Consequences of a Surveillance Strategy for Side-branch Intraductal Pancreatic Mucinous Neoplasms

Long-term Follow-up of One Thousand Cysts

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Objective: To quantify the rate of progression in surveilled cysts and assess what factors should indicate delayed resection.

Background: Side-branch intraductal papillary mucinous neoplasms (SB-IPMNs) are increasingly discovered, making it challenging to identify which patients require resection, thus avoiding inappropriate treatment. Most incidental lesions are surveyed, yet the consequences of that decision remain uncertain.

Methods: A prospectively maintained database of pancreatic cystic neoplasms was queried for patients with SB-IPMN. Patients with ≥ 2 imaging studies >6 months apart were included. Clinically relevant progression (CR-progression) was defined by symptoms, worrisome/high-risk stigmata, or invasive cancer (IC). Growth ≥ 5 mm in 2 years is considered CR-progression; size ≥ 3 cm alone is not.

Results: Between 1997 and 2023, 1337 patients were diagnosed with SB-IPMN. Thirty-seven (2.7%) underwent up-front surgery; 1000 (75.0%) had >6 months of surveillance. The rate of CR-progression was 15.3% (n = 153) based on size increase (n = 63, 6.3%), main-duct involvement (n = 48, 4.8%), symptoms (n = 8, 5.0%), or other criteria (n = 34, 3.4%). At a median follow-up of 6.6 years (interquartile range: 3.0–10.26), 17 patients (1.7%) developed IC. Those with CR-progression developed IC in 11.1% (n = 17) and high-grade dysplasia (HGD) in 6.5% (n = 10). Nearly half of the cancers were not contiguous with the surveyed SB-IPMN. Size ≥ 3 cm was not associated with HGD/IC ($P = 0.232$). HGD/IC was least common in CR-progression determined by size growth (6.3%) versus main-duct involvement (24%) or other (43%, $P < 0.001$) Patients with CR-progression demonstrated improved survival (overall survival) with resection on time-to-event ($P < 0.001$) and multivariate Cox regression (hazard ratio = 0.205, 0.096–0.439, $P < 0.001$) analyses. Overall survival was not improved with resection in all patients ($P = 0.244$).

Conclusions: CR-progression for SB-IPMNs is uncommon, with the development of cancer anywhere in the pancreas being rare. Initial size should not drive resection. Long-term and consistent nonoperative surveillance is warranted, with surgery currently reserved for CR-progression, knowing that the majority of these still harbor low-grade pathology.

Key Words: intraductal papillary mucinous neoplasm, pancreatic cancer, pancreatic cyst, side-branch IPMN, surveillance

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Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing cystic neoplasms of the pancreas. These lesions are at some risk to develop invasive cancer (IC) which initially led to the widespread adoption of surgical resection for all mucinous neoplasms at discovery.[1,2] The recognition of a high prevalence of incidental disease and understanding with observational experience that many lesions do not progress to malignancy, has led to an alternate strategy of observation for many patients.[3] IPMNs that involve the main pancreatic duct, main-duct (MN) or mixed-type, do convey a high risk of malignancy, and generally require resection.[2,4] Side-branch IPMN (SB-IPMN) are independent of the main pancreatic duct and present as single or multiple cysts of the peripheral ductal branches. These have a lower risk of malignancy.[3,5,6] Many of these patients are appropriate for a surveillance strategy, yet there are consequences to avoiding immediate resection as patients need to be followed at some unclear interval and duration to still identify patients before they develop IC.

There are 3 important concepts in the management of SB-IPMN. The first involves the pathology of the epithelium in IPMN. To be considered part of the spectrum of the disease, the epithelium must have some degree of dysplasia, from low-grade dysplasia (LGD) at a minimum to IC at the extreme.[7,8] LGD does not necessarily confer a malignant potential, which is validated by current surveillance protocols where the natural history has shown that the vast majority of patients will not develop cancer.[9–11] The next important outcome is the actual development of IC in the SB-IPMN being surveyed. This is clearly the most feared outcome and is frequently reported as the only outcome of importance as it represents a group of patients who, if accurately identified earlier in the course of disease progression, would warrant prophylactic resection. Ideally, those receiving surgical resection would constitute the group that have progressed pathologically to high-grade dysplasia (HGD).[2,9–11] The identification of these patients is the driving force behind a comprehensive initial evaluation and surveillance protocol. The third concept is the aspect of a genetic or acquired field defect in the pancreas represented by the presence of any SB-IPMN. This would account for

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the expected and inconsequential development of additional SB-IPMNs during surveillance, and potentially the increased incidence of SB-IPMN with advancing age in the general population.[12] Ominously, it may also explain the development of a pancreatic ductal adenocarcinoma independently arising distinct from the SB-IPMN being surveyed.[13]

There has been an evolution in the management of SB-IPMN away from immediate resection of all identified lesions. Incidental asymptomatic patients are generally surveyed, although there are challenges in properly balancing the risks and benefits of surgical resection versus missing the development of IC. A series of consensus guidelines have helped guide clinicians in caring for patients. The initial Sendai guidelines in 2006 have progressed to the Fukuoka and American Gastroenterological Association guidelines.[3,5,6] Controversy remains over the surveillance intervals for low-risk lesions, duration of surveillance, proper management of borderline-risk lesions, and bias for surgical resection.[14–16] In addition, certain Fukuoka criteria such as cyst size >3 cm remain controversial.[2,4,10] Overall, while advancement has occurred in the understanding of the natural history of disease, there remain significant gaps in our knowledge secondary to generally short follow-up intervals in small populations of surveyed patients.

An ideal management strategy would identify which cysts harbor the potential to develop cancer at initial assessment, indicating which patients require resection, and no surveillance for truly low-risk SB-IPMN. Current practice only allows for surveillance of all lower-risk patients, aiming to identify patients who progress towards a higher risk of IC. There are numerous ways to define progression of pancreatic cystic disease,[16,17] it is our principle aim to define clinically relevant progression (CR-progression) that will identify which symptoms and imaging-based changes warrant surgical resection. We also aim to add to the body of evidence on the natural history of SB-IPMN disease and aid the continued evolution of consensus guidelines.

METHODS

A prospectively maintained database of patients with pancreatic cystic neoplasms was queried to identify patients who were diagnosed with SB-IPMN between January 1997 and December 2022. SB-IPMN was defined by imaging and/or aspiration results as mucin-producing neoplasms communicating with, but not directly involved, the main pancreatic duct.[1,18] Patients aged ≥ 18 years were included if they had 2 sets of cross-sectional abdominal imaging >6 months from diagnosis. To consider the full spectrum of the natural history of disease, cysts were followed from the time of first detection on imaging, not when assessed by our subspecialty team, as well as the progression of disease whether specifically surveyed by our team or other practitioners. Thus, patients were also included in the surveillance cohort who had previous imaging evidence of SB-IPMN but received up-front resection upon presentation to our specialty group.

Our subspecialty team also utilized templated notes for initial and subsequent follow-up, data from which were retrievable. Patients were excluded who: (1) had a diagnosis of MN-IPMN or mixed-type IPMN, (2) did not have follow-up imaging at least 6 months from initial discovery, (3) underwent up-front surgical resection precluding traditional surveillance, or (4) were aged <18 years. The primary outcome of interest was pathologic evidence of HGD or invasive carcinoma (IC). Secondary outcomes include overall survival (OS) and rate of LGD in resected patients. This study was approved by the Cleveland Clinic Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Patient information was extracted from the electronic medical record, including clinical history, laboratory tests, imaging studies, endoscopic procedures, operative details, and pathology results. Imaging studies, including computed tomography and/or magnetic resonance imaging (MRI), were reviewed to identify the first abnormal scan demonstrating IPMN disease within the pancreas, regardless of whether this was the scan leading to the presentation. Radiographic features regarding the lesion, including cyst size, location, communication with the main pancreatic duct, and suspected diagnosis, were recorded. For endoscopic procedures, information regarding the lesion and appearance of the ampulla were noted. Aspiration and biopsy results were collected. Pathologic assessment was based on the revised classification from the Baltimore Consensus Meeting, and lesions were separated into LGD, HGD, and IC.[19] Lesions that were previously characterized as "borderline" or "intermediate-grade dysplasia" according to previous classification schema were considered in the LGD group.

Protocol for Management of Suspected Intraductal Papillary Mucinous Neoplasms

We define CR-progression in conjunction with the Fukuoka guidelines as the development of: (1) worrisome features, including enhancing mural nodules <5 mm, thick enhancing cyst walls, new main duct dilation (5–9 mm), abrupt change in MPD caliber, or rapid rate of cyst growth >5 mm/2 years or (2) high-risk stigmata such as symptoms (jaundice and pancreatitis), enhancing nodule ≥ 5 mm, or main duct dilation ≥ 1 cm.[2] It is critical to note that while size growth ≥ 5 mm in 2 years was considered CR-progression, size ≥ 3 cm alone was not. Patients with CR-progression are typically offered surgery if they meet standard criteria as operative candidates, while those who are not continued imaging surveillance. We also routinely discuss cases at a multidisciplinary Upper GI Conference that includes abdominal radiologists, gastroenterologists, and surgeons, and group consensus is used to determine disease type, surveillance interval, and resection recommendations. Most cysts receive yearly surveillance unless features warrant more frequent imaging. For analyses, a progression event was determined based on the date of the first positive imaging scan with the feature making the patient high-risk. Operative procedures are determined based on the location and extent of the disease. After surgical pancreatic resection, patients are typically followed with contrast-enhanced pancreas protocol computed tomography or MRI imaging every 6 to 12 months at the discretion of the surgeon. Endoscopic ultrasound fine-needle aspiration (EUS-FNA) is frequently used at a surgeon's or gastroenterologist's discretion at initial evaluation and during surveillance.

Endoscopic Ultrasound

EUS-FNA is employed at a surgeon's or gastroenterologist's discretion for cysts >2 cm in size,[9,10] cases of equivocal diagnosis, difficulty in ascertaining the risk

profile of the cyst, or in high-risk cysts in patients with prohibitive operative risk. Analysis in this study compared the findings of EUS-FNA as part of the initial evaluation with subsequent histopathologic data in cases that were resected. Cases receiving EUS-FNA that did not have subsequent histopathology were not included in the sensitivity analysis.

Statistical Analyses

Numerical values were reported as mean and SD or median and interquartile range where appropriate. Categorical values were reported as counts and percentages. Student t test or Mann-Whitney U tests were used as appropriate to assess differences in continuous variables, whereas Pearson χ^2 or Fisher exact test were used for categorical variables. Time-to-event analysis was conducted using the Kaplan-Meier estimate curve and log-rank test to determine differences in progression-free duration from resection between patients based on their high-risk stigmata. Multivariate Cox regression analyses were employed to determine individual associations between risk factors and patient survival. Patients who were not diagnosed with HGD or malignancy by tissue histopathology were assumed to have not developed these conditions for analyses unless otherwise noted. A P value of <0.05 was considered statistically significant for all tests. Data analysis was performed using SPSS version 28 (IBM Corp.).

RESULTS

In total, 2686 patients were diagnosed with pancreatic cystic neoplasms of any type during the study period. Of these, 1337 patients (49.7%) were diagnosed with suspected SB-IPMN. Thirty-seven (2.7%) patients underwent up-front surgery, of which 10 patients (27.0%) had IC on surgical pathology and 6 (16.2%) had HGD. Three hundred (22.5%) did not have adequate surveillance imaging. One thousand (75.0%) patients received >6 months of surveillance and were considered the study cohort.

The median cyst size at diagnosis in the 1000-patient surveillance cohort was 1.3 cm (interquartile range: 0.9–2); the maximum size was 7 cm. The median age at diagnosis was 68.6 years (60.2–76.2). Eighty-five (8.5%) had size ≥ 3 cm on initial imaging. Median imaging surveillance follow-up was 6.6 years (3.0–10.3; Table 1).

Four hundred fifty-five (45.5%) patients received endoscopic cyst assessment at some point in their clinical course. Fifty-one patients (7%) with SB-IPMN received up-front EUS-FNA and had a surgical pathology from definitive resection. FNA cytology revealed atypical cells (n = 30, 59%), HGD (n = 9, 17.6%), or concern for IC (n = 12, 23.6%). FNA demonstrated a sensitivity = 0.435 (95% CI: 0.232–0.637), specificity = 0.926 (0.827–1.02), positive predictive value = 0.833 (0.625–1.04), and negative predictive value = 0.658 (0.507–0.809) for cancer or HGD on final pathology.

The overall rate of CR-progression was 15.3% (n = 153/1000), and the median time to CR-progression was 3.4 years (1.7–6.4 years; Fig. 1A). The determination for CR-progression was based on size increase ≥ 5 mm/2 years (n = 63, 6.3%), MN involvement (n = 48, 4.8%), development of clinical symptoms (n = 8, 5.0%), or other Fukuoka criteria (n = 34, 3.4%). Other Fukuoka criteria were radiologic, including enhancing nodular component (n = 21), thick cyst walls (n = 11), abrupt duct cutoff (n = 1), or lymphadenopathy (n = 1). Symptom-based CR-progression during surveillance included jaundice (n = 4), pancreatitis (n = 4), and abdominal pain (n = 1). Those with CR-progression were offered surgical resection in 131 cases (85.6%) and received surgical resection in 61 (39.2%). Twenty-eight (18.3%) patients with CR-progression had EUS-FNA with findings of high-risk dysplasia that contributed to the indication for surgery.

In total, 1.7% (n = 17) of surveilled patients developed IC at a median time of 6.7 years (3.2–8.0; Fig. 1B). HGD was discovered in an additional 10 patients in the CR-progression cohort. Over three-quarters (78.9%, n = 7/9) of those with clinical symptoms developed HGD/IC. An additional 66 patients (43.1%) of those with CR-progression had evidence of LGD.

In those with IC (n = 17), 10 (58.9%) had IC arising within the cyst seen on previous imaging, whereas 7 (41.1%) had a noncontiguous IC arising in the pancreas, constituting a field defect carcinoma. Seven (43.8%) had positive lymph

Table 1. Demographic and Clinical Information for Included Patients

	Overall (n = 1000)	Without CR-progression (n = 847)	With CR-progression (N = 153)	P*
Age at diagnosis (yr)	68.6 (60.2–76.2)	69.5 (60.8–76.3)	68.4 (60.2–76.2)	0.859
Sex (M); n (%)	393 (39.4)	339 (40.0)	54 (35.3)	0.323
Race; n (%)				
White	855 (85.5)	724 (85.5)	130 (85.4)	0.756
Black	84 (8.4)	73 (8.6)	12 (7.8)	—
Asian/Pacific Islander	20 (2)	17 (2.0)	3 (2.0)	—
Mixed Race	16 (1.6)	14 (1.7)	2 (1.3)	—
Unknown/Declined	25 (2.5)	19 (2.2)	6 (3.9)	—
Ethnicity; n (%)				
Hispanic	15 (1.5)	14 (1.7)	1 (0.6)	0.353
Not Hispanic	985 (98.5)	827 (98.3)	152 (99.4)	—
Body mass index (kg/m^2)	27.1 (24.0–31.3)	27.2 (24.1–31.6)	26.1 (23.3–30.94)	0.236
Initial cyst size (cm)	1.3 (0.9–2)	1.3 (0.8–1.8)	1.7 (1.2–2.3)	**<0.001**
Cyst size >3 cm; n (%)	85 (8.5)	67 (7.9)	18 (11.9)	0.104
Imaging follow-up from diagnosis (yr)	6.6 (3.0–10.3)	6.3 (2.7–9.7)	7.9 (4.2–11.9)	**<0.001**

*Significant to $P < 0.05$.

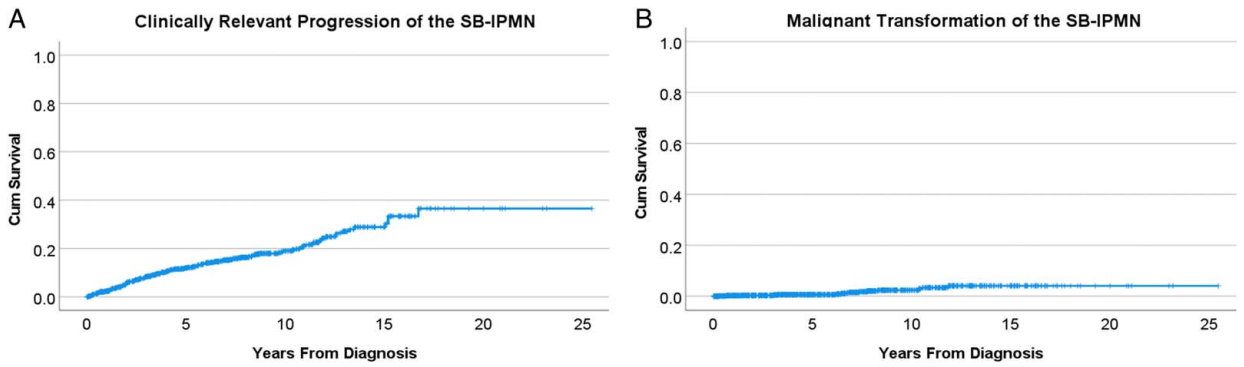

Fig. 1. Natural History of the Surveilled Side Branch IPMN. A, Overall rate of CR-progression in one thousand SB-IPMNs up to 20 years from diagnosis. B, Rate of malignant transformation up to 20 years from diagnosis.

nodes. Four patients had T1 cancers with negative lymph nodes, constituting a microscopic focus of adenocarcinoma within the cyst of interest. Nine (56.3%) of the patients with IC were consistently followed by our surgical team at the recommended intervals, and 7 (43.8%) had been temporarily lost to follow-up for >2 years preceding the diagnosis of IC, including the sole patient presenting with metastatic disease.

Cysts of initial size ≥ 3 cm were not more likely to develop HGD/IC (5.9% vs 4.3%, $P = 0.489$; Fig. 2A). Cysts with CR-progression determined by size criteria were the least likely to develop HGD/IC (n = 4/63, 6.3%) versus main duct involvement (n = 8/48, 24%) or other non–size-based criteria (n = 18/42, 42.9%, $P < 0.001$), and size-based CR-progression demonstrated the longest time without dysplastic transformation on time-to-event analysis (3.6 vs 2.9 years, $P < 0.001$; Fig. 2B). Only one patient progressed directly from low-risk imaging criteria to invasive IPMN, this occurred at a 1-year interval. All other patients developed imaging findings of disease progression of the SB-IPMN or a noncontiguous ductal carcinoma. The median time from diagnosis to progression in cysts <1 cm was 4.3 years (2.4–7.8 years) and 4.1 years (1.8–8.5) in those ≥ 1 cm. The years from cyst diagnosis to either CR-progression or last follow-up for all included cysts by initial cyst size is shown in Figure 2C, demonstrating that cysts of all sizes progress up to 15 years from diagnosis and that

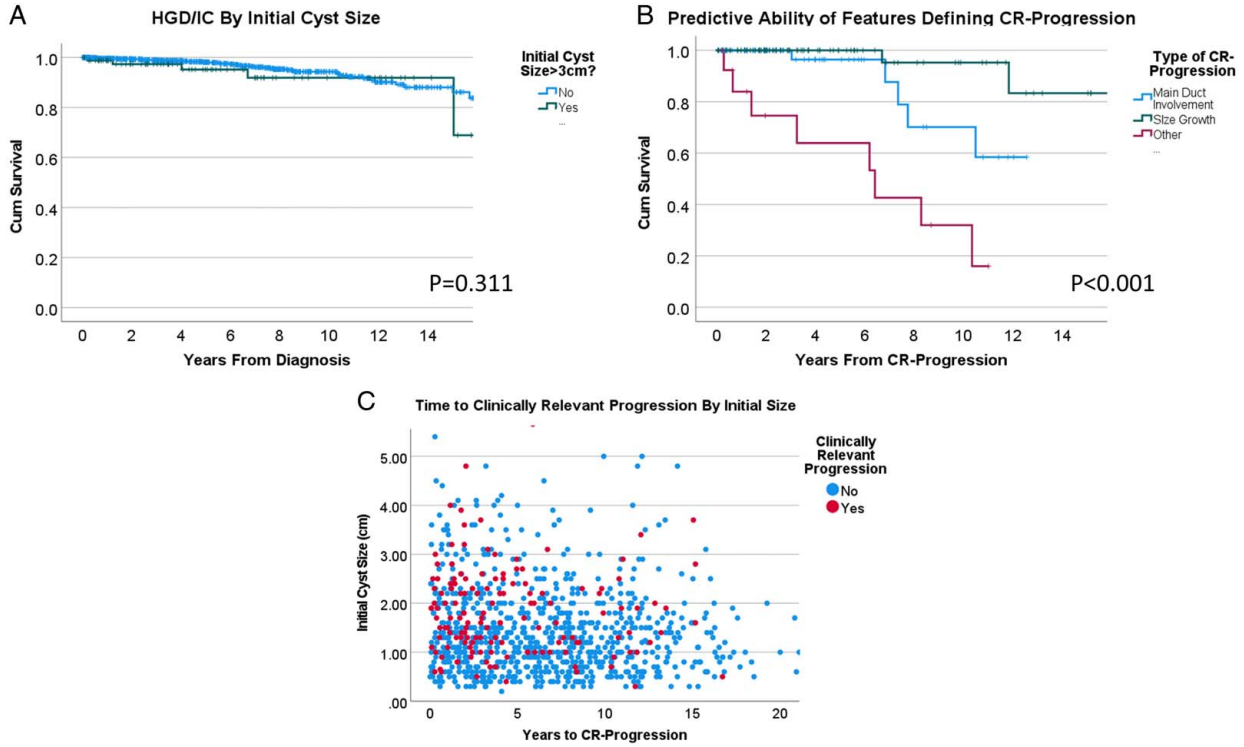

Fig. 2. Predicting malignant transformation of the SB-IPMN. A, Presence of HGD or IC over time by initial cyst size, demonstrating no association between cyst size at diagnosis and malignant potential ($P = 0.311$). B, Presence of HGD/IC over time in cysts with CR-progression by feature defining progression. Growth in size had the least correlation with dysplastic potential versus main duct involvement or other high-risk stigmata ($P < 0.001$). C, Time in years from cyst diagnosis to CR-progression for all included cysts by cyst size at presentation.

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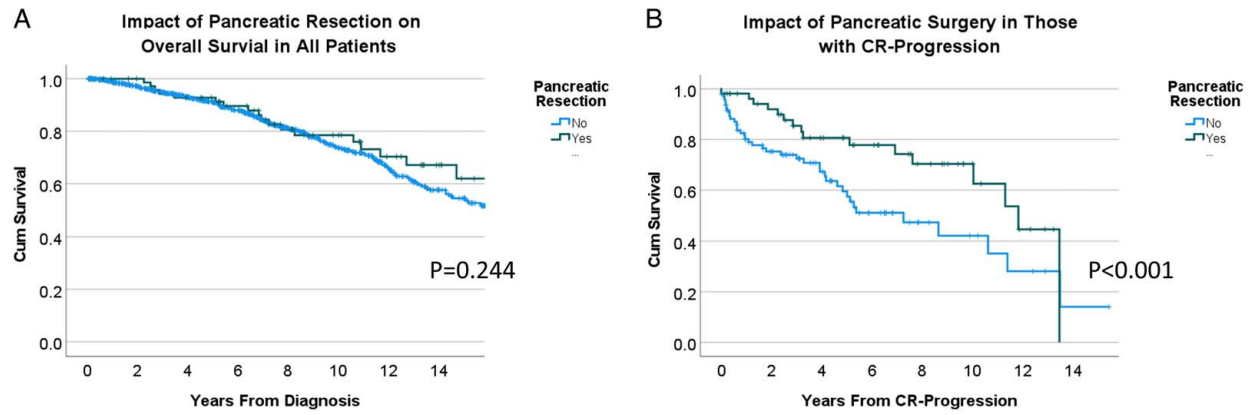

Fig. 3. Impact of surgical resection on OS. A, Surgical resection is not associated with improved survival from diagnosis among all comers with SB-IPMN ($P = 0.244$). B, Surgical resection is associated with improved survival in patients with CR-progression ($P < 0.001$).

initial size does not well predict when a cyst will develop CR-progression.

In the total cohort of patients with surveyed SB-IPMN, surgical resection was not associated with improved OS versus those who did not receive surgery ($P = 0.244$). However, patients with CR-progression who received surgical resection had improved survival from the time CR-progression was detected ($P < 0.001$; Fig. 3). On multivariate Cox-regression analysis in the total cohort, CR-progression [hazard ratio (HR) = 1.592, 95% CI = 1.138–2.227, $P = 0.007$] was the strongest negative predictor of OS from diagnosis followed by increasing age at diagnosis (HR = 1.029, 1.016–1.044, $P < 0.001$). Pancreatic resection (HR = 0.575, 0.336–1.076, $P = 0.062$) did not independently improve survival in the total population (Table 2). In patients with CR-progression, the strongest predictor of reduced survival was IC (HR = 8.036, 2.982–21.635, $P < 0.001$). HGD ($P = 0.498$), cyst size ($P = 0.083$), or type of CR-progression ($P = 0.238$, $P = 0.240$) were not associated with decreased survival. However, pancreatic resection was independently associated with improved survival in this sub-cohort (HR = 0.205, 0.096–0.439, $P < 0.001$; Table 2).

Table 2. Cox-regression Analysis of Factors Predicting Survival In Patients With SB-IPMN

	HR†	95% CI	*P*
OS from diagnosis in all-comers with SB-IPMN			
Cyst size ≥ 3 cm	1.254	0.806–1.952	0.316
CR-progression	1.592	1.138–2.227	**0.007***
Pancreatic resection	0.575	0.336–1.076	0.062
Age at diagnosis	1.029	1.016–1.044	**<0.001***
OS from the time of CR-progression in CR-progression cohort			
Pancreatic malignancy	8.036	2.982–21.635	**<0.001***
HGD	1.396	0.532–3.665	0.498
Increasing cyst size	1.914	0.919–3.989	0.083
Pancreatic resection	0.205	0.096–0.439	**<0.001***
Type of CRP			
Main duct dilatation	0.633	0.296–1.354	0.238
Growth in size	1.533	0.756–3.237	0.240
Age at diagnosis	1.026	0.996–1.057	0.087

*Significant to $P < 0.05$.
†Increasing HR is associated with reduced survival.
CRP indicates clinically relevant progression.

DISCUSSION

The diagnosis of pancreatic cancer carries an ominous implication within the general public and medical community alike. Despite remarkable achievements in advancing the surgical outcomes of pancreatic resection and the development of powerful chemotherapy regimens administered in both the neoadjuvant and adjuvant setting, the prognosis for resected pancreatic cancer is still measured by a median survival of ~2 years, and overall 5-year survival rate under 5%.[20] Understandably, patients and practitioners would both swiftly take any opportunity to prevent pancreatic cancer by treating a precursor lesion. The development and utilization of sensitive imaging modalities have led to the recognition of a vast population of patients with incidental and asymptomatic cysts, nearly all SB-IPMN. Acquired and increasing in incidence with advancing age, nearly a quarter of the elderly population will harbor this pathology of uncertain consequence.[21,22] Patients referred for evaluation of any pancreatic finding detected by imaging undoubtedly fear the worst and are susceptible to overtreatment during their evaluation, ongoing surveillance, and recommendation for surgery. All of these raise the specter of grave interventional outcomes, ongoing patient anxiety, and costs. It behooves us to carefully study cystic lesions and, specifically, the natural history of SB-IPMN when incidentally detected, to ideally identify only those patients who predictably will progress to high-risk pathology, HGD, or invasive carcinoma. This series adds valuable information to our understanding of SB-IPMN based on the longest interval of surveillance yet reported. The overall risk of developing IC during surveillance is rare at 1.7%. Nearly all ICs in SB-IPMN will develop imaging progression. This requires consistency in follow-up imaging if a surveillance program is to be entertained, and we demonstrate an impressive benefit of surveillance in the potential to diagnose ductal cancers associated with this pancreatic field defect. Resection undertaken during a surveillance program will not yield the same rate of high-risk pathology when careful initial assessment leads to up-front surgery, as this can identify a significant rate of high-risk cysts in our experience. As a surgical community, we can do better as the majority of resections for SB-IPMN yielded LGD, whose resection will not improve their OS but only the potential for adverse surgical outcomes.

This is the largest study to date reporting surveillance for SB-IPMN, twice the size of the next largest

experience,[4,10] and the study with the longest surveillance follow-up. We help define the natural history of the surveilled SB-IPMN, finding a 15% rate of CR-progression and a 1.7% rate of IC over a 7-year median follow-up. Only 1% of patients developed IC within the cyst of interest. We define a refined surveillance strategy based on CR-progression, a definition that attempts to separate lesions requiring surgical resection from traditional definitions of progression, such as any size increase or development of a new cyst, which should not prompt resection. Initial cyst size was not correlated with dysplastic potential, and size-based CR-progression had the lowest correlation with malignant transformation, which supports previous work by our group.[10] Finally, it seems that cysts may continue to progress up to 10 years from diagnosis, supporting the need for long-term surveillance.

Perhaps most importantly, we define a strategy for surveillance and potential resection of the incidental SB-IPMN, specifically following low-risk cysts with yearly scans for 10 years, or until evidence of CR-progression. The definition of CR-progression resembles published guidelines,[2,23] though it is notable that size ≥ 3 cm itself does not warrant intervention. We confirm that our refined definition of CR-progression, which is primarily based on imaging criteria, does predict HGD/IC, and, thus, patients that might benefit from surgical resection. Our strategy is supported by findings that patients undergoing resection in the total cohort experienced no survival benefit, yet resection did improve survival in those with CR-progression. This is the first time that a differential survival benefit has been demonstrated in the SB-IPMN, supporting surgical resection only in patients with CR-progression. Data from our cohort have shown that the remnant pancreas may develop a CR disease that requires further evaluation in 10% of patients after surgical resection at a time interval of 1 to 5 years. Explant pathology was not predictive of disease progression in the remnant pancreas. Thus, we recommend continuing yearly surveillance over this period after resection. Given the nature of SB-IPMN as a field defect, we prefer this approach to postresection patients of all grades of dysplasia.

One important consequence of managing SB-IPMN is the risk of overtreatment. This is potentially likely when patients are aware of the gravity of a diagnosis like pancreatic cancer and are willing to accept resection to presumably prevent that outcome. It is important to correctly identify only the patient that will achieve this benefit, otherwise this group of largely asymptomatic patients will be subjected to a high risk of surgical morbidity and even mortality. Specifically, there was a 1.7% rate of malignancy in our cohort, and there is a national unadjusted postpancreatectomy mortality of 1.3% to 2.5%.[24] Although our group only operated on $<10\%$ of patients with SB-IPMN, most of these patients still had LGD; other studies have also reported similar trends.[25,26] This outcome is also reflected in our OS curve (Fig. 3A), wherein the overall cohort did not show survival benefit with surgery. We did find that pancreatic cancer was independently predictive of reduced survival, yet HGD was not, which supports the aim of our protocol, namely, to identify and resect only those with HGD before it progresses to malignancy. Further progress in the field should identify those who are truly at risk, with the proposed definition of CR-progression representing one avenue of future research.

Most studies concerning SB-IPMN have reported outcomes of cysts undergoing resection, creating a population limited by selection bias, as cysts undergoing resection are likely inherently higher risk.[1,2,23,27,28] Indeed, some studies quote a rate of malignant transformation as high as 20% in the SB-IPMN, which would support more liberal resection if accurate.[23,28,29] However, a few studies of smaller size, such as those by Sahora et al[4] and Lee et al,[30] have reported HGD/IC in 3% to 4% of SB-IPMNs, a rate similar to this cohort. For this reason, modern guidelines recommend the observation of asymptomatic cysts without worrisome features.[1,2,23] Our findings support an active surveillance strategy. There is also currently no consensus regarding the duration of surveillance. As seen in Figure 1, we find the risk of both CR-progression and malignancy, while low, continues to increase slowly over 10+ years of follow-up, and half of patients developed CR-progression over 6 years from initiation of surveillance. This indicates that surveillance should be continued for 10+ years without a reduction in surveillance interval during that period. Further, many of the patients with IC had been lost to follow-up preceding the diagnosis of IC, underscoring the importance of frequent and consistent surveillance, which may have identified progression before the development of IC. Even cysts of a small size developed CR-progression as far as 15 years from diagnosis; however, it does seem that the progression of small, stable cysts is somewhat less common after 10 years of surveillance (Fig. 2C). Discontinuation of surveillance imaging for small cysts after 10 years is likely justifiable depending on patient age and clinical situation.

The relative importance of cyst size remains highly debated. While cyst size ≥ 3 cm is a worrisome feature by Fukuoka guidelines, previous studies by our group and others have addressed the arbitrary nature of this cutoff.[2,10] Yet other studies support the importance of size as a consideration but propose other size cut-offs, such as ≥ 1.5 or 2 cm, at which resection should be considered.[31,32] We find that initial size ≥ 3 cm is not correlated with high-risk dysplastic potential, providing additional evidence that this finding alone should not warrant resection. While we do not consider static cyst size ≥ 3 cm to be CR-progression, rapid cyst growth ≥ 5 mm/2 years is concerning based on our findings. Thus, we support the resection of cysts meeting size-growth criteria but not the resection of cysts above 3 cm alone.

While not the main focus of this work, the role of EUS and/or EUS-FNA also remains controversial. Fukuoka guidelines recommend surveillance with EUS-alone for "worrisome features." This necessitates invasive procedures, and we thus propose a strategy that focuses more on contrast-enhanced MRI and possible surgical resection. This would also aide with cyst surveillance in rural areas, who have reduced access to specialists performing advanced endoscopic procedures.[33] We also note a low sensitivity but high specificity for the detection of HGD/malignancy on EUS-FNA, which is in line with many previous studies on the topic.[34–36] Our center does not employ routine EUS-FNA to confirm the diagnosis of SB-IPMN but to add to cytopathology in cases of uncertain risk. The utility of negative FNA in patients with worrisome features seems limited based on the low reported sensitivity, and thus we would favor resection based on surgeon judgment in the presence of CR-progression. However, high-risk features on FNA do seem potentially useful in identifying high-risk cysts. Further work regarding molecular and genomic analysis of cyst fluid may continue to enhance the utility of endoscopy during surveillance.[37–39]

This study has limitations. We attempted to overcome selection biases, which confound survival analyses, with high patient volume and long-term follow-up, yet a low event rate makes definitive conclusions challenging. We assumed for this analysis that the absence of a diagnosis of carcinoma is equivalent to a true negative. However, without a tissue diagnosis, we cannot confirm that the presence of HGD or cancer is truly not present. In addition, patients may be assumed to be negative for carcinoma when they might instead be lost-to-follow-up before developing IC. Thus, we may underestimate the rate of CR-progression and/or IC. Despite reporting the longest follow-up to date, we show the risk of malignancy continues to increase at long follow-up periods. Thus, the study is limited by its follow-up period, as even longer surveillance would be ideal. Finally, outcomes are not known in patients who had >6 months surveillance, but were then lost to follow-up, as these patients are assumed to be negative for malignancy but may have indeed developed such transformation.

CONCLUSIONS

CR-progression for SB-IPMNs is uncommon, with the development of cancer anywhere in the pancreas being rare. Initial size should not drive resection. Long-term and consistent nonoperative surveillance is warranted, with surgery currently reserved for CR-progression, knowing that the majority of these still harbor low-grade pathology.

REFERENCES

1. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology*. 2006;6:17–32.
2. Tanaka M, Fernández-del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17:738–753.
3. Vege SS, Ziring B, Jain R, et al. Clinical Guidelines CommitteeAmerican Gastroenterology Association. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148:819–822.
4. Sahora K, Mino-Kenudson M, Brugge W, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg*. 2013;258:466–475.
5. Coronel E, Lanke G, Bhutani MS, et al. Clinical utility of the Fukuoka 2017 Consensus and 2015 American Gastroenterological Association Guidelines in the management of intraductal papillary mucinous neoplasms (IPMNs): 76. *Am J Gastroenterol*. 2018;113:S43.
6. Ge P, Muthusamy V, Gaddam S, et al. Evaluation of the 2015 AGA guidelines on pancreatic cystic neoplasms in a large surgically confirmed multicenter cohort. *Endosc Int Open*. 2017;5:E201–e208.
7. Hruban RH, Takaori K, Klimstra DS, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004;28:977–987.
8. Shi C, Hruban RH. Intraductal papillary mucinous neoplasm. *Hum Pathol*. 2012;43:1–16.
9. Walsh RM, Perlmutter BC, Adsay V, et al. Advances in the management of pancreatic cystic neoplasms. *Curr Probl Surg*. 2021;58:100879.
10. Walsh RM, Vogt DP, Henderson JM, et al. Management of suspected pancreatic cystic neoplasms based on cyst size. *Surgery*. 2008;144:677–684; discussion 684-685.
11. Lim J, Allen PJ. The diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas: has progress been made? *Updates Surg*. 2019;71:209–216.
12. Chang YR, Park JK, Jang JY, et al. Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21,745 individuals: Large-scale, single-center cohort study. *Medicine (Baltimore)*. 2016;95:e5535.
13. Uehara H, Nakaizumi A, Ishikawa O, et al. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. *Gut*. 2008;57:1561–1565.
14. Peisl S, Burckhardt O, Egger B. Limitations and prospects in the management of IPMN: a retrospective, single-center observational study. *BMC Surg*. 2023;23:3.
15. Tanaka M. Controversies in the management of pancreatic IPMN. *Nat Rev Gastroenterol Hepatol*. 2011;8:56–60.
16. Wood LD, Adsay NV, Basturk O, et al. Systematic review of challenging issues in pathology of intraductal papillary mucinous neoplasms. *Pancreatology*. 2023;23:878–891.
17. Marchegiani G, Pollini T, Andrianello S, et al. Progression vs cyst stability of branch-duct intraductal papillary mucinous neoplasms after observation and surgery. *JAMA Surg*. 2021;156:654–661.
18. Klöppel G, Solcia E, Longnecker DS, et al. *Histological Typing of Tumours of the Exocrine Pancreas*. 2nd edn. Springer Berlin Heidelberg; 1996.
19. Basturk O, Hong SM, Wood LD, et al. A revised classification system and recommendations from the baltimore consensus meeting for neoplastic precursor lesions in the pancreas. *Am J Surg Pathol*. 2015;39:1730–1741.
20. Yamamoto T, Yagi S, Kinoshita H, et al. Long-term survival after resection of pancreatic cancer: a single-center retrospective analysis. *World J Gastroenterol*. 2015;21:262–268.
21. Khan S, Sclabas G, Reid-Lombardo KM. Population-based epidemiology, risk factors and screening of intraductal papillary mucinous neoplasm patients. *World J Gastrointest Surg*. 2010;2:314–318.
22. Crippa S, Capurso G, Falconi M. IPMNs of the pancreas: more epidemiologically than clinically relevant. *JAMA Network Open*. 2023;6:e2338696–e2338696.
23. Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology*. 2012;12:183–197.
24. Hasan S, Abel S, Verma V, et al. Predictors of post-operative mortality following pancreatectomy: a contemporary nationwide analysis. *J Clin Oncol*. 2019;37(suppl 15):e15706–e15706.
25. Amini N, Habib JR, Blair A, et al. Invasive and noninvasive progression after resection of noninvasive intraductal papillary mucinous neoplasms. *Ann Surg*. 2022;276:370–377.
26. Zhang C, Al-Shaheri FN, Alhamdani MSS, et al. Blood-based diagnosis and risk stratification of patients with pancreatic intraductal papillary mucinous neoplasm (IPMN). *Clin Cancer Res*. 2023;29:1535–1545.
27. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg*. 2004;239:788–797; discussion 797-799.
28. Fritz S, Küper-Steffen R, Feilhauer K, et al. Resection of benign side-branch intraductal papillary mucinous neoplasm of the pancreas—is long-term follow-up indicated?: a case report and review of the literature. *Medicine*. 2018;97:e9894.
29. Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate. *Ann Surg*. 2004;239:651–657; discussion 657-659.
30. Lee CJ, Scheiman J, Anderson MA, et al. Risk of malignancy in resected cystic tumors of the pancreas $<$ or $=3$ cm in size: is it safe to observe asymptomatic patients? A multi-institutional report. *J Gastrointest Surg*. 2008;12:234–242.
31. Pergolini I, Sahora K, Ferrone CR, et al. Long-term risk of pancreatic malignancy in patients with branch duct intraductal papillary mucinous neoplasm in a referral center. *Gastroenterology*. 2017;153:1284–1294.e1.

32. Oyama H, Tada M, Takagi K, et al. Long-term risk of malignancy in branch-duct intraductal papillary mucinous neoplasms. *Gastroenterology*. 2020;158:226–237.e5.
33. Zahnd WE, Hung P, Shi SK, et al. Availability of hospital-based cancer services before and after rural hospital closure, 2008-2017. *J Rural Health*. 2023;39:416–425.
34. Pitman MB, Deshpande V. Endoscopic ultrasound-guided fine needle aspiration cytology of the pancreas: a morphological and multimodal approach to the diagnosis of solid and cystic mass lesions. *Cytopathology*. 2007;18:331–347.
35. Pitman MB, Genevay M, Yaeger K, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. *Cancer Cytopathol*. 2010;118:434–440.
36. Michaels PJ, Brachtel EF, Bounds BC, et al. Intraductal papillary mucinous neoplasm of the pancreas: cytologic features predict histologic grade. *Cancer*. 2006;108: 163–173.
37. Turner RC, Melnychuk JT, Chen W, et al. Molecular analysis of pancreatic cyst fluid for the management of intraductal papillary mucinous neoplasms. *Diagnostics (Basel)*. 2022;12: 2573.
38. Khalid A, Zahid M, Finkelstein SD, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc*. 2009;69:1095–1102.
39. Khalid A, Mcgrath K, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. *Clin Gastroenterol Hepatol*. 2005;3:967–973.

DISCUSSANT

Dr. Jeffrey Drebin (New York, NY)

The discussion will be started by Dr. Merchant.

Dr. Nipun Merchant (Miami, FL)

Thank you for a very nicely presented study. I really want to congratulate you and your authors for reporting on the largest series on the surveillance of these side-branch IPMNs with the longest surveillance period, a median of 6.6 years. This study clearly adds to our understanding of the natural history of these side-branch lesions, which is clearly needed. Several important aspects of these lesions are reinforced in this analysis, and I want to emphasize a few.

Number one, the overall risk of developing IC during surveillance is extremely rare at $<2\%$. The initial cyst size of >3 cm and size-based CR-progression do not correlate with dysplastic potential or malignant transformation, providing additional evidence that this finding alone should not warrant surgical resection. Half of the patients developed CR-progression over 6 years from the initiation of surveillance, and cysts continued to progress up to 10 years from diagnosis, supporting the need for long-term surveillance, and lastly, clearly, these lesions have an aspect of a genetic or acquired field defect in the pancreas represented by the presence of a noncontiguous IC away from the primary cyst in question in more than 40% of patients.

So, while these findings and others in the study add to the literature providing a better understanding of the natural progression of these lesions, sadly, it also highlights the fact that we are still far from finding the holy grail in operating only on patients that have progressed pathologically to HGD. This is highlighted by the fact that even in the patients that we would consider as having high-risk features of CR-progression, which is primarily based on imaging studies, you still had 43% of patients taken to surgery with CR-progression who only had LGD, and even in 37 patients that underwent up-front surgical resection, presumably based on high-risk features, more than half had LGD; so clearly we have much to learn to better predict the right patients to offer surgery to, and likely identifying optimal biomarkers is the way forward.

Currently, we have the Sendai and Fukuoka AGA guidelines to help guide us. However, they all have their shortcomings. As we continue to understand better the natural progression of these lesions, we still have controversy over surveillance intervals for low-risk lesions, duration of surveillance, and proper management of these borderline-risk lesions.

The EA2185 protocol comparing clinical surveillance of 2 different cyst surveillance programs may help answer some of these questions, but the study has had very slow accrual, and I believe it is because the surgical community does not have equipoise regarding limiting surveillance in these patients. Your study clearly helps further emphasize that a significant number of patients clearly progress well beyond 6 years and that active surveillance should likely continue long term as you suggest based on your data, which I also agree with.

My question, however, is regarding your recommendation for an annual imaging follow-up. Do we really need annual follow-ups in patients with small cysts that may continue to be stable for an extended period of time and have no symptoms? Even in your study, only one patient progressed directly from low-risk imaging criteria to invasive IPM within a 1-year interval. If we are going to continue long-term imaging follow-up and only 15% have CR-progression, almost half of which still do not have high-risk pathology, if we take 1000 patients as you had in your study over 10 years, of the 10,000 imaging studies, you will only have about 750 CR images that will alter the course of treatment in these patients, so perhaps should we consider prolonging the interval of imaging in patients with stable small cysts?

My next question comes back to those patients who underwent surgical resection and had HGD. How do you surveil these patients after surgery? Have you seen any recurrences in these patients, and if so, at what time intervals?

The next question I have is that you had 15% of patients that had CR-progression, but only 40% of those patients actually underwent surgical resection. What was the reason for not operating on those patients?

And for my last question, I would like to play devil's advocate and bring forth a controversial idea. While I agree that long-term surveillance is indicated, you show that only $<2\%$ of patients progress to IC, and as you know, the overall mortality rate of pancreatic resections, even inexperienced high-volume centers, is exactly that, $<2\%$, so should we come to a point and argue that maybe low-risk patients should not even be surveilled?

I want to congratulate you again on a very well-done study, a much-needed study that clearly adds to a better understanding of the natural progression of these lesions. Thank you.

Response from R. Matthew Walsh

Thank you, Dr. Merchant, for those very thoughtful questions, and I will admit that we do not have an ideal surveillance strategy as yet. I think part of the issue about the interval of imaging depends on several things. One is since these are acquired lesions, they always have to start at

a small size, and it is totally arbitrary when they are going to be found, so we would agree that there should be some surveillance.

Our current protocol is if they are <1 cm, we do it every 2 years and look for stability, but once they are over 1 cm, I think that the yearly surveillance, which is ultimately going to come down to cost, does society agree with that cost to do, but having looked at the ones who did have gaps, those 40%, you did get the sense that perhaps they did have intervening imaging changes that you wish you could have operated on.

So I think the other part of it is I think patients are very willing to have the surveillance. They all know pancreatic cancer is bad, and they are willing to come. It is a low-risk procedure, and I think if we emphasize that it is important that we see them, they will do it.

In terms of after-surgery surveillance of the remnant, we have a manuscript in process on that very topic of 500 IPMNs that we have surveyed the remnant, and very rarely does the pathology correlate with what happens in the remnant except for MN disease if there is HGD at the margin.

In terms of the patients who did not get operated on who had CR changes, you know, we did not force people to operate if they saw changes in the rate of growth, so a lot of patients fell into that category. We follow really everybody, and some patients really were not candidates for resection.

Lastly, your provocative question about what you would rather die from, pancreatic cancer or die from the Whipple? That is a way to look at it. Let us look at it on both sides. I think our group is trying to contribute to at least not having patients get a Whipple who do not need it. On the other side, I think again it is what, as a society, we want to spend our money on, and I would be equally provocative and say, why can not everyone have a low-cost MRI and diagnose their lung cancer, see their coronary disease and their renal cancer, as well as following their pancreas and go more to Star Trek where you get wanded once a year, and we will see what happens.

Dr. Jeffrey Drebin (New York, NY)

Yes, I want to congratulate you. Great presentation. We always like studies that confirm our own biases, and you tagged a number of mine. The 3 cm thing being nonsense may be the highest among them.

Also, it is important to recognize if you look online, if you look in various pathology texts, you will see things like side-brand IPMNs have a 10% incidence of cancer, and MN IPMNs have a 50% incidence—people come into the office absolutely terrified, and they do not understand why we do not operate on them, and you have shown us why we do not since the incidence of cancer is actually much lower. These are great data that I think will help all of us in dealing with patients.

I have a couple of questions. One thing, you have combined HGD and IC in your long-term follow-up, and I would argue those are very different. HGD means you hit the target perfectly. You got it just in time. IC means maybe you were a little late.

And then just the other question has to do with patients' genetic backgrounds and whether that guides you in any way. I see a lot of patients who are BRCA family members who have an 8 mm cyst and are convinced it is going to be cancer, so why do not we take it out today? Do you change your surveillance intervals based on your genetics of the patient?

Response from R. Matthew Walsh

Yes, great questions. You are right, exactly. The holy grail is to only resect patients with HGD. That would be the ideal. We combined the 2 because we still felt that those were the high-risk pathology. That is the ultimate outcome, I guess, so that is why we did it. We did separate out HGD, and that did occur twice as often, so we did somewhat better, versus cancer.

In terms of people who may have a family history or genetic risk, we do not change it primarily because, as you know, the pancreatic ductal pathway is probably different than the IPMN pathway, and we already have trouble knowing really how to surveil patients at increased genetic risk, so for this, we have not changed our protocol.

Dr. William Chapman (St. Louis, MO)

Will Chapman, St. Louis. Great paper to present. I think, as already said, this is a tricky area that we do not have a great idea of how to follow these patients.

Now I just want to get the message correctly. Annual surveillance for life with an MR/MRCP, to me, I would say, is not that easy, and one of the challenges is, you know, we are in the rural Midwest. Getting imaging locally, the MR/MRCP that we get when it is done locally for a patient, that is, 4 or 5 hours away, is often, not always, inadequate, poor quality, so I think many places, we review these patients at our pancreas imaging conference and look to the radiologists and say, "Okay, what do you think about follow-up?" and the first time it will be 6 months, then the next time it will be a year. We have tended to go to 2 years, and after the patient's out 6 years, many patients are saying, "Why are we still doing this?" and so your plan is annual for life as I hear it at your institution.

Response from R. Matthew Walsh

Well, I think it is a perfectly great point. Obviously, we see patients as well from varied distances, and we do like to partner with the local providers and get the imaging yearly. I think that is a practical solution. Obviously, the magnets are really different across the country, and they need to get a contrast to make it reliable to look for the enhancing nodule, but I do think that is a reasonable compromise is what I would say, and I know you are saying for life, but remember, most of these are going to be older patients already, and that is why the survival curve goes down, so I guess the people that I follow appreciate knowing that another year is great.

Dr. Jeffrey Drebin (New York, NY)

Dr. Asbun?

Dr. Horacio Asbun (Miami, FL)

Congratulations again. I want to echo the fact that this is a problem that we all face, and it is a difficult problem. I guess the Miami population is more smart than yours. They love the fact that we follow them, and they want to continue being followed.

My question is do you alternate EUS with MRI, and specifically because of the mural nodule, does it help you to know if it is a mucous plug or not a mucous plug? That is question number one.

Question number 2 is, where does fluid molecular analysis play a role here? We are now seeing it done more

and more, and it seems like the gastroenterologists, at least the ones that I work with, feel very comfortable with it. Do we really know if we can feel comfortable with that?

And the last question is, again, great study. What are you going to do differently in your practice with the results of this, or is this just confirming that what you are doing is the right thing to do?

Response from R. Matthew Walsh

Last question first, I am not sure it is the right thing, but we have not decided to change anything other than looking at the rate of growth more closely, so one of the reasons people are not getting operated is if they have a rate of growth, we are more likely to EUS them for cytology. That is what we are looking at. We are not looking at molecular genetics, and our data, I think, would suggest that it really is not helping find people who need surgery, which is the only thing I think that is useful for, and I think our radiologists, in general, are good at mucous plug versus enhancing nodules. That is why you need to have the IV contrast, and I do not like overutilizing EUS when they have a clear indication for surgery.

Dr. Horacio Asbun (Miami, FL)

Thank you very much.