Natural History of Branch Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas

A Multicenter Study in Japan

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Objective: The aim of this study was to evaluate the long-term follow-up results of patients with branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) without mural nodules (MNs) at 10 representative institutions in Japan.

Methods: We analyzed 349 follow-up BD-IPMN patients who had no MNs on endoscopic ultrasonography at initial diagnosis.

Results: Observation periods ranged from 1 to 16.3 years (median, 3.7 years). Sixty-two (17.8%) patients exhibited disease progression during follow-up. Twenty-two underwent surgery, leading to a pathological diagnosis of carcinoma in 9 and adenoma in 13. Although the remaining 287 (82.2%) showed no changes, 7 underwent surgery because of symptoms (n = 2), choice (n = 2), or development of pancreatic ductal adenocarcinoma (n = 3); all of them were diagnosed pathologically as adenomas. Of the 29 patients undergoing surgery, all 9 with carcinoma exhibited signs of progression, such as increased main pancreatic duct diameter and/or appearance of MNs. Pancreatic ductal adenocarcinomas and additional BD-IPMNs developed in 7 (2.0%) and 13 (3.7%), respectively. Overall, 320 (91.7%) patients were followed without surgery.

Conclusions: Most BD-IPMN patients who had no MNs on endoscopic ultrasonography could be managed without surgery. However, careful attention should be paid to disease progression and the development of pancreatic ductal adenocarcinomas during follow-up.

Key Words: branch duct, IPMN, natural history, follow-up, pancreatic ductal adenocarcinoma

Abbreviations: IPMN - intraductal papillary mucinous neoplasm, BD-IPMN - branch duct intraductal papillary mucinous neoplasm, MD-IPMN - main duct intraductal papillary mucinous neoplasm, MN - mural nodule, MPD - main pancreatic duct, PDA - pancreatic ductal adenocarcinoma, US - ultrasonography, ERCP - endoscopic retrograde cholangiopancreatography, MRCP - magnetic resonance cholangiopancreatography, EUS - endoscopic ultrasonography, CT - computed tomography

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are distinct pancreatic cystic neoplasms that have received increased recognition in recent years and are characterized by slow growth and a relatively favorable prognosis compared with ordinary pancreatic ductal adenocarcinomas (PDAs).[1–3] Intraductal papillary mucinous neoplasms are classified histologically as adenoma, borderline, and carcinoma, with carcinomas being further subcategorized as noninvasive and invasive. They can be subdivided into main duct IPMNs (MD-IPMNs) and branch duct IPMNs (BD-IPMNs), depending on the location of the lesion.[4–7]

In 2006, international consensus guidelines for the management of IPMNs were proposed by the Working Group of the International Association of Pancreatology (IAP) following the 11th Congress of the IAP held in Sendai, Japan.[8] The guidelines recommended surgical resection for all MD-IPMNs. In addition, surgery was recommended for patients with BD-IPMNs who have symptoms, mural nodules (MNs), a dilated main pancreatic duct (MPD), or a cyst size more than 30 mm. However, it is still controversial whether these BD-IPMNs should be resected immediately. Because most IPMNs are BD-IPMNs, and these neoplasms are being diagnosed with increasing frequency, it is important to elucidate their natural history for better management. The aim of this study was to evaluate the long-term follow-up results of BD-IPMN patients who had no MNs on initial imaging in a retrospective multicenter series in Japan.

MATERIALS AND METHODS

We retrospectively analyzed BD-IPMN patients without MNs based on endoscopic ultrasonography (EUS) at the time of initial diagnosis. All patients were followed for more than 1 year at 10 tertiary referral institutions. These 10 institutions were selected by the Working Group of the Japan Pancreas Society.

Definitions

The definition of IPMN was based on imaging as follows: on-face visualization of a patulous ampulla of Vater, called

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"fish-eye ampulla" because of mucin in the duct seen on endoscopic imaging; filling defects in the pancreatic duct during endoscopic retrograde cholangiopancreatography (ERCP); or cystic lesions communicating with the MPD seen on EUS, magnetic resonance cholangiopancreatography (MRCP), and/or computed tomography (CT). Branch duct IPMN was defined as a grapelike multilocular cystic lesion communicating with the MPD less than 10 mm. For patients who underwent surgery after follow-up, the diagnosis of IPMN was made histologically.

Patients and Follow-Up

Four hundred seventeen patients who underwent EUS at the time of initial diagnosis were initially recruited from the 10 institutions. Among them, 14 patients were excluded from the analysis because they did not satisfy this study's inclusion criteria: follow-up periods of less than 1 year in 4, MPD dilatation ≥10 mm in 5, histologically diagnosed as non-IPMN in 3, and incomplete description in 2 patients. Fifty-four patients who had apparent MNs on EUS at the time of initial diagnosis were also excluded. A total of 349 BD-IPMN patients without MNs were thus available for further analysis. At the time of initial diagnosis, ERCP was performed in 252 (72.2%) of 349 BD-IPMNs to determine if there was mucus in the pancreatic duct.

The maximum diameters of cysts and MPDs were measured by EUS in combination with ultrasonography (US), CT, and/or MRCP. Presence or absence of MNs in cysts was determined by EUS at the initial diagnosis. During the follow-up period, monitoring for MNs was performed by EUS, US, and/or CT at least twice. Endoscopic ultrasonography was performed in 176 (50.4%) cases at least twice during the follow-up period. In combination with EUS, CT, US, MRCP, and ERCP were carried out in 151, 119, 128, and 39 cases, respectively, during regular follow-up examinations. Changes on imaging modalities were regarded as progression if any of the following findings were observed: cyst size changes 10 mm or greater, MPD changes 2 mm or greater, and/or development of MNs 5 mm or greater in size. Surgery was performed principally in patients with symptoms or apparent MNs.

The database contained data regarding the patient's age, sex, date of examination, findings at the time of initial diagnosis, imaging modalities for follow-up study, histology of resected specimens, and whether or not the patient developed an additional neoplasm.

Statistical Analysis

Statistical significance was analyzed with the Mann-Whitney U and Fisher χ^2 tests, using SPSS II for Windows, version 11.0.1.J (SPSS). Differences were considered significant for $P < 0.05$.

RESULTS

Clinical Outcomes of 349 BD-IPMN Patients During Follow-Up Periods

The management and clinical outcomes of the 349 BD-IPMN patients during the follow-up periods are shown in Figure 1.

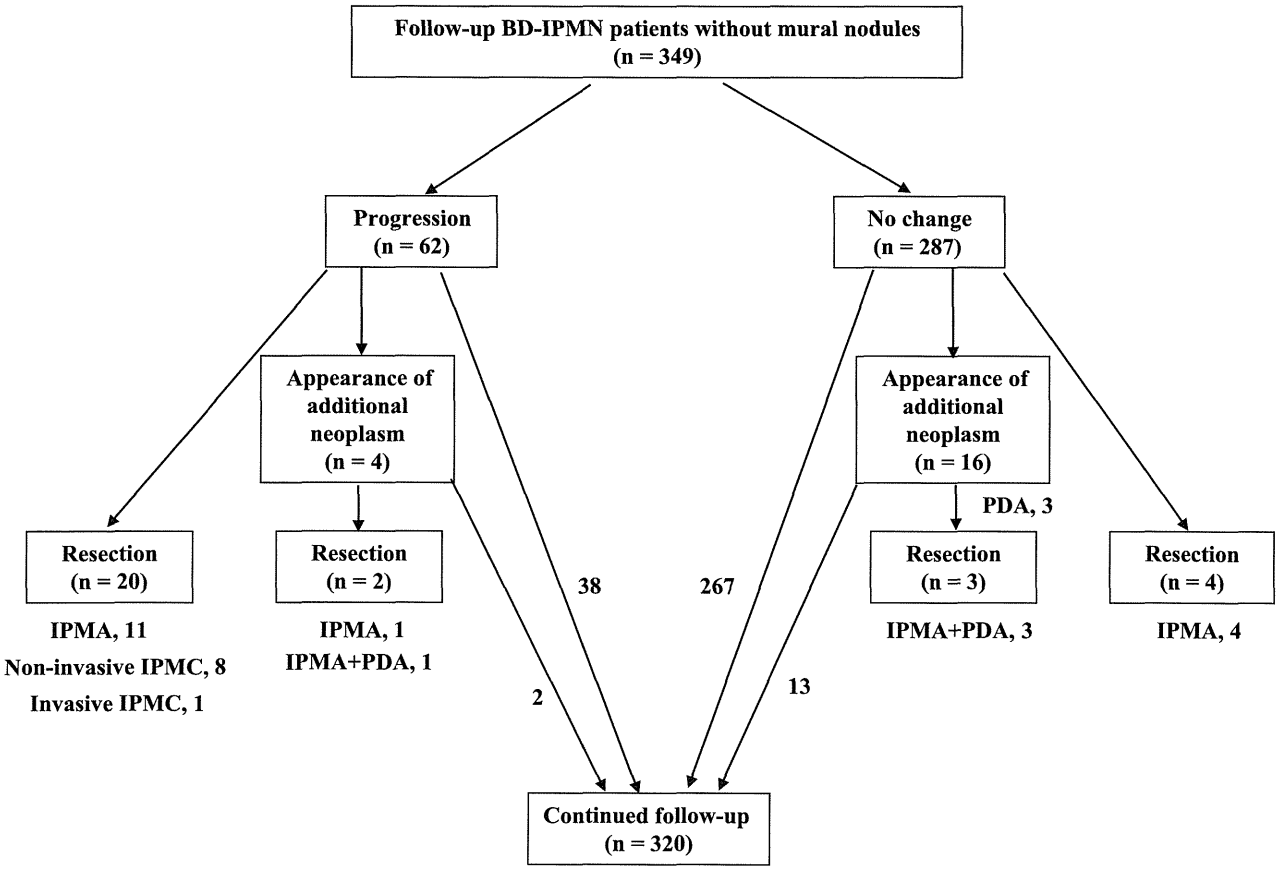

FIGURE 1. Management and clinical outcomes of BD-IPMNs during follow-up periods. IPMA indicates intraductal papillary mucinous adenoma; IPMC, intraductal papillary mucinous carcinoma; PDA, pancreatic ductal adenocarcinoma.

TABLE 1. Clinical Characteristics of the 349 Patients With BD-IPMNs

	Total (n = 349)	Progression of BD-IPMNs		*P* Value (Progression vs. No Change)
		Progression* (n = 62)	No Change (n = 287)	
Male, n (%)	179 (51.3)	41 (66.1)	138 (48.1)	0.010
Median age (range), yrs	66 (37–85)	65 (37–83)	67 (38–85)	0.453
Unifocal, n (%)	238 (68.2)	40 (64.5)	198 (69.0)	0.493
Location (head), n (%)	193 (55.3)	41 (66.1)	152 (53.0)	0.062
Symptomatic, n (%)	6 (1.7)	4 (6.5)	2 (0.7)	0.011
Median cyst size (range), mm	19 (3–60)	19 (3–55)	19 (4–60)	0.908
Median MPD diameter (range), mm	3 (1–9)	3 (1–9)	3 (1–9)	0.068
Median follow-up period (range), yrs	3.7 1.0–16.3	4.4 1.0–16.3	3.5 1.0–14.4	0.053

*Progression based on imaging findings during the follow-up period was defined as follows: cyst size changes ≥10 mm, MPD changes ≥2 mm, or appearance of MNs.

During follow-up, progression was found in 62 (17.8%) of 349 patients. Among the patients with findings of progression, 20 underwent surgery. The pathological findings were adenoma in 11, noninvasive carcinoma in 8, and invasive carcinoma in 1.

Four patients developed new neoplasms; there were additional BD-IPMNs in 3 and PDA in 1. Of these 4 patients, surgical resection was performed in 1 patient with an additional BD-IPMN and in 1 with PDA. Both 2 BD-IPMNs were diagnosed pathologically as adenomas. Collectively, a total of 22 patients underwent surgery. The remaining 40 patients continued to be followed without surgery.

Although 287 (82.2%) of 349 BD-IPMN patients showed no changes during the follow-up period, a total of 7 patients underwent surgery because 2 became symptomatic, 2 chose to receive surgery, and 3 had developed PDAs. All 7 BD-IPMNs were diagnosed histologically as adenoma. Overall, 320 (91.7%) patients continued to be followed during the median observation period of 3.7 years.

Clinical Characteristics of the 349 Patients With BD-IPMNs

Table 1 shows the clinical characteristics of the 349 BD-IPMN patients with or without progression. There were 179 men and 170 women, with a median age of 66 years (range, 37–85 years). There was a significant difference in the sex ratio between patients with and without progression ($P = 0.01$). Symptomatic BD-IPMN was significantly more frequent in patients with progression than in those without ($P = 0.01$). There were no significant differences in initial cyst size and MPD diameter between patients with and without progression. The median follow-up period was longer in patients with progression than in those without, although the difference did not reach statistical significance (4.4 vs. 3.5 years, $P = 0.053$).

Relationship Between Initial Imaging Findings and Progression of BD-IPMNs

A comparison of initial imaging findings and progression in BD-IPMNs is shown in Table 2. Initial cyst size was 30 mm or greater in 13 (21.0%) patients with progression and in 49 (17.1%) without ($P = 0.467$). Initial MPD diameter was 6 or greater mm in 6 (9.7%) patients with progression and in 14 (4.9%) without ($P = 0.123$). There were no significant differences in initial cyst size and MPD diameter between patients with and without progression.

Development of Additional Pancreatic Neoplasms and Progression of BD-IPMN During the Follow-Up Period

During follow-up, additional neoplasms distinct from the original BD-IPMNs developed in 20 (5.7%) of 349 patients, as summarized in Table 3. Of these patients, 13 had developed additional BD-IPMNs and 7 had developed PDAs. There was no significant difference in the frequency of additional neoplasms between patients with and without progression.

Comparison of BD-IPMNs in Patients With Progression Between Patients With and Without Surgical Resection

Among 62 patients with progression, 40 continued to be followed without surgery, whereas 22 underwent surgery (Fig. 1). Table 4 shows a comparison of BD-IPMNs with progression between patients with (n = 22) and without (n = 40) surgical resection. The cyst size measured at the time of resection was not different between the 2 groups. The MPD diameter in patients without surgery was significantly narrower than the diameter in patients with resection ($P = 0.003$). There was a

TABLE 2. Relationship Between Initial Imaging Findings and Progression of BD-IPMNs

Initial Imaging Findings	Total (n = 349)	Progression of BD-IPMNs		*P* Value (Progression vs. No Change)
		Progression (n = 62)	No Change (n = 287)	
Cyst size, n (%)				
<30 mm	287 (82.2)	49 (79.0)	238 (82.9)	0.467
≥30 mm	62 (17.8)	13 (21.0)	49 (17.1)	
MPD diameter, n (%)				
<6 mm	329 (94.3)	56 (90.3)	273 (95.1)	0.123
≥6 mm	20 (5.7)	6 (9.7)	14 (4.9)	

TABLE 3. Development of Additional Pancreatic Neoplasms and Progression of BD-IPMNs During the Follow-Up Period

New Neoplasms	Total (n = 349)	Progression of BD-IPMNs		*P* Value (Progression vs. No Change)
		Progression (n = 62)	No Change (n = 287)	
Additional BD-IPMN, n (%)	13 (3.7)	3 (4.8)	10 (3.5)	0.415
PDA, n (%)	7 (2.0)	1 (1.6)	6 (2.1)	0.639

significant difference in the frequency of MNs between the 2 groups ($P = 0.002$). The follow-up period was significantly longer in patients without surgery than in patients with resection ($P = 0.043$).

Histologic Findings of Resected BD-IPMNs With or Without Progression

Table 5 shows the pathological diagnosis in 29 patients who underwent resection during follow-up. Of 29 BD-IPMNs, 20 (69.0%) were diagnosed histologically as benign (adenoma in 20), and 9 (31.0%) were malignant (noninvasive carcinoma in 8 and invasive carcinoma in 1). The incidence of malignancy in patients with progression was higher than that in patients without progression, although the difference did not reach statistical significance ($P = 0.050$). In contrast, 7 BD-IPMNs in patients without progression were all diagnosed histologically as benign.

Relationship Between Imaging Findings at the Time of Resection and Malignancy in 29 Pathologically Confirmed BD-IPMNs

The relationship between the imaging findings at the time of resection and malignancy in the 29 patients with pathologically confirmed BD-IPMNs is shown in Table 6. Among the 16 resected BD-IPMNs with a cyst size of 30 mm or greater, 11 were diagnosed pathologically as benign, and 5 were malignant ($P = 0.647$). Malignancy was found in 5 of 11 BD-IPMN patients with an MPD diameters of 6 mm or greater and in 7 of 15 patients with MNs at the time of resection ($P = 0.184$ and $P = 0.068$, respectively). Two of 9 malignant BD-IPMNs without the appearance of MNs exhibited signs of progression, such as increasing MPD diameter or cyst size. Although all 349 patients had an MPD diameter of less than 10 mm at the time of initial diagnosis, 4 (1.1%) cases progressed to be more than 10 mm in diameter during follow-up.

Table 7 shows the comparison of changes in the imaging findings during the follow-up period in 29 patients pathologically confirmed to have malignant (n = 9) and benign (n = 20) BD-IPMNs. Changes in imaging findings were divided into 8 groups as follows: (1) increased cyst size alone; (2) increased MPD diameter alone; (3) appearance of MNs alone; (4) increased cyst size and MPD diameter; (5) increased cyst size and appearance of MNs; (6) increased MPD diameter and appearance of MNs; (7) increased cyst size, MPD diameter, and appearance of MNs; and (8) no changes. Between malignant and benign BD-IPMNs, a significant difference was observed in group 6 (increased MPD diameter and appearance of MNs; $P = 0.023$).

Prognosis of Patients With Malignant BD-IPMN Who Developed Additional PDA

One patient with invasive intraductal papillary mucinous carcinoma (IPMC) and 8 of 9 patients with noninvasive IPMCs were doing well without any signs of recurrence after a median follow-up period of 4.2 years (range, 0.7–9.8 years) after resection. Only 1 patient with noninvasive IPMC died of an unrelated cause. Among 7 patients who had developed PDAs, 4 underwent surgery. After surgery, 3 died of cancer after a median follow-up period of 1.4 years (range, 0.6–2.1 years), and 1 was alive with a follow-up of 3.3 years. The remaining 3 patients dying with unresectable PDA had a median survival of 0.8 years (range, 0.5–1.4 years) after PDA diagnosis.

DISCUSSION

We collected a large number of BD-IPMN patients without MNs for a retrospective analysis. The advantages of this study include ability to clarify the progression process in BD-IPMNs without MNs and a multicenter study design with a much larger sample size than that seen in previous studies.[9–11] Limitations include lack of common criteria for surgery and lack of a single imaging modality for follow-up among the 10 institutions, because of the retrospective nature of this multicenter analysis.

The most important finding in this study is that 287 (82.2%) of 349 BD-IPMN patients who had no MNs on EUS at the time of initial diagnosis showed no changes during the median follow-up period of 3.5 years (range, 1–14.4 years). There have been increasing numbers of reports published on follow-up data in patients with BD-IPMNs.[9–18] Rautou et al[18] reported that 88 (72.7%) of 121 patients without MNs showed no morphologic changes during a median follow-up period of 33 months.

TABLE 4. Comparison of BD-IPMN in Patients With Progression Between Patients With and Without Surgical Resection

Imaging Findings at the Time of Resection	BD-IPMN With Progression (n = 64)		*P* Value (Resection vs. No Resection)
	Resection (n = 22)	Follow-Up Without Surgery (n = 40)	
Median cyst size (range), mm	32.5 (6–65)	28.5 (6.0–50.0)	0.190
Median MPD diameter (range), mm	5.5 (2–13.0)	3.0 (1.0–10.0)	0.003
MNs			
Absent	7	29	0.002
Present	15	11	
Median follow-up period (range), yrs	2.7 (1.0–15.3)	4.6 (1.1–16.3)	0.043

TABLE 5. Histologic Findings of Resected BD-IPMNs With or Without Progression

Histology	Total (n = 29)	Resected BD-IPMN		*P* Value (Progression vs. No Change)
		Progression (n = 22)	No Change* (n = 7)	
Benign, n (%) (adenoma)	20 (69.0)	13 (59.1)	7 (100.0)	0.050
Malignant, n (%) (noninvasive cancer + invasive cancer)	9 (31.0)	9 (40.9)	0 (0.0)	

*Seven patients underwent resection; 2 became symptomatic, 2 desired to undergo surgery, and 3 developed additional pancreatic cancer.

Tanno et al[17] reported that 69 (84.1%) of 82 BD-IPMN patients without MNs had no progression during a median follow-up period of 61 months. Kobayashi et al[15] demonstrated that 36 (97.3 %) of 37 BD-IPMN patients without MNs showed no changes during a mean follow-up period of 41.8 months. Our findings, taken together with the other studies, demonstrate that 70% to 90% of BD-IPMN patients without MNs remain unchanged during a long period of time (range of median follow-up, 33–61 months). In addition, our study demonstrated that all 7 patients who underwent surgery without progression had histologic diagnosis of adenoma. This finding suggests that it may take a long time for malignant transformation of BD-IPMNs without MNs in patients without progression.

In this study, the remaining 62 patients (17.8%) exhibited progression as defined by a combination of the following findings: appearance of MNs, increased cyst size, and/or increased MPD diameter. Among 62 patients showing progression during follow-up, 22 underwent surgery, whereas the remaining 40 continued to be followed without surgery. The remaining 40 patients with progression did not undergo surgery because there were no prescribed common criteria for surgery among the 10 institutions taking part in this retrospective multicenter analysis. However, a retrospective assessment revealed that there were significant differences in the MPD diameters and the frequency of MNs at the time of resection between patients undergoing surgery and in patients who completed follow-up without surgery. Specifically, patients who underwent surgery exhibited more progression than did patients who were followed without surgery. The study showed that, of the 22 patients undergoing surgery because of marked progression, 13 (59.1%) had histologic adenoma and 9 (40.9%) had carcinoma. This suggests that the remaining 40 patients with progression who were followed without surgery could also develop carcinoma. Although the median observation period in the 40 patients with follow-up was significantly longer than the observation period in the 22 undergoing surgery, and malignant changes were not actually observed on imaging in the 40 follow-up patients, the absence of carcinoma cannot be definitively known. Therefore, these patients should be monitored closely by imaging modalities on an ongoing basis to enable the detection of changes, and surgery should be considered in patients with progressing BD-IPMNs.

The presence of MNs has been reported to be strongly suggestive of malignancy.[5,8,12,15,17] In addition, several authors have reported that malignancy was associated with increased MPD diameter and/or cyst size during follow-up periods.[3,7,13,14] In this study, 9 patients with BD-IPMNs diagnosed histologically as carcinoma exhibited obvious signs of progression, such as development of MNs or increased MPD diameter. In contrast, all 7 surgical patients with BD-IPMNs not progressing during follow-up had histologic adenoma. These multicenter study findings support the notion that malignancy is associated with signs of progression, such as appearance of MNs or increased MPD diameter. In particular, our data suggest that a combination of increased MPD diameter and appearance of MNs was a statistically significant predictor of malignancy development during follow-up of patients with BD-IPMN.

In this study, there was a significant difference in the sex ratio between patients with and without progression ($P = 0.01$); BD-IPMN in male patients progressed more frequently. Although the reason for this difference is unclear, hormonal status may play an important role in the development and pathogenesis of BD-IPMN. Indeed, sex has been reported to be associated with the development of colorectal cancer and pancreatic mucinous cystic neoplasms.[19,20]

With regard to errors in measurement because of the use of different modalities, EUS was performed in these 349 patients

TABLE 6. Relationship Between Imaging Findings at the Time of Resection and Malignancy in 29 Pathologically Confirmed BD-IPMNs

Imaging Findings at the Time of Resection	Total (n = 29)	Resected BD-IPMN		*P* Value (Malignant vs. Benign)
		Malignant (n = 9)	Benign (n = 20)	
Cyst size, n (%)				
<30 mm	13 (44.8)	4 (44.4)	9 (45.0)	0.647
≥30 mm	16 (55.2)	5 (55.6)	11 (55.0)	
MPD diameter, n (%)				
<6 mm	18 (62.1)	4 (44.4)	14 (70.0)	0.184
≥6 mm	11 (37.9)	5 (55.6)	6 (30.0)	
MNs, n (%)				
Absent	14 (48.3)	2 (22.2)	12 (60.0)	0.068
Present	15 (51.7)	7 (77.8)	8 (40.0)	

TABLE 7. Changes in Imaging Findings During the Follow-Up Period in 29 Pathologically Confirmed BD-IPMNs

Changes in Imaging Findings	Total (n = 29)	Resected BD-IPMN		*P* Value (Malignant vs. Benign)
		Malignant (n = 9)	Benign (n = 20)	
(1) Increased cyst size, n (%)	2 (6.9)	0 (0.0)	2 (10.0)	0.468
(2) Increased MPD diameter, n (%)	4 (13.8)	2 (22.2)	2 (10.0)	0.407
(3) Appearance of MNs, n (%)	6 (20.7)	2 (22.2)	4 (20.0)	0.629
(4) Increased cyst size and MPD diameter, n (%)	1 (3.4)	0 (0.0)	1 (5.0)	0.690
(5) Increased cyst size and appearance of MNs, n (%)	3 (10.3)	1 (11.1)	2 (10.0)	0.688
(6) Increased MPD diameter and appearance of MNs, n (%)	3 (10.3)	3 (33.3)	0 (0.0)	0.023
(7) Increased cyst size, MPD diameter, and appearance of MNs, n (%)	3 (10.3)	1 (11.1)	2 (10.0)	0.690
(8) No changes, n (%)	7 (24.1)	0 (0.0)	7 (35.0)	0.050

to confirm the absence of MNs at the time of initial diagnosis. Although we could not reexamine all patients during follow-up by EUS, it was performed at least twice in 176 patients during the follow-up period. Instead, CT, US, MRCP, and ERCP were performed for regular follow-up in 151, 119, 128, and 39 patients, respectively. Consequently, it is likely that there were several discrepancies in measurement because of the different modalities used in this multicenter study.

There have been several reports on the development of PDAs during the follow-up of patients with BD-IPMNs.[15,21–24] Recent studies have demonstrated that in 5.4% to 9.3% of patients with BD-IPMNs, PDAs were located at a distance from the original BD-IPMNs. In this study, PDAs distinct from original BD-IPMNs developed in 7 (2.0%) of 349 patients during the follow-up period. These data suggest that PDAs distinct from BD-IPMNs occur not infrequently in the pancreas and support the view that a BD-IPMN may be an indicator of a precancerous state of the pancreas.[15,21–24] Our study also showed that patients with PDAs distinct from BD-IPMNs had an extremely poor prognosis, whereas patients with malignant BD-IPMNs, including noninvasive and invasive carcinomas, had a relatively better prognosis after surgical treatment. Thus, special attention should be paid to the occurrence of PDAs in the entire pancreas when performing follow-up examinations in patients with BD-IPMNs.

As for the appearance of neoplasms other than PDAs, we found additional BD-IPMNs distinct from the original neoplasms during follow-up, with an incidence of 3.7%. With regard to the incidence of multifocal BD-IPMNs, Rodriguez et al[9] reported that 21 (14.5%) of 145 BD-IPMNs were multifocal. Tanno et al[23] reported that 17 (19.1%) of 89 BD-IPMNs were multifocal. These observations support the hypothesis that a field defect causing multiple primary neoplastic lesions exists in pancreata harboring BD-IPMNs.[25]

This multicenter study presented the long-term follow-up results of a large number of patients with BD-IPMN. In conclusion, most patients with BD-IPMN without MNs can be managed conservatively without surgery, but careful attention should be paid to monitoring for progression and the development of additional neoplasms in the pancreas, especially PDAs, during follow-up.

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ORIGINAL ARTICLE

Pancreatic Ductal Adenocarcinoma Derived From IPMN and Pancreatic Ductal Adenocarcinoma Concomitant With IPMN

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Objectives: Pancreatic ductal adenocarcinoma (PDAC) may derive from an intraductal papillary mucinous neoplasm (IPMN) of the pancreas or may develop in the pancreatic duct apart from IPMN. The purpose of this study was to define the clinicopathological features of these 2 entities and compare them with those of ordinary PDAC.

Methods: Of 765 patients who had surgical resection for IPMN, 122 were diagnosed as having PDAC derived from IPMN and 31 with PDAC concomitant with IPMN. In addition, 7605 patients with PDAC who were registered in the Japan Pancreas Society pancreatic cancer registry were compared with the above patients.

Results: Pancreatic ductal adenocarcinomas derived from IPMN and concomitant with IPMN were significantly smaller, less invasive, and less extensive than ordinary PDAC. The median survival of patients with the 2 conditions was significantly longer than for those with ordinary PDAC when compared overall or when limited to TS2 (2.0 cm < tumor size ≤ 4.0 cm) or TS3 (4.0 cm < tumor size ≤ 6.0 cm) cases.

Conclusions: These findings suggest that PDAC concomitant with IPMN and PDAC derived from IPMN may have more favorable biological behaviors or be diagnosed earlier than ordinary PDAC.

Key Words: IPMN, PDAC concomitant with IPMN, PDAC derived from IPMN

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Intraductal papillary mucinous neoplasm (IPMN) is characterized by papillary proliferation of atypical mucinous epithelium in the pancreatic ductal system, and the affected pancreatic ducts are often cystically dilated.[1,2] Intraductal papillary mucinous neoplasm is a spectrum of diseases ranging from adenoma, to in situ carcinoma, to invasive carcinoma (minimally invasive carcinoma and invasive carcinoma derived from IPMN).[3] On the other hand, pancreatic ductal adenocarcinoma (PDAC) develops independently of IPMN in the pancreatic duct.[4,5] When PDAC originates in the vicinity of IPMN, the distinction between PDAC derived from IPMN and PDAC concomitant with IPMN is sometimes difficult to make. In this collective series, we developed a definition of the 2 conditions and analyzed the incidence of the conditions in patients with IPMN. In addition, we compared the clinicopathological features between (1) ordinary PDAC and PDAC derived from IPMN and (2) ordinary PDAC and PDAC concomitant with IPMN.

MATERIALS AND METHODS

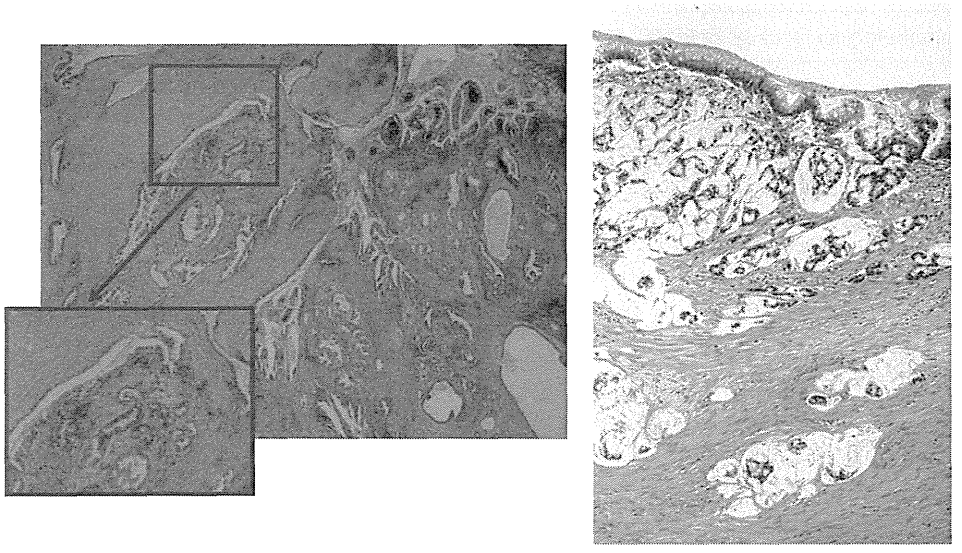
The Japan Pancreas Society (JPS) formed a committee to solve the clinical and pathological problems associated with PDAC derived from IPMN and PDAC concomitant with IPMN. The committee (Drs H. Maguchi, K. Hanada, Y. Noda, M. Tada, and A. Nakaizumi as internists; Drs K. Yamaguchi, T. Hatori, Y. Shimizu, and T. Nakagori as surgeons; and Drs Y. Kato, T. Furukawa, B. Nobukawa, and S. Ban as pathologists) discussed the definition of PDAC derived from IPMN and PDAC concomitant with IPMN and proposed a new definition of 3 categories (PDAC derived from IPMN, PDAC concomitant with IPMN, and PDAC of undetermined relationship with IPMN) based on the topological relationship of the 2 conditions and the presence or absence of a histological transition (Fig. 1) between the conditions as follows: F1

PDAC Derived From IPMN

Pancreatic ductal adenocarcinoma is evidently derived from IPMN, based on the findings of radiologic images and macroscopic or microscopic findings, and a histological transition is present between IPMN and PDAC.

PDAC Concomitant With IPMN

Intraductal papillary mucinous neoplasm is obviously different from PDAC, according to the radiologic images and macroscopic or microscopic findings.



From IPMN to tubular carcinoma From IPMN to mucinous carcinoma

FIGURE 1. Histological transition from IPMN to tubular carcinoma or mucinous carcinoma.

TABLE 1. Intraductal Papillary Mucinous Neoplasm, PDAC Derived From IPMN, and PDAC Concomitant With IPMN

IPMN	582 cases
Adenoma	381 cases
Carcinoma	201 cases
Noninvasive	157 cases
Minimally invasive	44 cases
PDAC derived from IPMN	122 cases
PDAC concomitant with IPMN	31 cases
PDAC undetermined derived from IPMN or concomitant with IPMN	30 cases
Total	765 cases

TABLE 2. Clinical Features of Patients With PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (Overall)

	PDAC	PDAC Derived From IPMN		PDAC Concomitant With IPMN	
	(n = 7605)	(n = 122)	*P*	(n = 31)	*P*
Age,* mean (SD), yr	63.5 (9.9)	66.5 (8.4)	<0.001	67.1 (8.2)	0.021
Sex,† n (%)					
Male	4674 (61.5)	77 (63.1)	0.67	21 (67.7)	0.457
Female	2931 (38.5)	45 (36.9)		10 (32.3)	
Follow-up duration,* mean (SD), mo	17.1 (22.0)	36.7 (36.0)	<0.001	37.3 (36.9)	<0.001

P value compared with PDAC.

*Two-sample *t* test.

†χ^2 test.

Undetermined Whether PDAC Is Derived From IPMN or Concomitant With IPMN

Intraductal papillary mucinous neoplasm and PDAC are evident, but whether PDAC was derived from IPMN or whether PDAC was concomitant with IPMN could not be determined because there was no histological transition between the 2 diseases. The histological transition might not be evident (1) because serial stepwise section examination of the resected specimens was not done in all the cases, (2) because the transition might have disappeared because of the extensive and massive growth of PDAC, or (3) because the 2 diseases developed independently and collided with each other. Thus, such cases were considered as undetermined whether PDAC was derived

TABLE 3. Comparison Among IPMN Types and IPMN, PDAC Derived From IPMN, and PDAC Concomitant With IPMN

	Main Duct (+Mixed) Type, n (%)	Branch Duct Type, n (%)	*P*
IPMN (n = 582)	181 (31.1)	401 (68.9)	—
PDAC derived from IPMN (n = 122)	61 (50.0)	61 (50.0)	<0.001
Tubular adenocarcinoma (n = 81, 66.4%)	38 (46.9)	43 (53.1)	0.004
Mucinous carcinoma (n = 41, 33.6%)	23 (56.1)	18 (43.9)	0.001
PDAC concomitant with IPMN (n = 31)	3 (9.6)	28 (90.4)	0.012
Tubular adenocarcinoma (n = 31, 100%)	3 (9.6)	28 (90.4)	0.012
Mucinous carcinoma (n = 0, 0.0%)	0 (0)	0 (0)	NA

P value compared with IPMN.

NA indicates not available.

TABLE 4. Clinicopathological Findings of PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (Overall)

		PDAC (n = 7605)		PDAC Derived From IPMN (n = 122)			PDAC Concomitant With IPMN (n = 31)		
		n	%	n	%	*P*	n	%	*P*
Histological diagnosis	Tubular adenocarcinoma	7484	98.4	60	69.0	<0.001	20	100	0.57
	Mucinous adenocarcinoma	121	1.6	26	29.9		0	0.0	
	Tubular + mucinous	0	0.0	1	1.1		0	0.0	
	Unknown	0		35			0		
Location	Head	5204	68.6	77	67.0	0.222	14	46.7	<0.001
	Body	974	12.8	10	8.7		11	33.3	
	Tail	420	5.5	9	7.8		5	16.7	
	All segments of pancreas	115	1.5	4	3.5		0	0.0	
	Two segments of pancreas	868	11.4	15	13.0		1	3.3	
	Unknown	24		7			1		
TS	TS1	882	12.0	9	7.4	0.005	15	48.4	<0.001
	TS2	3921	53.6	65	53.7		12	38.7	
	TS3	1837	25.1	25	20.7		4	12.9	
	TS4	681	9.3	22	18.2		0	0.0	
	Unknown	284		1			0		
T	Tis	0	0.0	0	0.0	<0.001	2	6.5	<0.001
	T1	229	3.2	8	6.6		9	29.0	
	T2	281	3.9	27	22.1		0	0.0	
	T3	1915	26.8	72	59.0		14	45.2	
	T4	4714	66.0	15	12.3		6	19.4	
	Unknown	466		0			0		
N	N0	2319	33.7	65	53.3	<0.001	14	45.2	0.01
	N1	1518	22.1	39	32.0		12	38.7	
	N2	1399	20.3	15	12.3		4	12.9	
	N3	1642	23.9	3	2.5		1	3.2	
	Unknown	727		0			0		
M	M (−)	5480	72.4	118	96.7	<0.001	31	100	0.001
	M (+)	2092	27.6	4	3.3		0	0.0	
	Unknown	33		0			0		
Stage	0	0	0.0	0	0.0	<0.001	2	6.5	<0.001
	I	146	2.2	6	4.9		8	25.8	
	II	167	2.5	26	21.3		1	3.2	
	III	1278	19.0	57	46.7		10	32.3	
	IVA	2250	33.4	22	18.0		8	25.8	
	IVB	2887	42.9	11	9.0		2	6.5	
	Unknown	877		0			0		

P value compared with PDAC.

from IPMN or PDAC was concomitant with IPMN and were excluded from further comparisons to examine the details of each discrete condition.

The clinicopathological data of 765 patients who underwent surgical resection for IPMN were collected from the following 7 representative Japanese institutions:

TABLE 5. Median Survival of PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (Overall)

PDAC (n = 7605)		PDAC Derived From IPMN (n = 122)		PDAC Concomitant With IPMN (n = 31)		Results of the Log-Rank Test (*P*)	
n	MST, mo	n	MST, mo	n	MST, mo	PDAC vs PDAC Derived From IPMN	PDAC vs PDAC Concomitant With IPMN
7359	12	122	46	31	57	<0.001	<0.001

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We had 4 committee meetings where we reviewed the radiologic images and hematoxylin-eosin–stained sections of the patients and discussed the differentiation of the tumors and determined the diagnostic criteria. All 765 patients underwent surgery from February 1987 to February 2009. They consisted of AQ3 381 patients with IPMA (49.8%), 201 with IPMC (26.3%) (157 with noninvasive IPMC and 44 with minimally invasive IPMC), 122 judged to have PDAC derived from IPMN (15.9%), 31 judged to have PDAC concomitant with IPMN (4.1%), and 30 for whom it could not be determined whether the PDAC derived from IPMN or was concomitant with IPMN (3.9%) (Table 1). T1

In addition, data from 7605 patients with PDAC who were registered in the JPS pancreatic cancer registry were obtained under the permission of the president of the JPS (Professor Masao Tanaka, MD, PhD, FACS, Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan). These patients underwent surgical resection in 168 Japanese institutions from November 1971 to January 2005.

Data were analyzed following the *Classification of Pancreatic Carcinoma* published by the JPS (Second English Edition, 2003, Kanehara & Co, Ltd, Tokyo, Japan).[6] Statistical analyses were done by *t* test, χ^2 test, and log-rank test. The mean follow-up period was determined when the final follow-up information was obtained. Mean follow-up period of the 7605 cases with PDAC was 17.1 months, that of the 122 cases with PDAC derived from IPMN was 36.7 months, and that of the

TABLE 6. Clinicopathological Features and MST (Overall Cases)

		PDAC (n = 7605)			PDAC Derived From IPMN (n = 122)			PDAC Concomitant With IPMN (n = 31)			
		n	%	MST, mo	n	%	MST, mo	%	n	%	MST, mo
All cases		7605	100.0	12	122	100.0	46	100.0	31	100.0	57
Histological diagnosis	Tubular adenocarcinoma	7484	98.4	13	60	69.0	44	69.0	20	100	51
	Mucinous adenocarcinoma	121	1.6	31	26	29.9	55	29.9	0	0.0	NA
	Tubular + mucinous	0	0.0	NA	1	1.1	30	1.1	0	0.0	NA
	Unknown	0			35				0		
TS	TS1	882	12.0	29	9	7.4	38	7.4	15	48.4	59
	TS2	3921	53.6	14	65	53.7	42	53.7	12	38.7	24
	TS3	1837	25.1	10	25	20.7	54	20.7	4	12.9	12
	TS4	681	9.3	9	22	18.2	61	18.2	0	0.0	NA
	Unknown	284			1				0		
T	Tis	0	0.0	NA	0	0.0	NA	0.0	2	6.5	138
	T1	229	3.2	45	8	6.6	50	6.6	9	29.0	42
	T2	281	3.9	25	27	22.1	39	22.1	0	0.0	NA
	T3	1915	26.8	19	72	59.0	62	59.0	14	45.2	62
	T4	4714	66.0	10	15	12.3	35	12.3	6	19.4	24
	Unknown	466			0				0		
N	N0	2319	33.7	20	65	53.3	54	53.3	14	45.2	73
	N1	1518	22.1	14	39	32.0	31	32.0	12	38.7	54
	N2	1399	20.3	11	15	12.3	47	12.3	4	12.9	24
	N3	1642	23.9	9	3	2.5	24	2.5	1	3.2	NA
	Unknown	727			0				0		
M	M (−)	5480	72.4	16	118	96.7	47	96.7	31	100	57
	M (+)	2092	27.6	9	4	3.3	36	3.3	0	0.0	NA
	Unknown	33			0				0		
Stage	0	0	0.0	NA	0	0.0	NA	0.0	2	6.5	138
	I	146	2.2	57	6	4.9	47	4.9	8	25.8	36
	II	167	2.5	36	26	21.3	42	21.3	1	3.2	54
	III	1278	19.0	23	57	46.7	60	46.7	10	32.3	60
	IVA	2250	33.4	15	22	18.0	39	18.0	8	25.8	24
	IVB	2887	42.9	9	11	9.0	44	9.0	2	6.5	12
	Unknown	877			0				0		

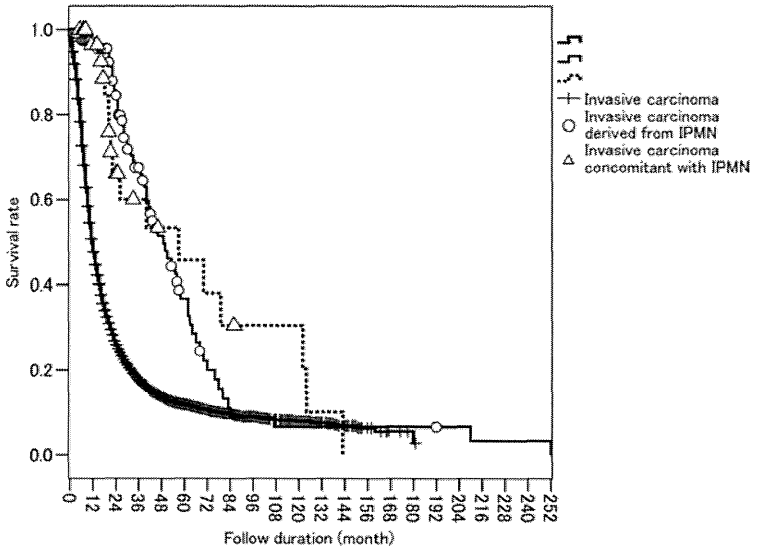
31 cases with PDAC concomitant with IPMN was 37.3 months (Table 2). Survival curves were made by the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological Comparison Between PDAC and PDAC Derived From IPMN and Between PDAC and PDAC Concomitant With IPMN

The mean ages of patients with PDAC derived from IPMN and PDAC concomitant with IPMN was 66.5 ($P < 0.001$) and 67.1 ($P = 0.021$) years, respectively, both of which were significantly higher than the mean age of 63.5 years of the PDAC patients. The male-to-female ratio was approximately 60% in all 3 groups (Table 2). The IPMN in the cases of PDAC derived from IPMN was significantly more frequently of the main duct type than when IPMN was detected alone, and most IPMNs in PDAC concomitant with IPMN were of the branch duct type, which was not the case when patients presented with IPMN only. Concerning the histological type, approximately one-third of the cases of PDAC derived from IPMN (41/122) were mucinous carcinomas, although most of the cases of PDAC concomitant with IPMN (28/31) were tubular adenocarcinomas, similar to ordinary PDAC (Table 3). Approximately 30% of the cases of PDAC derived from IPMN were mucinous carcinomas, which was significantly more frequent than is observed in patients with PDAC alone ($P < 0.001$; Table 4). More than 50% of the lesions of PDAC concomitant with IPMN were located in the body or tail of the pancreas, whereas approximately 70% of PDAC ($P < 0.001$) and PDAC derived from IPMN ($P = 0.002$) were in the head of the pancreas. About 50% of the cases of PDAC concomitant with IPMN were of TS1 (≤2 cm) in size, whereas approximately 10% of PDAC ($P < 0.001$) and PDAC derived from IPMN ($P < 0.001$) were of TS1. Lymph node metastasis in PDAC was significantly more frequent and more extensive than in patients with PDAC derived from IPMN and PDAC concomitant with IPMN. Distant metastasis was also more frequent in PDAC than in PDAC derived from IPMN and PDAC concomitant with IPMN. In addition, the stage at the time of the diagnosis of PDAC was more advanced than in patients diagnosed with PDAC derived from IPMN and PDAC concomitant with IPMN.

P for No. Cases			*P* for MST		
PDAC vs PDAC Derived From IPMN	**PDAC vs PDAC Concomitant With IPMN**	**PDAC Derived From IPMN vs PDAC Concomitant With IPMN**	**PDAC vs PDAC Derived From IPMN**	**PDAC vs PDAC Concomitant With IPMN**	**PDAC Derived From IPMN vs PDAC Concomitant With IPMN**
			<0.001	<0.001	0.808
<0.001	0.57	0.016	<0.001	0.003	0.354
			0.354	NA	NA
			NA	NA	NA
0.005	<0.001	<0.001	0.888	0.337	0.19
			<0.001	0.031	0.116
			<0.001	0.028	0.689
			<0.001	NA	NA
			<0.001	0.002	0.127
<0.001	<0.001	<0.001	NA	NA	NA
			0.732	0.301	0.815
			0.404	NA	NA
			<0.001	0.104	0.14
			0.001	0.007	0.831
<0.001	0.01	0.87	<0.001	0.136	0.601
			<0.001	0.015	0.404
			<0.001	0.036	0.369
			0.223	0.280	0.333
<0.001	0.001	0.307	<0.001	0.001	0.789
			0.017	NA	NA
<0.001	<0.001	<0.001	NA	NA	NA
			0.676	0.141	0.917
			0.986	0.957	0.625
			0.001	0.717	0.075
			<0.001	0.018	0.778
			<0.001	0.075	0.67



	survival rate		
	1-year	3-year	5-year
PDAC	51%	19%	12%
PDAC derived from IPMN	97%	68%	37%
PDAC concomitant with IPMN	97%	61%	46%

* p<0.001

FIGURE 2. Survival curves of PDAC, PDAC derived from IPMN, and PDAC concomitant with IPMN (overall).

The median survival times (MSTs) of the 122 patients with PDAC derived from IPMN and of 31 with PDAC concomitant with IPMN were 46 and 57 months, respectively, both of which were significantly longer than the 12 months of the 7605 patients with PDAC (Table 5). The MST of the 7605 patients with PDAC of the tubular type was 13 months, which was significantly shorter than the 44 months of the 122 patients with PDAC derived from IPMN ($P < 0.003$) and 51 months of the 31 patients with PDAC concomitant with IPMN ($P = 0.016$) (Table 6). The MSTs of patients with PDAC of TS1, TS2, TS3, and TS4 were significantly shorter than those of patients with PDAC derived from IPMN and PDAC concomitant with IPMN. The MSTs of patients with PDAC of stage I or II were similar to those of patients with PDAC derived from IPMN and PDAC concomitant with IPMN. However, the MSTs of patients with stage III, IVA, and IVB PDAC were significantly shorter than those of patients with PDAC derived from IPMN and concomitant with IPMN. The survival curve of the patients with PDAC was more unfavorable than that for patients with PDAC derived from IPMN ($P < 0.001$) and with PDAC concomitant with IPMN ($P < 0.001$) (Fig. 2). The 1-, 3-, and 5-year survival rates of PDAC were 51%, 19%, and 12%, respectively, all of which were significantly shorter than 97%, 68%, and 37% of patients with PDAC derived from IPMN and the 97%, 61%, and 46% of patients with PDAC concomitant with IPMN.

Clinicopathological Comparison of TS2 or TS3 PDAC and TS2 or TS3 PDAC Derived From IPMN and Concomitant With IPMN

Next, we compared the tumors that were TS2 (2.0 cm < tumor size ≤ 4.0 cm) or TS3 (4.0 cm < tumor size ≤ 6.0 cm) in size because TS2 and TS3 tumors were the most frequent

TABLE 7. Clinical Features of PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (TS2 or TS3)

	PDAC	PDAC Derived From IPMN		PDAC Concomitant With IPMN	
	(n = 5758)	(n = 90)	*P*	(n = 16)	*P*
Age,* mean (SD), yr	63.6 (9.9)	66.0 (8.7)	0.012	69.4 (6.4)	0.002
Sex†					
Male	3520 (61.1)	60 (66.7)	0.285	11 (68.8)	0.532
Female	2238 (38.9)	30 (33.3)		5 (31.3)	
Follow-up duration,* mean (SD), mo	15.8 (20.0)	34.7 (34.9)	<0.001	16.4 (7.5)	0.759

P value compared with PDAC.
*Two-sample *t* test.
†χ^2 test.

TABLE 8. Clinicopathological Findings of PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (TS2 or TS3)

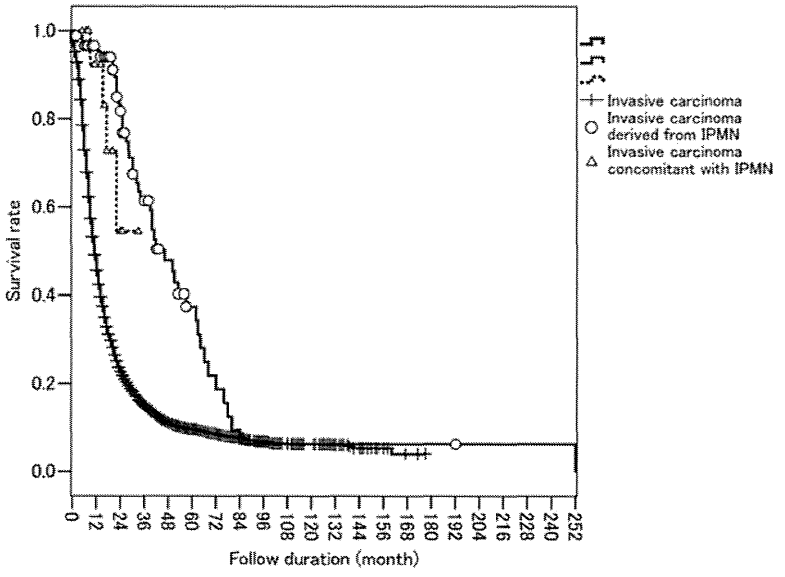
		IDC (n = 5758)		IDC Derived From IPMN (n = 90)			IDC Concomitant With IPMN (n = 16)		
		n	%	n	%	*P*	n	%	*P*
Histological diagnosis	Tubular adenocarcinoma	5686	98.7	51	73.9	<0.001	10	100	0.722
	Mucinous adenocarcinoma	72	1.3	17	24.6		0	0.0	
	Tubular + mucinous	0	0.0	1	1.4		0	0.0	
	Unknown	0		21			6		
Location	Head	4186	72.8	62	73.8	0.615	9	56.3	0.337
	Body	697	12.1	7	8.3		4	25.0	
	Tail	306	5.3	6	7.1		2	12.5	
	All segments of pancreas	24	0.4	1	1.2		0	0.0	
	Two segments of pancreas	537	9.3	8	9.5		1	6.3	
	Unknown	8		6			0		
TS	TS2	3921	68.1	65	72.2	0.404	12	75.0	0.554
	TS3	1837	31.9	25	27.8		4	25.0	
	Unknown	0		0			0		
T	Tis	0	0.0	0	0.0	<0.001	0	0.0	0.001
	T1	0	0.0	0	0.0		0	0.0	
	T2	239	4.4	26	29.4		0	0.0	
	T3	1434	26.5	52	58.4		11	68.8	
	T4	3742	69.1	11	12.2		5	31.3	
	Unknown	343		1			0		
N	N0	1629	30.9	46	51.1	<0.001	3	18.8	0.02
	N1	1251	23.8	33	36.7		9	56.3	
	N2	1160	22.0	10	11.1		3	18.8	
	N3	1225	23.3	1	1.1		1	6.3	
	Unknown	493		0			0		
M	M (−)	4177	72.8	88	97.8	<0.001	16	100	0.015
	M (+)	1560	27.2	2	2.2		0	0.0	
	Unknown	21		0			0		
Stage	0	0	0.0	0	0.0	<0.001	0	0.0	0.007
	I	0	0.0	0	0.0		0	0.0	
	II	113	2.2	25	27.8		0	0.0	
	III	925	18.0	41	45.6		7	43.8	
	IVA	1854	36.1	17	18.9		8	50.0	
	IVB	2244	43.7	6	6.7		1	6.3	
	Unknown	642		1			0		

P value compared with PDAC.

sizes diagnosed in patients with PDAC, PDAC derived from IPMN, and PDAC concomitant with IPMN of this series. A total of 5578 patients had TS2 or TS3 PDAC, 90 patients had TS2 or TS3 PDAC derived from IPMN and 16 had TS2 or TS3 PDAC concomitant with IPMN (Table 7). These 3 groups of PDAC were compared to examine whether the type TS2 or TS3 PDAC tumors were different from the TS2 or TS3 PDAC derived from IPMN or the TS2 or TS3 PDAC concomitant with IPMN. The T number in the TS2 or TS3 PDAC was significantly greater than for PDAC derived from IPMN and TS2 or TS3 PDAC

TABLE 9. Median Survival of PDAC, PDAC Derived From IPMN, and PDAC Concomitant With IPMN (TS2 or TS3)

PDAC (n = 5578)		PDAC Derived From IPMN (n = 90)		PDAC Concomitant With IPMN (n = 16)		Results of the Log-Rank Test (*P*)	
n	MST, mo	n	MST, mo	n	MST, mo	PDAC vs PDAC Derived From IPMN	PDAC vs PDAC Concomitant With IPMN
5578	11	90	46	16	24	<0.001	0.002



	Survival rate		
	1-year	3-year	5-year
PDAC	50%	16%	10%
PDAC derived from IPMN	96%	62%	38%
PDAC concomitant with IPMN	93%	60%	N.A.

*p<0.001 ** p=0.002

FIGURE 3. Survival curves of PDAC, PDAC derived from IPMN, and PDAC concomitant with IPMN (TS2 or TS3).

T8 concomitant with IPMN (Table 8). Lymph node and distant metastases were significantly more frequent and more extensive in TS2 or TS3 PDAC than in TS2 or TS3 PDAC derived from IPMN and TS2 or TS3 PDAC concomitant with IPMN. Distant metastasis was also more frequent in TS2 or TS3 PDAC than in TS2 or TS3 PDAC derived from IPMN and TS2 or TS3 PDAC concomitant with IPMN. The stages of TS2 or TS3 PDAC were more advanced than those of TS2 or TS3 PDAC derived from IPMN and TS2 or TS3 PDAC concomitant with IPMN.

The MST of patients with TS2 or TS3 PDAC was 11 months, being significantly shorter than the 46 months ($P < 0.001$) of the patients with TS2 or TS3 PDAC derived from IPMN and 24 months ($P = 0.002$) of those with TS2 or TS3 PDAC con-
T9 comitant with IPMN (Table 9). The MSTs of PDAC derived from IPMN and concomitant with IPMN were longer than those of ordinary PDAC for each stage. The survival curves of patients with TS2 or TS3 PDAC were more unfavorable than those of TS2 or TS3 PDAC derived from IPMN ($P < 0.001$) and of TS2 or TS3
F3 PDAC concomitant with IPMN ($P = 0.002$; Fig. 3). The 1-, 3-, and 5-year survival rates of ordinary TS2 or TS3 PDAC were 50%, 16%, and 10%, respectively, whereas those of TS2 or TS3 PDAC derived from IPMN were 96%, 62%, and 38%, respectively, and those of TS2 or TS3 PDAC concomitant IPMN were 93%, 60%, and NA (not available).

DISCUSSION

The definition of PDAC derived from IPMN and PDAC concomitant with IPMN was proposed in this study mainly with regard to the topological relationship between the 2 lesions and the presence or absence of a histological transition between the 2 conditions. This was a multi-institutional study, and we could not use *mucin profiles* and molecular biological examination for the differentiation. A total of 765 patients with IPMN were classified into 5 categories, that is, 381 (50%) with IPMA, 201 (26%) with IPMC (157 with noninvasive and 44 with minimally invasive disease), 122 (16%) with PDAC derived from IPMN, 31 (4%) with PDAC concomitant with IPMN, and 30 (4%) with PDAC of undetermined status with regard to IPMN. When the 2 groups composed of PDAC derived from IPMN and PDAC concomitant with IPMN were compared with ordinary PDAC, the mean ages of the 2 groups were higher than those of the non-IPMN PDAC group (Table 10). Mucinous carcinoma was more T10 frequently seen in the group of PDAC derived from IPMN than

TABLE 10. Pancreatic Ductal Adenocarcinoma, PDAC Derived From IPMN, and PDAC Concomitant With IPMN

	PDAC		PDAC Derived From IPMN		PDAC Concomitant With IPMN
Age, yr	64	<	67	≒	67
Sex, M/F	M: 60%	≒	M: 60%	≒	M: 60%
Site	H ≫ B, T		H ≫ B, T		H > B, T
Type (IPMN)			MPD Br		Br
Histological diagnosis	Tub		Muc (30%)		Tub
Tis	big	>	smaller	>	smallest
T	big	>	smaller	>	smallest
N (+)	70%	>	50%	≒	50%
M (+)	30%	>	3%	≒	0%
Stage	Advanced	>	Earlier	>	Earliest
MST, mo	12	<	46	≒	57

in the other 2 groups. Pancreatic ductal adenocarcinoma concomitant with IPMN was more frequently located in the body or tail of the pancreas than were PDAC derived from IPMN and ordinary PDAC. Pancreatic ductal adenocarcinoma derived from IPMN and concomitant with IPMN were significantly smaller than ordinary PDAC in size and showed less invasive and extensive growth than ordinary PDAC. The median survivals of the 2 groups were significantly longer than that of patients with typical PDAC when compared overall and when limited to TS2 or TS3 cases.

Intraductal papillary mucinous neoplasm progresses from adenoma to carcinoma (noninvasive, then minimally invasive, and finally to PDAC derived from IPMN).[1–3,7,8] Yamaguchi et al[5] first reported PDAC concomitant with IPMN in 2002. Thereafter, this combination has been reported mainly in Japan,[9,10] and the development of pancreatic cancer apart from IPMN has been also reported during the follow-up of branch duct IPMN.[11,12] When IPMN and PDAC are present near each other, the distinction between PDAC derived from IPMN and PDAC concomitant with IPMN is difficult to make. There has been some confusion about the definition of the 2 conditions. In this series, we proposed diagnostic criteria of the 2 diseases based on the topological relationship and the presence or absence of a transitional area between the 2 diseases. In this series, we did not perform *mucin profiles* and molecular biological examinations because the present study was a multi-institutional analysis. If we added molecular biology to the criteria, we might have been able to differentiate the 2 conditions more precisely, decreasing the number of patients included in the "undetermined" group.

The reported incidence of PDAC concomitant with IPMN was 9%[5] or 4%[10] in 2 series of surgically resected IPMN. Ingkakul et al[13] reported that 22 (9.3%) of 236 patients with IPMN had concomitant PDAC synchronously or metachronously, and their multivariate analysis revealed that worsening of diabetes mellitus and an abnormal serum CA 19-9 level are 2 significant predictors of the presence of PDAC in IPMN. The development of independent PDAC has been reported in the follow-up of patients with IPMN.[11,12,14] Tada et al[11] reported that PDAC developed in 5% of patients with IPMN during a 3.8-year follow-up. Uehara et al[12] showed an 8% incidence of PDAC developing in 60 patients with branch duct IPMN during the mean follow-up period of 87 months. The 5-year rate of development of PDAC was 6.9%, and the incidence of PDAC was 1.1% per year. Tanno et al[14] showed that 4 (4.5%) of 89 patients with branch duct IPMN developed PDAC during a median follow-up of 64 months. When the new definition is applied, the incidence of PDAC concomitant with IPMN in the present series was 4.1%, which was lower than in the previous reports. This difference might come from the strict definition in this series and the multi-institutional collection of surgically resected cases.

Some have reported that the clinical outcome of patients with PDAC derived from IPMN is better than that for patients with ordinary PDAC because PDAC derived from IPMN is diagnosed at an earlier phase[15] or because the clinicopathological features of PDAC derived from IPMN are different from those of ordinary PDAC.[16–18] A global genomic analysis of IPMN showed significant molecular features that were different from ordinary PDAC.[19] In this series, the clinical outcome of patients with PDAC derived from IPMN was better than that of ordinary PDAC when compared overall and when limited to TS2 or TS3 tumors in size. Patients with IPMN related to PDAC (PDAC derived from IPMN and PDAC concomitant with IPMN) showed a longer MST than those with ordinary PDAC in each stage. Therefore, the biological behavior of PDAC derived from IPMN may be different from ordinary PDAC.

We first reported that the clinical outcome of patients with PDAC concomitant with IPMN was better than that of ordinary PDAC because PDAC concomitant with IPMN was detected at an earlier stage because of the presence of IPMN.[5] In this series, we compared the clinical course of PDAC concomitant with IPMN and that of ordinary PDAC when compared overall and when limited to TS2 or TS3 tumors in size. The clinical course of PDAC concomitant with IPMN was better than ordinary PDAC. Thus, the biological behavior of PDAC concomitant with IPMN may also be different from that of ordinary PDAC.

Concerning pancreatic carcinogenesis, 2 main pathways have been considered: (1) from PanIN to PDAC[20–22] and (2) from IPMN to mucinous carcinoma.[23,24] Others have reported that mucinous carcinoma of the pancreas often originates from IPMN.[23,24] In the present series, mucinous carcinoma was more frequently present in PDAC derived from IPMN than PDAC alone or PDAC concomitant with IPMN. In minimally invasive foci of IPMC, IPMC invaded the stroma in the form of mucinous carcinoma in about a half of the patients.[3] With regard to the histological type, approximately one-third of the PDAC derived from IPMN (41/122) was mucinous carcinoma, although most of PDAC concomitant with IPMN (28/31) was tubular adenocarcinoma, which is similar to ordinary PDAC. These facts may support the hypothesis that most of the mucinous carcinoma of the pancreas originates from IPMC.

This series is a collective series of surgically resected IPMN, PDAC derived from IPMN, and PDAC concomitant with IPMN, and there are some biases that resulted from this limitation. In this series, the PDAC derived from IPMN or concomitant with IPMN were less invasive and showed less extensive growth than those of ordinary PDAC. The overall survival rates of PDAC derived from IPMN and PDAC concomitant with IPMN were significantly better than those of ordinary PDAC. Even when limited to TS2 or TS3 tumors, PDAC derived from IPMN and PDAC concomitant with IPMN showed less aggressive growth than TS2 or TS3 PDAC. Therefore, PDAC derived from IPMN and concomitant with IPMN may have more favorable biological features than ordinary PDAC. Further examination of the natural history of PDAC derived from IPMN and concomitant with IPMN is therefore necessary before any definitive conclusions can be made about the origins, behavior, and lethality of the different types of pancreatic cancer.

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