췌관내유두상점액종의 장기 추적관찰을 통한 자연경과의 고찰

Natural history of intraductal papillary mucinous neoplasm of pancreas during surveillance: focusing on cyst growth and manifestation of worrisome features

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Abstract

Natural history of intraductal papillary mucinous neoplasm of pancreas during surveillance: focusing on cyst growth and manifestation of worrisome features

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Background: To evaluate the natural history of branch-duct intraductal papillary mucinous neoplasms (BD-IPMN) of the pancreas under surveillance and to recommend optimal follow up intervals and duration.

Methods: We included only patients whose imaging studies showed classical features of BD-IPMN, and conducted follow-up periods of at least 3 years. We reviewed radiologic and pathologic findings, and performed linear and binary logistic regressions to estimate cyst growth.

Results: We identified 1,369 patients diagnosed with BD-IPMN. The

median annual growth rate of the cyst was 0.6 mm over a median follow-up time of 61 months. During surveillance, 46 patients (3.4%) underwent surgery due to disease progression after a median follow-up time (in this group) of 62 months. Worrisome features were observed in 171 patients (12.5%) during surveillance, including cyst size >3 cm (n=47, 3.4%), cyst wall thickening (n=51, 3.7%), main pancreatic duct (MPD) dilatation (n=78, 5.7%) and mural nodule (n=43, 3.1%). Along with annual cyst growth rate, incidences of MPD dilatation, cyst wall thickening and mural nodules were related to initial sizes of cysts at detection ($P<0.001$).

Conclusion: Most BD-IPMN appear indolent, but some exhibit rapid growth and progression. Therefore, surveillance protocols should be individualized with regards to the natural history of BD-IPMNs focusing on initial cyst size and growth rate.

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keywords : Intraductal papillary mucinous neoplasm of pancreas, IPMN, Natural history

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I. Introduction

 Detection of pancreatic cysts has increased over the last two decades due to wider screening and advances in radiologic diagnosis such as computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS).[1] [2] With increasing identification of pancreatic cysts and recognition of their malignant potential, whether to treat them with upfront surgery or watchful surveillance has been the subject of extensive research.

Intraductal papillary mucinous neoplasm (IPMN) is the most frequently detected premalignant lesion involving the main pancreatic duct (MPD) or branch ducts. 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, but accumulating evidence suggests that watchful surveillance is suitable for branch duct IPMN (BD-IPMN) with no high-risk stigmata features.[4] However, BD-IPMN requires continuous follow-up after initial diagnosis because of its reported annual malignancy conversion rate of 2% - 15%.[5] [6]

Several guidelines regarding surveillance of IPMN are available, including those from the International Association of Pancreatology (IAP), European Experts Consensus and American Gasteroenterological Association. However, these protocols vary greatly and show little agreement regarding follow-up intervals and duration. According to the 2012 IAP guideline for management of suspected BD-IPMN, patients with high-risk stigmata are recommended to have surgery, and patients who present with worrisome features should undergo EUS. However, close surveillance is recommended according to cyst size for those with nonspecific EUS findings and no worrisome features, such as over 3cm size cyst, mural nodule, cyst wall thickening and main pancreatic duct dilatation.[4]

However, the consensus guidelines and its recommendations regarding surveillance are based on expert opinions and lack evidentiary support. Also,

several recommendations on surveillance are based on other benign pancreatic cysts in addition to BD-IPMN, and thereby underestimate diagnoses of malignant IPMN. Therefore, this study aimed to evaluate the natural history of BD-IPMN and recommend an optimal surveillance protocol with respect to cyst growth and worrisome features that develop during follow-up.

II. Materials and Methods

1. Patient selection and data collection

We retrospectively reviewed clinicopathologic findings and radiologic images through a thorough search of electronic medical records, which were screened using codes defined by the International Classification of Diseases-10 (ICD-10). Patients diagnosed with pancreatic cyst (K862) and intraductal papillary mucinous neoplasm (D017, D136, D377, C259) were extracted. We also selected patients with pancreatic cystic lesions transcribed on image readings. Radiologic and pathologic data were reviewed by an experienced board-certified radiologist and pathologist who specialize in hepatobiliary and pancreas imaging and pathology (respectively) with more than 15 years of experience.

We identified 10,083 patients suspected to have IPMN at the Seoul National University Hospital from January 2001 and December 2016. We excluded 4,566 patients with uncertain diagnoses, 3,630 patients with follow-up periods of less than 3 years, 473 patients with only ultrasound follow-up images, and another 47 patients we considered to have MD-IPMN based on their radiological findings. Finally, a total of 1,369 patients with BD-IPMN were included and analyzed (Figure 1).

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital, which waived the requirement for informed consent (IRB number 1704-102-846).

Figure 1. Study design and patient selection
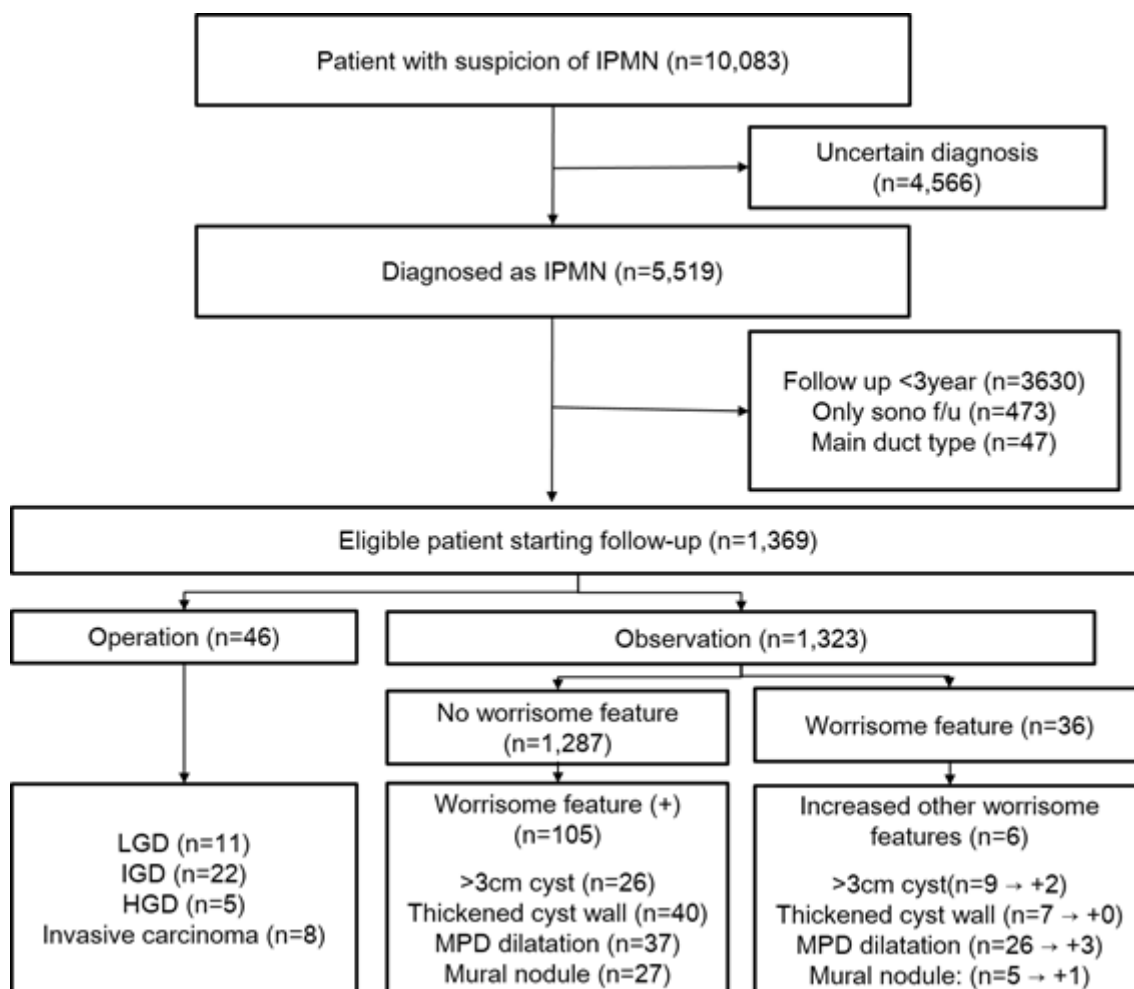
-IPMN: Intractal papillary mucinous neoplasm, f/u: follow-up, LGD: Low grade dysplasia, IGD: intermediate grade dysplasia, HGD: High grade dysplasia, MPD: Main pancreatic duct

2. Radiologic evaluation and follow-up

The diagnosis and follow-up of BD-IPMN includes computed tomography(CT), magnetic resonance imaging(MRI), endoscopic ultrasonography(EUS) and endoscopic retrograde cholangiopancreatography(ERCP). Initial diagnoses were made with CT scans because CT was considered as the standard modality for diagnosis and was used for cyst size measurements during follow-up. Most patients underwent CT or MRI during surveillance to observe any changes in

cystic features or to identify malignant transformation or progression. Additionally, EUS was performed to detect suspicious mural nodules or cyst wall thickening in patients with higher risks of malignancy.

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

BD-IPMN was diagnosed when typical features were observed, including pleomorphic shape, clubbed or finger-like appearance, and definite pancreatic ductal communication on CT, MRI or EUS.[7] Cyst size was defined as the average of the major and minor axis diameters on axial images. For multiple lesions, we mainly focused on the largest cyst during follow-up. Mural nodules were defined as enhanced hyperdense nodules that protruded into the dilated branch duct that enhanced after 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 and MPD dilatation was defined as diameter of main pancreatic duct over 5mm. All images were reviewed twice by a radiologist and a surgeon who were blinded to the final pathology. When discrepancies arose regarding radiologic findings, parameters were measured after 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 (average of the major and minor axis diameters); absolute differences in cyst sizes and absolute cyst growth rates (absolute size difference/follow-up period). In addition, we calculated time to increase to 150% of initial cyst size ([initial cyst size/2] ×

absolute cyst growth rate; i.e., half the doubling time), and time for the cyst to become > 3 cm ([30 mm − initial cyst size] × absolute cyst growth rate).

According to institutional policy, patients diagnosed with BD-IPMN underwent radiological follow up every 3‑6 months during the first year, with intervals lengthened to 9‑12 months if no progression or evidence of malignancy was seen. Surveilled patients underwent surgery if cyst size increased, they developed symptoms such as pancreatitis or obstructive jaundice, or when other factors associated with malignancy, such as mural nodules, appeared in follow-up imaging.

3. Statistical analysis

Statistical analysis was performed using R software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All variables are expressed in median and mean values, with standard deviations, ranges or percentages when appropriate. Categorical variables were compared using chi-square tests or Fisher's exact test, and continuous variables using t-tests or Wilcoxon rank-sum test. Univariate and multivariate analysis was performed. Linear regression and binary logistic regression were used to estimate cyst size and MPD size changes. Reclassification of development of worrisome features was performed using a net reclassification index(NRI). Survival analysis was performed to calculate risk of appearing worrisome features. $P < 0.05$ was considered significant.

III. Results

1. Patient demographics

We included 1,369 patients (Table 1) with a mean age of 62.5 years. They included 719 men (52.5%) and 650 women (47.5%). The median follow-up duration was 61 months. The mean initial cyst size was 11.1 mm and MPD was 1.8 mm and at final follow-up examination, the mean cyst size was 14.2 mm and MPD was 2.4 mm.

We detected a total of 171 new worrisome features during surveillance. At the end of surveillance, 47 (3.7%) cysts > 3 cm, 51 (3.7%) thickened cyst walls, 77 (5.6%) MPDs of 5‑9 mm, and 43 (3.1%) newly developed mural nodules.

Table 1. Patient Demographics

Variables		
Age (mean ± SD), years		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)], months		61 (36-189)

	Initial	Final
Cyst diameter (mean ± SD), mm	11.1 ± 5.4	14.2 ± 7.4
Main pancreatic duct (mean ± SD), mm	1.8 ± 1.0	2.4 ± 1.8
Worrisome feature development, n (%)		
Cyst size >3cm	9 (0.7%)	47 (3.4%)
Cyst wall thickening	71 (5.2%)	51 (3.7%)
MPD 5-9mm	26 (1.9%)	78 (5.7%)
Mural nodule	5 (0.4%)	43 (3.1%)
Multiplicity	241(17.6%)	326 (23.8%)

-SD: standard deviation, M: male, F: female, MPD: main pancreatic duct

2. Cyst growth and worrisome feature manifestation

Median annual cyst growth rate was 0.6 mm (Figure 2). Although 1,287 patients had no combined worrisome features at initial diagnosis, during surveillance, 105 patients (8.2%) developed newly or additional worrisome features, including 26 cysts that grew to >3 cm, 40 newly thickened cyst walls, 37 cases of MPD dilatation and 27cases of mural nodules. Among the 36 patients who showed worrisome features at diagnosis, during surveillance, 2 had cysts that grew to >3 cm, 3 developed MPDs of 5‑9 mm and 1 developed mural nodules (Figure 1).

Figure 2. Changes in cyst size
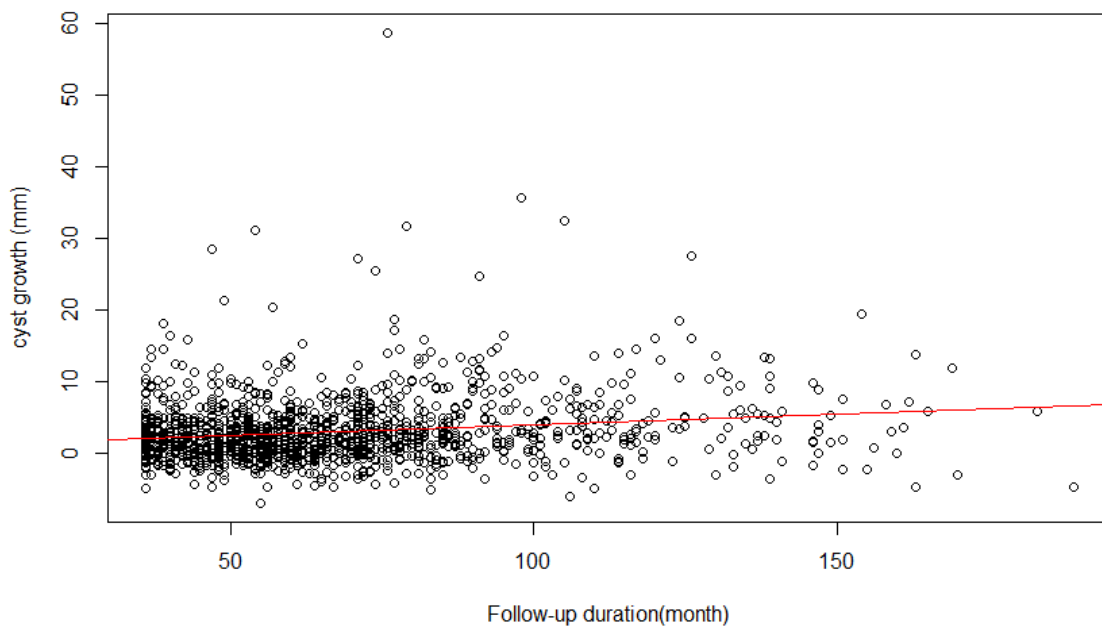
3. Surgery

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 malignancy. The 46 patients who underwent surgical resection did so after a median surveillance period of 62 months (Figure 1), and included 13 patients who were finally diagnosed with malignant IPMN (28.3% of the resection group, but only 0.9% of the entire BD-IPMN cohort), of whom five patients (10.9%) were pathologically diagnosed with high-grade dysplasia and eight patients (17.4%) with invasive carcinoma. Among the 33 other resection patients, 11 (23.9%) had low-grade dysplasia, and 22 (47.8%) had intermediate-grade dysplasia.

4. Cyst morphological changes by initial cyst size

We divided our subjects into four groups according to their initial cyst sizes, as Group 1: <10 mm (n=667), Group 2: 10 mm – <20 mm (n=608), Group 3: 20 mm – <30 mm (n=84), and Group 4: ≥30 mm (n=10; Table 2); their respective median annual growth rates (calculated relative to initial cyst size) were 0.6 mm, 0.5 mm, 1.0 mm and 1.0 mm (Figure 3). Because median annual growth rates differed significantly between Groups 1 and 2 and Groups 3 and 4 (P<0.001), we combined Groups 1 and 2 and Groups 3 and 4 into two groups (Group 1–2 [n=1275] and Group 3–4 [n=94]) to evaluate incidences of newly developed worrisome features. Of the 172 cases (12.6%) of newly developed or progressed worrisome features seen in the cohort as a whole 117 cases (9.2%) were found in Group 1–2, with a median development time of 65months; and 55 cases (58.5%) were seen in Group 3–4, with a median time of 26months.

MPD dilatation incidence and diameter also varied significantly with initial cyst size (P<0.001). MPD diameter was 1.7 ± 0.8mm, 1.9 ± 1.0 mm, 2.4 ± 1.3 mm and 2.7 ± 1.5 mm in Groups 1, 2, 3 and 4, respectively. Incidence of cyst wall thickening increased with cyst size as well, as Group 1: 15 patients (2.2%), Group 2: 44 patients (7.2%), Group 3: 11 patients (13.1%), and Group 4: 1 patient (10.0%; P<0.001). Incidence of mural nodules also differed significantly,

as Group 1: 0 patents, Group 2: 2 patients (0.3%), Group 3: 2 patients (2.4%); and Group 4: 1 patient (10.0%; *P*<0.001).

Figure 3. Cyst growth rate according to initial cyst size
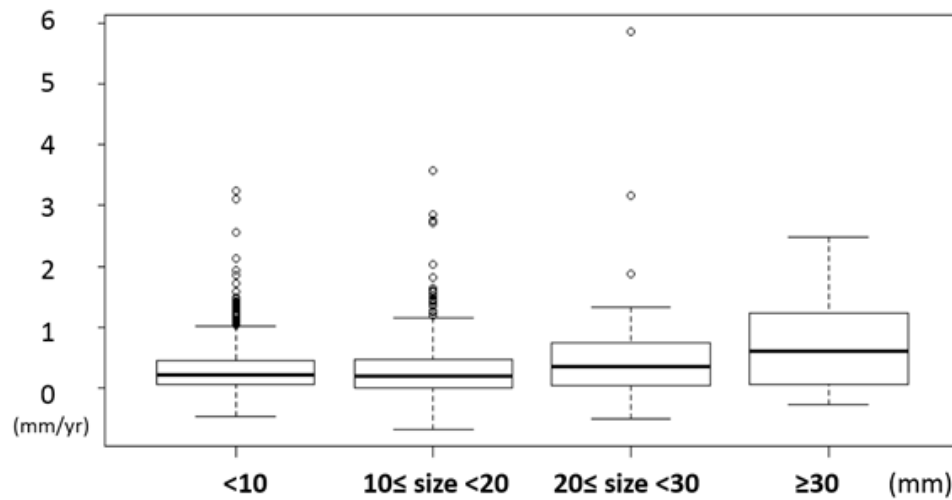
Patient demographics are also listed in Table 2. Patient's age(62.1 ± 9.2, 62.5 ± 9.9, 66.0 ± 9.5, 63.0 ± 8.6 years, respectively) and sex(p=0.016) were significant between the group. The presence of diabetes mellitus increased with cyst size, Group 1: 144 patients (12.6%), Group 2: 133 patients (21.9%), Group 3: 26 patients (31.0%), and Group 4: 6 patient (40.0%; *P*<0.001). Smoking history and family history of cancer had no difference between the groups.

Survival analysis was performed to calculate risk of worrisome feature according to group of initial cyst size. The median time for occurrence of worrisome feature were 169 months, 183 months, 35 months and 14, months, respectively. The risk of developed worrisome feature in BD-IPMN smaller than 1 cm was 0.5% at 1 year follow-up and 1.0% at 2 year. In group 2 (initial cysts 1-2 cm), 2.3% and 4.9% were calculated cumulative risk at follow-up period of one and two years respectively. The cumulative risk of cyst larger than 2cm was higher than that of smaller cyst groups(2.3% at 1year, 50% at 2year, Figure 4).

Figure 4. Occurrence rate of worrisome features according to initial cyst size groups
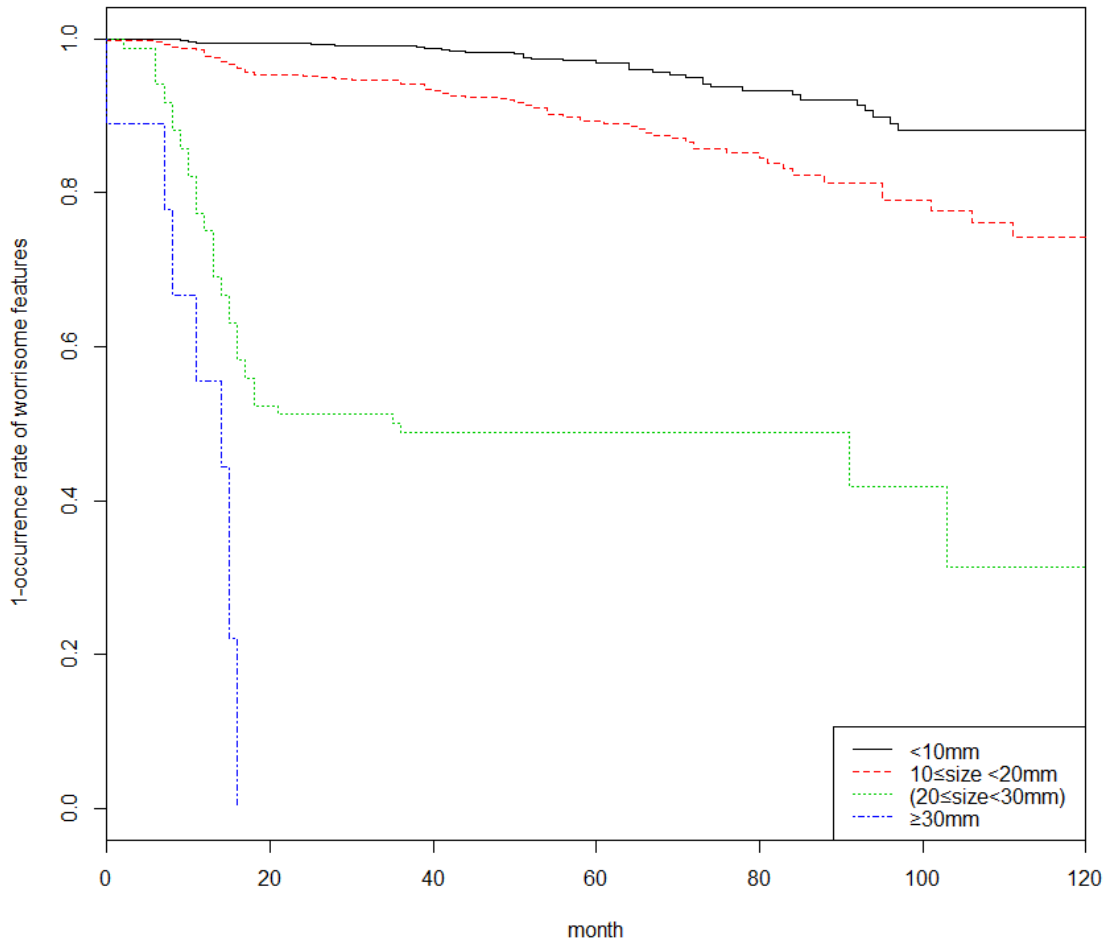
Conclusively, larger cysts, especially cysts larger than 2 cm, showed significantly faster annual growth rates, and likelihood of MPD dilatation and cyst wall thickening ($P<0.001$). Furthermore, initially larger cysts developed more worrisome features during surveillance and did so over shorter periods(Table 2)

Table 2. Difference in cyst feature and demograhics according to initial cyst size at detection

	Group 1 (<10mm)	Group 2 (10≤ size <20mm)	Group 3 (20≤ size<30mm)	Group 4 (≥30mm)	P-value
n (%)	667 (48.7)	608 (44.4)	84 (6.2)	10 (7.3)	
Age (mean±SD), years	62.1 ± 9.2	62.5 ± 9.9	66.0 ± 9.5	63.0 ±8.6	0.012
Sex (M/F), n (%)	324 (48.6%) / 343 (51.4%)	338 (55.6%) / 270 (44.4%)	50 (59.5%) / 34 (40.5%)	7 (70.0%) / 3 (30.0%)	0.016
Smoking history, n (%)	35 (5.2%)	30 (4.9%)	4 (4.8%)	0 (0.0%)	0.904
DM, n (%)	144 (21.6%)	133 (21.9%)	26 (31.0%)	6 (60.0%)	0.003
Family history of cancer, n (%)	74 (11.1%)	65 (10.7%)	16 (19.0%)	2 (20.0%)	0.100
Cyst size (mean ± SD), mm	7.0 ± 1.9	13.4 ± 2.6	23.3 ± 2.7	34.1 ± 9.4	<0.001
Location, n (%) Head Body & tail	257 (38.5%) 410 (61.5%)	594 (97.7%) 14 (2.3%)	50 (59.5%) 34 (40.5%)	7 (70.0%) 3 (30.0%)	<0.001
Type, n (%) BD Mixed	657 (98.5%) 10 (1.5%)	594 (97.7%) 14 (2.3%)	59 (70.2%) 25 (29.8%)	2 (20.0%) 8 (80.0%)	<0.001
Annual growth rate, mm/year	0.6 ± 0.7	0.5 ± 0.9	1.0 ± 1.5	1.0 ± 1.2	<0.001
MPD dilatation, n (%)	38 (5.7%)	71 (11.7%)	22 (26.2%)	4 (40.0%)	<0.001
MPD diameter, mm	1.7 ± 0.8	1.9 ± 1.0	2.4 ± 1.3	2.7 ± 1.5	<0.001
Wall thickening, n (%)	15 (2.2%)	44 (7.2%)	11 (13.1%)	1 (10.0%)	<0.001
Mural nodule, n (%)	0 (0.0%)	2 (0.3%)	2 (2.4%)	1 (10.0%)	<0.001
Worrisome feature development, n (%)	37 (5.5%)	80 (13.2%)	45 (53.6%)	10 (100.0%)	<0.001
Time to worrisome feature development, months (mean±SD)	68.6 ± 28.9	63.2 ± 28.0	40.9 ± 32.8	11.3 ± 5.4	<0.001

n: number of patient, SD: standard deviation, DM: diabetes mellitus M: male, F: female, BD: branch duct, MPD: main pancreatic duct

5. Prediction model of final cyst size and development of worrisome features

Correlation analysis was performed to evaluate the relationship between final cyst size and related factors including age, initial cyst size, MPD size and follow-up duration. Formulas using simple linear regression models were developed. Formulas and correlation coefficients R for each factors are as followed (Figure 5); $y=1.06x_1+2.45$, $R_1=0.6023$ (x_1: Initial cyst size), $y=1.44x_2+11.53$, $R_2=0.0369$ (x_2: MPD size), $y=0.09x_3+8.74$, $R_3=0.0128$ (x_3: age), $y=0.02x_4+12.87$, $R_4=0.0051$ (x_4: Follow-up duration).

Initial cyst size, age, follow-up duration and development of worrisome features were significantly associated with the final cyst size in multiple regression analysis with $P<0.001$ ($y=0.95x_1+0.05x_2+0.03x_3+4.76x_4-2.11$, x_1: initial cyst size, x_2: age, x_3: follow-up duration, x_4: development of worrisome features, table 3).

Figure 5. Correlation analysis of the final cyst size
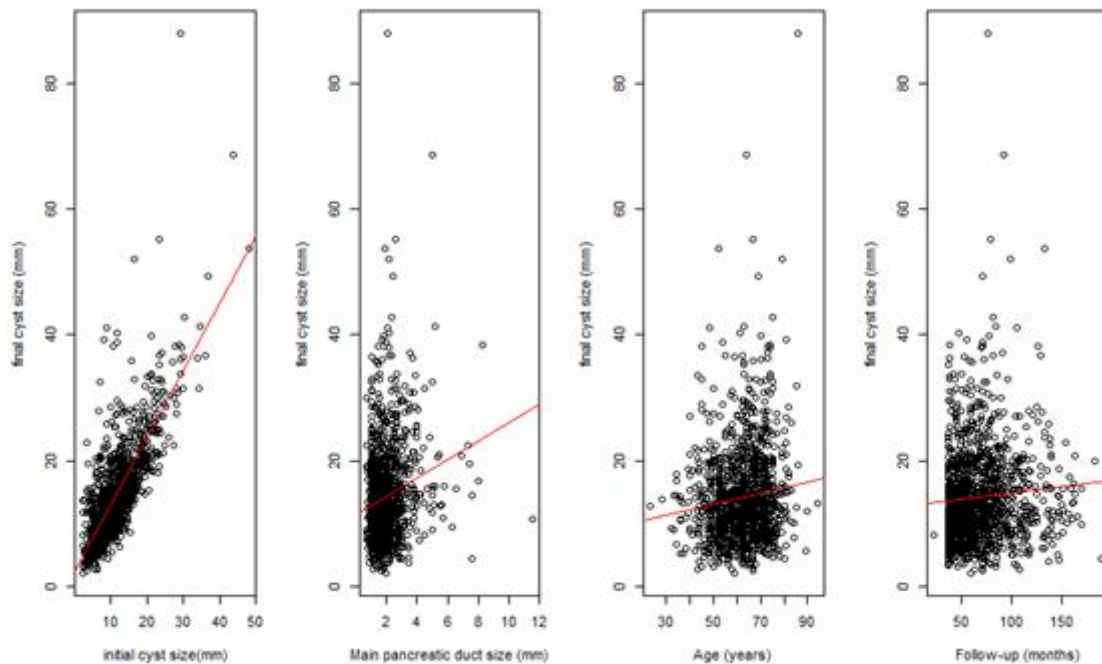
Table 3. Univariate and multivariate analysis for the final cyst size

	Univariate			Multivariate		
	estimate	SE	Pr(>|t|)	estimate	SE	Pr(>|t|)
Initial cyst size	1.06	0.02	<0.001	0.95	0.02	<0.001
MPD size	1.44	0.199	<0.001	0.16	0.13	0.198
age	0.09	0.02	<0.001	0.05	0.01	<0.001
follow-up duration	0.02	0.01	0.008	0.03	0.004	<0.001
development of worrisome features	10.81	0.53	<0.001	4.76	0.38	<0.001

-SE: standard error, MPD: main pancreatic duct

6. risk predictors of worrisome feature development

In the entire cohort of 1,369 patients, 171 cases (12.5%) developed newly or progressed worrisome features. On comparing presence of worrisome feature group and no worrisome feature group, proportion of male sex(60.2% vs 51.4%,; p=0.038), presence of diabetes mellitus(29.2% vs 21.6%; p=0.033) were higher in worrisome feature group, as were cyst size(16.6 vs 10.3mm; p<0.001), growth rate(1.3 vs 0.5mm/year; p<0.001) and initial presence of worrisome features. Linear regression analysis revealed higher age, longer follow-up duration, larger cyst size in worrisome feature group(Table 4).

Table 4. Univariate and multivariate analysis of worrisome feature appearing in IPMN during surveillance

	Univariate analysis			Multivariate analysis		
	no worrisome features (n=1198)	worrisome features (n=171)	p-value	OR	95%CI	p-value
Age(mean±SD), years	62.3 ± 9.5	63.8 ± 10.2	0.069	1.00	1.00-1.00	0.027
Sex (M:F)	616/582	103/68	0.038	1.01	0.98-1.04	0.407
Smoking, n(%)	58 (4.8%)	11 (6.4%)	0.482			
DM, n(%)	259 (21.6%)	50 (29.2%)	0.033	1.01	0.98-1.04	0.616
Family history of cancer, n(%)	136 (11.4%)	21 (12.3%)	0.820			
Follow-up duration, month	67.4 ± 26.9	68.5 ± 28.8	0.640	1.0	1.00-1.00	0.018
Cyst size, mm	10.3 ± 4.4	16.6 ± 8.2	<0.001	1.02	1.01-1.02	<0.001
MPD size, mm	1.7 ± 0.7	3.0 ± 1.7	<0.001	1.13	1.11-1.15	<0.001
Wall thickening, n (%)	0 (0.0%)	7 (4.1%)	<0.001	1.71	1.40-2.08	<0.001
Mural nodule, n (%)	0 (0.0%)	5 (2.9%)	<0.001	1.45	1.15-1.83	<0.001
growth rate ,mm/yr	0.5 ± 0.7	1.3 ± 1.6	<0.001	1.11	1.09-1.13	<0.001

IPMN: intraductal papillary mucinous neoplasm, n: number of patient, M: male, F: female, DM: diabetes mellitus, MPD: main pancreatic duct

According to IAP guideline, initial cyst size and worrisome features(MPD size, cyst wall thickening, mural nodule positivity) should be considered during surveillance. In order to understand the role of addition of patient's age, follow-up duration and annual growth rate of cyst to the conventional IAP guideline, we created two multivariate models: One with IAP guideline

covariates (Initial cyst size, main pancreatic duct size, cyst wall thickening, mural nodule) and another with IAP guideline covariates plus patient's age, follow-up duration and annual growth rate.

There was a net improvement in reclassification of age, follow-up duration, growth rate by 80.8%, which was statistically significant(p<0.001). Net upward reclassification for those who had an event(developing worrisome features) was 8.187% and net downward reclassification for those who did not have an event was 0.417% (Table 5).

Table 5. Reclassification table for nonevents and events in the worrisome feature in IPMN

Old Model	New Model 0-3% No.(%)	3-10% No.(%)	>10% No.(%)	Reclassification Up	Down
	Nonevents(n=1198)				
0-3%	876 (73%)	45 (4%)	0 (0%)	63	135
3-10%	116 (10%)	93 (8%)	18 (2%)		
>10%	2 (0%)	17 (1%)	31 (3%)		
	Events(n=171)				
0-3%	25 (15%)	6 (4%)	8 (5%)	36	13
3-10%	11 (6%)	10 (6%)	22 (13%)		
>10%	1 (1%)	1 (1%)	87 (51%)		

IPMN: Intraductal papillary mucinous neoplasm

IV. Discussion

Incidence of pancreatic cyst diagnoses, including IPMN, has increased dramatically.[1] [3] Since the first cases of IPMN in the 1980s, their diagnosis and management has been widely studied. Whereas resection is recommended for MD-IPMN and mixed-type IPMN due to their high malignant potential,[8] management of BD-IPMN is still evolving. Careful nonsurgical surveillance is generally suggested for BD-IPMN, as facilitated by improved imaging techniques

and better understanding of its natural history.

BD-IPMN has a low but persistent risk of malignancy, with a reported annual malignancy conversion rate of 2%‑3%.[5] Its surgical intervention rate was less than 10% and risk of an associated malignancy was lower than 5%.[9] Watchful surveillance in BD-IPMN with worrisome features shows tolerable outcomes with a 5-year survival rate at 81% and disease-specific survival (DSS) of 90% in patients who present worrisome features or high stigmata treated with nonsurgical monitoring. Patients with worrisome features showed better 5-year DSS than those with high-risk stigmata (96% vs 60%).[10] Our results indicate that patients with high-risk stigmata should undergo surgery whereas careful surveillance may be appropriate for patients with worrisome features, especially in elderly patients with shorter life expectancies.

Although our results accord with other reports that found tolerable DSS and persistent but low overall malignancy risk in BD-IPMN to justify close surveillance, most suggested surveillance protocols are based on short-term follow up and lack evidence regarding long-term safety. Currently, four guidelines are used in clinical practice. The 2012 IAP 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 thereafter for cysts 1‑2 cm; and EUS every 3‑6 months alternating with MRI for cysts 2‑3 cm.[4] The 2013 European Experts Consensus recommends follow-up with MRI or EUS twice a year in the first year and every 2 years thereafter for BD-IPMN without risk factors regardless of cyst size, then annual follow-up for 5 years for stable cysts with no changes.[11] The American College of Radiology and American Gastroenterological Association also suggest surveillance protocols.[12][13] However, all of these guidelines are based on expert opinions rather than supported by substantial evidence.[14][15] Additionally, pancreatic cysts can grow after an initial period of stability, which implies that current guidelines to discontinue surveillance after periods of

stability need reevaluation.[16] Therefore, a revised surveillance protocol, based on strong evidentiary support regarding 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 do not include IPMN with typical radiologic signs. Therefore, benign pancreatic cysts such as serous cystic neoplasm or pseudocyst are also included which can affect analytic results and surveillance protocols in turn.[17] [18]

To our knowledge, this is the one of the largest cohort investigation that exclusively includes BD-IPMN patients who presented with typical radiologic signs.[19] [20] In the present study, incidences of worrisome features varied over time differed by initial cyst size at detection. As with previous studies, we found initial cyst size to be an important parameter in determining BD-IPMN natural history.[17] Incidences of MPD dilatation, mural nodules and cyst wall thickening increased with cyst sizes, and the malignancy rate increased with initial cyst size. Larger cysts had higher risk of malignant transformation. During surveillance, 14% of our subjects developed new worrisome features and 0.9% developed malignant IPMN. New worrisome feature manifestation rates and growth rates differed by initial cyst size. The annual average growth rate was 0.6mm. New worrisome feature manifestation rates differed according to initial cyst size and growth rate. The annual cyst growth rate was 0.5mm annually in cysts smaller than 2cm developed worrisome features in 1.1% while growth rate was 1mm annually in cysts larger than 2cm with 14.9% manifesting new worrisome features. Accordingly, we devised a modified surveillance protocol based on initial cyst size and cyst growth rate.

Although the current medical trend for BD-IPMN is watchful surveillance, BD-IPMN has a risk of malignant transformation, and if malignant, 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 initial cyst size at diagnosis and

growth rate (Figure 3). Symptomatic BD-IPMN patients, and asymptomatic patients who present high risk stigmata should undergo upfront surgery as their initial management. The 5-year survival rate of invasive IPMN is reportedly 40%.[13] Therefore, preventive surgery is justified in high-risk patients. For asymptomatic patients who exhibit worrisome features, such as size > 3 cm, thickened or enhanced cyst wall and/or MPD of 5–9 mm, surgery should be considered if the patient is young or fit for surgery. However, for patients with no worrisome features, careful surveillance should be recommended, according to the initial cyst size.

With asymptomatic BD-IPMN with no worrisome features, we recommend a modified surveillance protocol based on initial cyst size, cyst growth rate, 150% growth time (Table 6) and time for occurrence of worrisome features (Figure 4). This protocol also accounts for some outliers that show rapid cyst growth as previously described (Figure 3). For example, for a BD-IPMN < 1 cm with an annual growth rate of 0.8 mm and a maximal annual growth rate of 7.4 mm annually, the time for the cyst to grow 150% (i.e., half the doubling time) is 9 years for a BD-IPMNs < 1 cm, whereas the minimal half-doubling time in a rapidly growing cyst is 6 months. Furthermore, 95% of the BD-IPMN <1 cm showed growth within 2 years. Therefore, BD-IPMN cysts <1 cm should be checked up 6 months after initial diagnosis and every 2 years with CT or MRI thereafter. Furthermore, we recommend that cysts 1–2 cm be managed with follow-up examinations every 6 months with CT or MRI for 1 year and every 1.5–2 years thereafter. Moreover, as cysts show accelerated growth according to their initial sizes at detection, cysts > 2 cm should receive follow-up examinations with MRI or EUS every 6 months for 1 year and then annually thereafter until the cyst size and features become stable. Cysts larger than 3 cm should receive close surveillance with MRI or EUS every 6 months; surgical resection can be considered in younger patients or in patients with other combined worrisome features.

Table 6. Optimal surveillance interval based on growth rate and cyst size

	Group 1 (<10mm)	Group 2 (10≤ size <20mm)	Group 3 (20≤ size<30mm)	Group 4 (≥30mm)
n (%)	667 (48.7)	608 (44.4)	84 (6.2)	10 (7.3)
Cyst size, mm	7.0 ± 1.9	13.4 ± 2.6	23.3 ± 2.7	34.1 ± 9.4
Growth rate, mm/year	0.6 ± 0.7	0.5 ± 0.9	1.0 ± 1.5	1.0 ± 1.2
Maximal growth rate	6.9	7.3	9.3	3.3
95% C.I.	2	2.3	3.9	3.3
Doubling time, year	11	26	23	34
Shortest doubling time	1	1.8	2.5	11.2
95% C.I.	3.6	5.8	5.9	11
50% increasing time, year	5	13	11	17
Shortest 50% increase	0.5 (6 month)	0.9 (10 month)	1.3	5.6
95% C.I.	1.8	2.9	3.0	5.5
Time taken to exceed 3cm	38	33	6	
Shortest time, year	3.3	2.3	0.7	
95% C.I.	11.6	7.1	1.7	
Recommended follow up interval	6 month à 2 year	6 month twice à 2 year	6 month twice à 1 year	Every 6 months

－C.I.: Confidence interval

Figure 6. Surveillance protocol for BD-IPMN
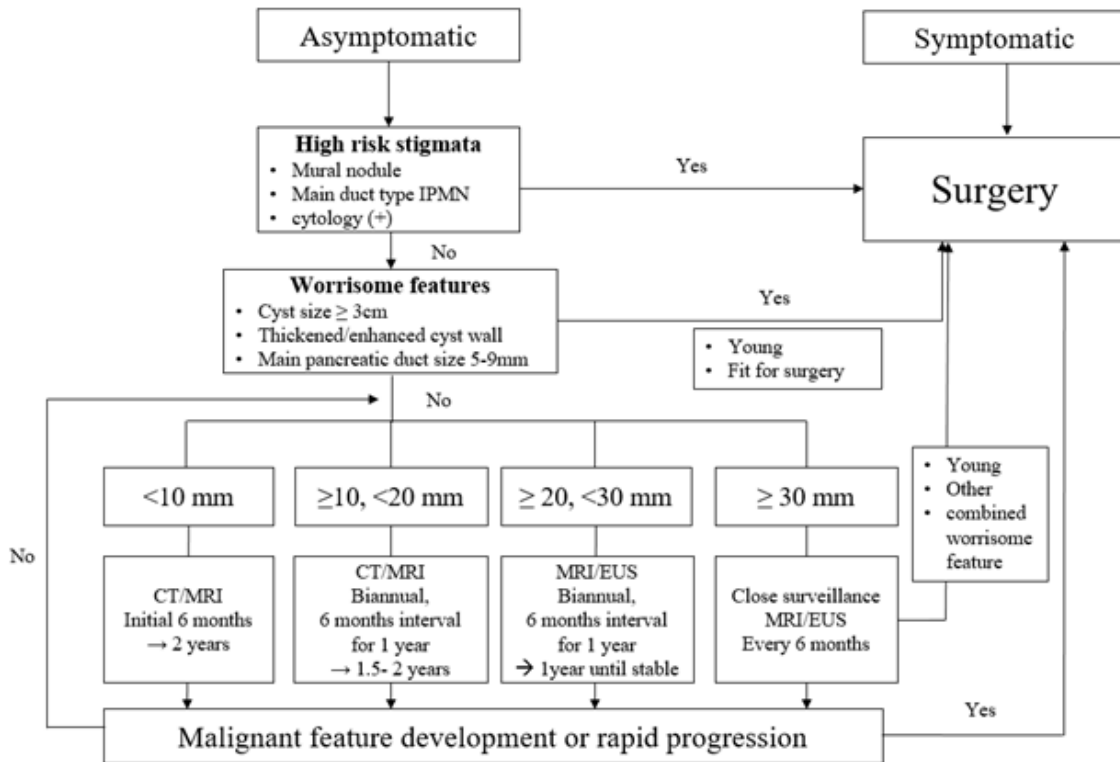
Overall, the radiological diagnostic rate between CT and MRI is comparable, both with high accuracy.[21][22] In the European and American guidelines, MRI is suggested for patients who require close surveillance, due to the radioactive exposure of CT. However, in some countries, diagnostic expenses greatly vary; MRIs can be more than 4‑5 times more expensive than CT use. Therefore, cost-effective diagnostic imaging modalities may depend on national policies regarding medical expense and actual cost. EUS is an alternative diagnostic modality in patients who need frequent surveillance or detailed assessments of their cysts.[23][24] In the surveillance protocol recommended in this study, patients with cyst sizes larger than 2 cm can undergo MRI or EUS. Since these patients need frequent checkups, MRI or EUS is recommended to reduce radiation hazards.

This study is somewhat limited by its retrospective design. However, it provides a judiciously planned surveillance protocol based on data from 1,369 patients

with BD-IPMN, in contrast to 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 including all types of benign pancreatic cysts,[17] [25] rather than BD-IPMN alone, and may thus underestimate the incidence of malignancy in BD-IPMN. However, this study exclusively includes patients with classical radiologic signs of BD-IPMN. Therefore, the natural history of BD-IPMN is well depicted in this study. This study also includes patients who were followed-up for at least 3 years, as there are only few studies that include patients with long-term follow-up. Overall, this study provides 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 provide patients evidence-based follow-up plans.

In conclusion, although most BD-IPMN is indolent and dormant, some cysts show unusually rapid growth with development of malignant signs. Therefore, follow-up intervals should be based on initial cyst size and growth rate.

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요약(국문초록)

췌관내유두상점액종의 장기 추적관찰을 통한 자연경과의 고찰

배경: 췌관내유두상점액종은 췌장암 전구병변으로 알려져 있다. 이에 췌관내유두상점액종의 자연경과를 관찰하고, 최적의 경과관찰 기간 및 간격을 제시하고자한다.

방법: 2001년부터 2016년까지 서울대학교병원에서 췌장낭성종양 진단을 받은 환자 중 영상검사상 전형적인 췌관내유두상점액종의 형태를 보이며 추적관찰 기간이 3년 이상인 환자를 대상으로 하였다. 진단시와 추적관찰 후 촬영한 모든 영상과 수술 후 병리결과를 확인하여 분석에 이용하였다.

결과: 췌관내유두상점액종으로 분석에 사용한 대상자는 1369명이었다. 경과관찰기간 중 췌관내유두상점액종은 연간 0.6mm 증가하였으며, 경과관찰기간의 중위값은 61개월이었다. 경과관찰기간 중 46명(3.4%)의 환자가 질병의 진행으로 수술을 받았으며, 수술 받은 환자의 경과관찰기간 중위값은 62개월이었다. 경과관찰기간 중 위험인자는 171명(12.5%)에서 발생했으며, 이는 3cm 이상 크기증가(n=47, 3.4%), 낭종벽비후(n=51, 3.7%), 주췌관확장 (n=78, 5.7%), 낭종내벽결절(n=43, 3.1%)을 포함하였다. 연간 낭종증가율과 위험인자의 발생은 발견당시 낭종의 크기와 관계가 있었다(P<0.001).

결론: 대부분의 췌관내유두상점액종은 무증상에 크기변화가 미미하나, 몇몇 환자에게서 낭종의 크기가 빠르게 증가하거나 췌장암으로 진행하는 경우가 있다. 그러므로 낭종 크기와 증가율에 따라 경과관찰을 진행하여야한다.

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