Should Patients With Cystic Lesions of the Pancreas Undergo Long-term Radiographic Surveillance?

Results of 3024 Patients Evaluated at a Single Institution

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Objective: In 2015, the American Gastroenterological Association recommended the discontinuation of radiographic surveillance after 5 years for patients with stable pancreatic cysts. The current study evaluated the yield of continued surveillance of pancreatic cysts up to and after 5 years of follow up.

Methods: A prospectively maintained registry of patients evaluated for pancreatic cysts was queried (1995–2016). Patients who initially underwent radiographic surveillance were divided into those with <5 years and ≥5 years of follow up. Analyses for the presence of cyst growth (>5 mm increase in diameter), cross-over to resection, and development of carcinoma were performed.

Results: A total of 3024 patients were identified, with 2472 (82%) undergoing initial surveillance. The ≥5 year group (n = 596) experienced a greater frequency of cyst growth (44% vs. 20%; $P < 0.0001$), a lower rate of cross-over to resection (8% vs 11%; $P = 0.02$), and a similar frequency of progression to carcinoma (2% vs 3%; $P = 0.07$) compared with the <5 year group (n = 1876). Within the ≥5 year group, 412 patients (69%) had demonstrated radiographic stability at the 5-year time point. This subgroup, when compared with the <5 year group, experienced similar rates of cyst growth (19% vs. 20%; $P = 0.95$) and lower rates of cross-over to resection (5% vs 11%; $P < 0.0001$) and development of carcinoma (1% vs 3%; $P = 0.008$). The observed rate of developing cancer in the group that was stable at the 5-year time point was 31.3 per 100,000 per year, whereas the expected national age-adjusted incidence rate for this same group was 7.04 per 100,000 per year.

Conclusion: Cyst size stability at the 5-year time point did not preclude future growth, cross-over to resection, or carcinoma development. Patients who were stable at 5 years had a nearly 3-fold higher risk of developing cancer compared with the general population and should continue long-term surveillance.

Keywords: intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, pancreas, pancreas cyst, pancreatic ductal adenocarcinoma, resection, serous cystadenoma, surveillance

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Cystic neoplasms of the pancreas represent an increasingly common radiographic diagnosis. The rising incidence of these lesions is due in large part to improvements in abdominal imaging that allow the diagnosis of small asymptomatic cysts.[1] As the population of patients with asymptomatic pancreatic cystic neoplasms continues to grow, new questions arise regarding appropriate long-term management of these patients. Although it was once deemed prudent to resect all such lesions given the risk of malignancy, studies demonstrating the safety of a selective approach to resection have led to a paradigm shift with respect to the care of these patients.[2,3] Currently, a selective approach to resection has been accepted as the standard of care for management of incidentally discovered pancreatic cysts without features concerning for malignancy.[4,5]

The adoption of a selective approach to resection directly translates to greater numbers of patients undergoing radiographic surveillance of their pancreatic cysts. Clinicians now face the question of how long to continue surveillance in this population. In 2015, the American Gastroenterological Association (AGA) published guidelines for the management of asymptomatic pancreatic cysts, in which a recommendation was made that radiographic surveillance could be discontinued after 5 years of follow up for patients with stable cysts because it was felt that these patients did not carry significant future risk of progression to malignancy.[6] However, the authors also acknowledged the dearth of published evidence in support of this recommendation, and identified this as an area that would benefit from additional study.[7] Although several groups have evaluated the outcomes of long-term surveillance of cystic pancreatic neoplasms, the results of these studies have been inconsistent and the sample size of many of these studies has been relatively small.[8,9]

The purpose of this study was to review our institutional database of patients evaluated for pancreatic cysts over the past 20 years. We hypothesized that patients with pancreatic cystic neoplasms represent a high-risk group when compared with the general population – including those patients who were radiographically stable at 5 years. Given that a significant number of these lesions represent intraductal papillary mucinous neoplasms (IPMN)—a premalignant neoplastic process—we hypothesized that the risks of cyst growth, cross-over to resection, and progression to pancreatic carcinoma would remain present over time.

METHODS

Patient Selection

A prospectively maintained database containing patients with radiographic evidence of pancreas cysts and who were evaluated for the ICD9 (577.2) and ICD10 (K86.2) codes for pancreas cyst was

queried for all patients between January 1995 and July 2016. These patients were then divided into an ''initial resection'' group, defined as those patients who underwent resection within 6 months of the first radiographic assessment, and an ''initial surveillance'' group, which contained the remainder of the patients. Information regarding demographics, presenting symptoms, and pertinent medical history was collected for all patients.

Patients Within Initial Surveillance Group

Patients in the initial surveillance group were divided into 2 groups based on the length of their radiographic follow up, defined by the number of months between the first and last radiographic assessment. Those patients followed for <5 years were compared with those patients followed for ≥5 years to determine differences in the proportions of each group with respect to cyst growth, cross-over to operation, and the development of pancreatic carcinoma—including pancreatic ductal adenocarcinoma (PDAC), colloid carcinoma, and carcinoma-in-situ (CIS) diagnosed either at resection or via biopsy. Cyst growth was defined as an increase in maximal cyst diameter of >5 mm. Secondary analyses included demographics and presence of presenting symptoms.

Determining 5-year Stability

The AGA's recommendation to discontinue surveillance after 5 years focused mainly on patients with stable cysts; we therefore targeted this group in our analyses. Patients within the group who had ≥5 years of follow up were further stratified by the detection of cyst progression at, or before, the 5-year time point. Patients who had not experienced cyst growth before 5 years of follow up were categorized as ''stable at 5 years''. These patients were compared with the <5 years follow-up group for radiographic progression, cross-over to operation, and development of pancreatic carcinoma.

Statistical Analysis

Comparisons between follow-up groups for associations between the length of follow up and specific patient and treatment factors were analyzed with a Wilcoxon rank sum test for continuous variables and a Fisher exact test for categorical variables. Observed-to-expected ratios for development of carcinoma were calculated for different subgroups based on the number of patients with PDAC, CIS, or colloid carcinoma. Expected cancer rates for comparison were calculated by using the age-specific incidence rates from the SEER database, corresponding to the age distribution of the patients in our cohort. Cumulative incidence graphs were created for patients who crossed-over to operation or developed carcinoma.

RESULTS

Patient Demographics, Cyst Characteristics, and Diagnostic Studies

Between 1995 and 2016, 3024 patients were identified who had been evaluated at our institution for a cystic lesion of the pancreas (Fig. 1). Patient and cyst characteristics are summarized in Table 1. Patients were predominantly female (n = 1911; 63%), and the median age was 66 years (range: 9–95 years). Twenty-seven percent were considered to be symptomatic at the time of presentation (n = 814), whereas 8% had a history of pancreatitis before identification of the cyst(s) (n = 257). The median initial cyst diameter was 1.6 cm (range: 0.1–23 cm) and the median final cyst diameter was 1.8 cm (range: 0–19.8 cm).

Radiographic assessment included CT imaging in 2701 patients (89%), whereas magnetic resonance imaging (MRI) was performed in 2212 patients (73%). Sixty-four percent of the patients underwent both computed tomography (CT) scan and MRI during surveillance (n = 1934). Endoscopic assessment was performed in 1685 patients (56%), endoscopic ultrasound in 1506 patients (50%), and fine needle aspiration (FNA) in 1290 patients (43%). A quarter of the patient cohort, representing 46% of those undergoing endoscopic ultrasound, had cyst fluid sent for carcinoembryonic antigen measurement (n = 688; 23%).

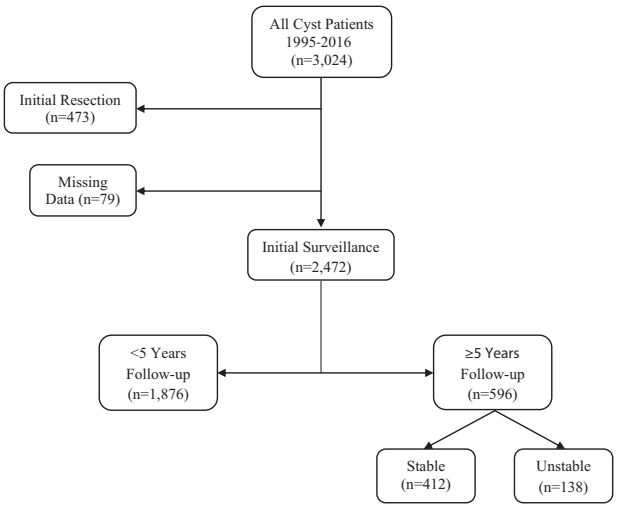

FIGURE 1. Patient Selection Criteria.

Management Recommendations

Initial operative resection was recommended for 473 of the 3024 patients evaluated (16%). Radiographic follow up could not be accurately determined in 79 patients, and these patients were excluded. The remaining patients (n = 2472) were placed in the initial surveillance category (Fig. 1). This cohort was predominantly female (n = 1568, 63%) and had a median age of 67 years (range: 15–95 years) (Table 2). The median length of radiographic follow up was 2.2 years (range: 0.0–21.5 years). Median initial cyst diameter was 1.5 cm (range: 0.1–16.0 cm), with a median cyst diameter

TABLE 1. Patient, Cyst, and Diagnostic Characteristics of the 3024 Patients Evaluated for Pancreas Cysts Between 1995 and 2016

Characteristic	Total (n = 3024)
Median age at presentation, yrs (range)	66 (9–95)
Sex, female, n (%)	1911 (63)
Symptomatic at diagnosis, yes, n (%)	814 (27)
History of pancreatitis, yes, n (%)	257 (8)
Median initial diameter, cm (range)	1.6 (0.1–23.0)
Median final diameter, cm (range)	1.8 (0.0–20.0)
Median change in diameter, cm (range)	0.1 (−13.0–9.3)
CT scan, n (%)	2701 (89)
MRI, n (%)	2212 (73)
CT and MRI, n (%)	1934 (64)
Endoscopy, n (%)	1685 (56)
EUS, n	1506 (50)
FNA, n	1290 (43)
Cyst fluid CEA, yes, n (%)	688 (23)

CEA indicates carcinoembryonic antigen; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; MRI, magnetic resonance imaging.

TABLE 2. Characteristics of Patients Initially Undergoing Surveillance (n = 2472)

Characteristic	Total (n = 2472)	<5 Years (n = 1876)	≥5 Years (n = 596)	*P*
Median age at presentation, yrs (range)	67 (15–95)	67 (15–95)	66 (31–88)	0.19
Sex, female, n (%)	1568 (63)	1180 (63)	388 (65)	0.35
Symptomatic at diagnosis, yes, n (%)	552 (22)	434 (23)	118 (20)	0.09
History of pancreatitis, yes, n (%)	183 (7)	145 (8)	38 (6)	0.32
Median follow up, yrs (range)	2.2 (0.0–21.5)	1.4 (0.0–5.0)	7.1 (5.0–21.5)	<0.0001
Median initial diameter, cm (range)	1.5 (0.1–16.0)	1.5 (0.1–16.0)	1.4 (0.2–12.8)	0.04
Median final diameter, cm (range)	1.7 (0.0–14.0)	1.6 (0.0–14.0)	1.8 (0.0–11.5)	<0.0001
Median change in diameter, cm (range)	0.1 (−12.0–9.3)	0.1 (−12.0–9.3)	0.5 (−6.0–8.7)	<0.0001
Increase in cyst size, yes, n (%)	619 (25)	357 (20)	262 (44)	<0.0001
Cross-over to Resection, yes, n (%)	262 (11)	214 (11)	48 (8)	0.02
Procedure, n (%)				
Whipple	97 (37)	79 (37)	18 (38)	
Distal pancreatectomy/splenectomy	85 (32)	67 (31)	18 (38)	
Distal pancreatectomy	28 (11)	26 (12)	2 (4)	
Enucleation	18 (7)	15 (7)	3 (6)	
Other	34 (13)	27 (13)	7 (15)	
Pathology, n (%)				
IPMN	110 (52)	88 (51)	22 (58)	
SCA	30 (14)	24 (14)	6 (16)	
MCN	27 (13)	21 (12)	6 (16)	
Pseudocyst	4 (2)	4 (2)	0 (0)	
Retention	16 (8)	14 (8)	2 (5)	
Other	25 (12)	23 (13)	2 (5)	
Carcinoma including CIS, yes, n (%)	73 (3)	62 (3)	11 (2)	0.07
Carcinoma type, n (%)				
PDAC	55 (75)	48 (77)	7 (64)	
Resected, n	25	22	3	
Unresected, n	30	26	4	
Colloid	3 (4)	2 (3)	1 (9)	
CIS	15 (21)	12 (19)	3 (27)	

CIS indicates carcinoma-in-situ; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PDAC, pancreatic ductal adenocarcinoma; SCA, serous cystadenoma.

change of 0.10 cm (range: −12.0–9.3 cm). Among patients undergoing surveillance, 25% experienced cyst growth (n = 619) during follow up. Operative resection was performed for 262 patients (11%). During follow up, 3% of all patients initially selected for surveillance developed pancreatic carcinoma or CIS (n = 73). Forty-one percent of the patients found to have carcinoma (n = 30) were diagnosed without resection. Alternative methods of diagnosis included: positive PET scan; imaging suggestive of unresectable disease; malignancy on FNA, core, or brush biopsy; and metastatic disease identified during diagnostic laparoscopy prior to planned resection.

Within the initial surveillance cohort, there were 1876 patients (76%) who had been followed for <5 years, whereas 596 patients (24%) had been followed for ≥5 years. Patients followed for ≥5 years had twice the proportion of patients with clinically significant cyst growth (n = 262; 44%) compared with the patients followed for <5 years (n = 357; 20%, $P < 0.0001$). When rates of cross-over to resection were compared, 8% of the patients followed ≥5 years underwent operation (n = 48), whereas 11% of patients followed for <5 years were resected (n = 214, $P = 0.02$). Pancreatic cancer developed in 11 patients (2%) in the ≥5 years group, and in 62 patients (3%, P = 0.07) in the <5 years group. At the time of our analysis, overall mortality for the patients followed <5 years was 13% (n = 235), whereas it was 9% (n = 55) for those followed ≥5 years. Approximately 1% of the <5 year group (n = 26) and <1% of the ≥5 year group (n = 4) had died from pancreatic cancer at the time of last follow up.

To evaluate our hypothesis that patients with 5 years of stability may still have risk of progression, the cohort of patients followed for ≥5 years was subdivided into those whose cyst(s) were stable at the 5-year time point, and those who had experienced growth before the 5 year time point. Stability at the 5 year time point was experienced by 412 of the 596 patients who had ≥5 years of follow up (69%). Table 3 outlines patient characteristics for this group of patients. This cohort was predominantly female (n = 276; 67%) and had a median age of 66 years (range: 31–88 years). Median radiographic follow up was 7.2 years (range: 5–16 years). Radiographic growth was identified in one-fifth of these patients (n = 80; 19%), 20 patients (5%) crossed-over to resection (n = 20), and 1% of these patients (n = 4) developed carcinoma.

Comparison between patients with ≥5 years of follow-up who were stable at the 5 year time point and patients with <5 years of follow-up did not demonstrate a statistically significant difference in the proportion of patients that experienced clinically significant cyst growth (19% vs. 20%; $P = 0.95$). Rates of cross-over to resection were significantly lower in the patients with initial 5-year stability compared with the patients followed for less than 5 years (5% vs. 11%; $P < 0.0001$). In addition, the patients with initial 5-year stability had a lower rate of developing carcinoma when compared with the patients followed for <5 years (1% vs 3%; $P = 0.008$). Table 4 provides a side-by-side outline of these comparisons.

Risk Assessment of Initially Stable Group

To determine the risk of our cohort in comparison to the general population, the estimated incidence of developing carcinoma was calculated and compared with the national ratio of 12.4 per 100,000 per year, and to age-specific incidence rates calculated from the SEER database.[10] We calculated incidence rates for pancreatic ductal adenocarcinoma only, as the national incidence rates only take

TABLE 3. Characteristics of Patients with Stable Cysts for the First 5 Years of Surveillance (n = 412)

Characteristic	Total (n = 412)
Median age at presentation, yrs (range)	66 (31–88)
Sex, female, n (%)	276 (67)
Symptomatic at diagnosis, yes, n (%)	83 (20)
History of pancreatitis, yes, n (%)	31 (8)
Median follow up, yrs (range)	7.2 (5.0–16.4)
Median initial diameter, cm (range)	1.4 (0.2–12.0)
Median final diameter, cm (range)	1.5 (0.0–11.5)
Median change in diameter, cm (range)	0.15 (−6.00–3.20)
Increase in cyst size, yes, n (%)	80 (19)
Cross-over to resection, yes, n (%)	20 (5)
Pathology, n (%)	
IPMN	12 (67)
MCN	4 (22)
Retention cyst	1 (6)
SCA	1 (6)
Carcinoma including CIS, yes, n (%)	4 (1)
Carcinoma type, n (%)	
PDAC	1 (17)
Colloid	1 (17)
CIS	2 (33)

CIS indicates carcinoma-in-situ; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PDAC, pancreatic ductal adenocarcinoma; SCA, serous cystadenoma.

into consideration invasive pancreas cancer. Colloid carcinoma and CIS were excluded from our calculations. The estimated incidence of developing cancer based on the number of patients in the initial surveillance cohort who developed carcinoma was 700 per 100,000 per year. The expected national incidence rate corresponding to the age distribution of this cohort was 45.8 per 100,000 per year. Patients followed for ≥5 years have an observed rate of 151 per 100,000 per year, whereas the expected national incidence rate was 10.6 per 100,000 per year. The observed rate of developing cancer in the group that was followed for ≥5 years and were stable at the 5 year time point was 31.3 per 100,000 per year, with an expected incidence rate of 7.04 per 100,000 per year.

To evaluate the ongoing risk of cross-over to resection and the development of carcinoma, cumulative incidence rates were calculated and graphed (Fig. 2). The cumulative incidence of developing carcinoma, including CIS, plateaued at nine years. Interestingly, cumulative incidence of cross-over to resection never reached a plateau. Review of those patients resected after the nine year time point demonstrated that they underwent resection primarily for an increase in cyst diameter to greater than 3 cm. Each curve had similar numbers of patients at risk at each time point.

DISCUSSION

The recommendation by the American Gastroenterological Association to cease radiographic surveillance after 5 years in patients with radiographically stable cystic lesions of the pancreas was contrary to typical surgical practice, and has prompted a great deal of debate regarding appropriate duration of radiographic surveillance in these patients.[6,7] Given that many of these patients have a pre-cancerous neoplastic process (IPMN), we hypothesized that the risk of progression would not disappear simply because malignancy had not developed within 5 years.

The current study presents the outcomes of greater than 3,000 patients diagnosed with pancreatic cysts. Patients initially assigned to radiographic surveillance were found to experience cyst growth nearly a third of the time, demonstrating an 11% rate of cross-over to resection, and a 3% rate of carcinoma development with a median follow up of just over 2 years. When our cohort was separated by length of follow-up, those patients who had 5 years of radiographic stability still had evidence of future growth, cross-over to resection, and carcinoma development. The observed rate of cancer development in this sub-group was nearly 6 times greater than what would be expected in the general population (age-adjusted). Although the rates of carcinoma development and cross-over to resection decreased during our follow-up period, the fact that patients continued to progress to carcinoma or resection suggests that long-term surveillance is warranted.

The results of the current study are similar to previously published reports from our database and from others. In a 2006 study, we previously reported an 8% rate of cross-over to resection and a 2% rate of cancer development, and in 2011 we reported on a cohort that experienced a 7% rate of cross-over to resection and a 1.1% rate of developing pancreatic carcinoma.[2,11] Studies from other centers have also presented data that would suggest a need for continued radiographic surveillance. A study from Crippa et al[12] evaluating a cohort of 144 patients who were followed for a median duration of 86 months found that 26 of 144 patients developed worrisome features and high risk stigmata. Nineteen of these 26 patients had stable cysts before development of worrisome features or high risk stigmata, eight patients underwent resection, and 5 patients were found to have pancreatic carcinoma or carcinoma-in-situ. Del Chiaro et al[13] presented a cohort of 395 patients undergoing surveillance of their pancreatic cysts, with 14% crossing-over to resection during follow-up, and a 26% cumulative risk for surgery at 5 years, and a 72% estimated risk of surgery at 10 years.

Several groups have attempted to identify a subpopulation of cyst patients in which follow up could be discontinued after 5 years, but none of these studies have had sufficient power to be conclusive. For example, Kwong et al reported on a cohort of 310 patients with pancreas cysts followed for greater than 5 years. Within this group, they identified a 0% rate of pancreas carcinoma in the 212 patients who did not have high-risk features at the 5-year mark.[14] This is not surprising, as the patients with the fewest risk features should, by definition, be low-risk. We hypothesize that such patients are still at risk after the 5-year time point, and that longer-term follow up is needed.

TABLE 4. Cyst Growth, Crossover to Resection, and Progression to Carcinoma by Length of Radiographic Follow Up

Characteristic	<5 Years (n = 1876)	≥5 Years (n = 596)	≥5 Years and Stable (n = 412)	P*	P†
Increase in cyst size, yes, n (%)	357 (20)	262 (44)	80 (19)	<0.0001	0.95
Cross-over to resection, yes, n (%)	214 (11)	48 (8)	20 (5)	0.02	<0.0001
Carcinoma including CIS, yes, n (%)	62 (3)	11 (2)	4 (1)	0.07	0.008

*Comparison between <5 years with ≥5 years.
†Comparison between <5 years with ≥5 years and stable.

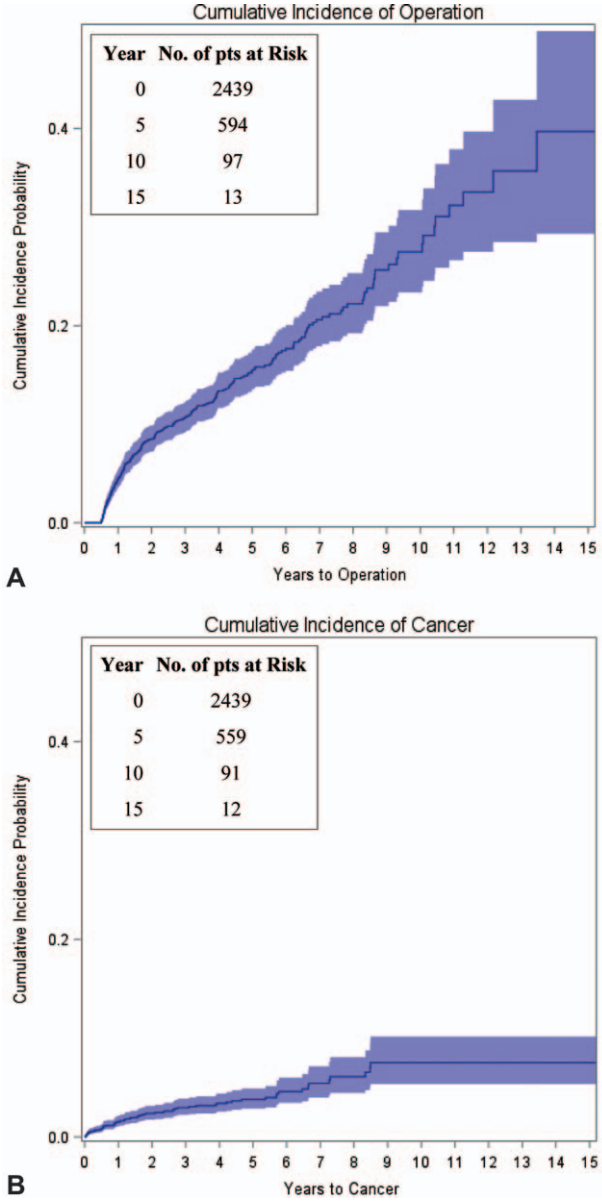

FIGURE 2. Cumulative incidence of progression to cancer and cross-over to resection. A, Cumulative incidence of cross-over to resection. B, Cumulative incidence of progression to carcinoma.

Many would argue that for routine screening of asymptomatic and average risk patients to be worthwhile, the screening test should be affordable and demonstrate a decrease in mortality of the screened population. Examples of this include mammography for breast cancer, colonoscopy or sigmoidoscopy for colorectal cancer, and the Papanicolau test for cervical cancer—all of which have been associated with decreased disease-specific mortality.[15] Mammography is generally recommended biennially from ages 40 to 74 years, a surveillance period of 35 years. Similarly, cervical cancer screening is typically recommended every 3 years over a 45 year span, from ages 21 to 65 years, and colorectal screening is recommended over a 25 year period, from ages 50 to 75, with varying frequency based on the chosen screening test.[16] These recommendations for long periods of surveillance are targeted to an asymptomatic population without known precursor lesions and presumed average risk. However, patients with known high-risk precursor lesions also benefit from enhanced screening/surveillance programs that are generally not discontinued. Some examples include endoscopic surveillance of patients with Barrett's esophagus, colonoscopy for patients with inflammatory bowel disease, and increased frequency of mammography in patients with pathological evidence of lobular carcinoma in-situ. All of these surveillance recommendations are accompanied by recommendations for aggressive surgical intervention at the earliest sign of progression to cancer.[17–19]

We believe that the results of this study suggest that patients with cystic lesions of the pancreas represent a high-risk group. Many of these patients will have IPMN, and one might presume that this neoplastic process may result in a prolonged risk of progression, much like Barrett's esophagus. As noted in the results, the annual incidence of pancreatic cancer in the general population is 12.4 per 100,000 per year.[10] The observed incidences for our population demonstrate that this cohort is at higher risk than the general population. If confined to the overall cohort, the observed risk of pancreatic cancer development was increased almost 70-fold when compared with what would be expected in an age-matched population cohort. We anticipated that this risk might decrease once we removed high-risk patients sent for resection, but would not decrease to the risk of the general population over time. As the length of surveillance increases, many patients with neoplastic cysts may experience growth and undergo resection. This will increase the percentage of patients in the surveillance group with non-neoplastic and benign cystic lesions such as serous cystadenoma, and thus decrease the likelihood of progression to cancer. When we limited our analysis to just those who had greater than 5 years of follow up, the observed incidence decreased to 151 cases per 100,000 per year, and when limited to those stable at the 5 year time-point the observed incidence decreased to 31.3 per 100,000 per year. When we age-adjusted the expected national incidence rate to match the age distribution of the different cohorts, we still saw that the observed rates were much higher than expected, a fact that we believe supports a policy of continuing surveillance.

The decline in the incidence over time, combined with the decreasing rates of both cancer and cross-over to resection, suggest that there may be a point in time when patients within the surveillance group will reach the risk of the general population and further surveillance may not be warranted. To explore this concept and attempt to define a proper duration of surveillance, cumulative incidence curves were created. These demonstrated a plateau of the rates for progression to cancer after 9 years of surveillance, but not for cross-over for resection. Although these data could argue for cessation of surveillance at this time point, the number of patients at risk at this time point was very low, with less than 100 patients at risk at 10 years. Not until larger numbers of patients have been followed for decades will this type of analysis be possible. In addition, the rate of cross-over to resection did not plateau, despite the decreased cancer incidence. A review of these patients revealed that the most frequent indication for resection after the nine year time point was increase in cyst size to greater than three centimeters. Further evaluation of this patient group will prove valuable in validating a recommended surveillance period.

There are many limitations to this study including its retrospective nature, as certain variables of interest may not have been collected at the time of patient presentation leading to instances of missing data. In addition, although our total cohort was quite large, several of our focused analyses were performed on smaller subgroups, reducing their power. For example, the patients with stable cysts after 5 years of follow up who then crossed-over to resection

and/or developed carcinoma was too small to confidently predict risk factors that may identify these patients prospectively. Although age and cyst size were identified as statistically significant characteristics for predicting which patients may be stable versus unstable at the 5 year time point, the differences in these characteristics were not clinically significant to assess risk. Identifying true risk factors would allow us to predict which patients are most likely to develop cancer or cross-over to resection many years after presentation. This knowledge could allow clinicians to tailor the patient's surveillance plan to match his or her level of risk.

We hope to address other issues pertinent to surveillance in future studies. For example, many groups have documented the presence of pancreas carcinoma at sites distinct from the cyst in question, a phenomenon known as concomitant PDAC. Tada et al. reported an incidence of 1% (n = 2) in his series of 197 patients, while Tanno et al. reported on a series of 168 patients with an incidence of concomitant PDAC reaching 5.4% (n = 9).[20,21] Unfortunately, information regarding the location of carcinoma in relation to the cyst in question was not present in our dataset and represents a limitation of the retrospective nature of our study. However, further investigation into the presence or absence of such an entity in our cohort may have important implications in regards to surveillance. Another area of interest is the long-term outcome of resected pancreas cyst patients found to have IPMN. The AGA guidelines also recommended that these patients did not need post-operative surveillance if high-grade dysplasia was not present in the resected specimen. Our cohort may provide valuable insight into the natural history of these patients and could help determine their future risk of cancer, and therefore, determine their need for continued surveillance.

CONCLUSION

The results of this study demonstrate that after 5 years of follow-up, patients with cystic lesions of the pancreas are still at risk for cyst growth, cross-over to operation, and developing cancer. This finding held true for patients that were stable at the 5 year time point, suggesting that surveillance should not cease even in patients with stable cysts who have been followed for 5 years. Patients would benefit from future studies that could aid in predicting which patients will cross-over to resection or progress to cancer.

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DISCUSSANTS

Dr Carlos Fernández–Del Castillo (Boston, MA):

In the field of pancreatic surgery, the management of incidentally discovered pancreatic cysts is guaranteed to fuel controversy and ignite passion. Positions as varied as passive minimal surveillance to frequent surveillance with routine endoscopic ultrasound aspiration, endoscopic ultrasound ablation, and surgical resection for the majority are seen in the current literature and are actively discussed in the national and international forums.

Two years ago, the American Gastroenterological Association had an exhaustive technical review that concluded that all the evidence regarding management of asymptomatic neoplastic pancreatic cyst was of very poor quality, and despite this poor evidence, came up with a new guideline for the diagnosis and management of these lesions. The AGA listed 10 recommendations. Some are sensible, but others have generated intense debate. In the latter group is a recommendation that surveillance be discontinued after 5 years if there is no significant change in the characteristics of the cyst.

In the article that was just presented, the Memorial Sloan Kettering group described their analysis of a database with over 3000

patients with pancreatic cysts. Some of those patients underwent surgical resection shortly after they were diagnosed, but close to 2500 underwent surveillance. This is a very large number of patients, and this study and subsequent analysis from this rich database have the potential to educate us on the natural history of branch duct IPMN's and other cystic lesions. As expected, most of these patients undergoing surveillance were asymptomatic and the cysts were small with a median size of 1.5 centimeters. Overall, they found growth, which was defined at 5 millimeters or more in 26% of patients; 11% of the patients eventually required surgery, and 3% of patients developed pancreatic malignancy.

Importantly, development of cancer was not limited to patients whose cysts had been stable for a period of time of 5 years.

I have a few questions for the presenters. First, you estimated the incidence of carcinoma in the patients who were radiographically stable at 5 years at 31 per 100,000. This is, of course, higher than the 12.4 incidence of pancreatic cancer in the United States. Did you adjust the incidence for age? Surely, you would expect the incidence in your cohort that has a median age of 66 to be higher than that of the general population.

You might also want to correct it for gender since there was a disproportion of females in your series (60%) and the risk of pancreatic cancer is lower in women.

I also do not recall seeing confidence intervals in your presentation. Was the increased incidence statistically significant? I was struck that all the diagnoses of malignancy were made in the resected specimens. Does this mean your surveillance did not miss timely diagnosis of a single cancer? Were all the cancers within the cyst, or did you find distinct or concurrent ductal adenocarcinomas in some patients as has been shown in many other series?

Second, this database includes patients seen over a span of 20 years, yet the median follow-up of the 2400 patients in the surveillance cohort is only 2.2 years. I suspect many of these patients had their pancreatic cysts discovered whereas being evaluated for other malignancies at Memorial, and perhaps they died. Do you have data on survival and cause of death of these patients, or were they simply lost to follow up?

Third, some of the cysts you followed were tiny, actually less than 1 millimeter. Did you see any difference in the likelihood of progression to malignancy in cysts that were small and remain small versus the rest? This is a very relevant question, because the number of patients with small cysts that are being identified is huge, and if we follow all of them forever, it's going to take a lot of resources.

In the same line, do you have presumed diagnosis for these patients that you are following? I imagine that for the very small ones you don't have a diagnosis, but you did do endoscopic ultrasound, remarkably on more than half of these patients, and just based on size and radiological appearance, some of those must have been serous cystadenomas. Were you able to show that the progression to cancer was absent or different on certain tumor types?

Finally, among the 473 patients who underwent surgery at the time of initial diagnosis and the 262 who were operated after some length of surveillance, there must have been many IPMNs, probably two-thirds, as you said. I realize this is not the focus of your study, but as you know, the AGA also gave recommendations after resection and states that if there is no malignancy, no further follow up is needed. Did you follow your nonmalignant IPMNs and found this recommendation to be safe, or is radiologic surveillance still warranted for these patients? Thank you.

Response from Dr Peter J. Allen (New York, NY):

First of all, I would like to thank Dr. Lawrence. She's a third year resident and she did a tremendous amount of work putting this large data set together in time for submission to this meeting. I believe she did an excellent job of presenting these data today.

The 4 questions are all good ones. We wanted to try to benchmark the risk of progression to cancer to some national norm, and we did use an estimated annual incidence as our initial benchmark. We've looked at it in other ways as well, and we will include this in the manuscript. With respect to age adjustment, we recently calculated expected rates from the National Registry in such a way that it matched the age distribution within our cohort. So it was an age adjusted assessment. If we look at the lowest risk group, when we age adjust, we would have expected seven cancers to develop, and yet we actually saw 32 cancers. So we still think that as we age adjust, it shows a high risk group.

With respect to your second question, our median follow up is short because as I'm sure you know, and you see, the number of patients we're seeing annually is exponentially increasing. So as we continue to see more and more patients, it's very hard for us to get our median length of follow up much longer. However, I would say that some of these patients do have other cancers, and within this subgroup, I think it's around 10% to 15% of patients did die of other causes with their cyst in place.

The third question with respect to size, we did find a couple of factors which predicted growth or development of cancer, and size was one of those. And that is something that we'll certainly tease out in the article. Age was another. If you look at dichotomizing those variables, you know, clinical relevance is maybe not there, but it is statistically significant.

With respect to following patients after resection of IPMN, I completely agree with you and disagree with the AGA. These patients, when we know they have IPMN, meaning they have undergone resection for IPMN, they are the highest risk group that we're following. In our group of patients who we've been following after resection for IPMN, we see radiographic progression in about 25% of patients after four or 5 years, and we see 4% of patients developing pancreatic cancer within 4 or 5 years in that subgroup. That's a very high risk subgroup. And the idea that you would not monitor those patients I don't think is wise.

Dr Vic Vellanovich (Tampa, FL):

Congratulations, Dr. Lawrence, on a beautifully presented study. My question has to do with the decision making, because how much of the decision making to resect was related to the surgeon giving the recommendation to resect versus the patient wanting to have a resection? Because some patients, even despite telling them that the risk of malignancy is quite low, just don't like the idea of having something abnormal in the pancreas. Was that evenly distributed among the groups? How did you handle that?

Response from Dr Peter J. Allen (New York, NY):

I think that's an impossible question for me to answer accurately. Obviously, each individual surgeon's practice is slightly different. I would say, however, that if you look at our data on who is resected and who is being followed, we generally are following these consensus guidelines, and that you would find it's a minority of patients who are resected outside of those guidelines.

I think it's up to us to educate the patients on what the risk is. And certainly a point that I didn't mention with respet to Dr. Fernandez's question, IPMN is a whole gland process. Even after we resect them, we don't know how much we have lowered their risk of developing pancreatic cancer. And as we follow these patients with pancreatic cysts, many of these who have IPMN, they're developing cancer in parts of the pancreas where the cyst is not located, and some of these patients are presenting with metastatic pancreatic cancer as

the initial presentation. So I do think it's up to us to educate them, particularly on the consensus guidelines.

Dr Charles Vollmer (Philadelphia, PA):

I would like to drill down on two things that Carlos brought up but we didn't hear an answer about yet. It gets back to age. The things we struggle with are the dichotomies of age, right? So the very young people, what do we do about them? And how long, and for how many years do we have to do this in the very old people who are 80 to 85 years? Can you tell us—and this has nothing to do with the risk adjustment to the population of having cancer—but did you do some risk analysis of the different stages of age to see what their behaviors are with this surveillance process? And can we make some decisions about not continuing on with older people or even with the younger people?

And then the second thing would have to do with serous cystadenoma. It seems like that was a component to the study, maybe 15% to 20% of these cases. Did that actually dilute or pollute your findings here? Or, alternatively, are you able to tell us something about surveillance of serous cystadenomas so that we can get a guideline as to when we can stop getting the scans in those cases?

Response from Dr Peter J. Allen (New York, NY):

Those are both good questions. Getting back to the issue regarding age, as we drill down into these numbers, the numbers get smaller and smaller, so it's very difficult for us to make definitive recommendations, and I don't think we can make definitive recommendations based on even this data set. I think we need more numbers and longer follow up.

We typically do follow patients as long as they are physically fit. I do not tell patients that we follow them for the rest of their life, but typically until they get to be 95 years old! And some of those patients argue to go to 96 on that last visit.

It would be nice to be able to say you have a branch duct IPMN in your pancreas. You're 46 years old. There are no concerning features here. We followed this many patients for 5 or 10 years. We've never seen a cancer develop. Come back in 10 years. Right? And that's what some of the data suggests, but that's really not what we've seen. So I think right now we're stuck with this approach, and hopefully we have a much better approach 5 or 10 years from now–with more data.

With respect to serous cystadenoma or IPMN, if you look at the number of patients who we initially followed and then resected, the vast majority of those patients have mucinous lesions. So there are some serous cystadenomas in there. Again, I think that gets back to our problem of preoperative diagnosis. Pancreatic cyst is a radiographic finding, it's not a histopathologic entity. Many times we think we're following an IPMN when we are following a serous cyst, and our ability to diagnose these lesions preoperatively is limited. It's getting better. And I hope that that will continue to improve. But it is the vast minority of people who are resected who had serous cysts.

Dr Rebecca Minter:

Thank you, Peter. Dr. Lawrence did a fantastic job presenting. Congratulations.

I wanted to drill down on one of the things that Dr. Fernandez Castillo talked about in terms of the small cyst. So your median cyst size is 1.6 centimeters. In our institution, we've been able to work with our radiology colleagues to develop a registry that's populated automatically for our prevention program for any patient found to have a pancreatic cyst on cross-sectional imaging. That's about 300 patients per year, and most of them are increasingly in the 2 millimeter range. As you noted in your presentation, it's a field defect, and we really have poor data to guide us..... So we do as you do. We surveil them every single year with an MRI which our radiology colleagues think is fantastic right now, but as we're moving into more of a population health model of health care delivery, the cost of this becomes immense and every year we have more and more patients coming.

With this in mind, have you done any sort of cost analysis in this population of patients? And do you have any thoughts as to how we move forward in these patients who have this seeming epidemic of 2 millimeter cysts that we previously weren't able to identify? What do we do with those patients? Do we surveil them every single year, or at a different interval? And what is the cost of that ultimately?

Response from Dr Peter J. Allen (New York, NY):

We have not subjected this to cost analysis. One of the challenges, though, is that probably the majority of these patients have IPMN. So even if we went back and said, well, let's resect all these cysts, we'd still follow these patients postoperatively because we think after pancreatectomy the pancreatic remnant is at increased risk.

I do think when we think about this process of IPMN, I think about Barrett's esophagus or ulcerative colitis or these other dysplastic processes that occur in the body, and how we monitor them. I do think that this is a process, contrary to what the AGA guidelines recommend, that has increased risk over time and thus rather than stop monitoring, we should continue with surveillance.

Dr Max Langham (Memphis, TN):

Thank you very much, Dr. Lillemoe. Again, congratulations to the authors for a really nice study.

As a pediatric surgeon, I was drawn to stand up by that patient on the low end at 9 years of age. At St. Jude Cancer Genetic Predisposition Clinic where we are following, and tracking people for cancer development, we've had a handful of pancreatic lesions that we didn't know what to do with. The pathology is all over the map.

I just wanted to see if you had any information about the teens or young adults and whether or not at Memorial Sloan Kettering you're doing any genetic evaluation of these patients before you start following them with ultrasound.

Thank you.

Response from Dr Peter J. Allen (New York, NY):

Yes, I would agree with you that my understanding of that pediatric population, the pathology is all over the map. In a few pediatric patients that I have evaluated we have applied the same testing that we apply to adults which is typically looking at cyst fluid CEA and now some molecular markers within the fluid which in the pediatric population many times is not particularly helpful.

Dr John Cameron (Baltimore, MD):

Peter, very nice study as all of your studies have been in pancreatic diseases. I rise as one of those old patients between 80 and 85 years that Dr. Vollmer mentioned. I have a pancreatic lesion, and I plan to continue to be followed for many, many more years, and I also continue to operate on these patients and perhaps will continue for more years.

I rise to talk about one specific group of patients that this study didn't really cover but you've mentioned, and that is those with IPMNs that were benign that were resected. How long should we follow them?

We've followed a substantial number of those patients for up to 10 years, and a few over 10 years. Our recommendation has been for a CT scan every 6 months for the first 5 years, and then every year thereafter. But I think we probably are going to change and make it

every year for the first 5 years and then every 6 months from 5 to 10 years because we've had 10% to 15% of those patients develop adenocarcinomas in the remnant. But they've all been out between 8 and 10 years. So I think maybe careful follow up is important, but probably after 5 years, even more important than before 5 years. And I wonder what your experience is with that group of patients.

Response from Dr Peter J. Allen (New York, NY):

I agree with you on 2 points. Number one is that these patients behave like early stage malignancy, meaning their recurrence is farther out from resection rather than early on, and thus you may want to say to your patient, I'll see you in 5 years, and then start following very intensively after that. But this is a very high risk group.

When we looked at our group of patients who were resected for IPMN, 25% will develop new lesions greater than a centimeter or double the size of lesions they have and 4% will develop pancreatic cancer within 4 or 5 years. That is a very high risk group. We follow hundreds of patients who are BRCA 2 positive who are presumed to be high risk for pancreatectomy cancer. Our most recent review of that group found that none of them developed pancreas cancer while we had been following them.

So this group of patients who have resected IPMN represent a very high risk group and this is a group we would strongly feel should be continued to be monitored.