Pancreatology 19 (2019) 1054–1060

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Main duct and mixed type intraductal papillary mucinous neoplasms without enhancing mural nodules: Duct diameter of less than 10 mm and segmental dilatation of main pancreatic duct are findings support surveillance rather than immediate surgery

Tae Hyeon Kim [a, 1], Tae Jun Song [b, 1], Seung Ok Lee [c], Chang Hwan Park [d], Jong Ho Moon [e], Gyu Young Pih [b], Dong Wook Oh [b], Sang Myoung Woo [f], Yun Jung Yang [g], Myung Hwan Kim [b, *]

[a] Department of Internal Medicine, Wonkwang University College of Medicine, Iksan, South Korea
[b] Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea
[c] Chonbuk National University Medical School, Jeonju, South Korea
[d] Department of Internal Medicine, Chonnam University College of Medicine, Kwangju, South Korea
[e] Department of Internal Medicine, Soon Chun Hyang University School of Medicine, Bucheon, South Korea
[f] Pancreatobiliary Cancer Clinic, Center for Liver Cancer, National Cancer Center, Goyang, South Korea
[g] Institute for Integrative Medicine, Catholic Kwandong University, International St. Mary's Hospital, Incheon, South Korea

ARTICLE INFO

Article history:
Received 6 May 2019
Received in revised form
14 September 2019
Accepted 22 September 2019
Available online 24 September 2019

Keywords:
Main duct intraductal papillary mucinous neoplasms
Mixed type intraductal papillary mucinous neoplasms
Mural nodule
Pancreatic cancer

ABSTRACT

Objective: The guidelines for pancreatic intraductal papillary mucinous neoplasms (IPMNs) recommend surgical resection of all main-duct (MD) and mixed-type IPMNs in surgically fit patients. We conducted this study to identify the rates of high-grade dysplasia (HGD) and invasive carcinoma according to the morphological features of the main pancreatic duct (MPD) in patients with MD and mixed IPMN.
Methods: We performed a retrospective study of 259 patients with histologically proven MD and mixed-type IPMNs who underwent surgery at six academic institutions.
Results: The rate of HGD and invasive carcinoma was 11.1% (24/216) in patients without enhancing mural nodules (MNs) and 69.8% (30/43) in patients with MNs. Multivariate analysis showed that MPD diameter of ≥10 mm [odds ratio (OR), 2.5; 95% confidence interval (CI), 1.155–5.505; $P = 0.02$], diffuse MPD dilatation (OR, 3.2; 95% CI, 1.152–8.998; $P = 0.02$), and presence of enhancing MNs in MPD (OR, 9.6; 95% CI, 3.928–23.833, $P < 0.0001$) were significant predictors of HGD and invasive carcinoma. Of the 216 patients without enhancing MNs, 79 patients (36.6%) having both segmental MPD dilatation and MPD diameter of <10 mm showed significantly lower rates of HGD and invasive carcinoma (3/79, 3.8%) than patients having both diffuse MPD dilatation and MPD diameter ≥10 mm (9/36, 25%, $P = 0.001$).
Conclusions: MD and mixed-type IPMNs having segmental MPD dilatation with MPD dilation <10 mm and no enhancing MNs on imaging showed a significantly lower rate of HGD and invasive carcinoma, and watchful follow-up instead of immediate surgical resection might be possible in these patients.

Introduction

Pancreatic main-duct (MD) and mixed-type intraductal papillary mucinous neoplasms (IPMNs) have been reported to show higher malignancy rate compared to branch-duct (BD) IPMNs [1–7]. Currently, surgical series of MD and mixed-type IPMNs included patients with mural nodules (MNs) or solid masses and most of them were symptomatic at presentation with a main pancreatic duct (MPD) diameter of ≥10 mm [2,3,5,7–9], leading to selection bias in assessing malignancy risk. According to the 2017 revised International Consensus guideline, and 2018 European evidence-based guideline (European guideline) all MD and mixed-

* Corresponding author. Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, South Korea.
E-mail address: mhkim@amc.seoul.kr (M.H. Kim).
[1] Drs. Tae Hyun Kim and Tae Jun Song contributed equally to this article.

https://doi.org/10.1016/j.pan.2019.09.010
1424-3903/

type IPMNs patients were recommended to undergo surgical resection regardless of the presence of symptoms, when surgically fit [10,11]. However, although surgical resection is a curative treatment, it has been reported to be related to significant morbidity and mortality [12–15]. Since MD and mixed-type IPMNs are usually diagnosed in patients older than 60 years of age, the surgical risk may increase further [16].

The 2017 revised International Consensus guideline and European guideline divided IPMN patients into two groups; high-risk stigmata and worrisome-features groups. Previous guidelines and meta-analysis agree that solid mass or enhancing MNs in the IPMNs is a high-risk stigma as well as an absolute surgical indication [10,11,17]. According to the guidelines, MPD diameter 5–9 mm was included in a worrisome feature group and diameter >10 mm was regarded as a high-risk stigma. The cutoff diameter of MPD dilatation for surgical resection or higher malignant potential has been reported ranging from 5 to 7 mm [4,18–21] However, there is insufficient evidence to prove the difference of malignancy rate between two groups; MPD dilatation 5–9 mm and >10 mm group [10,11]. Furthermore, since only a few reports for MD and mixed-type IPMNs patients without enhancing MNs has been reported, there is a lack of evidence to determine if surgery should be performed at the time of diagnosis especially in patients without MNs. Therefore, the present multicenter study included patients without MNs and aimed to identify the rate of high-grade dysplasia (HGD) and invasive carcinoma according to the morphological features of the MPD on imaging in MD or mixed-type IPMNs patients.

Methods

Patients selection

This study is a multi-institutional, retrospective study of clinical and radiographic data of patients who underwent pancreatic resection for confirmed MD IPMN and mixed-type IPMNs. Clinical data of patients treated at six academic medical institutions in South Korea between January 2002 and December 2016 were obtained. A total of 1,460 patients had a diagnosis of IPMN with surgical resection. Among them, 1,085 patients were identified with BD IPMN and 376 patients with MD or mixed-type IPMNs.

Following the 2017 revised International Consensus guideline, MD IPMNs were defined as MPD dilatation of >5 mm on preoperative contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) without other causes of obstruction. Mixed-type IPMNs were defined as dilated MPD (>5 mm diameter) communicating with a dilated BD (>5 mm diameter) [1,20]. We excluded patients with <5 mm MPD dilatation on preoperative radiological imaging despite pathologic diagnosis of MD or mixed-type IPMNs [22]. We also excluded patients with definitive enhancing MNs in BD cysts, but not in dilated MPD, and patients with either adjacent or remote solid mass in the pancreas parenchyma related to the IPMNs on contrast-enhanced CT or MRI, since enhancing MNs in the BD cysts and solid mass in the pancreas parenchyma is an absolute indication of surgical resection at clinical practice. After excluding these patients, we finally included 259 patients with pathologically diagnosed IPMN with MD involvement (Fig. 1). Radiological findings were based on contrast-enhanced CT) and/or MRI of the pancreas performed within two months before surgery. The study protocol was approved by the institutional review boards of each institution.

Data acquisition

We reviewed the medical records of all patients with MD or mixed-type IPMNs. Data collected included demographics; preoperative symptoms, such as the presence of acute pancreatitis or biliary obstruction; preoperative serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels; radiological findings; endoscopic findings; endoscopic ultrasound (EUS) findings; operative findings; and surgical pathological findings. Elevated serum CA 19-9 and CEA levels were defined as >37 U/mL and >5.0 ng/mL, respectively.

The following radiological features were assessed in both the pancreatic parenchymal and portal venous phases: maximal diameter of the dominant cyst, the presence of MNs, size of MNs or a solid component, maximal MPD diameter, morphology pattern of MPD dilatation, and a maximum diameter of the common bile duct. Maximal MPD diameter was measured based on the maximum cross-sectional diameter perpendicular to the MPD long axis. MNs were defined as protruding soft-tissue density, along with the cystic wall or the MPD in any phase of a dynamic study that was not thought to represent a confluence of septa. MPD dilatation was morphologically classified according to the extent (diffuse vs. segmental) and degree of dilatation (Fig. 2). The extent of MPD dilatation was defined as diffuse type if the length of the dilated MPD portion was greater than two-thirds of the total MPD length and segmental type if the length of the dilated portion was less than two-thirds of the total MPD length. The degree of MPD dilatation was classified according to the maximum diameter of the dilated MPD portion (5–9 mm vs. $\geq$ 10 mm), based on the 2017 revised International Consensus guideline.

Surgery and pathology

Each participating institution determined definite indications for surgical resection. Most tumors were generally managed according to international guidelines and expert opinion [1,23]. MPD involvement in all resected specimens was pathologically confirmed where histology showed a neoplasm with columnar, mucin-producing epithelium, with or without papillary proliferation, within the MPD epithelial lining [24]. The neoplasms were classified as low-grade dysplasia (LGD) or HGD, and IPMNs associated with invasive carcinoma [25]. If different grades coexisted in one lesion, the highest grade of dysplasia was recorded. For the analysis, IPMNs were grouped into LGD, or HGD and invasive carcinoma groups. This classification was based on the assumption that MD and mixed-type IPMNs with HGD or invasive carcinoma should be surgically resected, as recommended by International Consensus guidelines and other investigators.

Statistical analyses

Statistical analyses were performed with SPSS version 19.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as medians and ranges and compared by the Mann–Whiney *U* test. Categorical variables were compared by the chi-square and Fisher's exact probability tests. Multivariate logistic regression models were used to estimate the effects of possible predictive factors on malignant MD and mixed-type IPMNs. The inclusion of variables in the models was based on existing knowledge of risk factors for malignant MD and mixed-type IPMNs that were readily discernible on abdominal CT or MRI. The level of significance was set at $P < 0.05$. All *P* values were two-sided.

Results

Demographic, clinical and pathological data of all patients with MD and mixed-type IPMNs

The demographics and clinicopathological features of total of

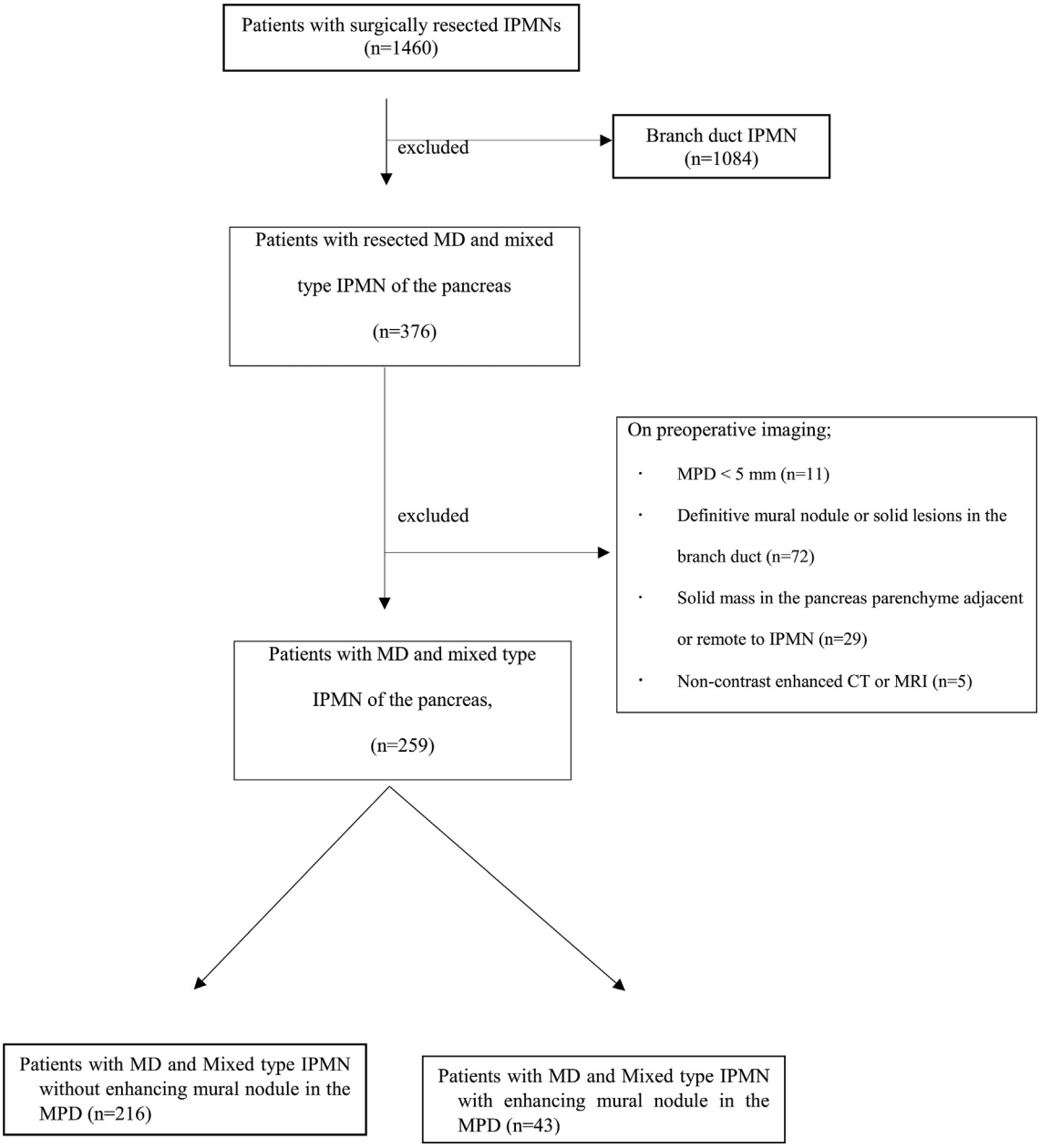

Fig. 1. Flow chart for the study population. MD-IPMN, main duct type IPMN; MPD, main pancreatic duct.

259 patients with MD or mixed-type IPMNs included in this study are shown in Table 1. The median age was 68 years (range, 37–87 years), and 68% were men. As an initial symptom, patients presented with abdominal pain in 25 (9.6%), weight loss in 5 patients (1.9%), and acute pancreatitis in 13 (5.0%). Of the 259 patients, forty-three patients (16.6%) had enhancing MNs within the MPD on preoperative imaging, and 216 patients (83.4%) had no enhancing MNs. The 160 patients (61.8%) showed diffuse MPD dilatation, and 99 patients (38.2%) showed segmental MPD dilatation. The MPD diameter was 5–9 mm and ≥10 mm in 183 (70.7%) and 76 (29.3%) patients, respectively. The median MPD diameter of malignant and benign MD and mixed-type IPMNs was 10 mm (range, 5–40) and 8 mm (range, 5–40), respectively ($P = 0.0001$). Pancreaticoduodenectomy underwent in 125 patients (48.3%), distal pancreatectomy in 119 (45.9%), and total pancreatectomy in 15 patients (5.8%).

The final pathological diagnosis among the 259 patients was LGD in 205 patients (79.2%), HGD in 33 (12.7%), and invasive IPMNs in 21 (8.1%) (Fig. 3). In MD and mixed type IPMNs patients without enhancing MNs, LGD was diagnosed in 192 patients (88.9%), HGD in 18 (8.3%), and invasive carcinoma in 6 patients (2.8%).

The rate of HGD and invasive carcinoma among the 259 patients with MD and mixed type IPMNs was 20.8% (54/259). Among patients without enhancing MNs, the rate of HGD and invasive carcinoma was 11% (24/216), and it was 69.8% (30/43) in patients with enhancing MNs. The rate of HGD and invasive carcinoma in patients without enhancing MNs and MPD with a diameter of 5–9 mm was 7.8% (13/166), and in patients without enhancing MNs and MPD with a diameter of >10 mm, it was 22% (11/50).

Predictors of high-grade dysplasia and invasive carcinoma among all patients with MD and mixed-type IPMNs (n = 259)

Univariate analysis showed that age, MPD diameter of

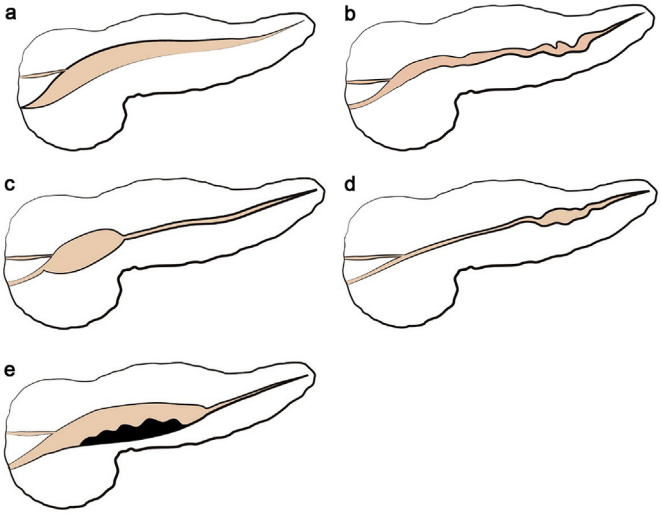

Fig. 2. Schematic classification of main pancreatic duct dilatation of the main duct and mixed type IPMNs. (a) and (b) shows diffuse and even dilatation of the main pancreatic duct. (c) and (d) shows segmental and even dilatation of the main pancreatic duct. (e) shows diffuse dilatation of the main pancreatic duct with a mural nodule.

≥10.0 mm, diffuse type of MPD dilatation, the presence of enhancing MNs in the MPD, maximal diameter of branch cyst, and MD IPMNs were significant predictors of HGD and invasive carcinoma in MD and mixed-type IPMNs patients with or without enhancing MNs (Table 2). In multivariate analysis, MPD diameter of ≥10 mm [odds ratio (OR), 2.5; 95% confidence interval (CI), 1.15–5.51; $P = 0.02$), diffuse type of MPD dilatation (OR, 3.2; 95% CI, 1.15–8.99; $P = 0.02$), and presence of enhancing MNs in the MPD on CT or MRI (OR, 9.6; 95% CI, 3.98–23.8; $P < 0.0001$) were significant predictors of HGD and invasive carcinoma.

Predictors of high-grade dysplasia and invasive carcinoma among patients with MD and mixed-type IPMNs without enhancing MNs (n = 216)

Enhancing MNs in the MPD are already known as definitive high-risk stigmatas of MD and mixed-type IPMNs in most guidelines. We wanted to identify predictors of HGD and invasive carcinoma in MD and mixed-type IPMNs without enhancing MNs in the MPD ($n = 216$). The univariate analysis showed that MPD diameter of ≥10 mm and diffuse type of MPD dilatation were significant predictors of HGD and invasive carcinoma (Tables 1 and 3). In the multivariate analysis, MPD diameter of ≥10 mm (OR, 2.5; 95% CI, 1.21–7.17; $P = 0.02$) and diffuse type of MPD dilatation (OR, 3.2; 95% CI, 1.05–8.42; $P = 0.04$) were significant predictors of HGD and invasive carcinoma (Table 3).

When we compared the patients according to the number of predictors (diffuse type of MPD dilatation and MPD diameter of ≥10 mm), we found that patients with zero predictors (dual negative group) showed significantly lower rates than patients with one predictor (3.8% vs. 15.3%; P = 0.01) or dual predictors (dual positive group) (3.8% vs. 25%, $P = 0.001$, Fig. 4). The negative predictive value of lesions with both segmental type of MPD dilatation and MPD diameter of 5–9 mm of malignancy was 96.2%.

Discussion

The revised guideline for pancreatic IPMNs has subdivided patients as a surveillance group with specific criteria decreasing the number of patients requiring immediate surgery. Surgery is an only curative method for MD or mixed-type IPMNs considering their malignant potential. However, surgery-related morbidity and mortality are still considerable especially in elderly patients in whom MD or mixed type IPMNs is frequently found. The revised 2017 International Consensus identified MPD dilatation of 5–9 mm

Table 1
Demographics and clinicoradiological characteristics of 259 all patients with main duct and mixed type IPMNs of the pancreas.

Characteristic	All Patients with IPMNs No. (%) (n = 259)	Patients with IPMNs without enhancing MN No, (%) (n = 216)	Patients with IPMNs with enhancing MN No, (%) (n = 43)	P value
Age, median (range), y	68 (37–87)	62 (32–80)	64 (40–78)	0.898
Male	176 (68.0%)	146 (67.6%)	29 (67.4%)	0.78
Episode of acute pancreatitis	13 (5.0%)	13 (6.0%)	0 (0%)	0.099
Presence of symptoms				
Body weight loss	5 (1.9%)	3 (1.4%)	2 (4.7%)	0.155
Abdominal pain	25 (9.6%)	19 (8.8%)	6 (13.9%)	0.296
Pathological diagnosis				
Low grade	205 (79.2%)	192 (88.9%)	13 (30.2%)	<0.0001
High grade	33 (12.7%)	18 (8.3%)	15 (34.9%)	<0.0001
Invasive cancer	21 (8.1%)	6 (2.8%)	15 (34.9%)	<0.0001
Background data on imaging findings				
Main duct vs. Mixed	73 (28.2%) vs 186 (71.8%)	49 (22.7%) vs. 167 (77.3%)	24 (55.8) vs 15 (44.2%)	<0.0001
MPD diameter, median (range), mm	8.0 (5–40)	7.0 (5.0–40.0)	8.0 (5.0–35.0)	0.0084
Cyst size, median (range), mm	2.0 (5–80)	2.0 (0.0–8.0)	2.0 (0.0–8.0)	0.141
Morphological classification of MPD and mural nodule status				
Dilatation extent (Diffuse vs. segmental type)	160 (61.8%) vs. 99 (38.2%)	121 (56.0%) vs 95 (44.0%)	39 (90.7%) vs 4 (9.3%)	<0.0001
Dilatation degree (≥10 mm vs. 5–9 mm)	76 (29.3%) vs. 183 (70.7%)	50 (23.1%) vs. 166 (76.9%)	26 (60.5%) vs 17 (39.5%)	<0.0001
Presence of enhancing mural nodule	43 (16.6%) vs. 216 (85.3%)		43 (100%)	
Elevated serum				
CEA level, median (range), U/mL	1.7 (0.4–12)	1.8 (0.4–12)	1.5 (0.4–12.0)	0.978
CA19-9 level, median (range), U/mL	12 (0.6–6800)	12 (0.6–320)	15 (1.5–6812)	0.008
Operation type				
Pancreaticoduodenectomy	125 (48.3%)	95 (44.0%)	30 (69.8%)	0.002
Distal pancreatectomy	119 (45.9%)	11 (51.4%)	8 (18.6%)	0.002
Total pancreatectomy	15 (5.8%)	10 (4.6%)	5 (11.6%)	0.072

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MD, main duct; MPD, main pancreatic duct; MRI, magnetic resonance imaging.

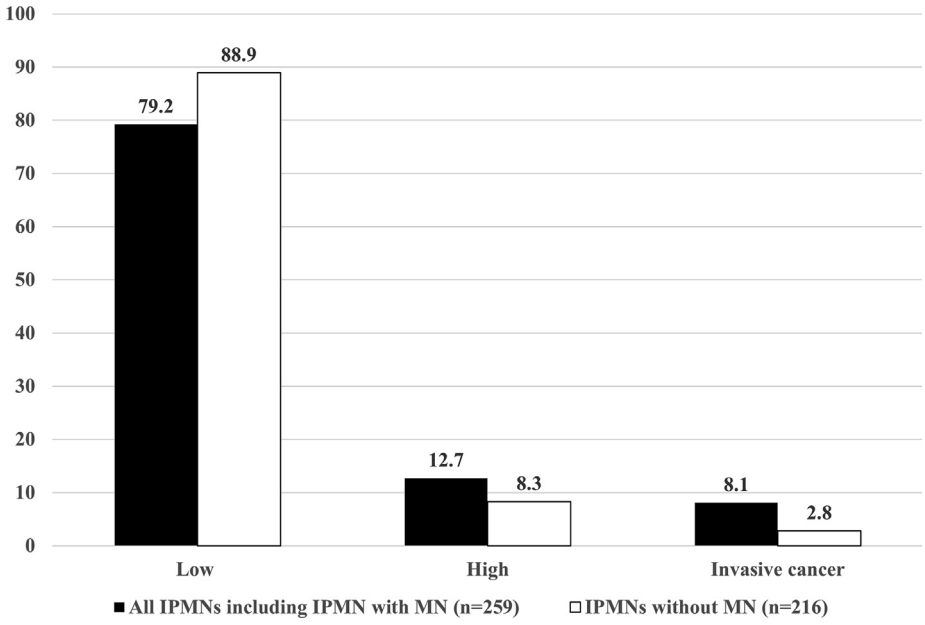

Fig. 3. Histologic distribution of MD and mixed type IPMN in all patients.

Table 2
Risk analysis for high-grade dysplasia and invasive carcinoma in all patients with MD and mixed type IPMNs (n = 259).

characteristics	No. (%)		*P* value		Odds ratio (95% CI)
	Benign IPMN (n = 205)	Malignant IPMN (n = 54)	Univariate analysis	Multivariate analysis	
Clinical characteristics					
Age	64 (32–83)	66 (31–78)	0.02	0.55	NA
Male	137(66.8)	39 (72.2)	0.51	NA	NA
Episode of acute pancreatitis	11 (5.4)	2 (3.7)	0.61	NA	NA
Background data on imaging findings					
Maximal diameter of branch cyst, median (range), mm	20 (0–70)	17 (0–80)	0.008	0.73	NA
MD IPMN vs. Mixed IPMN	50 (24.4)	23 (42.6)	0.004	0.66	NA
Morphological classification of MPD on imaging findings					
Dilatation extent (Diffuse vs. segmental type)	113 (55.1)	47 (87.0)	<0.0001	0.02	3.2 (1.152–8.998)
Dilatation degree (≥10 mm vs. 5–9 mm)	45 (21.9)	31 (57.4)	<0.0001	0.02	2.5 (1.155–5.505)
Presence of enhancing mural nodule in MPD	13 (5.2)	30 (55.6)	<0.0001	<0.0001	9.6 (3.928–23.833)

Table 3
Risk analysis for high-grade dysplasia and invasive carcinoma in IPMN patients without enhancing mural nodules on CT or MRI (n = 216).

Characteristics	No. (%)		*P* value		Odds ratio (95% CI)
	Low-grade dysplasia (n = 192)	High-grade dysplasia and invasive carcinoma (n = 24)	Univariate analysis	Multivariate analysis	
Background data					
Age	63 (32–80)	65 (44–74)	0.407	NA	NA
Male	127 (66.1)	19 (79.2)	0.251	NA	NA
Episode of acute pancreatitis	11 (5.7)	2 (8.3)	0.642	NA	NA
Background data on imaging findings					
Maximal diameter of branch duct cyst, median (range), mm	20 (0–70)	20 (0–80)	0.966	0.73	NA
MD IPMN vs. Mixed IPMN	50 (26.0)	5 (20.8)	0.632	0.66	NA
Morphological classification of MPD dilatation					
Dilatation extent (Diffuse vs. segmental type)	102 (53.1)	19 (79.2)	0.017	0.04	3.2 (1.054–8.416)
Dilatation degree (≥10 mm vs. 5–9 mm)	39 (20.3)	11 (45.8)	0.0009	0.02	2.5 (1.205–7.169)

as a 'worrisome feature' that requires further workup with EUS and the 2018 European guidelines classified it as a relative indication for surgery [10,11]. MPD dilatation of ≥10 mm is a high-risk stigmata that requires surgical resection [1,11]. In the previously reported surgical series on MD or mixed-type IPMNs, most of the patients had high-risk stigmata and showed high malignancy rate [2,3,5,8,9]. However, there are limited data on the risk of HGD and invasive carcinoma in MPD diameters of 5–9 mm. Hackert et al. [20] reported that the malignancy rate of IPMNs with MPD diameters of 5–9 and ≥10 mm were 59% and 73%, respectively. Sugimoto et al. [6] also showed similar results in their study (53.7% and 67.7%, respectively). In the present study, however, when we

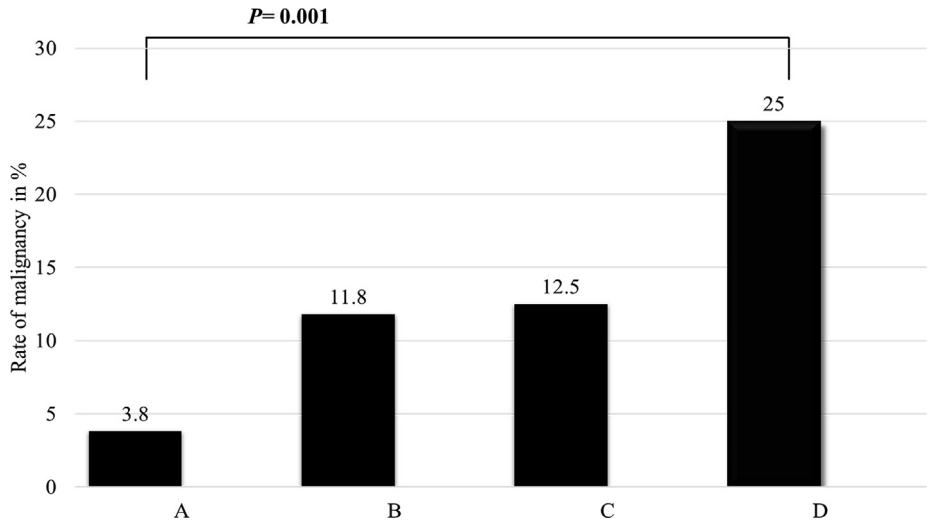

Fig. 4. Rates of high-grade dysplasia and invasive carcinoma in the main duct and mixed type IPMNs according to the degree and extent of dilatation of the main pancreatic duct (study population, n = 216). A was defined as IPMN with segmental type dilatation and main pancreatic duct (MPD) diameter 5–9 mm; B was defined as IPMN with diffuse-type dilatation and MPD diameter 5–9 mm; C was defined as IPMN with segmental type dilatation and MPD ≥10 mm; and D was defined as IPMN with diffuse-type dilatation and MPD ≥10 mm.

evaluated the rate of HGD and invasive carcinoma in MD or mixed-type IPMNs without enhancing MNs, the rate of HGD and invasive carcinoma in the MPD diameter of 5–9 mm group was significantly lower than that in the MPD ≥10 mm group (7.8% vs. 22%, P = 0.005). These results support the revised 2017 International Consensus and 2018 European guidelines that MPD dilation of 5–9 mm should be considered as a worrisome feature, supporting close observation without immediate surgical resection.

In our study, the rate of HGD and invasive carcinoma of MD or mixed-type IPMNs patients was only 20.8%, which is lower than the malignancy rate of 50%–90% reported in a previous surgical series [21,26,27]. Two main reasons can explain this difference. First, previous surgical series may have selection bias, as more patients with MNs might have been included in the previous study. Compared with the previous studies, which accounted for 46.2–62.9% of patients with MNs or a solid mass in the pancreas [20,27], our study only included 16.6% of patients with enhancing MNs. In our study, the rate of HGD and invasive carcinoma was 11.1% (24/216) in patients without enhancing MNs, and 69.8% (30/43) in patients with enhancing MNs. The difference in the proportion of MNs may result in a difference in the rate of HGD and invasive carcinoma.

Second, in terms of malignancy potential, the MD and mixed-type IPMNs may not be a homogeneous group. There may be a group of patients who have a relatively lower risk of malignancy. In the present study, enhancing MNs, MPD dilatation of >10 mm, and diffuse MPD dilatation were significant predictors of HGD and invasive carcinoma, and dual positivity with two predictors (MPD dilatation of >10 mm and diffuse MPD dilatation) resulted in significantly higher rates of HGD and invasive carcinoma than those observed in the dual negative group. Diffuse MPD dilatation has been reported as an independent risk factor of HGD and invasive carcinoma in mixed-type IPMNs [28]. Diffuse MPD dilatation may reflect a diffuse and extensive involvement of disease. However, the International Consensus guidelines have not adopted the disease extent as criteria in the treatment algorithm. In the present study, 79 patients (36.6%) of MD or mixed-type IPMNs without enhancing MNs were in the dual negative group (segmental MPD dilatation and MPD diameter of <10 mm), and the rate of HGD and invasive carcinoma among these patients was significantly lower than that of patients with one predictor (3.8% vs. 15.3%; $P = 0.01$) or two predictors (3.8% vs. 25%, $P = 0.001$). These results may imply that watchful follow-up may be considered in the dual negative group if there are no enhancing MNs.

Currently, the natural chronological change of MPD-involved IPMN remains unclear. Segmental dilatation may progress to diffuse dilatation with time and become indistinguishable from the diffuse form [29]. In addition to the maximal MPD diameter, differential change of disease involvement from a segmental to diffuse extent may be a more important factor predicting HGD and invasive carcinoma.

The current study has several limitations. First, its retrospective design using multicenter data might affect the results. Since the data was obtained from five centers, preoperative imaging modalities and surgical indications might have differed between centers. However, most patients in each hospital underwent surgery according to the 2006 Sendai Guidelines and/or the 2012 International Consensus Guidelines. Large-scale studies of long-term surveillance of patients with MD and mixed-type IPMNs are mandatory in the future. This study can be fundamental for further long-term prospective study. Second, this study only included patients who underwent surgical resection. This might lead to selection bias. However, the strength of this study is that MPD involvement and its correlation with preoperative imaging was pathologically confirmed in all included patients Third, different pathologists from each hospital conducted a pathologic assessment of IPMNs according to 2010 WHO classification. This might cause bias in the determination of the dysplasia grade of the IPMNs. In the present study, we could not describe the detailed histological subtypes of IPMNs.

In conclusion, MD and mixed-type IPMNs without enhancing MNs that have MPD dilatation less than 10 mm and segmental MPD dilatation on imaging had significantly lower rates of HGD and invasive carcinoma. These results will help identify MD and mixed-type IPMNs with low HGD and a risk of invasive carcinoma, and imaging and clinical surveillance without immediate surgery might be a reasonable strategy in such cases.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.09.010.

References

[1] Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012;12:183–97.

[2] Schmidt CM, White PB, Waters JA, Yiannoutsos CT, Cummings OW, Baker M, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg 2007;246:644–51. discussion 51-4.

[3] Ceppa EP, Roch AM, Cioffi JL, Sharma N, Easler JJ, DeWitt JM, et al. Invasive, mixed-type intraductal papillary mucinous neoplasm: superior prognosis compared to invasive main-duct intraductal papillary mucinous neoplasm. Surgery 2015;158:937–44. discussion 44-5.

[4] Hwang DW, Jang JY, Lee SE, Lim CS, Lee KU, Kim SW. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. Langenbeck's Arch Surg 2012;397:93–102.

[5] Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg 2004;239:678–85. discussion 85-7.

[6] Sugimoto M, Elliott IA, Nguyen AH, Kim S, Muthusamy VR, Watson R, et al. Assessment of a revised management strategy for patients with intraductal papillary mucinous neoplasms involving the main pancreatic duct. JAMA Surg 2017;152:e163349.

[7] Sahora K, Fernandez-del Castillo C, Dong F, Marchegiani G, Thayer SP, Ferrone CR, et al. Not all mixed-type intraductal papillary mucinous neoplasms behave like main-duct lesions: implications of minimal involvement of the main pancreatic duct. Surgery 2014;156:611–21.

[8] Suzuki Y, Atomi Y, Sugiyama M, Isaji S, Inui K, Kimura W, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. Pancreas 2004;28:241–6.

[9] Serikawa M, Sasaki T, Fujimoto Y, Kuwahara K, Chayama K. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. J Clin Gastroenterol 2006;40:856–62.

[10] Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017;17:738–53.

[11] European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018;67:789–804.

[12] Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. Dig Surg 2001;18:453–7. discussion 8.

[13] Park HM, Park SJ, Shim JR, Lee EC, Lee SD, Han SS, et al. Perioperative transfusion in pancreatoduodenectomy: the double-edged sword of pancreatic surgeons. Medicine (Baltim) 2017;96:e9019.

[14] Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006;10:1199–210. discussion 210-1.

[15] Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:824–48 e22.

[16] Salvia R, Crippa S, Partelli S, Armatura G, Malleo G, Paini M, et al. Differences between main-duct and branch-duct intraductal papillary mucinous neoplasms of the pancreas. World J Gastrointest Surg 2010;2:342–6.

[17] Elta GH, Enestvedt BK, Sauer BG, Lennon AM. Acg clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol 2018;113:464–79.

[18] Shin SH, Han DJ, Park KT, Kim YH, Park JB, Kim SC. Validating a simple scoring system to predict malignancy and invasiveness of intraductal papillary mucinous neoplasms of the pancreas. World J Surg 2010;34:776–83.

[19] Seo N, Byun JH, Kim JH, Kim HJ, Lee SS, Song KB, et al. Validation of the 2012 international consensus guidelines using computed tomography and magnetic resonance imaging: branch duct and main duct intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 2016;263:557–64.

[20] Hackert T, Fritz S, Klauss M, Bergmann F, Hinz U, Strobel O, et al. Main-duct intraductal papillary mucinous neoplasm: high cancer risk in duct diameter of 5 to 9 mm. Ann Surg 2015;262:875–80. discussion 80-1.

[21] Abdeljawad K, Vemulapalli KC, Schmidt CM, Dewitt J, Sherman S, Imperiale TF, et al. Prevalence of malignancy in patients with pure main duct intraductal papillary mucinous neoplasms. Gastrointest Endosc 2014;79:623–9.

[22] Fritz S, Klauss M, Bergmann F, Strobel O, Schneider L, Werner J, et al. Pancreatic main-duct involvement in branch-duct IPMNs: an underestimated risk. Ann Surg 2014;260:848–55. discussion 55-6.

[23] Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6:17–32.

[24] Shi C, Hruban RH. Intraductal papillary mucinous neoplasm. Hum Pathol 2012;43:1–16.

[25] Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, et al. A revised classification system and recommendations from the baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol 2015;39:1730–41.

[26] Machado NO, Al Qadhi H, Al Wahibi K. Intraductal papillary mucinous neoplasm of pancreas. N Am J Med Sci 2015;7:160–75.

[27] Tamura K, Ohtsuka T, Ideno N, Aso T, Shindo K, Aishima S, et al. Treatment strategy for main duct intraductal papillary mucinous neoplasms of the pancreas based on the assessment of recurrence in the remnant pancreas after resection: a retrospective review. Ann Surg 2014;259:360–8.

[28] Roch AM, Ceppa EP, Al-Haddad MA, DeWitt JM, House MG, Zyromski NJ, et al. The natural history of main duct-involved, mixed-type intraductal papillary mucinous neoplasm: parameters predictive of progression. Ann Surg 2014;260:680–8. discussion 8-90.

[29] Lana S, Vallara M, Bono NE, Russo G, Artioli G, Capretti G, et al. MRI findings of intraductal papillary mucinous neoplasms (IPMNs). Acta Biomed 2016;87(Suppl 3):28–33.