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CLINICAL—PANCREAS

Progression of Pancreatic Branch Duct Intraductal Papillary Mucinous Neoplasm Associates With Cyst Size

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BACKGROUNDS & AIMS: Most guidelines for management of patients with intraductal papillary mucinous neoplasms (IPMN) vary in proposed surveillance intervals and durations—these are usually determined based on expert opinions rather than substantial evidence. The progression of and optimal surveillance intervals for branch-duct IPMNs (BD-IPMN) has not been widely studied. We evaluated the progression of BD-IPMN under surveillance at a single center, and determined optimal follow-up intervals and duration. **METHODS:** We performed a retrospective analysis of 1369 patients with BD-IPMN seen at Seoul National University Hospital in Korea from January 2001 through December 2016. We included only patients whose imaging studies showed classical features of BD-IPMN, and collected data from each patient over time periods of at least 3 years. We reviewed radiologic and pathologic findings, and performed linear and binary logistic regressions to estimate cyst growth. **RESULTS:** The median annual growth rate of the cyst was 0.8 mm over a median follow-up time of 61 months. During surveillance, 46 patients (3.4%) underwent surgery because of disease progression after a median follow-up time (in this group) of 62 months. Worrisome features were observed in 209 patients (15.3%) during surveillance, including cyst size of 3 cm or more (n = 109, 8.0%), cyst wall thickening (n = 51, 3.7%), main pancreatic duct dilatation (n = 77, 5.6%), and mural nodule (n = 43, 3.1%). Along with annual rate of cyst growth, incidences of main pancreatic duct dilatation and mural nodules associated with the sizes of cysts at detection ($P < .001$). **CONCLUSIONS:** In a retrospective analysis of patients with BD-IPMN followed for more than 5 years, we found most cysts to be indolent, but some rapidly grew and progressed. Surveillance protocols should therefore be individualized based on initial cyst size and rate of growth.

Keywords: Pancreatic Cystic Neoplasm; Natural History; Monitoring; Invasive Carcinoma.

The detection of pancreatic cysts has increased over the last 2 decades because of a wide range of screening methods and advances in imaging tests, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS).[1,2] With the increasing identification of pancreatic cysts and recognition of their malignant potential, whether to treat them with upfront surgery or cautious surveillance has been the topic of interest in numerous studies.

Intraductal papillary mucinous neoplasm (IPMN) is the most frequently detected premalignant lesion that involves the main pancreatic duct (MPD), branch duct, or both. According to an observational study, IPMN is detected in approximately 80% of patients with pancreatic cysts.[3] Resection is recommended for main duct IPMN (MD-IPMN) and mixed-type IPMN because of their high malignant potential. However, studies suggest that cautious surveillance is suitable for branch duct IPMN (BD-IPMN) with no high-risk stigmata features.[4] However, BD-IPMN requires continuous follow-up after its initial diagnosis because of its reported annual malignancy conversion rate of 2–3%.[5,6]

Several guidelines regarding the surveillance of IPMN are available, including those from the International Association of Pancreatology, European Experts Consensus, and American Gastroenterological Association. However, these protocols significantly vary and are inconsistent in terms of follow-up intervals and duration. According to the 2012 International Association of Pancreatology guidelines for the management of suspected BD-IPMN, patients with high-risk stigmata are recommended to undergo surgery, and those who present with worrisome features should undergo EUS. However, a close surveillance of the cyst size for patients with non-specific EUS findings and no worrisome features is recommended.[4]

However, the consensus guidelines and its recommendations regarding surveillance are based on expert opinions, and data that will support these guidelines and recommendations are limited. In addition, several recommendations on surveillance are based on other benign pancreatic cysts in addition to BD-IPMN, and the diagnosis of high-grade dysplasia or IPMN-associated invasive carcinoma is underestimated.[7–9] Therefore, this study aimed to

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Abbreviations used in this paper: CT, computed tomography; EUS, endoscopic ultrasound; MD, main duct; MPD, main pancreatic duct; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Because of the lack of reports on the natural history of intraductal papillary mucinous neoplasm (IPMN) of the pancreas, guidelines regarding optimal surveillance of branch duct (BD)-IPMN vary in their suggested intervals and durations, and most are primarily based on experts' opinions.

NEW FINDINGS

The number of worrisome features increases relative to the size of the cyst at detection. While most BD-IPMNs appear dormant, some show extraordinary growth and malignant features that develop over a short period of time. The authors suggest optimal surveillance intervals based on the natural history of BD-IPMN.

LIMITATIONS

This study is somewhat limited by its retrospective design.

IMPACT

Nonoperative surveillance is suitable for patients with BD-IPMN detected incidentally. Follow-up duration and surveillance interval should be customized based on the size and growth rate of the cyst at detection, considering cost effectiveness and detection of malignant IPMN.

evaluate the natural history of BD-IPMN to achieve an optimal surveillance protocol on cyst growth and worrisome features that develop during follow-up.

Materials and Methods

Patient Selection and Data Collection

We retrospectively reviewed clinicopathologic findings and radiologic images through a thorough search of electronic medical records that were screened using codes defined by the International Classification of Diseases-10 (ICD-10). Patients who were diagnosed with pancreatic cyst (K862) and intraductal papillary mucinous neoplasm (D017, D136, D377, and C259) were evaluated. Moreover, those with pancreatic cystic lesions as seen on imaging studies were also included in the study. Radiologic and pathologic data were reviewed by an experienced board-certified radiologist (L.J.M.) and pathologist (L.K.B.) with more than 15 years of experience who specialize in hepatobiliary and pancreatic imaging and pathology, respectively. All pathologic reports were reviewed and revised according to the Verona consensus meeting.[10,11]

We identified 10,083 patients who were suspected with IPMN at Seoul National University Hospital from January 2001 to December 2016, and those with concomitant pancreatic ductal adenocarcinoma (PDAC) were excluded beforehand. In addition, 4566 patients with uncertain diagnoses, 3630 patients with follow-up periods of less than 3 years, 473 patients with only ultrasound follow-up images, and another 47 patients with MD-IPMN based on radiologic findings were not included in the study. Lastly, a total of 1369 patients with BD-IPMN were included and evaluated (Figure 1).

This study was approved by the Institutional Review Board of the Seoul National University Hospital, which waived the requirement of an informed consent (IRB no. 1704-102-846).

Radiologic Evaluation and Follow-up

CT, MRI, EUS, and endoscopic retrograde cholangiopancreatography were carried out for the diagnosis and follow-up of patients with BD-IPMN. Initial diagnoses were made based on the results of CT scans because it was considered as the standard modality for diagnosis. Furthermore, CT was carried for the measurement of cyst size during follow-up. CT or MRI were performed during surveillance to observe any changes in the patients' cystic features or to identify malignant transformation or progression. EUS was also performed to detect suspicious mural nodules or cyst wall thickening in patients who were at high risk for high-grade dysplasia or invasive carcinoma.

Based on the results of CT scans, we used a Multidetector CT with LightSpeed Ultra (GE Healthcare, Milwaukee, WI), Sensation 16 (Siemens Medical Solutions, Erlangen, Germany), or Brilliance 64 (Philips Medical Systems, Cleveland, OH) to obtain 3-mm triple-phase contrast-enhanced axial and coronal images. Late arterial and portal venous phases were reviewed using picture archiving and communication system workstation (PACS workstation and m-view, Marotech Ltd., Seoul, South Korea).

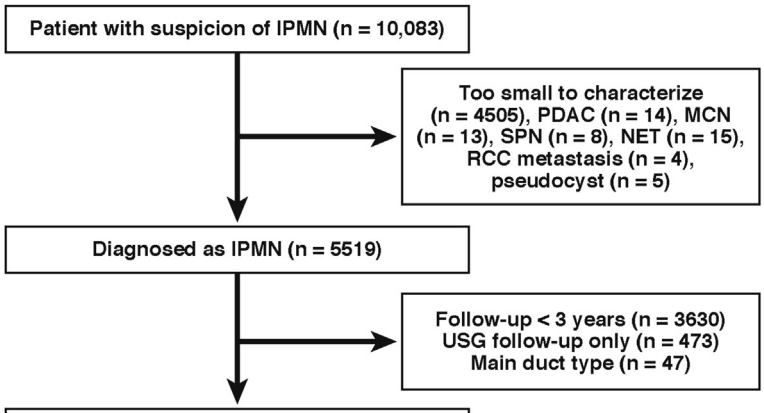
A patient with BD-IPMN was diagnosed when typical features were observed, including pleomorphic shape, clubbed or finger-like appearance, and definite pancreatic ductal communication of the cyst on CT, MRI, or EUS.[12,13] Cyst size was defined as the major axis diameter on axial or coronal view. For multiple lesions, we mainly focused on the largest cyst during follow-up. Mural nodules were defined as hyperdense nodules that protruded into the dilated branch duct that enhanced after the use of contrast agents during CT or as hypoechoic blood flow-supplied protrusions on EUS. The size criteria were not used to evaluate the presence of mural nodules. Cyst wall thickening was defined as cyst walls thicker than 2 mm. All images were reviewed twice by a radiologist and a surgeon who were blinded to the final pathology. When discrepancies on radiologic findings were observed, the parameters were measured after an extensive discussion between the radiologist and surgeon.

After obtaining data from follow-up images, we used the following parameters in the analysis: initial and final absolute cyst sizes defined as the maximal diameter and absolute differences in cyst sizes and growth rates (absolute size difference/follow-up period). In addition, we calculated the time it takes for the cyst to increase its initial size by 150% ([initial cyst size/2] $\times$ absolute cyst growth rate; ie, half the doubling time) and grow $>$ 3 cm ([30 mm - initial cyst size] $\times$ absolute cyst growth rate).[14]

According to the Seoul National University Hospital policy, patients diagnosed with BD-IPMN should undergo radiologic follow-up every 3–6 months during the first year, with lengthened intervals of 9–12 months if no progression or evidence of high-grade dysplasia or invasive carcinoma was observed. Moreover, patients should undergo surgery during surveillance if their cyst size increased, they developed symptoms, such as pancreatitis or obstructive jaundice, or when other factors associated with invasiveness, such as mural nodules, are observed during follow-up imaging.

Statistical Analysis

Statistical analysis was performed using R software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).



Patients without worrisome feature (n = 1310)

Worrisome features	Cases (n = 194)
Size ≥ 3cm	75
MPD 5–9mm	42
Cyst wall thickening	42
Mural nodule	35
Total patient number	150

Patients with worrisome feature (n = 59)

Worrisome features	Initial cases (n = 69)	Additional cases (n = 17)
Size ≥ 3cm	31	3
MPD 5–9mm	26	9
Cyst wall thickening	7	2
Mural nodule	5	3
Total patient number	59	17

Figure 1. A total of 10,083 patients with suspicious IPMN were identified, and only 1369 eligible patients were identified for follow-up after a careful exclusion. IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic ductal adenocarcinoma; MCN, mucinous cystic neoplasm; SPN, solid pseudopapillary neoplasm; NET, neuroendocrine tumor; RCC, renal cell carcinoma; USG, ultrasonography; MPD, main pancreatic duct.

All variables are expressed in median and mean values, with standard deviations, ranges, or percentages when appropriate. Categorical variables and continuous variables were compared using chi-square tests and *t*-tests, respectively. Linear regression and binary logistic regression were used to estimate the changes in cyst and MPD sizes. A *P*-value $<.05$ was considered statistically significant.

Results

Patient Demographics

A total of 10,083 patients with suspicious BD-IPMN were identified (Figure 1). Among these patients, 4564 were excluded because of the following reasons: 4505 patients have cysts that are extremely small to characterize or lack specific radiologic features, such as definite pancreatic ductal communication or pleomorphic and clubbing, 14 patients had PDAC, 13 patients had mucinous cystic neoplasm, 8 patients had solid pseudopapillary neoplasm, 15 patients had neuroendocrine tumors, 4 patients had renal cell carcinoma metastasis, and 5 patients had pseudocysts. A total of 5519 patients were diagnosed with IPMN. However, those with follow-up periods of less than 3 years, without CT or MRI, and MD-IPMN were further excluded.

In total, 1369 patients with a mean age of 62.5 years were included (Table 1), of which 719 were men (52.5%) and 650 were women (47.5%). Median follow-up duration was 61 months. Mean initial cyst size was 12.8 mm and MPD was 1.8 mm. At the final follow-up examination, the mean cyst size was 17.0 mm and MPD was 2.4 mm.

We detected a total of 280 worrisome features in 209 patients during surveillance. At the end of surveillance, 109 (8.0%) cysts $\geq$ 3 cm, 51 (3.7%) with thickened cyst walls, 77 (5.6%) MPDs of 5–9 mm, and 43 (3.1%) mural nodules were identified.

Cyst Growth and Manifestation of Worrisome Features

The median annual rate of cyst growth was 0.8 mm (Figure 2). A total of 1310 patients had no combined worrisome features at initial diagnosis, whereas 150 patients had newly developed 194 worrisome features during surveillance. Seventy-five cases of cysts larger than 3 cm, 42 cases of MPDs of 5–9 mm, 42 cases of cyst wall thickening, and 35 cases of mural nodules were observed in these patients. On the other hand, 59 patients presented with 69 worrisome features at initial diagnosis with 31 cases of cysts larger than 3 cm, 26 cases of MPDs of 5–9 mm,

Table 1. Patient Demographics

Variables	
Age (mean ± SD), ***y***	62.5 ± 9.6
Sex (M/F), n (%)	719 (52.5)/650 (47.5)
Location, n (%)	
Head	626 (45.7)
Body-tail	743 (54.3)
Follow-up [median (range)], ***mo***	61 (36–189)
Serum CEA (mean ± SD), ***ng/mL***	1.9 ± 1.3
Serum CA 19-9 (mean ± SD), ***U/mL***	21.2 ± 118.5

	Initial	Final
Cyst diameter (mean ± SD), ***mm***	12.8 ± 6.5	17.0 ± 9.2
Main pancreatic duct (mean ± SD), ***mm***	1.8 ± 1.0	2.4 ± 1.8
Worrisome feature development, n (%)		
Cyst size > 3 cm	31 (2.3)	109 (8.0)
Cyst wall thickening	7 (0.5)	51 (3.7)
MPD 5–9 mm	26 (1.9)	77 (5.6)
Mural nodule	5 (0.4)	43 (3.1)
Multiplicity	241 (17.6)	326 (23.8)

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; F, female; M, male; MPD, main pancreatic duct; SD, standard deviation.

7 cases of cyst wall thickening, and 5 cases of mural nodules. After the follow-up, 17 patients of these 59 patients further developed (3, 9, 2, and 3, respectively) worrisome features. Therefore, at initial diagnosis, 59 patients manifested 69 worrisome features, whereas at final surveillance, a total of 209 patients had newly developed or additionally manifested 280 worrisome features (Figure 1).

Surgery

All patients included in this study underwent surveillance for at least 3 years. Patients underwent resection if they presented with symptoms, high incremental cyst growth, or other signs of invasiveness. A total of 46 patients underwent surgical resection after a median surveillance period of 62 months, of which 13 patients were diagnosed with high-grade dysplasia (n = 5, 10.9%) or IPMN-associated invasive carcinoma (n = 8, 17.4%), which accounts for 28.3% of patients in the resection group but only 0.9% of the entire BD-IPMN cohort. Among the 33 (71.7%) patients who underwent resection, all were diagnosed with low-grade dysplasia.

Morphologic Changes in the Cysts in Terms of Initial Size

The participants were classified into 4 groups according to their initial cyst sizes: group 1, <10 mm (n = 501); group 2, 10 mm– <20 mm (n = 712); group 3, 20 mm– <30 mm (n = 125); and group 4, ≥30 mm (n = 31; Table 2). Their respective median annual growth rates (calculated relative to initial cyst size) were 0.7 mm, 0.8 mm, 1.1 mm, and 1.2 mm.

The annual growth rates differed among all 4 groups ($P = .046$). In addition, the incidence of newly developed

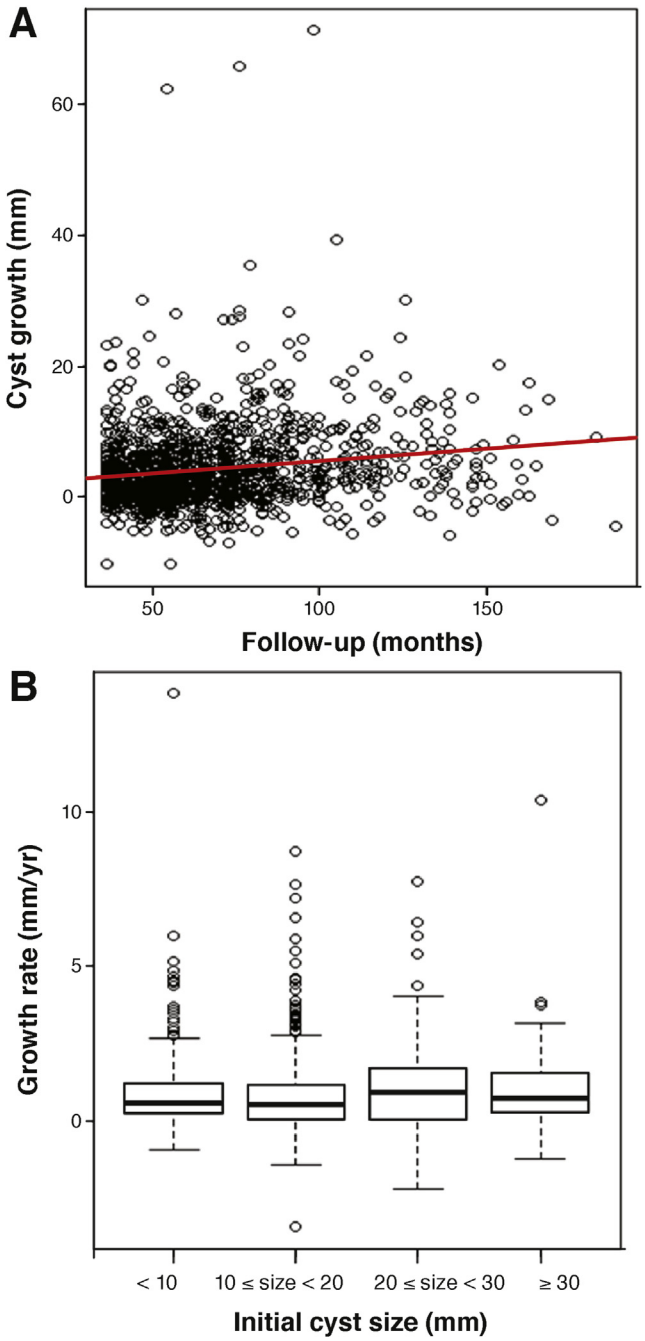


Figure 2. The median annual cyst growth rate was 0.8 mm, and rapidly growing cysts were observed according to the initial cyst size at detection. (*A*) Depiction of the changes in cyst size and (*B*) of cyst growth rate according to the initial cyst size.

worrisome features significantly differed ($P < .001$). Of the 167 cases of newly developed or progressed worrisome features in the cohort, 24 (4.8%), 71 (10.0%), 61 (48.8%), and 11 (35.5%) were observed in groups 1, 2, 3, and 4, respectively. Median time taken for the worrisome feature to develop was 54 months, 55 months, and 23 months in groups 1, 2, and 3, respectively.

The incidence of MPD dilatation and diameter also significantly varied with the initial cyst size ($P < .001$). The

Table 2. Difference in Cyst Feature According to Initial Cyst Size at Detection

	Group 1 (<10 mm)	Group 2 (10≤–<20 mm)	Group 3 (20≤–<30 mm)	Group 4 (≥30 mm)	*P* value
Total patient number, n (%)	501 (36.6)	712 (52.0)	125 (9.1)	31 (2.3)	
Cyst size (mean ± SD), *mm*	7.1 ± 1.8	14.0 ± 2.7	23.6 ± 2.7	35.4 ± 7.3	
Location, n (%)					<.001
Head	181 (36.1)	348 (48.9)	78 (62.4)	19 (61.3)	
Body & tail	320 (63.9)	364 (51.1)	47 (376)	12 (38.7)	
Type, n (%)					<.001
BD	493 (98.4)	697 (97.9)	123 (98.4)	23. (74.2)	
Mixed	8 (1.6)	15 (2.1)	2 (1.6)	8 (25.8)	
Annual growth rate, *mm/y*	0.8 ± 1.1	0.7 ± 1.1	1.1 ± 1.5	1.2 ± 2.1	.046
MPD dilatation, n (%)	7 (1.4)	12 (1.7)	2 (1.6)	5 (16.1)	<.001
MPD diameter, *mm*	1.7 ± 0.9	1.9 ± 1.0	2.0 ± 0.9	3.0 ± 1.8	<.001
Wall thickening, n (%)	0 (0.0)	3 (0.4)	3 (2.4)	1 (3.2)	<.001
Mural nodule, n (%)	0 (0.0)	2 (0.3)	2 (1.6)	1 (3.2)	<.001
Lymphadenopathy, n (%)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	.924
Suspected malignancy in cytology, n (%)	1 (0.2)	2 (0.3)	1 (0.8)	0 (0.0)	.005
Worrisome feature development, n (%)	24 (4.8)	71 (10.0)	61 (48.8)	11 (35.5)	<.001
Time to worrisome feature development, *mo* (median)	54	55	23		
Serum CEA (mean ± SD), *ng/mL*	2.0 ± 1.1	1.9 ± 1.4	1.9 ± 1.3	2.8 ± 2.3	.270
Serum CA 19-9 (mean ± SD), *U/mL*	17.9 ± 50.0	24.4 ± 157.2	14.8 ± 15.6	23.5 ± 44.4	.804

BD, branch duct; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; MPD, main pancreatic duct; SD, standard deviation.

MPD diameters of groups 1, 2, 3, and 4 were 1.7 ± 0.9 mm, 1.9 ± 1.0 mm, 2.0 ± 0.9 mm, and 3.0 ± 1.8 mm, respectively. The incidence of cyst wall thickening differed with cyst size: group 1, none; group 2, 3 patients (0.4%); group 3, 2 patients (1.6%); and group 4, 1 patient (3.2%) ($P < .001$). The incidence of mural nodules also remarkably differed: group 1, none; group 2, 2 patients (0.3%); group 3, 2 patients (1.6%); and group 4, 1 patient (3.2%) ($P < .001$).

Conclusively, larger cysts, particularly those larger than 2 cm, showed significantly faster annual growth rates and likelihood of MPD dilatation and cyst wall thickening ($P < .001$). Furthermore, patients with initially larger cysts developed more worrisome features during surveillance and over shorter periods of time (Figure 3). Worrisome features were observed in 1.4%, 2.4%, 4.0%, and 22.4% of patients in groups 1, 2, 3, and 4, respectively. After the follow-up, worrisome features developed in 6.2%, 11.8%, 51.2%, and 77.4% of patients accordingly. The number of patients with cysts >3 cm and cysts initially >3 cm is not presented in the total number of worrisome features observed.

Discussion

Tolerable outcomes were observed in BD-IPMN patients with a 5-year survival rate of 81% and disease-specific survival (DSS) of 90% who present with worrisome features or high stigmata treated with nonsurgical monitoring. Patients with worrisome features showed better 5-year disease-specific survival than those with high-risk stigmata (96% vs 60%).[15] Our results indicate that patients with high-risk stigmata should undergo surgery, whereas careful surveillance may be appropriate for patients with worrisome features, particularly in elderly patients with shorter life expectancies.

Although our results are in accordance with those of other reports that found tolerable disease-specific survival and persistent but low overall malignancy risk in patients with BD-IPMN to verify the importance of close surveillance, most studies suggested that surveillance protocols are

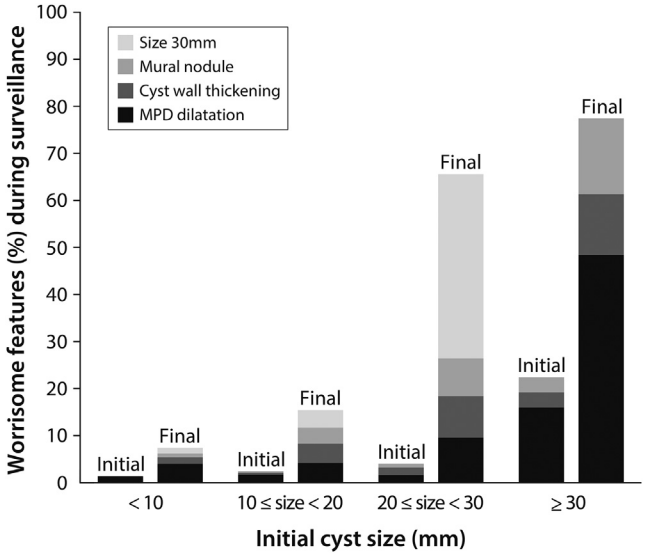


Figure 3. Changes in cystic features and worrisome features increase according to the initial cyst size. The number of patients with cysts >3 and those who were initially diagnosed with cysts >3 cm is not presented in this figure.

based on short-term follow-up, and evidence on its long-term safety is limited. Currently, 4 guidelines are used in clinical practice. The 2012 international Association of Pancreatology guideline recommends a surveillance interval based on the size of the largest cyst, with CT or MRI every 2–3 years for cysts <1 cm; follow-up every year for 2 years and lengthened follow-up thereafter for cysts 1–2 cm in size; and EUS every 3–6 months that should be alternated with MRI for cysts 2–3 cm.[4] The 2013 European Experts Consensus recommends follow-up with MRI or EUS in patients without risk factors twice a year in the first year, every year for the next 2–5 years regardless of cyst size, and then biannually after 5 years for patients with stable cysts or those without changes or with changes only in size.[16] The American College of Radiology and American Gastroenterological Association also recommended surveillance protocols.[17,18] However, all of these guidelines are based on expert opinions rather than substantial evidence.[19,20] Moreover, pancreatic cysts can grow after an initial period of stability, which implies that current guidelines in discontinuing surveillance after the periods of stability should be re-evaluated.[21] Therefore, a revised surveillance protocol that is based on evidence that supports the natural history of BD-IPMN is needed.

Although some surveillance protocols regarding pancreatic cystic neoplasms have been reported in several studies, most of these studies did not include IPMN patients with typical radiologic signs. Therefore, benign pancreatic cysts, such as serous cystadenoma or pseudocyst, are also included, which can in turn affect the analytic results and surveillance protocols.[9,22]

In this study, a total of 14 patients diagnosed with PDAC were excluded in the initial patient selection process. A total of 7 patients with IPMN and concomitant PDAC were identified. Four patients initially presented with concomitant PDAC, while 3 patients underwent surveillance for IPMN for at least 6 months. These patients were excluded because they did not meet the inclusion criteria of 3 years of surveillance period. Furthermore, patients diagnosed with invasive IPMN did not have concomitant PDAC.

To the best of our knowledge, this study is one of the largest cohort investigations that exclusively included BD-IPMN patients who presented with typical radiologic signs.[23,24] In the present study, the incidence of worrisome features differed over time according to the initial cyst size at detection. Based on previous studies, we found that the initial cyst size is an important parameter in determining the natural history of BD-IPMN.[9] In addition, the incidence of MPD dilatation and mural nodules increased with cyst sizes, and the rate of invasiveness increased with initial cyst size. Patients with larger cysts were at higher risk for malignant transformation. During surveillance, 14% of our participants developed new worrisome features and at least 0.9% developed high-grade dysplasia or invasive carcinoma, although the accurate rate of malignancy remains unknown because high-grade dysplasia and invasive carcinoma are rare but can exist without presenting any worrisome features. The incidence rate of new worrisome features and growth rates differed by initial cyst size. The annual average growth rate was 0.8 mm. Based on the annual growth rate and incidence of worrisome features in each size groups, a modified surveillance protocol was devised.

Although the current medical management for patients with BD-IPMN is cautious surveillance, these patients with BD-IPMN are at risk for malignant transformation, and if diagnosed with invasive carcinoma, poor prognosis is expected. Well-considered surveillance protocols are thus needed. Therefore, we suggest the following modified surveillance protocol based on the natural history of BD-IPMN with respect to the initial cyst size at diagnosis and growth rate (Figure 4). Symptomatic BD-IPMN patients and asymptomatic patients who present with high-risk stigmata should undergo upfront surgery as their initial management. The 5-year survival rate of patients with invasive IPMN is 40%[18]; therefore, preventive surgery is recommended for high-risk patients. For asymptomatic patients who exhibit worrisome features, such as those with cysts ≥3 cm, thickened or enhanced cyst wall, or MPD of 5–9 mm, surgery should be considered if the patient is young or fit for the procedure. Furthermore, surgery is also recommended in patients with lymphadenopathy, increased tumor marker levels, or other worrisome features, including abrupt ductal caliber change with distal pancreatic atrophy or rapid cyst growth.[25] However, for patients with no worrisome features, careful surveillance should be recommended according to the initial cyst size.

With asymptomatic BD-IPMN patients with no worrisome features, we recommend a modified surveillance protocol based on the initial cyst size, growth rate, and 200% growth time (doubling time; Table 3). This protocol also accounts for some outliers that show rapid cyst growth as previously described (Figure 2). For example, for a patient with BD-IPMN <1 cm with an annual growth rate of 0.8 mm and BD-IPMN <1 cm with a maximal annual growth rate of 13.8 mm, the time it takes for the cyst to grow by 200% (ie, the doubling time) is 25.6 years, whereas the minimal doubling time in a rapidly growing cyst is 6 months. Furthermore, 95% of the patients with BD-IPMN <1 cm showed growth within 2 years. Therefore, patients with BD-IPMN cysts <1 cm should be monitored 6 months after the initial diagnosis and every 2 years with CT or MRI thereafter. Furthermore, we recommend that cysts that are 1–2 cm in size should be managed with follow-up examinations every 6 months with CT or MRI for 1 year and every 1.5–2 years thereafter. Moreover, because the cysts show accelerated growth according to their initial sizes at detection, patients with cysts that are >2 cm in size should undergo follow-up examinations with MRI or CT or EUS every 6 months for 1 year and then annually thereafter until the cyst size and features become stable. Those with cysts that are larger than 3 cm should be closely monitored with MRI or CT or EUS every 6 months. Surgical resection can be considered in younger patients or those with other combined worrisome features.

Overall, the radiologic diagnostic rate based on CT and MRI is comparable, with high accuracy.[26,27] Based on the European and American guidelines, MRI is suggested for patients who require close surveillance because of the radioactive feature of CT. However, in some countries,

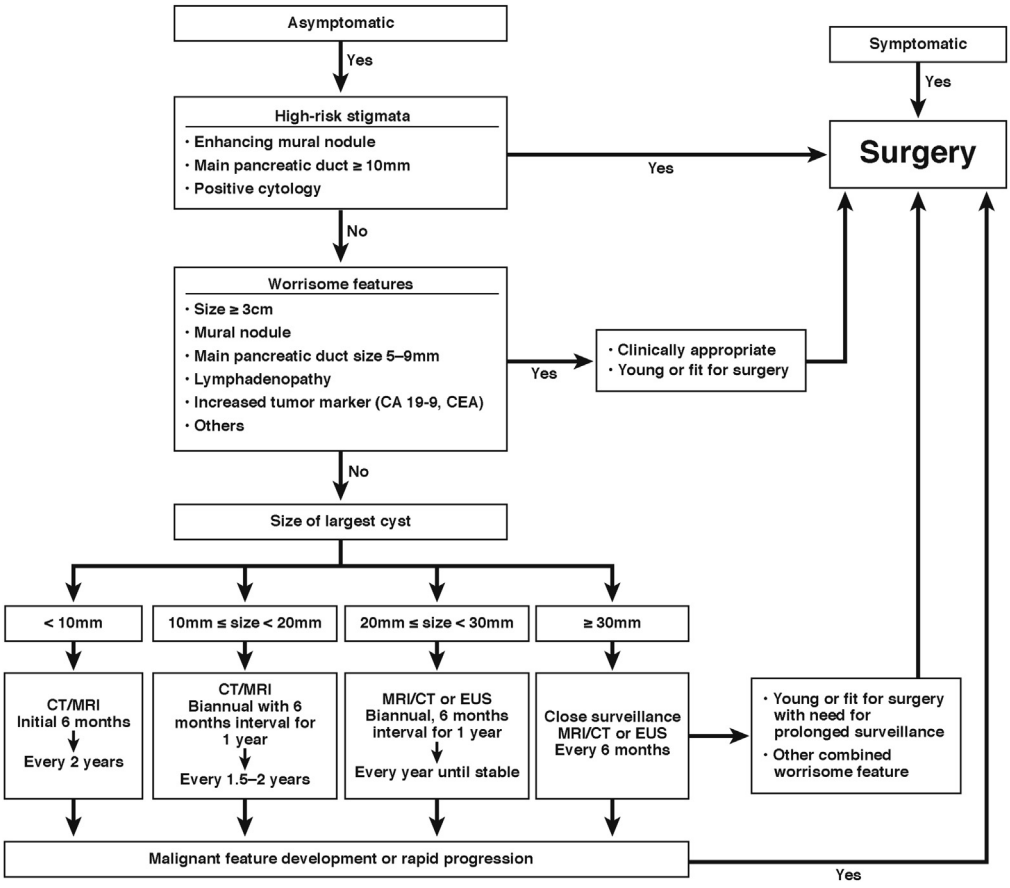


Figure 4. A new surveillance protocol was devised for BD-IPMN patients without high-risk stigmata or worrisome features based on the initial cyst size and growth rate. The selection of diagnostic modality and follow-up period should be based on the cyst size at detection.

diagnostic expenses significantly vary. MRI is 4–5 times more expensive than CT. Therefore, cost-effective diagnostic imaging modalities may depend on national policies on medical expense and actual cost. EUS is an alternative diagnostic modality in patients with cysts who need frequent surveillance or detailed assessments.[28,29] Based on the surveillance protocol recommended in this study, patients with cyst sizes >2 cm can undergo MRI or EUS. Because these patients need frequent check-ups, MRI or EUS is recommended to reduce radiation hazards.

In this study, CT or MRI was used during follow-up, whereas MRI was utilized to help physicians visualize the

Table 3. Optimal Surveillance Interval Based on Growth Rate and Cyst Size

	Group 1 (<10 mm)	Group 2 (≤10–<20 mm)	Group 3 (≤20–<30 mm)	Group 4 (≥30 mm)
Total patient number, n (%)	501 (36.6)	712 (52.0)	125 (9.1)	31 (2.3)
Cyst size, *mm*	7.1 ± 1.8	14.0 ± 2.7	23.6 ± 2.7	35.4 ± 7.3
Growth rate, *mm/y*	0.8 ± 1.1	0.7 ± 1.1	1.1 ± 1.5	1.2 ± 2.1
Maximal growth rate	13.8	8.7	7.7	10.4
95% CI	2.9	2.9	4.0	5.3
Doubling time, *y*	25.6	43.1	127	46.6
Shortest doubling time	0.5	1.6	3.1	3.4
95% CI	2.5	4.9	5.9	6.6
50% increasing time, *y*	12.8	21.5	64	23.3
Shortest 50% increase	0.3	0.8	1.5	1.7
95% CI	1.2	2.4	2.9	3.3
Time taken to exceed 3 cm	81.8	48.4	49.4	
Shortest time, *y*	1.7	1.8	0.8	
95% CI	8.0	5.6	1.6	
Recommended follow-up interval	6 month → 2 year	6 month twice → 2 year	6 month twice → 1 year	Every 6 months

CI, confidence interval.

whole figure and maximal size of the cyst. However, MRI cannot be routinely performed in all patients with BD-IPMN, primarily because of financial constraints compared with CT, which is readily undergone by most patients with BD-IPMN. To address the problems concerning cysts that are long and slender with an upward or downward traction, various CT protocols based on thickness were utilized. Furthermore, 3-dimensional reconstructions were routinely provided, based on CT protocols, to provide a better evaluation of the cyst morphology.

This study has several limitations. First, it has a retrospective design. In addition, despite the increasing importance of tumor markers, including carbohydrate antigen 19-9 and carcinoembryonic antigen,[25] serial follow-up of the tumor marker levels was insufficient. In general, carbohydrate antigen 19-9 was 21.2 ± 118.5 U/mL and carcinoembryonic antigen was 1.9 ± 1.3 ng/mL in patients with BD-IPMN. Tumor marker levels did not significantly differ according to the initial cyst at detection ($P = .270$ and .804, respectively). Furthermore, cytopathology results are not sufficient because such studies are not routinely performed at our institute because of their low sensitivity and the risk of complications, including tumor spillage and resultant peritoneal seeding.[30] Despite such limitations, this study provided a meticulously planned surveillance protocol based on data from 1369 patients with BD-IPMN compared with the current guidelines, which are based on expert opinion. Furthermore, previous studies of the natural history of pancreatic cysts were based on a full range of diagnoses of cysts, including all types of benign pancreatic cysts,[9,31] rather than BD-IPMN alone, and may thus underestimate the incidence of high-grade dysplasia or invasive carcinoma in patients with BD-IPMN. However, this study exclusively included patients with classical radiologic signs of BD-IPMN, and images were reviewed to obtain more accurate results. Therefore, the natural history of BD-IPMN is well depicted in this study. Moreover, patients who were followed-up for at least 3 years were also included in this study because there are few studies that included patients with long-term follow-up periods. Overall, this study provided a meaningful and representative natural history of BD-IPMN in a large patient cohort with a long follow-up period. Although further validation is needed, the proposed surveillance protocol can provide physicians more insight into the natural history of BD-IPMN and patients' evidence-based follow-up plans.

In conclusion, although most BD-IPMNs are indolent and dormant, some cysts rapidly grow with the development of other worrisome features. Therefore, follow-up intervals should be based on the initial cyst size and growth rate.

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Conflicts of interest
The authors disclose no conflicts.

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