patient and physician, with a willingness to commit to long-term imaging and assessment. When patients live in parts of the country, or world, where routine surveillance is not feasible or when they are unwilling to

commit to this approach, operative resection may be warranted. This is particularly true for patients in which a known mucinous cyst has been documented. Imaging should be pancreatic dedicated contrast enhanced (either CT or MRI). Interpretation of this imaging by dedicated radiologists is essential, and discussion of equivocal lesions within a multidisciplinary framework is highly recommended. Careful discussion of the risks of both approaches, operative and surveillance, should be performed before agreement on an informed treatment/surveillance decision.

In summary, the data presented in this study further demonstrated the increasing number of patients being identified with asymptomatic cystic lesions of the pancreas. Over the past 15 years, the patients evaluated at MSKCC have presented with lesions that are smaller and less likely to be symptomatic. These lesions are less likely to present with concerning radiographic features of malignancy such as a solid component or ductal dilation. Patients selected for radiographic surveillance were generally older patients with greater comorbidities (personal history of malignancy) who presented with small (<2 cm) asymptomatic cysts. With a median follow-up of 28 months, patients selected for initial surveillance had a 6.5% likelihood of developing changes that prompted resection and 1% chance of developing pancreatic malignancy. The risk of operative mortality within the group of patients who underwent initial resection was 1%. With the dramatic increase in the number of patients identified with incidentally discovered cysts smaller than 2 cm, the clinical challenge will be to further refine these recommendations for patients with premalignant mucinous lesions and to determine which imaging should be performed in those undergoing surveillance, over what time period, and how frequently it should be obtained.

Author Contributions

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Analysis and interpretation of data: Brennan, Gonen, D'Angelica, DeMatteo, Fong, Schattner, DiMaio, Janakos, Jarnagin, Allen

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Discussion

DR JOHN L CAMERON (Baltimore, MD): Congratulations on an excellent presentation of a very important database. Intraductal papillary mucinous neoplasms (IPMN) have been recognized by many of us in many institutions since the early 1980s as unusual mucinous tumors, but it wasn't really until 1984 that they were catalogued and categorized and given the name *intraductal papillary mucinous neoplasm.*

In the manuscript, there's a comparison between the first time period, 1995 to 2005, and then 2005 to the present with management of cystic lesions. During the first time period, many of the lesions resected were serous cystadenomas. I think we all agree now that small, asymptomatic, nonenlarging serous cystadenomas can be followed. But the second time period, the last 5 years, IPMNs have been the focus. Most of us have accepted the Tanaka criteria for deciding which of these IPMNs to follow and which to resect.

The Tanaka criteria were established in Sendai, Japan, in 2004, and they were published in 2006. I think most of us, including the Memorial group, have pretty much followed these criteria as indications of which of these many IPMNs that we're all seeing should be resected. The criteria, of course, are if the pancreatic duct is increased to 5 mm or greater, it's a main duct IPMN and should be resected. If the lesion is symptomatic, whether it's main duct or branch duct, it should be resected. And if it's a branch duct, a cystic lesion, if it has a solid component, or is more than 3 cm in diameter, it should be resected.

I would like to ask 2 questions. First, we have resected more than 400 IPMNs, and we find no correlation between the size of a branch duct lesion and malignancy. The other criterion, if there's an increased pancreatic duct diameter of 5 mm, there's a 60% incidence of malignancy. If there's a mural nodule in a cystic lesion, it has a 60% chance of being malignant, or if it's symptomatic, it probably has a 30% chance of being malignant.

But when we look at size alone, we have branch ducts of 6 and 7 cm without a malignancy. In fact, we don't have a single branch duct cystic lesion just on size alone that was malignant. So I would like to ask Dr Allen whether size alone, without any other criteria, resulted in finding malignancy in the lesion.

The second question is, in their series, it appears that of those IPMNs that they followed, particularly in the last 5 years, 28% were symptomatic, 6% had a solid component in the cyst, and 12% had an associated increase in pancreatic diameter of 5 mm or greater. Why did they decide to follow those lesions when they met the Tanaka criteria for resection? And did any of the 8 patients who ended up having cancer, who initially were followed, fall into that group?

Their mean follow-up was just about 2 years. I think the best data suggest that from the time of diagnosis with imaging of an IPMN that's not malignant, they all have the potential to become malignant. For those that become malignant, it takes at least 6 or 8 years and perhaps as many as 10 or 12 years for that evolution. So obviously, this early report with this length of follow-up, is just the beginning, and is not long enough to really determine the natural history of IPMNs.

The second thing is, the end point should not be the development of pancreatic cancer. We should be resecting these lesions when they