

Validation of the American Gastroenterological Association guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up

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Abstract

Objectives Recent guidelines suggest that imaging surveillance be conducted for 5 years for patients with at most one high-risk feature. If there were no significant changes, surveillance is stopped. We sought to validate this follow-up strategy. **Methods** In study 1, data were analysed for 392 patients with intraductal papillary mucinous neoplasms (IPMNs) and at most one high-risk feature who were periodically followed up for more than 1 year with imaging tests. In study 2, data were analysed for 159 IPMN patients without worsening high-risk features after 5 years (stop surveillance group). **Results** In study 1, pancreatic cancer (PC) was identified in 12 patients (27.3%) in the endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) indication group and none in the non-EUS-FNA indication group ($P < 0.01$). In the EUS-

FNA indication group, 11 patients (25%) died, whereas 29 (8.3%) died in the non EUS-FNA indication group ($P < 0.01$). In study 2 (stop surveillance group), PC was identified in three patients (1.9%) at 84, 103 and 145 months. **Conclusions** PC risk and mortality for IPMNs not showing significant change for 5 years is likely to be low, and the non-EUS-FNA indication can provide reasonable decisions. However, three patients without worsening high-risk features for 5 years developed PC. The stop surveillance strategy should be reconsidered.

Key points

- The AGA guidelines provide reasonable clinical decisions for the EUS-FNA indication.
- In stop surveillance group, PC was identified in 3 patients (1.9%).
- In stop surveillance group, 2 of 3 PC patients died from PC.
- Risk of pancreatic cancer in “stop surveillance” group is not negligible.

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Keywords Pancreatic cyst · Pancreatic neoplasms · Pancreatic ductal carcinoma · Cohort studies · Validation studies

Abbreviations

AGA	American Gastroenterological Association
BD-IPMN	branch-duct intraductal papillary mucinous neoplasm
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
HR	hazard ratio

HRS	high risk stigmata
ICG	International Consensus Guidelines 2012 for the Management of IPMN and MCN of the Pancreas
IPMNs	intraductal papillary mucinous neoplasms
IPMT	intraductal papillary mucinous tumour
IQR	interquartile range
MDCT	multidetector computed tomography
MD-IPMN	main-duct intraductal papillary mucinous neoplasm
MPD	main pancreatic duct
MRCP	magnetic resonance cholangiopancreatography
PC	pancreatic cancer
SCN	serous cystic neoplasm
SHR	subdistribution hazard ratio
SPN	solid-pseudopapillary neoplasm
WF	worrisome feature

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are well-defined premalignant lesions of pancreatic cancer (PC) [1, 2]. The 5-year rate of PC development is reported to be in the range of 1.4–6.9% [3–5]. In 2015, the American Gastroenterological Association (AGA) presented guidelines on the diagnosis and management of asymptomatic neoplastic pancreatic cysts [6], recommending examination with endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for pancreatic cysts with two or more high-risk features—including cyst size at least 3 cm, a dilated main pancreatic duct (MPD) or the presence of an associated solid component—and that imaging surveillance be conducted for 5 years for pancreatic cysts with at most one high-risk feature [6]. Any significant imaging changes that occur during these 5 years of surveillance indicate the need for EUS-FNA. However, for pancreatic cysts that have shown no significant imaging changes over the 5-year period, the AGA recommends stopping surveillance rather than continuing it. This guideline for a “stop surveillance strategy” based on imaging findings over a specified follow-up period may help medical practice and explanations of stopping surveillance to IPMN patients. However, there are no validation data for this strategy as yet. There are, however, data available on the natural history of IPMNs, particularly in regard to long-term follow-up for more than 5 years [3, 7]. In a previous study, we reported on the natural history of main-duct intraductal papillary mucinous neoplasm (MD-IPMN) and branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) according to the International Consensus Guidelines 2012 for the Management of IPMN

and MCN of the Pancreas (ICG) [4, 8], but the small number of IPMN cases was not sufficient to validate the AGA follow-up strategy of IPMN after 5 years, particularly in patients without worsening high-risk features. The present study includes 123 patients with IPMNs newly added to our previous database, and we have revised the follow-up period and outcomes accordingly. We have used the current data in the database to evaluate high-risk features, as defined in the AGA guidelines. This study sought to determine whether the AGA guidelines provide reasonable clinical decisions and ensure positive results in a real-world setting.

Materials and methods

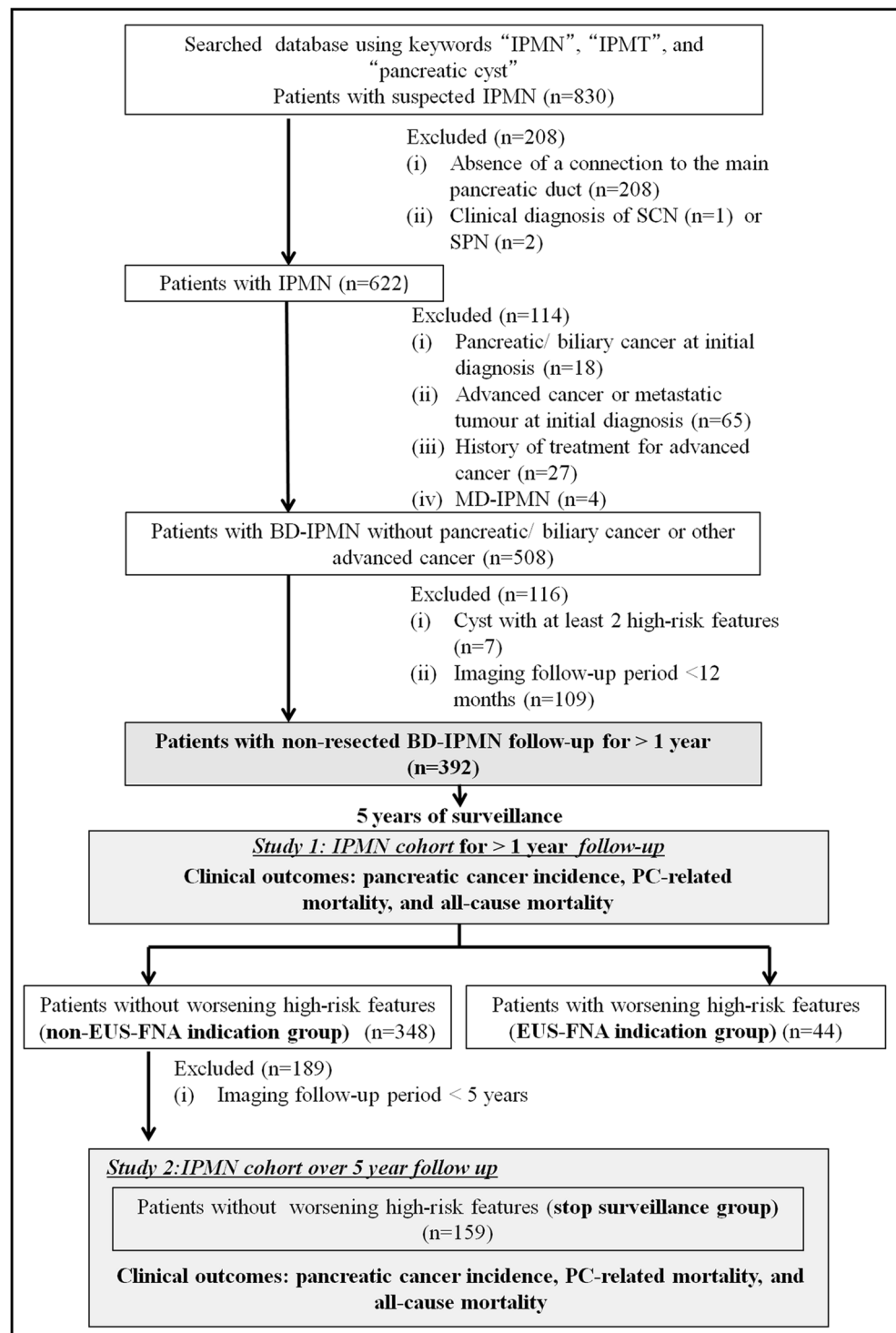
Patient selection

We retrospectively reviewed data on patients with IPMNs who underwent multidetector computed tomography (MDCT) and/or magnetic resonance cholangiopancreatography (MRCP) at the National Centre for Global Health and Medicine (NCGM), Japan, from February 1996 to August 2015. The data had been prospectively recorded in an electronic database (MegaOak online imaging system, NEC, Japan) which provides a searchable collection of records of MDCT and MRCP findings that radiologists prospectively input. We supplemented this review with data in the medical records and conducted two studies.

In study 1, a search of the database using the key terms “IPMN”, “IPMT” and “pancreatic cyst” identified 830 consecutive patients suspected of having IPMNs (Fig. 1). Second, we reviewed the radiologic and clinical findings of all 830 patients using the electronic medical record system and excluded patients with IPMNs that met the definition of IPMN given below. Of the 830 patients, we excluded 438 as follows: (i) absence of a connection to the MPD ($n = 208$); (ii) clinical diagnosis of serous cystic neoplasm ($n = 1$) or solid-pseudopapillary neoplasm ($n = 2$); (iii) clinical diagnosis of pancreatic or biliary cancer at initial diagnosis ($n = 18$); (iv) clinical diagnosis of advanced cancer or metastatic tumour ($n = 65$); (v) treatment history of advanced cancer. ($n = 27$); (vi) MD-IPMN ($n = 4$); (vii) at least two high-risk features mentioned below ($n = 7$) or (ix) imaging follow-up period less than 12 months ($n = 109$). This left a cohort of 392 IPMN patients with at most one high-risk feature who were periodically followed up for more than 1 year with MDCT and/or MRCP for analysis in study 1. In study 2, we analysed data for a subcohort of 159 patients with IPMN who did not show worsening high-risk features on imaging after 5 years of surveillance (stop surveillance group).

This study was approved by the institutional review board. The need to obtain informed consent from patients was waived for this retrospective study.

Fig. 1 Study flow chart. *IPMN* intraductal papillary mucinous neoplasm, *IPMT* intraductal papillary mucinous tumour, *SCN* serous cystic neoplasm, *SPN* solid-pseudopapillary neoplasm, *MD-IPMN* main-duct intraductal papillary mucinous neoplasm, *BD-IPMN* branch-duct intraductal papillary mucinous neoplasm



Definitions of IPMN and high-risk features

IPMNs were diagnosed on the basis of MDCT and/or MRCP findings of a dilated cyst and communication between the cyst and the MPD, in accordance with ICG [8]. Also, when endoscopic retrograde cholangiopancreatography (ERCP) and EUS were needed clinically, the findings defined as high-risk features were cyst size at least 3 cm, a dilated MPD (at

least 10 mm) and the presence of an associated solid component, based on the AGA guidelines [6].

Follow-up and outcomes

Outcomes were the development of PC, PC-related death and all-cause death that occurred in the follow-up period. Patients with IPMNs were followed up periodically by imaging

(MDCT/MRCP more than two times) and serologic marker tests, ultrasonography (US), ERCP and EUS as deemed necessary clinically. PC was defined as intraductal papillary mucinous carcinoma or concomitant pancreatic adenocarcinoma. Death was categorised as PC-related or other cause (disease diagnosed from laboratory test, imaging or autopsy findings). On the basis of the AGA strategy, during 5 years of surveillance, patients with worsening high-risk features of the cyst were assigned to the EUS-FNA indication group and patients without worsening of high-risk features were assigned to the stop surveillance group [6].

Statistical analysis

In study 1, we assessed the validity of the EUS-FNA indication according to the AGA guidelines [6]. In study 2, we assessed the validity of the stop surveillance strategy after 5 years of surveillance. For imaging follow-up analysis, the data were censored at the time of the last MDCT or MRCP. The endpoint was the development of PC. For survival analysis, data for patients lost to follow-up were censored at the time of the patient's last visit. The endpoint was death. The Kaplan–Meier method was used to estimate the cumulative PC development and mortality. Cox's proportional hazards modelling was used to estimate hazard ratio (HR) and 95% confidence intervals. The log-rank test was used to compare patients with worsening high-risk features and those with non-worsening high-risk features during the 5 years of surveillance. Additionally, we used Gray's test [9] in the competing risk analysis and calculated the subdistribution hazard ratio (SHR) with 95% CI, with death as a competing risk in study 1. Statistical analysis was performed using Stata version 13 software (Stata, College Station, TX).

Results

Study 1: validation of the EUS-FNA indication

Patient characteristics

The characteristics of a total of 392 IPMNs patients with at most one high-risk feature who were followed up for more than 1 year (185 men, 47.2%; median age, 70.5 years) are shown in Table 1. Fifty-two patients (13.3%) had a high-risk feature on imaging of the cyst.

Changes seen in imaging findings and PC development are shown in Table 2. During follow-up, a total of 1907 MDCT and 1193 MRCP imaging studies were done. During 5 years of surveillance, 44 patients (11.2%) had a worsening high-risk feature.

Pancreatic cancer development

During a median follow-up period of 53.6 months, PC was identified in 12 (27.3%) of 44 patients in the EUS-FNA indication group and in none of the 348 patients in the non-EUS-FNA indication group. The cumulative PC incidence in the two groups was 34.0% and 0% at 5 years, respectively (Fig. 2a). The log-rank test revealed significantly high PC incidence in the EUS-FNA indication group ($P < 0.01$). After adjustment for sex and age, the HR for PC development in the EUS-FNA indication group was 48.4 (95% CI, 13.1–179; $P < 0.01$). Competing risk analysis also revealed an increased risk of PC development in the EUS-FNA indication group (SHR, 42.3; 95% CI, 12.7–141; $P < 0.01$) (Fig. 2b).

Table 1 Baseline characteristics

	Study 1: IPMN cohort >1 year ($n = 392$)	Study 2: IPMN cohort >5 years ($n = 159$)
Median age (IQR), years	70.5 (63–76)	68.0 (62–75)
Male/female, n (%)	185 (47.2)/207 (52.8)	76 (47.8)/83 (52.2)
Initial imaging findings		
Cyst in head/body or tail/whole pancreas, n (%)	122 (31.1)/169 (43.1)/101 (25.8)	54 (34.0)/64 (40.3)/41 (25.8)
Median cyst size (IQR), mm	12 (7.7–20)	14 (9–21)
Cyst ≥ 30 mm, n (%)	43 (11.0)	22 (13.8)
Median MPD diameter (IQR), mm	2 (1.7–2.76)	2 (1.7–2.7)
MPD diameter ≥ 10 mm, n (%)	3 (0.77)	3 (1.89)
MPD diameter ≥ 5 mm, n (%)	16 (4.1)	5 (3.14)
Solid component, n (%)	6 (1.53)	4 (2.52)
High-risk features, n (%)	52 (13.3)	29 (18.2)

Solid component was defined as thickened cyst walls and mural nodules. High-risk feature was defined as having ≥ 1 of the following features: cyst size ≥ 30 mm, a dilated MPD (≥ 10 mm) and the presence of an associated solid component

IQR interquartile range, MPD main pancreatic duct

Table 2 Outcomes during survival follow-up with periodic imaging (study 1, $n = 392$)

Imaging follow-up ^a	
Median follow-up period, months [range] (IQR)	53.6 [9.9–222] (30.7–81.7)
Total no. of MDCT/MRCP studies	1907/1193
Median times patient underwent imaging, n (IQR)	7 (4–10)
Additional ERCP, n (%)	62 (15.8)
Additional EUS, n (%)	108 (27.6)
Dilation of MPD, n (%)	29 (7.4)
Increasing cyst size, n (%)	13 (3.32)
New appearance of solid component, n (%)	9 (2.3)
Worsening high-risk features ^b within 5 years of surveillance (EUS-FNA indication group), n (%)	44 (11.2)
Pancreatic cancer development, n (%)	15 (3.83)
Survival follow-up ^c	
Median follow-up period, months [range] (IQR)	64.4 [12.4–238] (39.2–97.7)
Death ^d , n (%)	40 (10.2)
PC-related death, n (%)	10 (2.6)

MDCT multidetector computed tomography, MRCP magnetic resonance cholangiopancreatography, ERCP endoscopic retrograde cholangiopancreatography, EUS endoscopic ultrasonography, PC pancreatic cancer

^a For imaging follow-up analysis, the endpoint was the development of PC

^b Worsening high-risk feature was defined as cyst size increasing to >3 cm, increasing main pancreatic duct size or the development of a solid component in the cyst on MDCT or MRCP imaging

^c For survival follow-up analysis, the endpoint was the date of the patient's death or the patient's last visit

^d Causes of death except PC were other cancers ($n = 11$), organ failure due to noncancerous disease ($n = 16$), and infectious disease ($n = 3$)

All-cause mortality and PC-related mortality

During a median survival follow-up period of 64.4 months, 40 patients (10.2%) died, 10 due to PC (Table 2). Eleven of 44 patients (25%) died in the EUS-FNA indication group, compared with 29 of 348 patients (8.3%) who died in the non-EUS-FNA indication group. Cumulative all-cause mortality in the groups were 15.3% and 3.8% at 5 years, respectively (Fig. 2c). The log-rank test revealed significantly high all-cause mortality in the EUS-FNA indication group ($P < 0.01$). After adjustment for sex and age, the HR for mortality in the group was 5.06 (95% CI, 2.47–10.4; $P < 0.01$). As

to PC-related mortality, eight patients (18.2%) died from PC in the EUS-FNA indication group, compared with 2 (0.57%) in the non-EUS-FNA indication group.

Study 2: validation of the stop surveillance strategy

Patient characteristics

During the 5 years of follow-up, 159 patients were categorised into the stop surveillance group (76 men, 47.8%; median age, 68.0 years). Their characteristics are shown in Table 1. Changes of imaging findings and PC development are shown

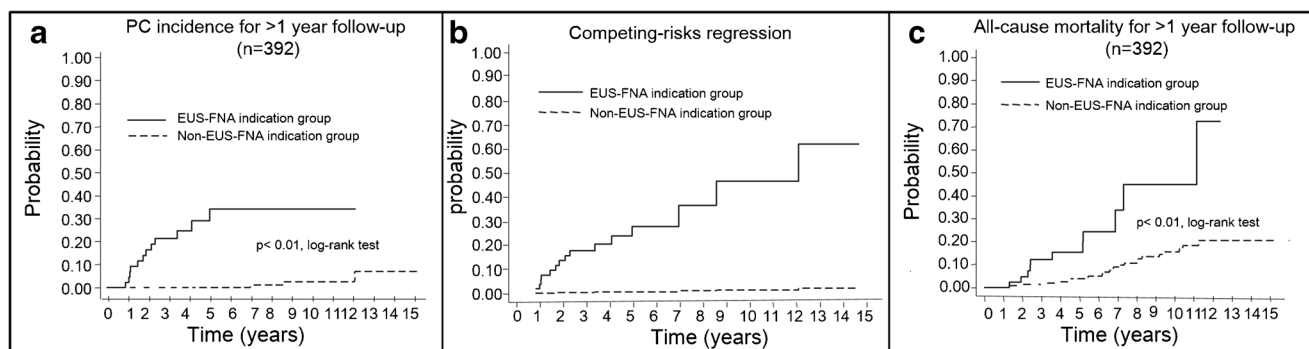


Fig. 2 Pancreatic cancer development and all-cause mortality in study 1. **a** Cumulative PC incidence (95% confidence interval [CI]) at 5 and 10 years in the EUS-FNA indication group and non-EUS-FNA indication group was 34.0% (20.0–53.8) vs 0% and 34.0% (20.0–53.8) vs 2.66% (0.66–10.4), respectively. **b** Competing risk analysis revealed

that the sex- and age-adjusted subdistributional hazard ratio (SHR) for PC development in the EUS-FNA indication group was 42.3 (95% CI, 12.7–141; $P < 0.01$). **c** Cumulative all-cause mortality (95% CI) at 5 and 10 years in the two groups was 15.3% (7.13–31.2) vs 3.8% (2.13–6.84) and 44.8% (22.9–74.11) vs 15.6% (10.44–22.9), respectively

in Table 3. During follow-up, a total of 952 MDCT and 624 MRCP imaging studies were performed.

Pancreatic cancer development and mortality in the stop surveillance group

Images in a patient who developed PC during surveillance are shown in Fig. 3. After at least 5 years of follow-up, PC was identified in three of 159 IPMN patients (1.9%) at 84, 103 and 145 months: one received surgery and two received best supportive care, with two patients (1.3%) dying from PC. Moreover, three patients underwent pancreatic surgery; two had IPMNs and one had a neuroendocrine tumour. Cumulative PC incidence at 10 years was 2.7% (Fig. 4a).

All-cause mortality and PC-related mortality

During a median survival follow-up period of 106 months, 15 patients (9.4%) died (Table 3). Cumulative all-cause mortality at 10 years was 11.2% (Fig. 4b).

Discussion

This study sought to evaluate the IPMN follow-up strategy recommended in the AGA guidelines. We conducted a long-term cohort study that followed low-risk IPMN patients with at most one high-risk feature at initial examination. In study 1, the sex- and age-adjusted hazard ratio for PC development was 48.4, and the

Table 3 Outcomes during survival follow-up with periodic imaging (study 2, $n = 159$)

Imaging follow-up ^a	
Median follow-up period, months [range] (IQR)	89.6 (72.0–120)
Total MDCT/MRCP studies	952/624
Median times patient underwent imaging, n (IQR)	9 (7–13)
Additional ERCP, n (%)	23 (14.5)
Additional EUS, n (%)	41 (25.8)
Pancreatic cancer development, n (%)	3 (1.9)
Survival follow-up ^b	
Median follow-up period, months [range] (IQR)	106.5 (81.3–135)
Death ^c , n (%)	15 (9.4)
PC-related death, n (%)	2 (1.3)

MDCT multidetector computed tomography, MRCP magnetic resonance cholangiopancreatography, ERCP endoscopic retrograde cholangiopancreatography, EUS endoscopic ultrasonography, PC pancreatic cancer

^a For imaging follow-up analysis, the endpoint was the development of PC

^b For survival follow-up analysis, the endpoint was the date of the patient's death or the patient's last visit

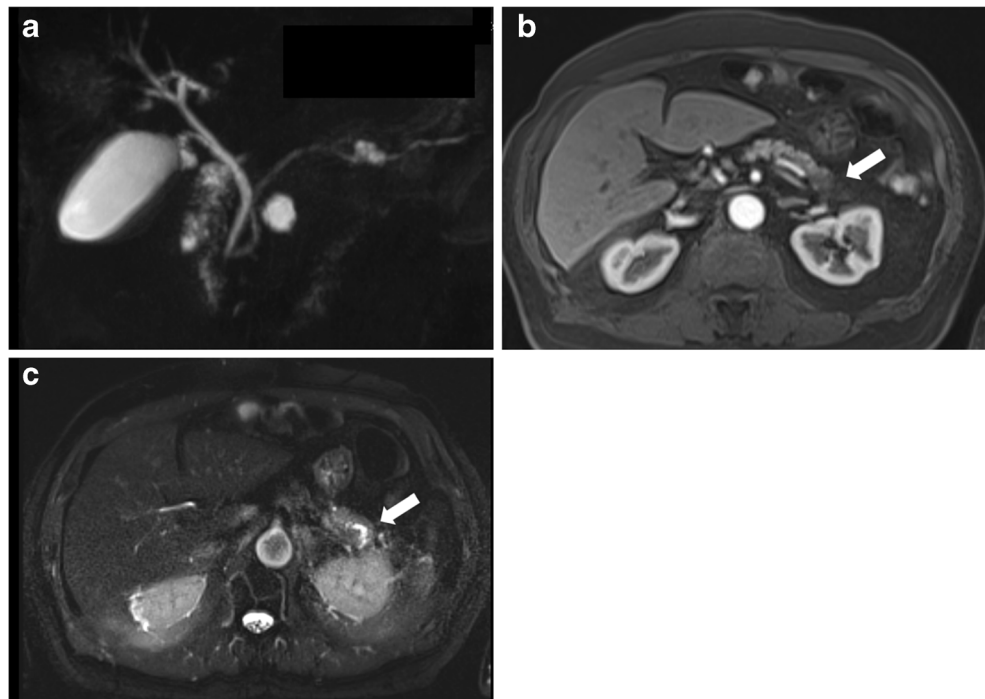
^c Causes of death except PC were other cancers ($n = 3$), organ failure due to noncancerous disease ($n = 7$), and infectious disease ($n = 3$)

HR for mortality was 5.1 in the EUS-FNA indication group compared with the non-EUS-FNA indication group, confirming the validity of the AGA guideline for the indication of EUS in patients with a worsening high-risk feature during surveillance. In study 2 of the stop surveillance group, however, three of 159 patients (1.9%) developed PC and two of the three patients who had not shown significant changes in imaging findings for 5 years later died from PC. Such cases, albeit very few, suggest that the stop surveillance strategy is not necessarily applicable to all patients who meet the stop surveillance criteria.

The ICG classify the risk of malignancy determined from imaging findings as, for example, “high risk stigmata” (HRS) and “worrisome feature” (WF) [8]. The AGA guidelines determine risk according to “high risk features” on imaging [6]. Several studies have validated the ICG recommendation. Shimizu et al. evaluated 66 MD-IPMN patients and 144 BD-IPMN patients who had undergone surgery and showed that the area under the receiver operating characteristic curve of the IPMN nomogram for prediction of malignancy was 0.747 in MD-IPMN and 0.752 in BD-IPMN [10]. Jang et al. examined 350 BD-IPMN patients who had undergone surgery and found that MPD dilation of at least 5 mm and the presence of mural nodules were independent predictors of malignancy [11]. The present study is the first to confirm the validity of the EUS-FNA indication based on high-risk features as set out in the AGA guidelines. Both sets of guidelines are useful, but they are causing confusion because of their differences in imaging finding criteria: standardisation of the two is awaited.

The ICG state that the follow-up of low-risk patients who showed no worsening images for 2 years is controversial [8]. Cahalane et al. verified five sets of guidelines [12], and they reported that the 2014 ‘Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms’ were found to be the most methodologically sound guidelines. According to the Italian consensus guidelines, after 2 years from initial diagnosis the BD-IPMN is stable and follow-up timing can be modified depending on the diameter of the cyst [13]. Furthermore, Yoen et al. postulated that cysts smaller than 15 mm without pancreatic ductal change could be followed up at an interval of at least 3 years [14]. No data are yet available as to how long we should follow up such patients. Recently in 2015, AGA recommended stopping surveillance when low-risk patients have shown no changes in imaging findings during the first 5 years of follow-up [6]. The strategy is supported by an annual rate of malignancy of 0.24% in pancreatic cysts reported by Scheiman et al. in the same year [15]. In this study, PC was identified in three patients (1.9%) at 84, 103, and 145 months in the stop surveillance group. Several cohort studies have also been reported. Malleo et al. retrospectively examined 569 BD-IPMN patients for a median follow-up of 56 months and found PC in nine patients, two of whom (0.35%) developed cancer at least 5 years later [5]. Tanno et al. followed up 89 BD-IPMN patients for a mean duration of 64 months and confirmed PC development

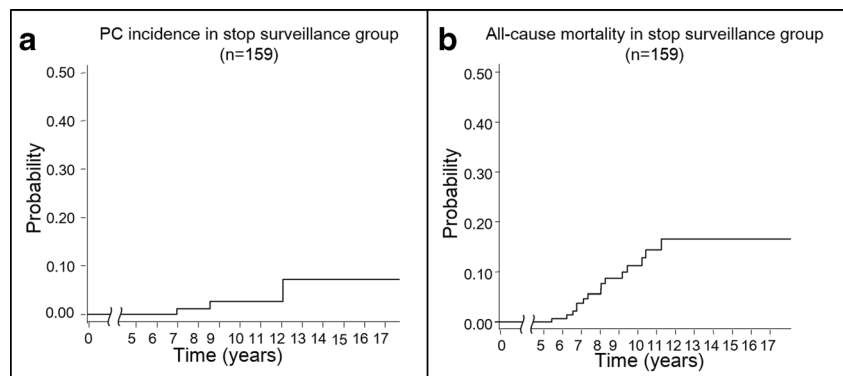
Fig. 3 Pancreatic cancer that occurred in the stop surveillance group. **a** MRCP image from a 68-year-old man in the stop surveillance group. There are no high-risk features. **b** After follow-up for 103 months from initial diagnosis, axial contrast-enhanced MRI image showing hypoaffectuating area (*arrow*). **c** Axial MRI image (HASTE) showing dilated MPD (*arrow*) immediately caudal to the mass. EUS-FNA revealed the lesion to be adenocarcinoma. The patient underwent surgery



in four patients, two of whom (2.24%) had late onset PC (at least 5 years) [7]. Further, Uehara et al. followed up 60 BD-IPMN patients for a mean 87 months and confirmed PC development in five cases (8.3%), one of which (1.67%) had late onset disease (at least 5 years) [3]. Not all subjects in these studies had at most one high-risk feature, and the studies were not all long-term cohort studies of more than 5 years' duration. Nevertheless, the PC incidence rate occurring over 5 years was 0.35–2.24%, which is in good agreement with our findings in this study. Whether or not these incidence rates are acceptable in clinical practice remains controversial, but we believe they are not negligible. The duration of follow-up for low-risk IPMN patients is an important clinical issue. Pancreatic surgery can be challenging because complications following surgery are numerous [16], and surgeons might be hesitant to operate on elderly patients, particularly those over 80 years old. Nevertheless, a report involving 300 pancreatic surgeries has shown that age is not an independent risk factor for mortality [17]. In addition, Marmor et al. state that patients aged

80 years or more who have no severe comorbidities received a survival benefit from PC treatment [18]. Therefore, in our opinion, follow-up until at least age 80 years may be warranted for low-risk IPMN in the absence of severe comorbidities, particularly in Japan. This is because the average life expectancy in Japan is 84 years [19]. Another epidemiological review has shown that 85% of Japanese people aged 60 years or more had no impediments in their daily life, compared with 65% or less of American, German and French people [20]. Additionally, 83% of Japanese women aged 65 years survive until 80 years, 3% higher than in any other country (70% in the USA and 72% in the UK) [21]. Thus, regarding how long such patients should be followed up, it is important to consider the various living conditions in each country. In this study, we excluded patients who had advanced cancer or received chemotherapy, because these conditions might influence PC development or mortality. The stop surveillance strategy might be acceptable for such patients, elderly patients or patients with multiple comorbidities.

Fig. 4 Pancreatic cancer development and all-cause mortality in study 2. **a** PC was identified in 3 patients at 84, 103 and 145 months. Cumulative PC incidence (95% CI) at 7.5 and 10 years was 1.11% (0.16–7.63) and 2.66% (0.66–10.4), respectively. **b** Cumulative all-cause mortality (95% CI) at 7.5 and 10 years was 5.55% (2.67–11.34) and 11.2% (6.42–19.2), respectively



This study is limited by the fact that it is a single-centre retrospective study and that the incidence rate of PC was too low to conduct multivariable analysis with adjustment for risk factors. Almost all patients had follow-up radiological examinations at our hospital, but some might have been followed up at another hospital. Nevertheless, this study involved a considerable number of patients who were followed up over the long term, providing a large number of images obtained from 1907 MDCT and 1193 MRCP imaging studies. Walter et al. reported the usefulness of these modalities in distinguishing benign from malignant forms of IPMN [22].

In conclusion, the risk of PC and all-cause mortality in IPMNs that do not show a significant change on imaging for 5 years is likely to be low, and the non-EUS-FNA indication can provide a reasonable clinical decision. However, three patients (1.9%) without worsening high-risk features for 5 years and thus classified in the stop surveillance group went on to develop PC, two of whom ultimately died from the disease. The stop surveillance strategy should be reconsidered.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Naoyoshi Nagata.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

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Statistics and biometry Dr. Takuro Shimbo has significant statistical expertise.

Informed consent Written informed consent was waived by the institutional review board.

Ethical approval Institutional review board approval was obtained.

Study subjects or cohorts overlap Our cohort was previously reported in *Radiology*. 2015:150131. In a previous study, we reported on the natural history of MD-IPMN and BD-IPMN according to the Fukuoka Consensus Guidelines. However, this present study includes 123 patients with IPMNs newly added to our previous database, and we have revised the follow-up period and outcomes accordingly. We have used the current data in the database to evaluate high-risk imaging features, as defined in the AGA guidelines, and validated the AGA follow-up strategy for low-risk BD-IPMNs.

Methodology

- retrospective
- observational
- performed at one institution

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